Clin Orthop Relat Res (2009) 467:1146–1153
DOI 10.1007/s11999-009-0734-9

SYMPOSIUM: CLUBFOOT: ETIOLOGY AND TREATMENT

Update on Clubfoot: Etiology and Treatment

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Published online: 18 February 2009

Abstract Although clubfoot is one of the most common congenital abnormalities affecting the lower limb, it remains a challenge not only to understand its genetic origins but also to provide effective long-term treatment. This review provides an update on the etiology of clubfoot as well as current treatment strategies. Understanding the exact genetic etiology of clubfoot may eventually be helpful in determining both prognosis and the selection of appropriate treatment methods in individual patients. The primary treatment goal is to provide long-term correction with a foot that is fully functional and pain-free. To achieve this, a combination of approaches that applies the strengths of several methods (Ponseti method and French method) may be needed. Avoidance of extensive soft-tissue release operations in the primary treatment should be a priority, and the use of surgery for clubfoot correction should be limited to an "a la carte" mode and only after failed conservative methods.

Level of Evidence: Level V, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

The authors are supported by NIH NINDS K12 Award (NS01690), the Children's Discovery Institute, and March of Dimes Basil O'Connor Award (CAG); and by the Shriners Hospital for Children, the Saint Louis Children's Hospital Foundation, and the Pediatric Orthopaedic Society of North America (MBD).
Each author certifies that his or her institution has 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 talipes equinovarus, also referred to as clubfoot, occurs in one in 1000 live births [74] and is one of the most common birth defects involving the musculoskeletal system. Although clubfoot is recognizable at birth, the severity of the deformity can vary from mild to an extremely rigid foot that is resistant to manipulation. Two classification systems are widely used in the initial evaluation of clubfoot deformities. One of these classification systems was developed by Dimeglio et al. [17] and the second by Pirani [52]. Both systems apply a point score based on a number of different physical findings, which when totaled lead to a score that correlates with clubfoot severity. Good correlation between the two systems has been demonstrated [25].

Idiopathic clubfoot is an isolated deformity of the foot and leg that is identifiable in utero and consists of four components: equinus, hindfoot varus, forefoot adductus, and cavus. When untreated, children with clubfoot walk on the sides and/or tops of their feet, resulting in callus formation, potential skin and bone infections, inability to wear standard shoes, and substantial limitations in mobility and employment opportunities.

The first aim of this review is to provide the readers with an overview of what is known regarding the etiology of clubfoot. Because of recent advances in terms of understanding clubfoot on a genetic level, emphasis will be

placed on reviewing these advances and discussing the implications of how a genetic classification could lead to improved and individualized treatment strategies. The second aim is to give a historical perspective on the evolution of treatment strategies for clubfoot emphasizing how predominantly non-surgical strategies have become the gold standard [18, 43]. The poor long-term results of extensive soft-tissue release surgery for clubfoot will be discussed as well as what the role for surgery is in the modern day treatment of clubfoot.

Etiology

Clubfoot deformity may be associated with myelodysplasia, arthrogryposis, or multiple congenital abnormalities, but is most commonly an isolated birth defect and considered idiopathic [74]. The prevalence of additional congenital anomalies or chromosomal abnormalities in patients with clubfoot varies substantially across studies, depending on the population and ranges from 24% to 50% [3, 30]. Of the known etiologies for clubfoot, disorders specifically involving the nervous system comprise the greatest number. The most common known etiologies are distal arthrogryposis and myelomeningocele. Given the vastly different etiologies of this condition, clubfoot likely represents a final common pathway for disruption anywhere along the neuromuscular unit, including the brain, spinal cord, nerve, or muscle [27].

Many theories have been proposed to explain the etiology of idiopathic clubfoot including vascular deficiencies [34], environmental factors, in utero positioning [23], abnormal muscle insertions [9], and genetic factors [28, 30]. While it is becoming more clear that clubfoot is multifactorial in origin, genetic factors clearly play a role as suggested by the 33% concordance of identical twins and the fact that nearly 25% of all cases are familial [44]. Additional evidence for a genetic etiology is provided by differences in clubfoot prevalence across ethnic populations with the lowest prevalence in Chinese (0.39 cases per 1000 live births) and the highest in Hawaiians and Maoris (seven per 1000) [5, 13]. Though the exact genetic mechanism of clubfoot has not yet been determined, a multifactorial and possibly polygenic causation has been suggested [44, 75]. Earlier studies using complex segregation analyses suggested a single incompletely dominant disease gene with unmeasured factors contributing to incomplete penetrance [56, 71]. In a different study, segregation analysis suggested a recessive mixed model [16], and a complex segregation analysis in Pacific and Maori people demonstrated a single dominant gene with 33% penetrance [11]. A polygenic threshold model was also supported by the finding of the Carter effect, in which females require a greater genetic load in order to inherit the disorder than males [42]. However, the physiological cause of this sex dimorphism, in which males are twice as likely to be affected as females, is currently unknown.

Environmental factors may play a role in some cases of clubfoot. Early amniocentesis (< 13 weeks gestation) was associated with an increased risk in talipes equinovarus compared to midgestational amniocentesis or chorionic villus sampling [51]. Increased risk of clubfoot was partially associated with amniotic fluid leakage, suggesting that oligohydramnios occurring at a critical gestational period may be detrimental to foot development [66]. However, amniocentesis is an uncommon risk factor among patients with idiopathic clubfoot. Unlike positional foot deformities, such as metatarsus adductus, that occur at increased frequency in twin pregnancies, there are little data to support an association of clubfoot with late gestational uterine compression [75].

Environmental exposure to cigarette smoke in utero is another independent risk factor for clubfoot. In a study of over 3000 patients, Honein et al. reported an association of smoking with clubfoot, with an adjusted odds ratio of clubfoot of 1.34 for smoking only, 6.52 for family history only, and 20.30 for combined exposure to smoking and family history [33]. Variants in genes responsible for the metabolism of tobacco [31], seasonal viral infections [44], elevated maternal homocysteine [39], and methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms [59] have also been associated with an increased risk of clubfoot.

It is not yet known to what degree clubfoot will result from the inheritance of common genetic variants (such as single nucleotide polymorphisms which, by definition, are present at an allele frequency of > 5%) or rare mutations in susceptibility genes. Using a candidate gene approach, common genetic variants have been associated with clubfoot including variants in homeodomain transcription factors HOXD12 and HOXD13 [72], and several apoptotic genes including the caspase genes [32]. However, these genetic variants are all of relatively small effect, contribute only slightly to an individual's risk of clubfoot, and will require replication in larger cohorts to confirm their importance. Future genome-wide association studies will provide an unbiased approach to the identification of clubfoot susceptibility genes and with the use of large sample sizes, will be able to identify both major and minor susceptibility genes if they are present.

The importance of genes involved in early limb development was recently shown by the identification of a rare mutation in the transcription factor PITX1 in a large family with idiopathic clubfoot [28]. PITX1 is the first gene implicated in clubfoot that explains the specific involvement of the foot, since PITX1 is expressed nearly exclusively in

the hindlimb and is responsible for rapid evolutionary changes in pelvic morphology in lower vertebrates [58]. Specific involvement of the foot also appears to exclude many of the skeletal muscle contractile genes that are responsible for distal arthrogryposis [62, 63, 65, 70] in the causation of idiopathic clubfoot, as mutations in these genes cause both upper and lower extremity involvement and were not identified in idiopathic clubfoot patients [29].

There is increasing evidence that clubfoot severity and treatment outcomes may vary by etiology [8, 30]. Thus, identification of the exact etiology of clubfoot may eventually be helpful in determining both prognosis and the selection of appropriate treatment methods in an individual patient.

Treatment of Clubfoot

Surgeons have struggled over the years to identify the best method of treatment for the congenital clubfoot deformity. This struggle has lessened over the last decade as the Ponseti method of clubfoot manipulation and casting, Achilles tendon tenotomy, and foot abduction bracing has become the primary treatment for idiopathic clubfoot around the world [54]. This is due to both the excellent short-term results reproduced at multiple centers as well as the long-term results published from the University of Iowa using this method [14, 43]. In addition, there is increasing evidence that extensive surgical releases for clubfoot result in painful, arthritic feet in adulthood [21].

Early attempts at primarily nonoperative strategies relied on forceful manipulations [20]. One of the most notable devices for forceful clubfoot manipulation was the Thomas wrench developed by Hugh Owen Thomas (1834–1891) who studied medicine at Edinburgh and University College, London [20]. These types of manipulations often resulted in incomplete corrections as well as iatrogenic deformities. As a result, Kite in 1939 introduced a more gentle method of manipulation that primarily involved serial manipulations and casting [40, 41]. Kite attempted to correct each component of the clubfoot deformity separately instead of simultaneously. Correction of the heel varus was attempted by abducting the foot at the midtarsal joints and by applying direct pressure on the calcaneocuboid joint. However, by abducting the forefoot in this manner, the calcaneus was actually blocked from adducting under the talus and the heel varus persisted. Therefore, because of this fundamental flaw in technique, this method of correction was often quite lengthy with children being casted for up to 2 years. In addition, 50% to 75% of patients still required soft tissue release surgery because of incomplete corrections [46].

With the introduction of anesthesia and aseptic techniques in the late 1800's, surgical treatments for clubfoot were developed. Most of the surgeries involved different types of soft-tissue release operations but the reported good results with these techniques were around 45% [24, 50]. During this same time period, surgeons were also experimenting with different osteotomy procedures for the correction of clubfoot but, again, with disappointing results [38].

In the 1970s, extensive soft-tissue release surgery for clubfoot again became popular in part due to the efforts of Turco [67, 68]. In his single-stage release procedure, emphasis was placed on the medial release of the subtalar joint, ankle and talonavicular joint. Release of the posterolateral aspect of the ankle and subtalar joint was not performed and, as a result, one of the complications of this procedure was the development of hindfoot valgus deformity due to lateral translation of the hindfoot. Many variations of extensive soft tissue release operations were promoted in the 1980s and 1990s [35, 47, 60]. Even though extensive soft tissue release operations can provide definitive correction, there are many reported short-term complications including incomplete corrections, overcorrections, as well as neurovascular injuries [2, 73]. The few long-term followup studies that are available on clubfeet treated with extensive soft tissue releases illustrate that the results often deteriorate with time [1, 21, 36, 37]. Reported long-term complications include stiffness of the ankle and subtalar joints [21, 37], arthritis [21, 37], muscle weakness [1, 21, 37], pain [21, 37], and residual deformity [1, 21, 37]. Because of these poor long-term results, intraarticular soft tissue release surgery as primary treatment for clubfoot deformity should be avoided.

Ponseti Method

Ignacio Ponseti developed and refined his treatment method for clubfoot in the late 1940s. The method was developed in part as a response to the observation that patients treated with extensive surgeries for clubfoot often developed painful feet with residual deformities over time. Ponseti was convinced there should be a more effective and less invasive way of correcting clubfoot. As a result, he studied extensively to better understand the functional and pathological anatomy of both the normal foot and the clubfoot. His studies led to the development of the Ponseti method of clubfoot correction.

The Ponseti method is a specific method of serial manipulation, casting, and tenotomy of the Achilles tendon to achieve correction of the clubfoot [43]. Included in the method is the use of a foot abduction brace to prevent relapses as well as strategies to treat relapses once they occur based on age of the child. The importance of communication with the family early in the treatment process

as to what is involved in terms of casting and brace wear cannot be overemphasized. Parents need to be aware that this treatment method lasts for at least 4 years and requires a serious commitment from the parents to make it successful.

In general, treatment is ideally started within the first few weeks of life and consists of gentle manipulation of the foot in an office setting followed by serial application of a long leg cast as described by Ponseti [43, 54]. Though Ponseti advocates the use of plaster for the cast material as it is easier to mold, there are reports on the successful use of fiberglass materials for achieving clubfoot correction [15, 53]. Regardless of the casting material used, the casts are changed every 5 to 7 days [48]. As the Ponseti method has spread around the world there is increasing experience and success with the use of this method in children older than 1 year of age with neglected clubfoot [22, 45, 61, 64]. The upper age limit to which this method can be applied remains a moving target. In some children older than 15 months of age, serial casting may need to be performed under sedation because of the difficulty in keeping the child still enough to apply a good cast [22].

Although the Ponseti method has traditionally been applied only to individuals with idiopathic clubfoot, the Ponseti method is now being used successfully for the treatment of severe nonidiopathic clubfoot deformities such as clubfoot occurring with arthrogryposis [8], myelomeningocele [12], a host of different genetic syndromes [30], as well as neuromuscular disorders [8, 30]. The method is also being applied to the treatment of complex clubfeet recently defined by Ponseti [55] and for clubfeet that have been previously treated with extensive soft tissue release surgery but have suffered a relapse [26].

In all patients, the cavus deformity is corrected first by supinating the forefoot with direct pressure under the first metatarsal. The cavus deformity is corrected with a single cast in most cases. The hindfoot varus, forefoot adduction, and hindfoot equinus are simultaneously corrected in the next three to four casts by gently abducting the foot in supination while counterpressure is applied to the head of the talus. In most cases, after the fourth clubfoot cast all deformities are corrected with the exception of some remaining hindfoot equinus. The foot should be able to be abducted to 50° at this point and the hindfoot varus should be corrected. A tenotomy of the Achilles tendon is performed at this point to correct the remaining equinus contracture. In the author's experience a tenotomy is required in over 90% of cases. The tenotomy is performed in the clinic setting under a local anesthesia for patients under 1 year of age and under formal sedation in the operating room for those children over 1 year of age. The authors prefer to use a topical anesthetic before the tenotomy and an injectable local anesthetic only after the tenotomy is performed. If local anesthetic is injected prior to the tenotomy, the surgeon may have difficulty palpating the tendon which makes the risk of damaging the neurovascular bundles more likely [19]. The Achilles tenotomy is a complete sectioning of the tendon and not a lengthening procedure. The final long leg cast is applied after the tenotomy and the foot is positioned in 70° of abduction and only 5° to 10° of dorsiflexion. One ultrasound study suggests the tendon heals within 3 weeks of casting [4].

After the final cast is removed, the patient goes directly into a foot abduction brace to prevent relapse. Many different braces are available today that all share the same principle with shoes attached to a bar of approximately the length between the child's shoulders. Many improvements have been made based on parental reports of difficulties with earlier braces. One example is the development of a dynamic bar that allows independent movement of each leg rather than a solid bar. The dynamic bar has the potential to improve patient comfort thus resulting in improved bracing tolerance [8, 12, 30]. The rotation of the shoes on the bar is set at around 70° of external rotation for the clubfeet and around 40° of external rotation for the normal feet. The brace is worn full time (23 hours a day) for 3 months and then at sleeping time (12 to 14 hours a day) until the age of 4 years. To improve compliance with brace wear, the authors have a designated nurse educator who instructs parents on brace wear and makes followup phone calls during the first week the child goes into the brace to troubleshoot any problems that may occur [12, 22, 30]. If the parents are having trouble with the brace, they are brought back into the clinic for a potential brace adjustment and re-education. If parents are doing well with the brace, the child is seen back in clinic 1 month after initiating brace wear and then at 3-month intervals. The nurse educator also instructs parents on range-of-motion exercises to be performed on the ankle and foot several times a day to improve flexibility.

Clubfoot relapses continue to be a problem in caring for the child with clubfoot. Brace intolerance is the primary reason for recurrence [10, 22, 49], though it may also occur with successful brace wear in some patients. Most early relapses occur in the hindfoot and are clinically evident by the development of equinus and varus deformities of the heel. Early relapses can usually be treated with repeat casting followed by the use of the foot abduction brace. If there is less than 15° of ankle dorsiflexion after casting, then a repeat tenotomy of the Achilles tendon may be needed. Children over 3 years of age who present with hindfoot varus in combination with a dynamic supination of the forefoot observed while walking require a different approach. The varus of the heel and adduction of the foot are first corrected with serial casting. Once these deformities are corrected a full tibialis anterior tendon transfer to the third cuneiform is performed. The child is casted for

6 weeks postoperatively, but there is no need for use of the foot abduction brace after this procedure. The authors incorporate formal physical therapy into the postcasting regime for these patients to help with gait training and muscle strengthening.

French Method

Another popular method of clubfoot treatment that also avoids extensive surgical treatment is the French or functional method [6]. This method requires daily manipulations of the newborn clubfoot by a skilled physiotherapist followed by immobilization with adhesive taping to maintain the correction achieved with stretching. The taping holds the foot in the corrected position but also allows some motion, unlike the casting used by Ponseti. The French method also focuses on peroneal muscle strengthening as a way to maintain long-term correction. A continuous passive motion machine was added to the treatment regimen in the 1990s to help with further stretching during sleeping hours. Daily treatments are continued for the first 2 months. The treatment frequency then decreases to three times a week until the child is 6 months of age. Once the program is successful in achieving correction, parents continue both the home exercises and night splints until the child reaches walking age.

The reported success rate with the French method has varied. Dimeglio et al. in 1996 reported that 74% of patients were successfully treated with the French method, without the need for surgical intervention [18]. Others have reported a much higher need for surgical intervention following application of the French method [57, 69]. Most of the surgery required was posterior release operations for residual equinus. Another potential disadvantage of the French method is the large time commitment for the parents as the children undergo daily formal physical therapy for 2 months.

Role of Surgery in Clubfoot Correction Today

The use of surgery for primary clubfoot correction today should be limited to an "a la carte" approach [7], where structures are released only as needed to obtain correction as an adjunct to a more conservative treatment approach. The vast majority of idiopathic clubfeet should be treated with casting and a percutaneous Achilles tendon tenotomy alone [43]. For those resistant idiopathic cases, as well as some syndromic and neurogenic clubfeet, more extensive soft tissue releases may be necessary [8, 30] if casting and bracing are not sufficient. This can usually be limited to a posterior release operation as the tight medial structures even in severe clubfeet typically respond to serial casting [30]. Another indication for surgery in the clubfoot correction is for recurrent clubfoot deformities that do not respond to casting alone. Many recurrent deformities, in both clubfeet that were initially treated with casting [54] and clubfeet that were treated initially with extensive soft tissue release operations, can be corrected with casting alone or casting followed by limited "a la carte" procedures [26]. The final role for surgery in clubfoot treatment is for those feet that have been initially treated with extensive soft tissue release operations and have residual deformities either from an incomplete correction, an overcorrection, or from residual muscle imbalance.

Discussion

Despite the fact that clubfoot is one of the most common musculoskeletal birth defects there is still much unknown regarding its etiology and continued controversy regarding optimal treatment strategies. This purpose of this review was to provide an update on the recent advances made in understanding the genetic etiology of clubfoot and explore what future studies are needed to arrive at a genetic classification system for this disorder. The second purpose was to review the history of clubfoot treatment and explain how the Ponseti method has revolutionized the care of children with clubfoot around the world.

While multiple theories have been proposed to explain the etiology of clubfoot [9, 23, 34], it is becoming increasingly clear that genetic factors play a major role [28, 30]. A recent study points toward a polygenic threshold model for clubfoot inheritance where multiple genes and environmental factors will be found to play a role [42]. Variants in genes responsible for a variety of environmental factors have been associated with an increase risk of clubfoot [31, 39, 44, 59]. In addition, using a candidate gene approach, other genetic variants have been associated with clubfoot including variants in homeodomain transcription factors HOXD12 and HOXD13 [72], and several apoptotic genes including the caspase genes [32]. Of note, however, is the fact that these genetic variants are all of relatively small effect, contribute only slightly to an individual's risk of clubfoot, and will require replication in larger cohorts to confirm their importance. The next step in unraveling the genetic etiology of clubfoot will be a genome-wide association study. This type of study will provide an unbiased approach to the identification of clubfoot susceptibility genes and, with the use of large sample sizes, will be able to identify both major and minor susceptibility genes.

The ideal treatment of clubfoot has been a matter of debate for hundreds of years. There are historical reports of both primarily operative and nonoperative strategies

utilized [20]. In more recent times, Kite introduced his method of primarily cast correction of clubfoot in the 1940s [40]. His method in most surgeon's hands resulted in incomplete corrections and a high rate of surgery for residual deformities [46]. Turco then popularized a single-stage extensive soft tissue release operation for clubfoot correction in the 1970s [67, 68]. While this surgery could result in initial correction of the clubfoot deformity reported long-term results were not good with a high rate of ankle stiffness and arthritis [21, 37]. The French method is primarily nonoperative and involves daily manipulations and splinting. Though this method can be successful [6], it has been reported to result in a substantial amount of residual equinus requiring posterior release operations [57].

Though Ponseti published on his primarily nonoperative method of clubfoot correction in the 1960s [43], it did not become the gold standard until the last 10 years. His method of treatment has excellent long-term results reported for idiopathic clubfeet [14]. In addition, his method is being used with a high rate of success in very stiff clubfeet associated with distal arthrogryposis [8], myelomeningocele [12], and a host of different genetic syndromes and genetic disorders [30]. Success has also been reported in treating older children with neglected clubfoot [45, 61] and clubfeet that have relapsed after initial treatment with extensive soft-tissue release surgery [26]. There is a report combining the principles of stretching emphasized in the French method [6] with the casting and bracing method of Ponseti [22]. The stretching exercises are taught to the parents and are performed three to four times a day while out of the foot abduction brace, emphasizing dorsiflexion of the ankle. A long-term study is needed to see if the addition of therapy can reduce the number of relapses seen with the Ponseti method.

Although current treatment methods appear to be effective for most patients irrespective of etiology, knowledge of etiology may be helpful for prognosis, risk of comorbidities (ie, hip dysplasia), and response to treatment. Personalized treatment based on etiology may also allow reduced brace wear if risk of relapse correlates with etiology or genetic profile. The primary treatment goal is to provide long-term correction with a foot that is fully functional and pain-free. To achieve this, a combination of approaches that applies the strengths of several methods (Ponseti method and French method) may be needed.

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