Skeletal Muscle Abnormalities and Genetic Factors Related to Vertical Talus

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Abstract

Background/rationale Congenital vertical talus is a fixed dorsal dislocation of the talonavicular joint and fixed equinus contracture of the hindfoot, causing a rigid deformity recognizable at birth. The etiology and epidemiology of this condition are largely unknown, but

some evidence suggests it relates to aberrations of skeletal muscle. Identifying the tissue abnormalities and genetic causes responsible for vertical talus has the potential to lead to improved treatment and preventive strategies.

Questions/purposes We therefore (1) determined whether skeletal muscle abnormalities are present in patients with vertical talus and (2) identified associated congenital anomalies and genetic abnormalities in these patients.

Methods We identified associated congenital anomalies and genetic abnormalities present in 61 patients affected with vertical talus. We obtained abductor hallucis muscle biopsy specimens from the affected limbs of 11 of the 61 patients and compared the histopathologic characteristics with those of age-matched control subjects.

Results All muscle biopsy specimens ($n = 11$) had abnormalities compared with those from control subjects including combinations of abnormal variation in muscle fiber size ($n = 7$), type I muscle fiber smallness ($n = 6$), and abnormal fiber type predominance ($n = 5$). Isolated vertical talus occurred in 23 of the 61 patients (38%), whereas the remaining 38 patients had associated nervous system, musculoskeletal system, and/or genetic and genomic abnormalities. Ten of the 61 patients (16%) had vertical talus in one foot and clubfoot in the other. Chromosomal abnormalities, all complete or partial trisomies, were identified in three patients with vertical talus who had additional congenital abnormalities.

Conclusions Vertical talus is a heterogeneous birth defect resulting from many diverse etiologies. Abnormal skeletal muscle biopsies are common in patients with vertical talus although it is unclear whether this is primary or secondary to the joint deformity. Associated anomalies are present in 62% of all cases.

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Each author certifies that his or her institution approved the human protocol for this investigation and 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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Introduction

Congenital vertical talus is a fixed dorsal dislocation of the talonavicular joint and fixed equinus contracture of the hindfoot, causing a rigid flatfoot deformity that is present at birth although not always recognized in the newborn owing to difficulty in differentiating it from other more common and benign positional foot anomalies [10]. Left untreated, vertical talus causes considerable deformity and disability with pain and callus formation along the talar head. Treatment of vertical talus can be long, difficult, and fraught with complications. A new approach emphasizing serial casting rather than extensive soft tissue releases has been used successfully to achieve initial correction of the deformity [1, 10, 11], although the long-term results are not known.

Although not definitively known, vertical talus has an estimated incidence of one in 10,000 [19]. We suspect lack of recognition of the condition has led to underestimation of the true incidence. There also is no consensus regarding whether there is a gender predilection for this disorder. This uncertainty, as with many other demographic variables for vertical talus, stems from the lack of published studies of large series of patients with this disorder. Several small series in published studies, two of which are only in abstract form, reported a predilection for males [6], whereas another showed an equal occurrence in males and females [19]. Fifty percent of children in one series had bilateral involvement [19]. Knowing more accurately the male to female ratio for vertical talus has important implications when investigating potential genetic causes of this disorder.

The etiology of vertical talus in most cases is not known. Previous studies have suggested that approximately ½ of all cases of vertical talus occur in association with neurologic abnormalities [25] or genetic syndromes [29, 30]. The most common associated neurologic disorders (neuromuscular and central nervous system) are distal arthrogryposis and myelomeningocele [20, 25]. Other common genetic defects identified before the use of the more sensitive chromosomal microarray analysis include trisomy 18 and trisomy 13 [29, 30]. Evidence for genetic causes of vertical talus includes familial occurrence with an autosomal dominant pattern of inheritance in 12% to 20% of otherwise idiopathic cases [9, 12, 19, 23]. Specific gene mutations have been identified in a few patients. A mutation in the *HOXD10* gene encoding, a homeobox transcription factor gene expressed early in limb development, was associated with vertical talus in two families with autosomal dominant inheritance [8, 26]. Variable hand and foot anomalies, including isolated vertical talus, were associated with *GDF5* (cartilage-derived morphogenetic protein-1) gene mutations in several large families [9, 24].

Given the diversity of known genetic causes of congenital vertical talus, the pathophysiologic mechanisms responsible for its development are likely heterogeneous. Imbalances in muscle strength have been proposed to cause vertical talus in patients with myelomeningocele because of the combination of a weak tibialis posterior and strong ankle dorsiflexors [25], and in other neuromuscular conditions owing to relative weakness of the intrinsic foot muscles [28]. In utero limb immobility, a mechanism of disease pathogenesis in distal arthrogryposis [17], also may play a role in isolated idiopathic vertical talus. Although skeletal muscle abnormalities resulting from sarcomeric gene mutations are present in patients with distal arthrogryposis [5], it is not known whether skeletal muscle abnormalities are present in patients with congenital vertical talus.

We therefore asked whether (1) patients with vertical talus have a difference in mean skeletal muscle fiber size (type I versus type II) and/or muscle fiber type proportion compared with an age-matched historical control population, and (2) what types of additional congenital anomalies and genetic abnormalities are present in children with sporadic and familial vertical talus.

Patients and Materials

We prospectively followed all 61 children with vertical talus (101 feet) seen at St Louis Children's Hospital and St Louis Shriners Hospital between August 2001 and September 2009. The diagnosis of congenital vertical talus was confirmed in all patients by (1) a lateral radiograph, made with the foot in maximum plantar flexion, showing persistent dorsal translation of the forefoot on the hindfoot caused by fixed dorsal dislocation of the navicular on the head of the talus, and (2) a lateral radiograph, made with the foot in maximum dorsiflexion, showing a persistently decreased tibiocalcaneal angle, which indicates a fixed equinus contracture of the hindfoot. There were more boys than girls, nearing a 2:1 ratio (Table 1). Forty (66%) had bilateral involvement, whereas the remaining 21 (34%) had unilateral involvement with the right foot involved in seven and the left foot involved in 14. Removing the 10 patients who also had clubfoot did not affect the gender or racial distributions.

From the medical records we recorded demographic data including gender, ethnicity, bilaterality or unilaterality of vertical talus, and presence and type of comorbid congenital anomalies. Imaging studies, genetic testing results, and clinical consultation notes from orthopaedic surgery, neurology, and genetics counseling were reviewed.

Clinical genetic testing including karyotype and chromosomal microarray analyses were performed on a subset

Table 1. Demographics of entire patient population with congenital vertical talus

Demographic variable	Entire population (n = 61)	Population excluding those without clubfoot (n = 51)	Familial vertical talus (n = 20) ⁺
Gender			
Male	38/61 (62%)	33/51 (65%)	9/20 (45%)
Female	23/61 (38%)	18/51 (35%)	11/20 (55%)
Ethnicity			
White	44/61 (72%)	38/51 (74%)	18/20 (90%)
African-American	10/61 (17%)	8/51 (16%)	1/20 (5%)
Asian	5/61 (8%)	3/51 (6%)	1/20 (5%)
Other	2/61 (3%)	2/51 (4%)	0/20 (0%)
Side affected*			
Left	14/61 (23%)	6/51 (12%)	2/20 (10%)
Right	7/61 (11%)	5/51 (10%)	5/20 (25%)
Bilateral	40/61 (66%)	40/51 (78%)	13/20 (65%)

* Children with one limb affected by vertical talus and the other limb affected by congenital clubfoot deformity are considered to have unilateral deformity on the side affected by vertical talus; ⁺family history was unavailable for 15 patients.

of patients with associated congenital anomalies seen through the Division of Genetics and Genomic Medicine at St Louis Children's Hospital. To gain additional insight into the etiology of vertical talus, we performed muscle biopsies in a subgroup of 13 patients with vertical talus, between August 2006 and May 2008. Parents of these 13 patients provided informed consent at the time of surgical correction of the vertical talus. The mean age of the patients at the time of biopsy was 18 months (range, 2–54 months). Biopsy specimens were obtained by one surgeon (MBD). All biopsy specimens were taken from the abductor hallucis muscle in the affected foot for comparison with available muscle biopsy results from the same muscle in a group of historical control subjects. In patients affected bilaterally, biopsy was performed in only one limb. Two biopsy specimens (two patients) were excluded from this study because not enough muscle was obtained at the time of biopsy to perform analysis. Of the remaining 11 patients, six were considered to have idiopathic anomalies (two with contralateral clubfoot and one with a contralateral calcaneovalgus foot deformity), two had additional congenital abnormalities and known chromosomal duplications, one had myelomeningocele, one had distal arthrogryposis, and one had associated ray deficiencies.

All specimens were processed and evaluated in the Washington University Neuromuscular Laboratory. The biopsy specimens were rapidly frozen in isopentane cooled with liquid nitrogen. Cryostat-cut sections of muscle were processed for histochemistry with 13 stains (standard in our laboratory) [22]. The biopsy specimens were interpreted by

a neuromuscular specialist (AP). Abnormalities in fiber sizes and fiber type proportions were interpreted based on comparisons with control age-matched abductor hallucis muscle biopsy specimens taken from autopsy samples of patients without neuromuscular disease [27].

We determined differences in mean muscle fiber size (type I versus type II) in our cohort with vertical talus compared with the difference in mean muscle fiber size seen in historical control subjects using percent difference as a measure. We also determined differences in the proportion of type I versus type II muscle fibers in our cohort with vertical talus compared with differences in the proportion of type I versus type II muscle fibers in historical control subjects using the chi square statistic. Demographic variables and frequencies of comorbidities are expressed as percentages. All statistical analyses were performed using SPSS Version 16.0 software (SPSS Inc, Chicago, IL, USA).

Results

All muscle biopsy specimens showed morphologic abnormalities compared with specimens from historical control biopsy specimens of the same muscle taken at autopsy of otherwise healthy children [27] (Table 2). Six of 10 specimens from children with vertical talus showed small type I muscle fibers (Fig. 1A), defined as greater than 12% difference in mean fiber diameter [13]. Seven specimens showed abnormal muscle fiber size variation (Fig. 1B) that included both fiber types and was defined by fiber diameters in which the smallest fibers were less than $\frac{2}{3}$ the size of the largest fibers [21]. Four of the specimens with abnormal fiber size variation also had type I fiber smallness (Table 3). Abnormalities of fiber type proportion were noted in six idiopathic cases, including two with type I muscle fiber predominance and three with type II fiber predominance (Table 4). The most extreme example of fiber type predominance occurred in a 28 month-old child with greater than 90% type I fibers (Fig. 1C). All of these specimens also showed abnormal variation in muscle fiber size [27]. Two other muscle biopsy abnormalities occurred in patients with known comorbid diagnoses. One specimen, taken from the child with chromosome 12q duplication, showed no structural changes, but had decreased COX staining, suggestive of a mitochondrial disorder (Table 4). In one patient with myelomeningocele, the specimen showed fiber-type grouping consistent with a neuropathic injury and reinnervation (Fig. 1D).

Congenital vertical talus occurred as an isolated deformity in 23 of the 61 patients (38%) (Table 5), and occurred in association with congenital abnormalities of the nervous system or musculoskeletal system in 38 (62%), 10 of whom

Table 2. Muscle biopsy findings for patients with vertical talus and for control subjects

Patient number	Fiber size comparison			Muscle fiber type proportion	
	Mean type I diameter (μm)	Mean type II diameter (μm)	Difference in fiber size (type I compared with type II) (%)	Percentage of type I fibers (%)	Percentage of type II fibers (%)
Control [27]	14.84	13.39	+9.8	48	52
01	8.70	11.83	−26.5	25	75
02	8.64	8.82	−2.0	33	67
03	14.00	18.40	−23.9	66	34
05	13.67	18.51	−26.1	58	42
06	15.07	22.75	−33.8	48	52
07	11.00	14.07	−21.8	33	67
08	9.14	20.39	−55.2	53	47
09	21.91	24.00	−8.7	94	6
10	13.67	15.06	−9.2	73	27

Fig. 1A–D Abductor hallucis muscle biopsy specimens from patients with vertical talus are shown. With ATPase staining, type I fibers stain dark and type II fibers stain light. Histologic analysis showed (A) type I muscle fiber atrophy in 7-month-old infant, (B) abnormal fiber size variation in an 11-week-old infant, (C) marked type I muscle fiber predominance (> 90%) in child aged 2 years and 4 months, and (D) fiber type grouping characteristic of nerve injury with reinnervation in a child aged 4 years and 5 months with myelomeningocele. The loss of the normal mosaic pattern of muscle fibers with type I fibers clustered in the lower left and type II fibers in the upper right of this illustration are evident (Stain, ATPase pH 4.3; magnification, ×400). Bars in lower right corner of each image = 25 microns.

had anomalies of both. Ten of the patients with unilateral affection also had clubfoot deformity in the contralateral limb, comprising 16% of the patients in this series. In eight of 10 patients with vertical talus and clubfoot, the right foot had clubfoot and the left had vertical talus (two of these patients were considered to have idiopathic anomalies). Two patients had myelomeningocele, one of whom also had right-sided polydactyly. Two patients had caudal regression syndrome, one of which was associated with maternal diabetes. The remaining four patients had various abnormalities, including chondrodysplasia punctata, cerebral palsy with developmental hip dysplasia, cleft lip, and

Table 3. Abductor hallucis muscle biopsy abnormalities

Biopsy finding	# (n = 11)*
Type I muscle fiber smallness	6
Abnormal muscle fiber size variation	7
Type I muscle fiber predominance	2
Type II muscle fiber predominance	3
Mitochondrial disorder, decreased COX staining (patient with chromosome 12q duplication)	1
Fiber type grouping (patient with myelomeningocele)	1

* Number of abnormalities does not add up to 11, as multiple morphologic abnormalities were present in some specimens.

Table 4. Patient-specific muscle biopsy findings

Patient number	Comorbid diagnoses	Biopsy findings
01	Contralateral TEV (idiopathic)	Type II fiber predominance Type I fiber smallness
02	Right calcaneovalgus	Type II fiber predominance Fiber size variation
03	Distal arthrogryposis attributable to MYBPC1 mutation	Type I fiber smallness Fiber size variation
04	Multiple congenital abnormalities; chr 12q duplication	Decreased COX staining → mitochondrial disorder
05	None (idiopathic)	Type I fiber smallness Fiber size variation
06	Missing phalanges	Type I fiber smallness Fiber size variation
07	None (idiopathic)	Type II fiber predominance Type I fiber smallness Fiber size variation
08	Multiple congenital abnormalities; chr 16p duplication	Type I fiber smallness
09	Contralateral TEV (idiopathic)	Type I fiber predominance Fiber size variation
10	None (idiopathic)	Type I fiber predominance Fiber size variation
11	Myelomeningocele, contralateral TEV	Fiber type grouping

TEV = talipes equinovarus.

congenital heart disease. None of the patients with vertical talus and clubfoot had a known genetic or genomic abnormality.

Chromosomal abnormalities, all complete or partial trisomies, were identified in three patients with vertical talus who had additional congenital abnormalities (Table 2). One patient with hydrocephalus and vertical talus at birth had duplication of the long arm of chromosome 12. Another patient with vertical talus, congenital heart disease, ear skin tags, and hearing difficulties had a small duplication of approximately 2.8 megabases at chromosome 16p13.3, near the Rubinstein-Taybi locus. No patients had trisomy 18 or 13. One had trisomy 21.

Of 46 patients whose family histories were known, 20 (43%) had a history of congenital vertical talus, defined as at least one affected first- or second-degree relative (Table 2). Confirmation of the affected status of relatives was confirmed by physical examination, medical records, and, in some cases, radiographic evaluation. Eight of these familial cases (40%) had no associated anomalies. The proportion of patients with positive family histories and

Table 5. Congenital anomalies associated with vertical talus

Congenital anomalies	Number of patients = 61 (%) [*]	Bilateral** n = 40 (%)	Familial vertical talus n = 20 (%)
No associated anomalies	23 (38%)	17/40 (43%)	8/20 (40%)
Neuromuscular	22 (36%)	15/40 (38%)	5/20 (25%)
Cerebral palsy	5	4	0
Myelomeningocele	5	2	0
Caudal regression syndrome	4	2	1
Arthrogryposis	5	4	3
Multiple pterygium syndrome	2	2	1
Hydrocephalus	1	1	0
Orthopaedic	21 (34%)	8/40 (20%)	5/20 (25%)
Contralateral clubfoot	10	0	2
Hip dysplasia/dislocation	4	2	1
Missing phalanges	2	2	1
Leg-length discrepancy	2	0	0
Contractures	2	0	0
Polydactyly	2	0	0
Intrinsic-minus of hand	1	1	0
Syndactyly	1	1	1
Contralateral calcaneovalgus	1	0	0
Chondromalacia punctata	1	1	0
Pectus carinatum	1	1	0
Syndromic/chromosomal anomalies	5 (8%)	5/40 (13%)	3/20 (15%)
Chromosome 12q duplication	1	1	unknown
Chromosome 16p13.3 duplication	1	1	1
Trisomy 21 (Down syndrome)	1	1	0
GDF5 mutation	1	1	1
HOXD10 mutation	1	1	1
With other major congenital anomalies	5 (8%)	5/40 (13%)	3/20 (15%)
Cleft lip/palate	2	2	1
Congenital heart disease	3	3	3

^{*} Patients frequently had multiple associated anomalies, which were counted individually. They may be included in more than one category so subcategories may not equal the overall totals listed in each heading and percentages may not total 100%; ^{**}patients with bilateral affections, by definition, exclude those affected with contralateral clubfoot deformity.

associated neuromuscular and orthopaedic anomalies was less than in the overall study population (25% vs 36%, and 25% vs 34%, respectively).

Discussion

Despite the relative frequency of vertical talus [19] and the strong evidence for a genetic basis of the disorder [8, 9, 12, 23, 26], it is not known for most cases whether abnormalities are primarily in the muscle, bone, nerve, or vasculature. An exception to this uncertainty is in the case of distal arthrogryposis, a limb contracture syndrome in which vertical talus is a common feature [15]. Distal arthrogryposis is associated with skeletal muscle abnormalities resulting from sarcomere gene mutations [5, 15]. As the phenotype of distal arthrogryposis is similar to that of isolated vertical talus, we chose to investigate whether similar skeletal muscle abnormalities are present in muscle biopsy specimens of a subset of patients with vertical talus (six of whom had idiopathic vertical talus). We therefore asked whether (1) patients with vertical talus have a difference in mean skeletal muscle fiber size (type I versus type II) and/or muscle fiber type proportion compared with an age-matched historical control population, and (2) what types of additional congenital anomalies and genetic abnormalities are present in children with sporadic and familial vertical talus.

We recognize limitations to our study. First, skeletal muscle biopsies were limited to 11 patients, six of whom had idiopathic vertical talus. Biopsy specimens from additional patients with idiopathic vertical talus might provide stronger support for the association of skeletal muscle abnormalities with idiopathic vertical talus. Second, the genetic testing, including chromosomal microarray, was performed on only a subset of patients, and a more complete evaluation is needed to assess whether genomic alterations (ie, deletions or duplications) also are responsible for isolated larger percentages of cases of vertical talus.

The most common findings in patients with idiopathic vertical talus were abnormal variations in muscle fiber size and type I muscle fiber smallness. Although these skeletal muscle morphologic variations are not specific for any one disease, they are common in congenital myopathies and distal arthrogryposis [18]. One patient with distal arthrogryposis type 1 (DA1) [15], vertical talus, and a mutation in skeletal muscle myosin binding protein C1 (MYBPC1) was included in this series. His biopsy specimen characteristically showed type I fiber atrophy. Thus, our muscle biopsy observations suggest patients with idiopathic vertical talus may have underlying skeletal muscle abnormalities. However, none of our patients (with the exception of the patient with DA1) had generalized weakness or upper extremity involvement that would be expected with myopathy or distal arthrogryposis. Substantial phenotypic variability is present in distal arthrogryposis [4]; therefore, it is possible that individuals

with vertical talus may have a mild or limited form of distal arthrogryposis type 1.

Although myelomeningocele is a relatively common cause of vertical talus, muscle biopsy results do not support a similar pathophysiologic mechanism for idiopathic vertical talus. The muscle biopsy specimen from a patient with myelomeningocele had fiber-type grouping that is consistent with chronic denervation with reinnervation, but this pattern was not present in any other biopsy specimen, suggesting that denervation is not a common mechanism of disease in patients with idiopathic vertical talus. We also detected an abnormality consistent with a mitochondrial disorder (decreased COX staining) in the specimen from a patient with partial trisomy 12q, but as far as we know, vertical talus has not been associated with mitochondrial disorders. Furthermore, there was no evidence for mitochondrial dysfunction in the specimens from children with idiopathic vertical talus, suggesting that this is uncommon in vertical talus.

There are several similarities between this cohort of patients with vertical talus and patients with clubfoot that may be informative to understanding etiologies of both disorders. Contrary to some reports that described a similar prevalence in males and females [19, 23], we found a male predisposition to vertical talus, which parallels that found in clubfoot, with an approximate 2:1 male to female ratio. Also, 10 patients in our series have clubfoot on one side and vertical talus on the other making clubfoot the most common associated orthopaedic anomaly in this series. However, a major difference is that patients with vertical talus have a higher incidence of additional congenital anomalies compared with patients who have clubfoot. In this series, only 38% of patients with vertical talus had no associated anomalies, whereas approximately 75% of patients with clubfoot have an isolated condition [14]. Although it is recognized that vertical talus may be associated with conditions such as myelomeningocele and distal arthrogryposis, we noted an equally high occurrence of associated orthopaedic anomalies such as hip dysplasia. The presence of additional orthopaedic anomalies suggests that a generalized defect in limb development may be present in these patients.

Several chromosomal anomalies were identified in patients with vertical talus with associated birth defects. Although vertical talus is part of the clinical presentation of trisomy 18 (Edward syndrome) and trisomy 13 (Patau syndrome) [2, 32], vertical talus was present in two patients with partial trisomy of chromosomes 12q and 16p. The association of vertical talus with trisomic chromosomal conditions suggests the possibility that limb development is particularly sensitive to gene dosage effects. With the development and routine use of chromosomal microarray analysis (CMA) in clinical diagnosis, many small

chromosomal deletions and duplications now are identified in children with limb birth defects [3, 7, 31].

Isolated vertical talus was familial in nearly 20% of patients of this series who had detailed pedigree analysis data available, which is consistent with other reports [8, 23]. Although the genetic defects are not known for most individuals with idiopathic vertical talus, a specific genetic diagnosis was made for two patients included in this series. We previously identified a HOXD10 mutation in one patient with a strong family history of isolated vertical talus [8] and a GDF5 mutation in a patient with a family history of incompletely penetrant hand and foot abnormalities, predominantly brachydactyly type C [9]. However, HOXD10 and GDF5 mutations are relatively rare in patients with vertical talus [8, 16], and neither genetic test currently is available clinically in the United States.

Congenital vertical talus is a birth defect associated with diverse etiologies. Our data suggest that skeletal muscle biopsy abnormalities are common in patients with vertical talus. Although nondiagnostic, these abnormalities frequently are seen in patients with congenital myopathy and distal arthrogryposis, and suggest the possibility that idiopathic vertical talus may be related to an underlying muscle or movement abnormality.

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