

Impact of congenital talipes equinovarus etiology on treatment outcomes

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DOI: 10.1111/j.1469-8749.2008.03016.x

Although congenital talipes equinovarus (CTEV) is often idiopathic, additional birth defects occur in some patients that may have an impact on the treatment of this disorder. The purpose of this study was to determine the prevalence of associated malformations, chromosomal abnormalities, or known genetic syndromes, and to compare treatment outcomes of children with idiopathic CTEV with children with non-idiopathic CTEV. Of 357 children evaluated, 273 (76%) had idiopathic CTEV (179 males, 94 females; mean age 2y 1mo [SD 1y 2mo], range 0–18y) and 84 (24%) had non-idiopathic CTEV (51 males, 33 females; mean age 2y 5mo [SD 2y], range 0–16y). Disorders affecting the nervous system were found in 46 (54%) children with non-idiopathic CTEV. In a subgroup of patients treated entirely at our institution ($n=196$), children with non-idiopathic CTEV ($n=47$) required more casts for correction than those with idiopathic CTEV ($n=149$; 5.3 vs 4.6; $p=0.016$). There was also a greater risk of recurrence in non-idiopathic CTEV (14.9% vs 4%; $p=0.009$), but no significant difference in the need for extensive surgery (2.7% vs 8.5%; $p=0.096$). Treatment was initiated at a mean age of 13 weeks (range 1wk to 2y 6mo) for both idiopathic and non-idiopathic patients, and treatment was assessed during a minimum 2-year follow-up. Non-idiopathic CTEV can be successfully treated with the Ponseti method of serial casting, with low recurrence rates or need for surgery.

Congenital talipes equinovarus (CTEV), also referred to as clubfoot, occurs in 1 in 1000 live births¹ and is one of the most common birth defects involving the musculoskeletal system. It is recognizable at birth and is readily distinguishable from positional foot anomalies because the foot is rigid and does not correct with passive movement. In contrast to metatarsus adductus and calcaneovalgus foot anomalies, both positional in nature, there is less evidence to suggest that CTEV results from intrauterine crowding or positional effects.¹ When untreated, children with CTEV walk on the sides of their feet instead of the soles, resulting in infections, callus formation, arthritis, and significant limitations in mobility and employment opportunities.² Successful treatment entails months of serial manipulations, castings, and surgical procedures, followed by bracing for several years. Most cases of CTEV occur as an isolated birth defect and are considered idiopathic. A genetic component is suggested by the 33% concordance of identical twins³ and familial occurrence in 25% of cases,⁴ but the causes are currently unknown. The pathophysiological basis of idiopathic CTEV may be better understood by studying the known causes of this birth defect.

One purpose of this study was to determine the current prevalence of additional malformations, chromosomal abnormalities, or known genetic syndromes in a hospital-based orthopedic clinic CTEV population. CTEV is a common component of several neurological disorders, including distal arthrogryposis, myotonic dystrophy, and myelomeningocele. Chromosomal abnormalities, including chromosome 2q deletion and trisomy 18, have also been associated with CTEV.⁵ In previous series the prevalence of associated anomalies in patients with CTEV varied from 11 to 48%, depending on the population and method of study.^{1,6,7} However, recent advances in neuroimaging and genetic testing have improved the ability to diagnose underlying diseases associated with CTEV.

Current treatment of idiopathic CTEV consists of serial casting using the Ponseti method to gradually correct the deformity, followed by several years of bracing to maintain correction.⁸ When initiated in the first few years of life, patients treated with the Ponseti method rarely require extensive surgical treatment and have excellent long-term outcomes.⁹ Despite the reported successful treatment of idiopathic CTEV with the Ponseti method,^{8,10–12} there is no report, to our knowledge, of the use of the Ponseti method in non-idiopathic CTEV. On the contrary, patients with non-idiopathic CTEV are often treated primarily with extensive surgical releases because the deformities in these patients are felt to be too rigid to correct with casting alone.^{13,14} Therefore, the second purpose of this study was to determine whether non-idiopathic CTEV could be corrected by the Ponseti method with a high success rate and low recurrence risk, similar to idiopathic CTEV.

Method

CLINICAL DATA COLLECTION

Children ($n=357$) evaluated for CTEV (by MBD) at St Louis Children's Hospital and Shriners Hospital St Louis, MO, USA between 2000 and 2006 were included in this study. Institutional Review Board approval was obtained for this research and informed consent was obtained from parents. Charts were reviewed for demographic data, including sex,

bilaterality or unilaterality of CTEV, age at treatment onset, number of casts required for initial correction, complications (cast slippage), compliance with foot bracing, and need for extensive surgical treatment. Patients with any apparent additional anomalies underwent evaluation by a clinical geneticist or neurologist. Most of these children had already been evaluated by these clinicians before being seen in the pediatric orthopedic clinic. However, 12 patients were referred to these consultants by the orthopedic surgeon due to the presence of additional anomalies or developmental delay. Hospital discharge summaries, genetics and neurology clinical consultations, genetic testing, imaging studies, electrodiagnostic testing, and muscle biopsy results were all reviewed. Genetic testing was not uniform across all patients, but generally consisted of routine karyotype and chromosomal microarray.

Treatment was documented for a subgroup of patients with CTEV ($n=196$) whose care was initiated and completed by a single orthopedic surgeon (MBD). This included 149 patients with idiopathic CTEV and 47 patients with non-idiopathic CTEV. Treatment outcomes of 11 of these patients with distal arthrogyriposis are being reported elsewhere.¹⁵ Patients were excluded from this portion of the study if any previous treatment of the affected limb (casting, bracing, or surgery) had occurred before our evaluation. Patients were not excluded on the basis of age at which treatment was started; several study participants whose treatment was started at more than 2 years of age were included in both idiopathic and non-idiopathic groups. Radiographs were not routinely obtained and, therefore, not used to assess outcome. Outcome measures utilized were clinical correction of the CTEV deformity components and total number of casts required for initial correction for each patient. Patients were followed up for a minimum of 2 years in order to determine the number of recurrent CTEV deformities and the number of recurrences requiring surgical correction.

TREATMENT REGIMEN

The following summarizes the use of the Ponseti method at our institution. Treatment is started as soon as possible after referral, preferably shortly after birth, and consists of gentle manipulation of the foot and application of serial long leg plaster casts. Casts are changed weekly in the clinic for an average of 4 to 6 weeks.¹⁰ Before the last cast is applied, a percutaneous lengthening of the heel cord (Achilles tendon) is performed in the clinic setting under local anesthetic. This allows restoration of normal ankle motion. Following the heelcord lengthening, a final cast is applied which remains on for 3 weeks to allow the tendon to heal. Upon removal of the last cast, the patient is fitted with an orthosis to prevent relapse of the deformity. The orthosis consists of open-toed shoes attached to an aluminum bar of approximately the length between the patient's shoulders. The shoes are attached to the bar in 60° of external rotation to prevent recurrence of the CTEV. This is used during sleeping hours until the patient is 4 years old. The parents are also instructed on gentle exercises to perform on the corrected feet to maintain foot flexibility. These exercises are to be performed daily during changes. Compliance with casting is critical to prevent recurrence of the deformity.¹⁰ Recurrent CTEV is diagnosed clinically when the ankle has decreased flexibility and the patient begins to walk on the outside of the heel. These

relapses can often be treated with repeat castings. If correction cannot be achieved with repeat casting, then a more extensive surgical release is performed.

STATISTICAL ANALYSIS

Continuous data (number of casts required to treat) are expressed as mean (SD) and the rest of variables are presented as percentages (frequency). Group differences (number of casts required to treat) were compared using the *t*-test. Categorical variables were compared with the χ^2 test, and Fisher's exact test was used when the numbers were too small (<5). For all statistical analyses, a *p* value of <0.05 was considered to be significant.

Results

Of 357 patients evaluated for CTEV, 273 (76%) had idiopathic CTEV (179 males, 94 females; mean age 2y 1mo [SD 1y 2mo], range 0–18y) with no known etiology or associated malformations and the remaining 84 patients (24%; 51 males, 33 females; mean age 2y 5mo [SD 2y], range 0–16y) had associated malformations or genetic syndromes and were classified as having non-idiopathic CTEV (Table I). There were significantly more males than females in both groups, nearing a 2:1 ratio. Bilateral CTEV was more common than unilateral in both groups. The majority of unilateral CTEV was idiopathic (108/129 patients). There did not appear to be a preference for either right or left foot involvement when the condition was unilateral.

Disorders affecting the nervous system were found in 46 out of 84 (54%) patients with non-idiopathic CTEV. Of these 84 patients, 12 (14%) had abnormalities of the central nervous system, 19 (23%) of the spinal cord, and 15 (18%) of muscle (Table II). Other brain abnormalities included three patients with severe intractable infantile seizures of unknown etiology with normal brain magnetic resonance imaging, and two patients with mental retardation,* also of unknown etiology. Many patients with multiple organ system involvement also had central nervous system abnormalities. These patients were categorized as having a probable genetic syndrome; therefore the number of patients with nervous system involvement is even greater than 54%. There were only one or two patients in each of the etiologies for non-idiopathic CTEV in this series (Table II).

Myelomeningocele, a disorder predominantly affecting the distal spinal cord, was the single diagnosis responsible for the largest number of patients with non-idiopathic CTEV (17/84 patients). Arthrogyriposis was the second most

*UK usage: learning disability.

Table I: Demographic data of patients with idiopathic and non-idiopathic CTEV

	<i>Idiopathic</i>	<i>Non-idiopathic</i>	<i>p</i>
Nr of patients (%)	273/357 (76)	84/357 (24)	NA
Male/Female	179/94	51/33	0.417
Bilateral (%)	159/273 (58)	63/84 (75)	0.006
Unilateral-right (%)	56/273 (20)	10/84 (12)	0.076
Unilateral-left (%)	52/273 (18)	11/84 (13)	0.211

CTEV, congenital talipes equinovarus; NA, not applicable.

Table II: Etiologies of non-idiopathic CTEV (additional malformations, chromosomal abnormalities, genetic syndromes)

Central nervous system, <i>n</i> (%)	12/84 (14)
Dandy Walker	2
Septo-optic dysplasia	1
Perisylvian syndrome	2
Neuroblastoma	1
Choroid plexus papilloma	1
Other	5
Spinal cord, <i>n</i> (%)	19/84 (23)
Myelomeningocele	17
Spinal muscular atrophy-like (SMN negative)	1
Tethered cord	1
Muscle, <i>n</i> (%)	15/84 (18)
Distal arthrogryposis	6
Arthrogryposis multiplex	4
Congenital myotonic dystrophy	3
Congenital muscular dystrophy	2
Chromosomal abnormality, <i>n</i> (%)	10/84 (12)
Trisomy 18	2
Trisomy 21	1
Ring chromosome 18	1
Partial trisomy 4, monosomy X	1
Partial trisomy 1q and monosomy 10q	1
Partial trisomy 13q and monosomy 5p	1
22q11.2 deletion	2
Subtelomeric deletion 13q	1
Known genetic syndromes, <i>n</i> (%)	5/84 (6)
Costello syndrome	1
Carpenter syndrome	1
Toriello Carey syndrome	1
Osteogenesis imperfecta	1
X-linked chondrodysplasia punctata	1
Probable genetic syndrome, <i>n</i> (%)	19/84 (23)
Orthopedic <i>n</i> (%) (fibular hemimelia, polydactyly, hip dysplasia, ulnar longitudinal deficiency)	6/84 (7)
Multiple congenital anomaly	13/84 (15)
Amniotic band sequence, <i>n</i> (%)	4/84 (5)

CTEV, congenital talipes equinovarus; SMN, survival motoneuron gene.

common diagnosis (10/84 patients). Genetic diagnosis of congenital myotonic dystrophy (CTG trinucleotide repeat expansions in the myotonin protein kinase gene) was made in three patients (Table II).

Chromosomal abnormalities were identified in 10 patients with multiple congenital anomalies. Three patients with small chromosomal abnormalities (one patient with subtelomeric deletion of chromosome 13q and two with 22q11.2 deletion) were detected with chromosomal microarray analysis. Twenty-four patients had multiple congenital anomalies and suspected or known genetic syndromes. Several of these patients had additional isolated orthopedic reduction deficiencies, including three with fibular hemimelia and one with ulnar longitudinal deficiency. Of the four patients with amniotic band sequence, two also had polydactyly. Two additional patients with multiple congenital abnormalities had evidence of amniotic bands.

Treatment outcomes with the Ponseti method were compared in a subgroup of patients treated entirely at our institution. This group consisted of 149 patients with idiopathic and 47 patients with non-idiopathic CTEV (Figs. 1a and 1b). Treatment was initiated at a mean age of 13 weeks (range 1wk–2y 6mo) for both idiopathic and non-idiopathic groups. There was a large range in the number of serial casts required for CTEV correction (range 1–13; Fig. 2a). Non-idiopathic CTEV required significantly more casts for correction than idiopathic CTEV (mean 5.3 vs 4.6; $p=0.016$). Initial correction was achieved in all patients with idiopathic CTEV and in all but two patients (four affected feet) in the non-idiopathic group using the Ponseti method.

Increased recurrence rate of the deformity was noted in the non-idiopathic group compared with the idiopathic group (14.9% [7/47] vs 4% [6/149]; $p=0.009$). In seven patients (five non-idiopathic and two idiopathic) recurrent deformities were successfully treated with repeat casting alone. Need for surgical treatment did not differ significantly between patients with non-idiopathic CTEV compared with idiopathic CTEV (8.5% [4/47] vs 2.7% [4/149]; $p=0.096$; Fig. 2b). Of the four patients with idiopathic CTEV that



Figure 1: (a) Bilateral congenital talipes equinovarus deformity occurring in a male patient with trisomy 18, before treatment at age 1 month and (b) after treatment at age 3 years. This patient was treated with the Ponseti method of serial casting which required a total of six casts applied weekly between the ages of 1 and 3 months.

required further surgery, two (three affected feet) required extensive soft tissue release operations while two patients (four affected feet) required tibialis anterior tendon transfers. Three patients (five affected feet) in the non-idiopathic group had extensive soft tissue release operations while one patient had a tibialis anterior tendon transfer. The extensive soft tissue release surgeries in the idiopathic CTEV group occurred in patients who were non-compliant with bracing, whereas the same surgery in non-idiopathic CTEV ($n=3$) was required because the feet were too stiff and contracted to obtain correction with the Ponseti method of serial casting.

Discussion

The prevalence of additional congenital anomalies or chromosomal abnormalities in patients with CTEV varies significantly across studies, depending on the population. The current study consisted of patients treated in an orthopedic tertiary referral center and found 24% to have known etiologies of their CTEV. In contrast, the prevalence of associated abnormalities was much higher (48.6%) in an obstetric population using ultrasound and/or postnatal examinations.⁶ A South Australian study of birth records (including stillbirths and termination of pregnancy) also demonstrated a 40% prevalence of associated birth defects.⁷ Differences in the prevalence of associated abnormalities between these two populations probably reflect the higher rates of poor pregnancy outcomes, including stillbirth, termination of pregnancy, and neonatal death, in the antenatally diagnosed CTEV.⁶

Many different etiologies and associated anomalies may be identified in patients with CTEV, although disorders specifically involving the nervous system comprise the greatest number of patients with known etiologies of their CTEV. The CTEV foot may, therefore, represent a final common pathway for disruption anywhere along the neuromuscular unit, including the brain, spinal cord, nerve, or muscle.¹⁵ Interestingly, peripheral nerve lesions (congenital neuropathies) that could lead to isolated lateral foot weakness were not identi-

fied in this series, which is consistent with a previous study that demonstrated normal motor nerve conduction studies in a group of 25 patients with idiopathic CTEV.¹⁶ However, motor neuropathy may cause a nearly identical acquired CTEV-like deformity (foot inversion) in early childhood (Dobbs MB, unpublished material). In fact, many of the conditions associated with congenital CTEV in this series (e.g. muscular dystrophy, tethered cord) may be associated with acquired forms of CTEV in childhood.

CTEV is not a requisite feature of any of the disorders found to be associated with this condition, suggesting that additional environmental, genetic, or epigenetic factors may be required for the development of contractures. The degree of muscle weakness, which is often difficult to evaluate reliably in infants with contractures, may correlate with the development of CTEV. However, not all patients born with muscle weakness have CTEV or contractures. For example, patients with spinal muscular atrophy type 1 (caused by homozygous deletions in the survival motor neuron [SMN] gene) are often quite weak at birth, yet contractures are uncommon features of this disorder and none was identified in this series. Although contractures have been reported in patients with SMN-negative spinal motor neuron disease, these are primarily found in patients with spinal muscular atrophy with respiratory distress type 1 that is associated with recessive mutations in the immunoglobulin mu binding protein 2 gene.¹⁸ Of note is the fact that patients with congenital myotonic dystrophy often have only mild weakness, yet frequently have CTEV.

Many theories have been proposed regarding the etiology of idiopathic CTEV, including primary abnormality of muscle, nerve, spinal cord, and connective tissue. Pathological evidence of retracting fibrosis with shortening of tendons and ligaments in CTEV have suggested a primary connective tissue abnormality,¹⁸ although these changes may be secondary to abnormalities of the neuromuscular unit. Recent identification of embryonic myosin heavy chain mutations in distal arthrogryposis syndromes (Freeman-Sheldon

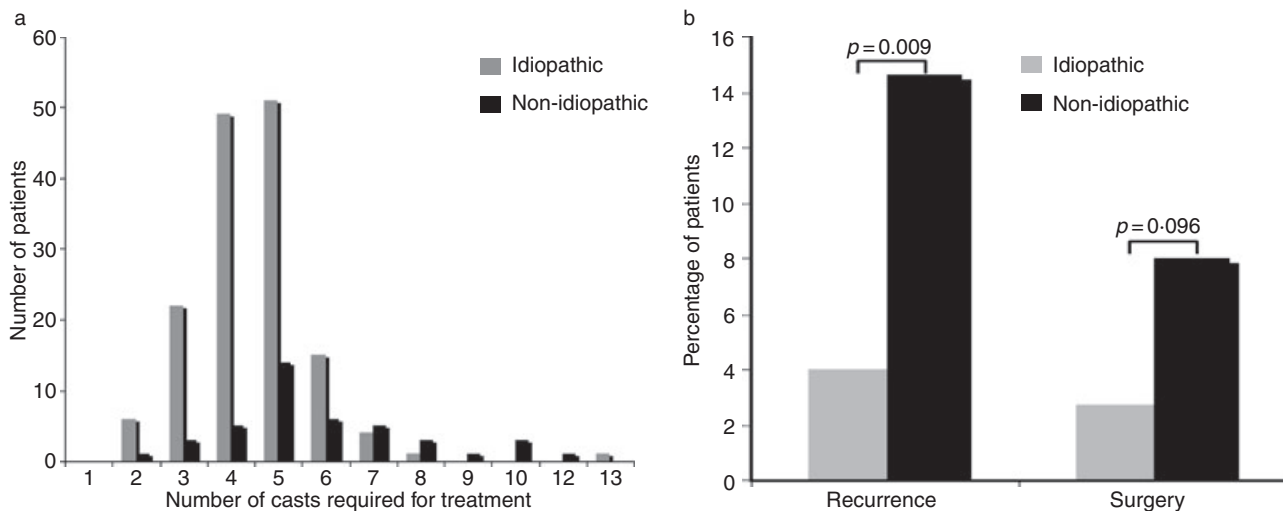


Figure 2: Differences in treatment response for idiopathic versus non-idiopathic clubfoot. (a) Number of serial casts required for initial correction of the congenital talipes equinovarus (CTEV) deformity with the Ponseti method. (b) Percentage of children who developed recurrence and percentage who required surgical correction of CTEV after initial success with the Ponseti method.

syndrome and Sheldon-Hall syndrome¹⁹) suggests that contractures may result from brief periods of embryonic akinesia.²⁰ However, it is unclear whether fetal weakness or excess contractile function causes contractures in distal arthrogryposis, as human mutations in fast skeletal muscle regulatory proteins (troponin I, troponin T, and beta-tropomyosin) appear to increase contractile activity in vitro.²¹ Muscle abnormalities limited to the embryonic or fetal period are consistent with the natural history of most cases of treated idiopathic CTEV, in which the contracture does not recur and the foot demonstrates relatively normal strength.^{9,10} However, the diverse etiologies of CTEV identified in the current study suggest that the pathophysiological basis of idiopathic CTEV may be likewise complex and multifactorial.

Excellent outcomes with the use of the Ponseti method of serial casting have been documented in patients with idiopathic CTEV, but this treatment method has rarely been applied to patients with non-idiopathic CTEV. To our knowledge, no study has reported CTEV treatment outcomes with the Ponseti method in patients with non-idiopathic CTEV. Common practice has been to treat CTEV arising from non-idiopathic CTEV with extensive soft tissue release surgery,^{13,14} an assumption based on severe rigidity often associated with these conditions. As a surrogate measure of the severity of the CTEV, we counted the number of serial casts required for correction with the Ponseti method. Although a significantly greater number of casts was required for initial correction of idiopathic compared with non-idiopathic CTEV, treatment with the Ponseti method was successful in obtaining initial correction in the majority of patients. The need for additional surgery in idiopathic versus non-idiopathic CTEV was not significant in the current study. However, certain subgroups (i.e. distal arthrogryposis) appear to be more susceptible to recurrences requiring surgical intervention. Even in this difficult population, the number of patients requiring surgery was small (<10%). The ultimate measure of success will be longer follow-up demonstrating maintenance of CTEV correction without the need for more extensive surgery. Our data support the use of the Ponseti method of treatment in all children with CTEV, irrespective of the etiology.

Conclusion

Although the vast majority of patients with CTEV are idiopathic, in this tertiary clinic series, 24% were non-idiopathic. Non-idiopathic CTEV is associated with a long list of associated malformations, chromosomal abnormalities, or known genetic syndromes; more than half are associated with abnormalities of the nervous system. Although common practice has been to treat non-idiopathic clubfoot CTEV with extensive soft tissue release surgery, we demonstrate here that non-idiopathic CTEV can be successfully treated with the Ponseti method of serial casting, with low recurrence rate and need for surgery.

Accepted for publication 19th December 2007.

Acknowledgements

CAG is supported by NIH NINDS K12 Award (NS01690) and the Children's Discovery Institute. MBD is supported by the Shriners Hospital for Children and the St Louis Children's Hospital Foundation.

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