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Mini review article

CONGENITAL CLUBFOOT: ETIOPATHOGENETIC MECHANISMS AND TREATMENT CHALLENGES

EKVINOVARUS DEFORMITET STOPALA: ETIOPATOGENETSKI MEHANIZMI I TERAPIJSKI IZAZOVI

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Abstract

Clubfoot is recognized as one of the most frequent musculoskeletal deformities. Being characterized by equinus and varus hindfoot, adduction and inversion of the forefoot, cavus and calf muscles' atrophy, it occurs in 1 to 2 per 1000 newborns. The concrete etiology of the deformity is not completely known but different studies suggest multifactorial pathogenesis, including numerous genetic and environmental risk factors. The most frequent clubfoot clinical presentation is isolated while it may also be associated with other neurologic conditions as part of a syndrome. The disease is easy seen at birth and its degree may vary from mild to an extremely rigid foot that is not reducible to manipulation. The challenge of identifyng the best clubfoot treatment method has become less demanding as Ponseti invented his method that is today thought to be the gold standard, including weekly stretching and casting while following tenotomy of the Achilles tendon is mandatory for rigid equinus. Foot abduction brace treatment for four to five years is indicated to prevent relapse. Surgical soft-tissue releases might be necessary for those resistant clubfeet, where conservative treatment is not sufficient. If untreated, clubfoot leads to lifelong disability, so it is essential to aware parents of the importance of persistent and patient commitment and compliance during the treatment period.

This paper aims to show the significance of multifactorial clubfoot etiology as well as different clubfoot therapeutic modalities.

Keywords:
clubfoot deformity,
clubfoot etiology,
Ponseti method,
Achilles tenotomy

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Sažetak

Ekvinovarus je jedan od najčešćih mišićnoskeletnih deformiteta. Karakterišu ga ekvinus, varus, aduktus i kavus stopala, zajedno sa atrofijom mišića zadnje lože potkolenice. Prosečno se javlja u 1 do 2 na 1.000 novorođene dece. Tačan uzrok oboljenja nije poznat, ali različite studije ukazuju na multifaktorsku patogenezu, tj. značaj niza genetskih i faktora sredine. Najčešća je izolovana forma oboljenja, mada se može sresti udruženo i sa drugim neurološkim stanjima, u sklopu niza sindroma. Ekvinovarus se lako prepoznaje na rođenju, a stepen samog deformiteta može varirati od blagog do veoma teškog – ekstremno rigidnog stopala, otpornog na manipulaciju. Odgovor na težak izazov u pronalaženju najboljeg terapijskog rešenja za ovaj deformitet dao je Ponseti, koji je razvio sopstveni terapijski metod ekvinovarus deformiteta, danas zlatni terapijski standard. Ovaj metod podrazumeva serijsko istezanje mekih tkiva i plasiranje korektivnih natkolenih longeta, dok je tenotomija Ahilove tetive namenjena za slučajeve rigidnog ekvinusa. Za preveciju naknadnih relapsa se, u trajanju od četiri do pet godina, koriste abdukcione ortoze. Hirurško lečenje ekvinovarusa namenjeno je slučajevima rigidnog deformiteta koji nije dobro odreagovao na inicijalni konzervativni tretman. U slučaju neadekvatnog lečenja ili izostanka lečenja ekvinovarus vodi dugotrajnoj funkcionalnoj onesposobljenosti, zbog čega je vrlo važno upozoriti roditelje na značaj uporne i strpljive saradnje za vreme trajanja tretmana.

Cilj ovog rada je da prikaže značaj multifaktorske etiologije ekvinovarus deformiteta, kao i terapijske modalitete njegovog lečenja.

Ključne reči:
ekvinovarus deformitet,
etiologija ekvinovarusa,
Ponsetijev metod,
tenotomija Ahilove tetive

Introduction

Clubfoot is recognized as one of the most frequent musculoskeletal deformities. Being characterized the equinus and varus hindfoot, adduction and inversion of the forefoot, cavus and calf muscles' atrophy it occurs in around 1 to 2 in 1000 live births approximately (1-8) (**Figure 1**). This deformity and the importance of its treatment were first described by Hippocrates (370 BC), while Ignacio Ponseti described the modern concept of conservative clubfoot treatment in 1972 (1). As a structural deformity, clubfoot is clinically recognizable at birth, so it is rarely difficult to identify it in a newborn. The severity of clubfoot deformity can range from a mild, flexible condition to a significantly rigid foot that is difficult to correct through manipulation (2, 9). The most common clubfoot form is isolated although it may be related to numerous syndromic abnormalities as the part of neurologic disease (3). Idiopathic clubfoot is present as a single musculoskeletal deformity in an infant with no other neuromuscular abnormalities (2). The concrete etiology of the deformity is not completely known but different studies suggest multifactorial pathogenesis, including numerous genetic and environmental risk factors, such as vascular deficiencies, in-utero positioning and abnormal muscle insertions. Over the past decade, the challenge of identifying the most effective treatment for clubfoot has diminished significantly with the development of the Ponseti method. This method, which involves serial stretching and casting, is now recognized as the gold standard for treating clubfoot. In a certain number of cases, there is residual equinus deformity, which can be easily corrected by Achilles tendon percutaneous tenotomy. Surgical interventions, such as medial tissue releases, are generally reserved for clubfeet that are resistant to conservative treatments, thanks to the excellent outcomes achieved with non-surgical approaches (2, 4, 9, 11, 12). Following the initial correction of the deformity, the focus of treatment shifts to preventing its recurrence through the use of various braces and footwear. This follow-up period can extend up to 10 years. It is crucial to inform parents that clubfoot active treatment spans at least three to four years and success hinges on their compliance and strict adherence to the treatment protocol. Initiating treatment within the first few weeks of life significantly improves the long-term prognosis for clubfoot deformity. Delaying treatment beyond the first six months increases the likelihood of requiring surgical intervention to correct the deformity, along with its associated complications (3, 4, 13).

This paper aims to show the significance of multifactorial clubfoot etiology as well as different clubfoot therapeutic modalities.

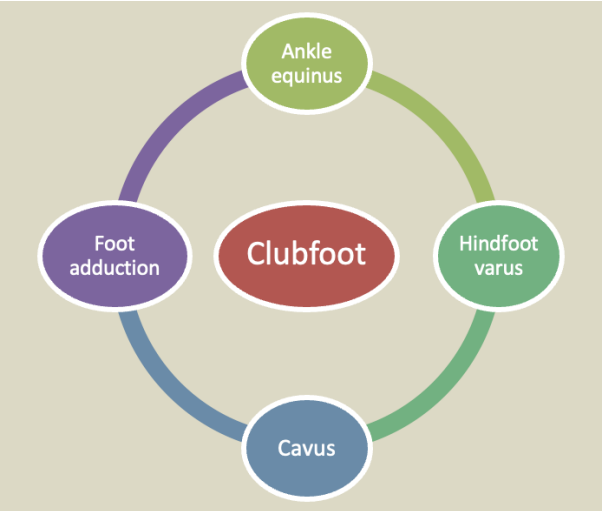

Figure 1. Clubfoot components

Epidemiological and socio-demographic characteristics

Being described as one of the most frequent musculoskeletal deformities, where approximately 90% of the affected children come from low-income or middle-income countries, clubfoot affects around 174.000 children annually (8, 10). Structural and functional deformities within this disease are part of congenital dysplastic changes of all tissues distal to the knee (2, 4, 14). If left untreated, clubfoot can result in a lifelong impairment, affecting the patient's social life and ability to walk (8, 15). Literature suggests that around 80% of clubfoot cases are idiopathic, with the remaining 20% associated with syndromic malformations observed in conditions such as arthrogryposis, cerebral palsy, and myelomeningocele. Moreover, syndromic clubfoot, which is four times less common, presents greater challenges in treatment and carries a higher risk of recurrence (2, 3, 16, 17). Additionally, while the incidence of clubfoot is approximately 1 to 2 per 1000 births among Caucasian children, there is a significant variation in its occurrence across different ethnic groups. Notably, high incidences have been reported at 7 per 1000 births among Hawaiian and Maori children, whereas lower rates of 0.5 to 1 per 1000 births are observed in Japanese and Filipino children. Secondly, between 30% to 50% of clubfoot cases are bilateral, with the right-sided clubfoot being more prevalent in unilateral instances (3, 4, 9, 18-20). Finally, the exact reason for 2:1 male predilection remains unclear (3, 21, 22) but some studies (9) point out on Carter effect, describing that females probably require a greater genetic burden to inherit the disorder.

Genetic and environmental risk factors

Given that the precise cause of clubfoot remains unidentified, its pathogenesis continues to be a subject of scientific inquiry. As previously noted, the most common clinical manifestation of clubfoot is the isolated form. Therefore, it is important to differentiate these idiopathic cases from the syndromic ones, which appear as part of neurological diseases (4, 9). There are numerous theories in the literature (9, 23-27) describing the etiology and pathogenetic mechanisms of clubfoot, including both genetic and environmental factors (**Figure 2**).

The genetic contribution to clubfoot is evidenced by a concordance rate of approximately 35% in affected identical twins, coupled with the fact that nearly one-quarter of clubfoot cases have a familial occurrence. This has led numerous researchers to assert the significant role of genetics in the pathogenesis of clubfoot (3, 9, 28). Consequently, the likelihood of offspring inheriting both structural and functional foot and ankle deformities is notably increased if both parents are affected (1, 3, 18, 19). Furthermore, the genetic component is thought to be polygenic and complex so the deformity is not determined by one gene but by several genes and a large spectrum of loci (2). However,

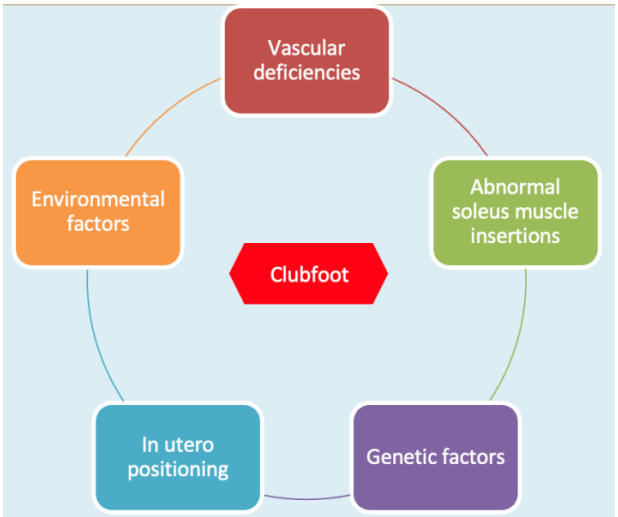

Figure 2. Clubfoot etiology

some authors (2, 29, 30) point out that an arrest in embryonic foot development might be responsible for the structural abnormality noted at birth. Secondly, arteriography in children affected with clubfoot deformity are showing the importance of anterior tibial artery hypoplasia or the fact that dorsalis pedis or posterior tibial artery are completely non-developed in the majority of cases (1, 31, 32). Whether this is the cause or the consequence of the deformity remains unknown. Some other studies (1, 33) have previously described the impact of intrauterine peroneal nerve compression as a risk factor, as abnormal somatosensory and motor potentials have been reported in nearly 50% of observed patients. Anatomical abnormalities, such as shortening of the lateral talofibular or calcaneofibular ligaments, accompanied by shortening of the deltoid ligament due to fibromatosis are described to be possible factors for clubfoot (1, 34). A study from Khansour et al. (35) has pointed out on genetic association of previously unstudied FSTL5, whose encoded product is thought to have potential role in tissue morphogenesis. Additionally, Ding et al. (36) have published the results of research in which 37 genes were selected for further analysis of clubfoot etiopathogenesis. Furthermore, as it is already known that smoking during pregnancy increases the risk for clubfoot, several genes whose encoded products have an impact on modulating tobacco smoke were studied, such as N-acetylation genes (NAT1, NAT2) as well as other xenobiotic metabolism genes (CYP1A). Genes whose products in the form of contractile proteins of skeletal myofibers are involved in muscle morphogenesis and limb development (HOXA, HOXD, IFGBP3, CAND2, WNT7α, TBX4), have also been studied as their mutations may increase the risk of clubfoot (2, 9). Finally, oligohydramniosis, accompanied with fluid leakage and early amniocentesis is an environmental factor that might be related with an increased risk for clubfoot (37, 38) as well as viral infections, increased homocysteine levels during pregnancy and methylenetetrahydropholate reductase (MTHFR) gene polimorphisms (9). This type of congenital foot deformity as well as metatarsus adductus is also significantly related to developmental dysplasia of the hip (39).

Clinical and pathoanatomical features

Clubfoot is characterized by a series of pathoanatomical changes affecting multiple structures of the foot and leg (1,2,4,14). The talus exhibits the primary deformity, with its anterior section, specifically the talar neck, deviating medially and plantarly. This deviation results in an increased angle between the trochlea and the talar neck, a feature more pronounced in neonates and even more so in clubfoot cases. Additionally, the talus is overall smaller, with delayed ossification and an inward rotation of the anterior articular surface (1,4,40,41). The calcaneus, while less deformed than the talus, shows slight medial deviation and hypoplasia of the sustentaculum tali. The metatarsal and forefoot bones present with mild hypoplasia, being shortened yet normal in width. Computed tomography (CT) studies have indicated a reduction in the physiological external rotation of the tibia in clubfoot, with the lower leg's appearance of external rotation often masked by the posterior displacement of the fibula. Ankle and subtalar joint alterations include forward displacement of the talus out of the ankle mortise and medial rotation and ventrocaudal tilting of the calcaneus relative to the talus, respectively. The talonavicular and metatarsal joints are affected by medial and plantar displacement, contributing to the adduction and inversion of the forefoot (42). Despite these substantial bone and joint changes, soft tissue alterations are equally significant, with anteromedial and posterolateral soft tissues around the talus being shortened. Histological studies have highlighted changes in all tissue types (skin, ligaments, tendons, muscles, blood vessels, nerves) in clubfoot patients, suggesting these alterations are secondary and affect various structures, including specific ligaments and muscles, notably the posterior tibial muscle, often referred to as the "clubfoot muscle" (1-2). This comprehensive pathoanatomical landscape underlines the complexity of clubfoot, involving both bone and soft tissue structures, leading to the condition's distinct clinical presentation (1). Research involving fetal development (43) has demonstrated that the foot maintains a physiological clubfoot position until the 11th week of pregnancy. It is only after this period that the foot begins to adopt its normal alignment. Clubfoot can be diagnosed prenatally during the first expert ultrasound examination of the pregnancy, typically conducted between the 20th and 24th weeks of gestation. If a clubfoot deformity is identified, further evaluation is required to screen for hereditary diseases and other genetic anomalies (2,3). Postnatally, clubfoot deformity is readily apparent through its distinctive clinical features (1). There are two main classification systems for assessing the severity of clubfoot deformity: the Dimeglio system and the Pirani system. The Dimeglio classification is often considered more reliable due to its more objective and reproducible method for scoring. It categorizes clubfoot into four grades: Grade I, a soft clubfoot which is reducible without significant resistance; Grade II, a moderate clubfoot reducible with some resistance; Grade III, a severe clubfoot reducible only against significant resistance; and Grade IV, a very severe or syndromic clubfoot (1). Children with clubfoot deformity that presents late may exhibit a gait where they walk on the outer aspect of their affected foot or display a limp, attributed to pain or the challenge of bearing weight on the foot (3,4). The natural history of untreated clubfoot deformity encompasses progressive worsening, leading to significant long-term complications. Early onset arthritis is a common outcome, as the abnormal foot and ankle alignment accelerates joint wear and tear. The physical deformity may intensify, complicating the ability to wear standard footwear or engage in physical activities. Persistent pain, a direct consequence of the deformity, can severely restrict walking and standing capabilities. Furthermore, the reduced mobility stemming from the deformity can hinder daily activities, affecting the individual's quality of life and independence (9,13).

Treatment challenges

The consensus among orthopedists is that nonoperative approaches should be the first line of treatment for idiopathic clubfoot, with the understanding that starting treatment early enhances its success due to the newborn foot's viscoelastic properties (9,44). This nonoperative strategy, primarily through methods like the Ponseti method, aims to be definitive, significantly reducing or even eliminating the need for surgical intervention and the associated risks of scarring and stiffness that surgery can entail. This approach is grounded in the lessons learned from earlier surgical outcomes, which often resulted in a scarred and stiff foot. Effective nonoperative correction follows a systematic process, with the acronym CAVE (cavus, adductus, varus, equinus) guiding the sequence of deformity correction (2,4,9,11,12). Typically, the plaster cast is changed weekly, over a period of five to six weeks, each time adjusting to correct the deformities in the specified order, with equinus being the final adjustment. Often, to expedite correction, a subcutaneous heel cord tenotomy is performed in the majority of cases, following the correction of varus and adduction, enhancing the effectiveness of the nonoperative treatment (4,9,45,46). Following the initial correction and removal of the last plaster cast, the treatment enters its maintenance phase, which requires the child to wear abduction orthoses or plastic splints. For the first three months, these are to be worn all day, except during hygiene activities, transitioning to nighttime use only thereafter. Upon the child beginning to walk, anti-varus shoes are prescribed, which are then gradually replaced with normal footwear. The duration of this maintenance phase, specifically the wearing of braces and splints, remains a topic of debate, but the general recommendation is for it to last for a minimum of two years or until the child reaches the age of ten (2,4,9,47). The French method, developed in the early 1970s by Masse and Bensahel and their colleagues, represents an alternative nonoperative approach to clubfoot correction, involving daily manipulations of the newborn's clubfoot, stimulation of surrounding

muscles (especially the peroneal muscles) to sustain the correction achieved through passive manipulation, and the temporary immobilization of the foot with nonelastic adhesive strapping. Despite its encouraging outcomes, the method has been criticized for its intensive demand on time and expertise, heavily relying on the skill level of physical therapists. The effectiveness of this approach also hinges on the cooperation and availability of families, posing a challenge when they reside far from treatment centers (4, 9, 11, 12, 48, 49). Due to these concerns, the Ponseti method is the preferred treatment option in our region, recognized for its efficiency and lower reliance on such variables (**Figure 3**).

When a clubfoot deformity is resistant, persistent, or relapses and does not improve with further non-operative interventions, surgical treatment becomes necessary to achieve a plantigrade foot. This entails performing a surgical release that targets all the pathological anatomical structures involved in a resistant clubfoot. The procedure, which includes a comprehensive release of both the hindfoot and midfoot, is considered among the most complex surgeries in orthopedics (3, 4, 13).

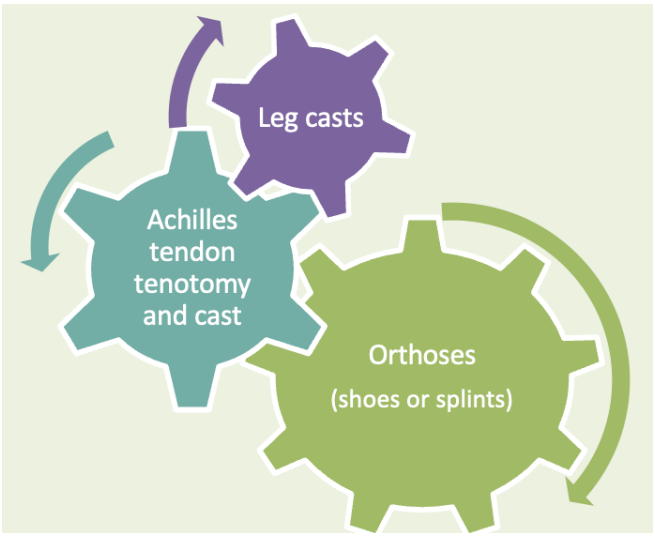

Figure 3. Ponseti method phases

Conclusion and future directions

The management and understanding of clubfoot have evolved significantly, with the Ponseti method emerging as the gold standard for treatment due to its high efficacy and nonoperative nature. Despite this advancement, the exact cause of clubfoot remains elusive, suggesting a multifactorial etiology involving a complex interplay of genetic and environmental factors. This underscores the need for further research into the genetic underpinnings of clubfoot, particularly in exploring the polygenic aspects of its pathogenesis and the variation in prevalence across different genders and ethnic populations. Future research directions could also focus on the development of predictive models to identify infants at high risk for clubfoot, facilitating early intervention and potentially reducing the need for surgical correction. Additionally, the varying success rates of nonoperative treatments like the Ponseti method and the French method highlight the importance of personalized treatment plans that consider the individual patient's condition, family capabilities, and access to healthcare services. Investigating the long-term outcomes of these treatments, including the psychological and social impact on patients and families, is crucial for optimizing care. In terms of treatment, innovations in brace design and the integration of new technologies for monitoring brace adherence and correcting deformities could enhance treatment outcomes. Even today, there is a trend in developing minimally invasive techniques (surgical as well as non-surgical) for resistant or relapsed cases that could improve recovery times and reduce complications. Ultimately, a multidisciplinary approach that incorporates genetic counseling, advanced imaging techniques, and novel therapeutic interventions could offer a more comprehensive strategy for managing clubfoot. This approach would not only aim to correct the deformity but also address the potential long-term challenges faced by individuals with clubfoot, enhancing their quality of life and mobility.

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