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Congenital Talipes Equinovarus: Requires Investigative Curiosity to Understand the Definition for Detection, Prevalence, Etiology, Treatment, and Outcomes

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Abstract

Introduction: Investigative curiosity is required following the identification of Congenital Talipes Tquinovarus (CTEV) to identify the etiology for appropriate prenatal and post-natal counseling as it has an important impact on reproductive decisions, treatment management and recurrence risk.

Material and Methods: This review article is a structured review using Pub Med with CTEV key word identifiers for consideration of the detection, prevalence, etiology, treatment, and outcomes. Review for isolated and complex CTEV was used as CTEV is common with many genetic syndromes/associations/sequences. Review period was concentrated for 2000 to 2020 but earlier cohorts were included for prevalence evaluation.

Results: The prevalence for CTEV was 0.4 to 7.0 per 1000 live births with ethic differences (Chinese 0.39; Polynesian/Pacific Islanders 7.0). Etiologies were variable considering idiopathic and non-idiopathic (fetal environment-fetal mechanical-fetal external exposure-fetal genetic) for both isolated and complex-multiple anomaly cohorts. Genetic etiologies included chromosomal, molecular mutation, and syndromes (dominant; recessive; X-linked). Consensus for neonatal treatment is use of manipulation and serial casting initially with surgical techniques for primary treatment failure and post ambulation recurrence.

Conclusion: Maternal smoking and a family history of CTEV have been identified as risk factors in affected children. The etiologies for complex CTEV have been shown to have multiple fetal environmental, mechanical, external exposure, and genetic/molecular etiologies. Many genetic syndromes have CTEV as a component of the syndrome multiple anomalies. Treatment supports the use of a non-surgical approach (Ponseti)

Method: Manipulation, casting, bracing) initially prior to the consideration of surgical techniques.

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Introduction

Congenital Talipes Equinovarus (CTEV), commonly termed 'clubfoot', is typically an isolated and idiopathic musculoskeletal system anomaly but with multiple causative etiologies and variable recurrence risk. As a congenital anomaly, CTEV can have an etiology of a primary malformation or a secondary deformation/disruption. This etiologic factor is highlighted with comparison of idiopathic and non-idiopathic (additional birth defects, chromosomal abnormalities, genetic syndromes) CTEV.

Investigative curiosity is required to identify the etiology for appropriate prenatal and post-natal counseling as it has an important impact on reproductive decisions, treatment management and recurrence risk.

This review article will consider the definition for detection, prevalence, etiology, treatment, and outcomes. The counseling and management approach for isolated and complex CTEV is important as CTEV is common with many genetic syndromes/associations/sequences and requires a coordinated multidisciplinary review team.

The anatomical features for CTEV

Definitions and associated lower limb features CTEV- clubfoot is a structural deformity of the foot and ankle with hindfoot equinus (plantar flexion), varus of the heel (inward rotation), supination, and adduction of the forefoot (plantar cavus). The anomaly presents as rigid 'inward

Table 1: Prevalence of Talipes from Mixed Populations and Time Intervals 3b, [7-16].

Reference	Time Interval Location	Cohort	Prevalence/1000 Live birth (95th confidence interval)	Other
Symthe et al. [7]	*Systematic Review/Meta-analysis* (1960-2015) *20 countries*	48 studies/13,962,989 children	*Pooled estimate* *0.51-2.03* Africa 1.11 (0.96; 1.26) Americas 1.75 (1.69; 1.80) SE Asia 1.21 (0.73; 1.68) India 1.19 (0.96; 1.42) Turkey 2.03 (1.54; 2.53) E Mediterranean 1.19 (0.98; 1.40) West Pacific 0.94 (0.64; 1.24) China 0.51 (0.50; 0.53)	comparison of low to middle income countries
Wang et al. [8]	*Europe* (1995-2011)	18 population -based congenital anomaly registries; 48 million births	*Data used total births*/5458 congenital talipes with 5056 live born (93%) *Total* *1.13 (1.10; 1.16)* N/chromosome 1.08 (1.05; 1.11) Isolated talipes 0.92 (0.90; 0.95) isolated talipes 82% associated major anomalies 11%	prenatal detection was 22%/95% confirmed after birth
Parker SE et al. [9]	*USA* 2001-2005	4.7 million live born	*Total* *1.29*	
Alderman [10]	*USA*		Non-Hispanic white 1.38 Hispanic 1.30 African-American 1.14 Asian 0.87	racial/ethnic differences
Wynne-Davis [3]/ Barker [11]	*UK*		UK 1.2 Scotland 2.0	
Ching [12] **Chung [13]** **Moorthi [14]**			Polynesian 6.8 Caucasian 1.12 Hispanic 0.68 Chinese 0.39	racial/ ethnic differences
Brougham et al. [15]/ Chapman et al. [16]	*New Zealand* *Pacific Islanders*		Maori 6-7.0 Hawaiian Tongan	increased population prevalence

turning' of the foot towards the midline of the body resembling a persistently contracted foot [1].

Hypoplasia of the lower leg muscles is a common finding, present at birth, and remains even after corrective treatment [2]. CTEV can be associated with joint laxity, congenital dislocation of the hip, tibial torsion, ray anomalies of the foot, absences of some tarsal bones, and a family history of other foot anomalies in the family [3].

Talipes are unilateral (30% to 40%) and bilateral (60% to 70%) and can be further classified as either isolated (50% to 70%) or complex with other structural or genetic anomalies (30% to 50%). Bilateral CTEV involvement is usually more severe than unilateral with presentation at delivery [4] and the unilateral cases tend to be located on the right side [5].

The structural anomalies frequently associated with CTEV are CNS/spinal (52%), other MSS (28%), and thoracic anomalies (12%) [6].

Prevalence

CTEV is identified in 0.4 to 7.0/1000 live births, occur twice as often in males compared to females (2.0-2.5 to 1) but is dependent on the population cohort evaluated. Table 1 summarizes CTEV cohorts from different ethnic populations, identifying Chinese with a low prevalence of 0.39 per 1000 live births and the Polynesian/Maori with a high prevalence of 7.0 per 1000 live births [3,7-16].

Shi et al. [17] reported on a large cohort of 4,088 fetuses with 144 (3.52%) fetuses diagnosed with limb abnormalities and CTEV-clubfeet- talipes present in 51 (35.4%) cases.

Detection, Genetic Testing, and Obstetrical Management for CTEV (isolated/Complex) prenatal assessment by detailed ultrasound can identify CTEV as early as 13 weeks of gestation but 85% of the detection is made between 13 to 23 weeks of gestation. Additional fetal MRI can assist with differentiation between isolated and complex CTEV. While MRI may not be indicated, following ultrasound imaging with an isolated CTEV assessment, MRI is most useful for additional imaging when a complex CTEV is identified by ultrasound [18].

The optimal clinical approach recommends comprehensive Ultrasound (US) to determine isolated or complex categories; diagnostic genetic analysis (CMA) with complex/additional features with amniocentesis or chorionic villus sampling; MRI can be used for

Table 2: Summarized Clinical Screening Indications and pathogenic copy number variants (<10Mb) detected by CMA highlighting the ultrasound abnormality prenatal diagnosis indication [19].

Screening Indication for possible prenatal diagnosis	Publication cohort numbers	Cases with positive CNV (<10Mb)	Literature cohort numbers	Cases with positive CNV (<10Mb)	Total combined cohort numbers	Cases with positive CNV (<10Mb)
High Risk - **US +** - aneuploidy screen + - **Family hx** - **NIPS +**	1365	61 (4.5%)	7931	197 (2.5%)	9296	258 (2.8%) **191 (4.1%)** 36 (1.1%) **24 (2.0%)** **7 (7.2%)**
Low Risk - AMA - Anxiety - other	145	0 (0%)	14,424	117 (0.8%)	14,569	117 (0.8%) 79 (0.8%) 18 (0.5%) 20 (1.6%)
Total	1510	61 (4.0%)	22,355	314 (1.4%)	23,865	375 (1.6%)

evaluation of the fetal central nervous system for additional predictive features; serial US surveillance for any additional or progressive structural changes; and comprehensive newborn assessment (or autopsy for pregnancy loss or termination). Obstetrical and delivery management requires an individualized approach based on the previous maternal obstetrical/adverse events/delivery history and the impact of the congenital anomalies in the present pregnancy. Isolated CTEV does not require a cesarean delivery unless there is a history of previous cesarean delivery and vaginal birth after cesarean delivery is not a delivery option. Complex CTEV will require comprehensive obstetrical considerations for delivery planning based on the sequential assessment of the anomalies and pregnancy status.

The additional clinical screening of maternal risk by clinical assessment categories is highlighted by Chau et al. [19] and shows that a positive Copy Number Variant (CNV) genomic result is variable between clinical risk categories (Table 2).

Invasive diagnostic genetic testing for complex fetal anomalies is commonly recommended and the 'gold-standard' has moved from a karyotype (for whole chromosome or large genetic anomaly identification) to Chromosomal Micro-Array (CMA) /Copy Number Variation (CNV) technology (for detailed smaller pathogenic and micro-deletion-duplication genetic anomaly identification). Whole Exome Sequencing (WES) can be considered when the pattern of anomalies is consistent with a specific syndrome or an associated group of clinical syndromes [19-22].

Non-Invasive cell-free Placental DNA Screening (NIPS) is generally limited to screening for the common autosomal trisomy [21,18,13] and sex chromosomes but would not be a recommended technique when fetal structural anomalies (isolated or complex) are identified.

At birth, a detailed neonatal examination is recommended, as 70% to 75% of the isolated CTEV are confirmed with an antenatal ultrasound false positive rate of 10% to 20% and 5% to 13% of the CTEV cases (false negative) are confirmed to be complex rather than the anticipated isolated status [6].

Etiologies associated with the anatomical diagnosis of CTEV-talipes

CTEV cases have been reviewed for epidemiology factors (maternal smoking; seasonality; early amniocentesis) and for etiological theories (mechanical-positional; bone-joint; connective tissue; vascular; neurological; developmental arrest) [1]. An additional etiological classification uses extrinsic (intrauterine-pressure, placental, amnion-chorion, toxins, drugs, infection, temperature) and intrinsic (genotype, polygenic, chromosomal, single gene inheritance (dominant, recessive, sex-linked)) factors [11].

Hester et al. [23] proposed that the underlying factor in all cases of CTEV is the lack of fetal movement. Fetal movement is a key developmental signal in the development of joints. The model starts at cellular differentiation moving to bone, muscle, and connective tissue formation and anatomical movement. Interference can occur at the cellular level (retinoic acid/toxins) or bone, muscle, connective tissue formation (neuromuscular blockade/physical restriction) or movement (abnormal musculature). From the existing etiology discussions for CTEV, genetic (multifactorial, polygenic, major gene), developmental, and structural (muscular, bone, vascular, nerve, abnormal tendon insertion) categories have been considered. The variable etiologies for CTEV can be shown to have an underlying disease process that acts to reduce the movement in the forefoot (or more generally). Reduced or unbalanced movement will fail to induce normal forefoot morphogenesis. Joint and bone abnormalities will result from the reduced fetal movement and the variation in severity will be due to the stage of development and the nature of the impairment. Fibrotic and vascular changes may be primary (causing defective movement) or secondary (related to abnormal development and intrinsic reduced movement). Genetic conditions will impact through similar mechanisms due to the genomic neuromuscular or developmental effects.

A Systematic Review for the diagnosis of Idiopathic Congenital Talipes Equinovarus (ICTEV) reported major limitations, in terms of heterogeneity and the lack of high-profile studies. Genetic etiologies and maternal smoking are reported to be strongly associated with the ICTEV etiology but more studies are needed to understand the complex and multifactorial etiologies for this common congenital lower-limb anomaly [24].

Table 3 summarizes the broad number of etiological categories for the isolated (idiopathic) and complex (non-idiopathic) CTEV-talipes clinical scenarios [2,6,11,20,24-30]. No major gene has been identified for isolated/idiopathic CTEV but the data supports an association with various causative genetic variants [30]. The fetal environment is associated with maternal exposure (smoking, drugs, medications, peri-natal infection), maternal anomalies (uterine malformations), and pregnancy related adverse events (oligohydramnios, amniotic-chorionic membrane rupture).

Early amniocentesis (<15 weeks gestation; procedure 'window' of 11+0-12+6 weeks) was reported in CEMAT (randomized trial-early amniocentesis 16.3/1000 live births compared to traditional amniocentesis 1.2/1000 live births) to be associated with an increased

Table 3: Etiologies for CTEV/Talipes/Clubfoot [2,6,11,20,24-30].

	Isolated CTEV (unilateral / bilateral)	**Complex** (multiple lower and upper anomalies including CTEV)	**Reference**
Idiopathic (congenital with no identified factor)	Polygenic/multifactorial: 1-4/1000 live births bilateral in 50% males /females ration: 2/1 higher concordance monozygotic (32%) with dizygotic (2.9%) recurrence 10%-20%	Developmental vascular-muscular-bony	Barker [11] Bacino [2] SMFM [6] Honein [25]
Non-Idiopathic (probable or definite etiology identified)		Greater association with central nervous system anomalies/ multifactorial/syndromes (neural tube defect; holoprosencephaly; hydranencephaly)	
Fetal Environmental	Maternal smoking alone (with family history risk increase x20) Placental insufficiency		Barker [11] Dodwell [26]
Fetal Mechanical (deformation)	Oligohydramnios (transient or continued) Uterine malformation Amniotic bands	Oligohydramnios (physiological or iatrogenic)	CEMAT [27]; Tredwell [28] Barker [11]
Fetal External Exposure (disruption)	Perinatal infection Maternal toxin Maternal drug or medication Maternal temperature	misoprostil	Barker [11] Bacino [2] SMFM [6]
Fetal Chromosomal	Isolated Unilateral Bilateral 3.1% (1/32) 0 Chromosomal 0%-5.9%	Complex Unilateral Bilateral 24% (6/25) 50% (4/8)	De le Segno [20] Swamy [29]
Fetal Molecular	Isolated/non-syndromic talipes equinovarus: associated candidate genes genome wide association genes copy number variations identified positive linkage analysis positive exome sequencing early limb transcription PITX1-TBX4 pathway muscle contracture genes	Syndromes (dominant; recessive; X-linked) Copy Number Variants / Mutation Candidate Gene Association Genome-wide Association Linkage Analysis (detailed syndrome list Table 4)	Barker [11] Bacino [2] SMFM [6] Basit and Khoshal [30] Pavone [24]

Genomic/CNV analysis duplication and/or deletion: TARP (mutations RMB 10 gene); HOX genes (HOXA/HOXD); T BOX-4 gene duplication; mutations or deletions PITX1 gene); *PITX1-TBX4* pathway; 17q23.1; 5q31; *WGS*FLNB gene; *muscle contracture gene complex*
Candidate Gene Association: HOXD12; HOXD13; HOXA9; CASP10; MTHFR; COL9A1; NAT2; TPM1; TPM2; TNNC2; GL13
Genome – wide association: NCOR2; ZNF664; FOXN3; SORC51; MMP7
Linkage analysis: 3p25.1; 13q22.1

prevalence of talipes. The etiology for the early amniocentesis CTEV was proposed to be due to a probable transient oligohydramnios, secondary to amniotic fluid leakage out of the amnion sac into the space between the amnion and chorion due to the non-fused membrane status at the procedure gestational age. Normally the amnion cavity membrane expands out to meet the chorion membrane so that space between the membranes is occluded by 15 weeks of gestation [27,28].

The traditional amniocentesis procedure (>/=15 weeks of gestation) and the CTEV risk was evaluated by a case-control study nested within a population-based cohort with linkage to a Scottish Congenital Anomalies Linked Database with 564,299 singleton births (1992-2001). The study concluded there was a modest association between CTEV and amniocentesis conducted at >/=15 weeks gestation but this was mainly confined to children with non-isolated CTEV and for mothers who had the test at >20 weeks gestation. Evaluation suggested that the association is most likely accounted for the need of an amniocentesis to be conducted because of the earlier ultrasound screening test identified a fetal anomaly. Therefore, second trimester amniocentesis is unlikely to contribute to the development of CTEV in the offspring [31].

Genetic etiologies for CTEV

Basit and Khoshhal have reviewed the genetics of clubfoot/Talipes Equinovarus (TEV) and while a better understanding of the diagnosis and management is available, there is a limited understanding of the early developmental molecular (PITX1-TBX4 genes) and signaling (HOX) pathways involved [30]. Evaluation of the genes involved in isolated and syndromic TEV disorders and experiments on model organisms have provided more insights into normal foot development. While rodent and human foot development shares major characteristics, they are dependent on close interaction between the lateral plate mesoderm cells and the outer ectodermal *via* different signaling pathways.

A. Chromosomal Etiology (Table 3) [2,6,11,20,24-30]

De le Segno et al. [20] reported, from 90 prenatally diagnosed fetuses with talipes (isolated 62%/complex 38%), that chromosomal abnormalities were present in 1.8% (1 of 56) and 29.4% (10 of 34) respectively [20]. The talipes anomaly was unilateral (31%) and bilateral (69%). Chromosomal etiologies in unilateral (isolated and complex) cases were 3.1% (1 of 32) and 24% (6 of 25) while in bilateral (isolated and complex) cases were 0% and 50% (4 of 8) respectively. The isolated chromosomal case was 47, XXY and complex chromosomal cases were five cases of trisomy 18, two cases of triploidy, and single cases of 47, XYY, 46, XX der8 t (8:11), 46, XY inv [4].

From an UK cohort, a chromosomal etiology was reported only with talipes and additional anomalies [29].

Other reports for isolated talipes have a variable prevalence for chromosomal findings (0% to 5.9%) which included genetic conditions with minimal to no antenatal ultrasound anomalies such as Klinefelter syndrome or a small area of duplication on chromosome

Table 4: Genetic Syndromes with CTEV as part of the complex anomalies [38,40].

Syndrome	Autosomal Dominant	Autosomal Recessive	X-Linked
Atelosteogenesis Type 1 Type 2 Type 3	X/new mutation X/new mutation	 X	
Abetalipoproteinemia		X	
Barth			X
Bruck (Kuskokwin)		X	
Camptomelic dysplasia	X/new mutation		
CHST3-related skeletal dysplasia		X	
Adducted thumb-clubfoot CHST14 gene	X		
Diastrophic dysplasia		X	
Distal 18q deletion	X/new mutation Majority		
Duane-radial ray	X/new mutation		
Ehlers-Danlos Type 1 CHST14 gene Type 2 DSE gene Vascular COL3A1 gene			
Freeman-Sheldon	X	X	
Genitopatellar	X/new mutation		
Kniest dysplasia	X		
Larsen FLNB gene CHST3 gene	X	 X	
Loeys-Dietz	X/new mutation 75%		
Multiple epiphyseal dysplasia		X	
Myotonic dystrophy Type 1 congenital	X		
PITX1 gene	X/mutations- Deletions		
Saul-Wilson	X/new mutation		
Sheldon-Hall	X/new mutation		
Spinal muscular atrophy with lower extremity predominance	X		
Spondylocarpotarsal FLNB gene		X	
Spondylo-epimetaphyseal dysplasia Strudwick type	X		
Spondylo-epiphyseal dysplasia congenita	X		
Spondylo-peripheral dysplasia	X		
Yuan-Harel-Lupski	X (*de novo*)		
22q11.2 deletion	X/new mutation		

[11,32-37].

B. Additional Birth Defect Association/Sequence Etiologies (Table 3)

After removing the talipes cases with a chromosomal etiology, De le Segno et al. [20] evaluated the other etiologies in the isolated (4 cases/3 bilateral) and complex (21 cases/17 bilateral) cohorts. The prenatally identified isolated CTEV cohort had two cases with CNS anomalies and single cases of arthrogryposis and fetal alcohol syndrome. The prenatally identified complex cohort had eight cases of Myelomeningocele (MMC) and single diagnosis for VACTERL sequence (vertebral-anal-cardiac-tracheo-esophageal fistula-renal-limb), arthrogryposis, Dandy-Walker malformation, Caudal-regression syndrome, Fryns syndrome, Moebius syndrome, CHARGE sequence (coloboma-heart-atresia of nasal choanae-growth restriction-ear/deafness), Fowler syndrome, cystic hygroma-hydrocephaly, esophageal atresia without TEF (Trachea-Esophageal Fistula) [20].

The 22q11.2 deletion syndrome has a variety of associated congenital anomalies (Congenital Heart Disease (CDH) (Tetralogy of Fallot); palatal deficiencies (Cleft Palate (CP)). In a retrospective study from two specialized 22q11.2 Deletion Centers, clubfoot was identified in 48/1466 cases (3.3%). Neither the CDH and/or a CP were significantly associated with the clubfoot anomaly but the prevalence of clubfoot in the 22q11.2 deletion population was 30 times higher than that observed in the general population [38].

Carroll et al. [36] summarized the clinical outcome etiologies,

Table 5: Treatment of isolated and complex talipes cases [4,29,36,37,41-48].

Cohort			
Antenatal US<20 weeks gestation Tillet et al. [46]	14 fetuses 9 bilateral 5 unilateral	23 feet antenatal 22 feet at birth - 7 grade 1 - 9 grade 2 - 6 grade 3 (2 lobster-claw)	6 (23%) no treatment 3 (13%) serial plastering (grade 2) 14 (61%) serial plastering and surgery (grade 2; grade 3; 2 lobster-claw)
Antenatal US<20 weeks gestation (mean) (range 13-34 weeks) Carroll et al. [36]	76 talipes cases isolated 17 complex 59	Isolated cases - all 17 LB Complex - TOP 26 - IUD 3 - NND 7 - LB 23	Unilateral 16 *(15 bony defect / 1 positional)* **Treatment** Physio 15 Surgery 13 (single) Bilateral 13 *(11 bony defect /2 positional)* **Treatment** Physio 12 Surgery 8 (single 5; double 3) Median age at surgery 12 months (6-30)
Impact of congenital talipes equinovarus etiology on treatment outcomes Garnett [45]	357 children with CTEV: Idiopathic 273 Non-idiopathic 94	Non-idiopathic cases had 54% with nervous system disorders Mean age at treatment start for both groups 13 weeks (1 wk-2 y 6 mon) with 2 y follow-up	Non-idiopathic patients can be treated with the Ponseti method of casting with low recurrence or need for surgery
Antenatal US and congenital cases (1990-2006) Swamy et al. [29]	**Cohort I**: 46 fetal cases of talipes from 75,933 *pregnancies* **Cohort II**: 69 congenital cases of talipes from 35,132 *deliveries*	**Cohort I** fetal unilateral 21 (45%) bilateral 25 (55%) termination 11 (6 trisomy 18-3; 21-2; 13-1) **Cohort II** (identified) antenatal 22 (32%) no antenatal 47 (68%)	**Cohort I** LB 10 no surgery (30%) 24 surgery (70%) **Cohort II** surgery 16 (73%) surgery 21 (45%)
Clinical Review Current management of clubfoot Bridgens [47]	UK cohort 1/1000 live births Majority idiopathic	Best treatment uses casting and bracing according to the Ponseti method	Results with manipulative methods are better than surgical release; recurrences secondary to non-compliance with bracing
Antenatal US<20 weeks gestation Hartge et al. [37]	106 / 46735 (0.23%) 55 live born isolated 37/55 complex 18/55 51 termination complex 46/51 **fetal karyotype** *live born* 25/55 - 5 all with NND (trisomy 14, 18, 21; ring 13; inversion 11) *stillborn* 30/51 - 11/30 (aneuploidy 6 trisomy 18, 1 trisomy 21, 1 trisomy 5, 2 triploidy, 1 dup 11)	Isolated 23/37 bilateral 7/37 left or right Complex 13/18 bilateral 3/18 left 2/18 right Termination (TA) 41/51 bilateral 5 / 51 left or right *Male gender* *-isolated LB 22/37* *-complex LB 11/18* *- isolated TA 2/5* *-complex TA 25/46*	Classified using subjective orthopedic outcome score (SOOS) 5=excellent 4=very good 3= good *6/55 were not treated i NND* *33/49 conservative* *16/49 surgery* *21/49 excellent* *19/49 very good* *1/49 good*
Review Article Conservative Management of clubfoot Balasanker [42]	UK 1/1000 live births	Four complex foot: forefoot adductus midfoot cavus hindfoot varus ankle equinus	Pre-treatment classification of severity is essential Conservative treatment best: manipulation serial casting braces

Retrospective analysis Machida et al. [41]	57 patients with 84 idiopathic clubfeet; higher surgical volume related to pediatric referral volume	Weekly gentle manipulation of the foot and serial casting using a long-leg cast; re-evaluation was after 10 serial casts; if uncorrected or relapsed after walking the posteromedial release surgical technique was used	Follow-up was >15 years with feet rated as good or excellent by International Clubfoot Study Group score; forefoot movement was 81% in conservative group while in surgery group >1 year 74% and <1 year 65%; Achilles tendon was introduced in 2007 and less PMR was found 40% *vs.* 60%
Retrospective analysis Matar et al. [44]	16 children (10 male / 6 female) with 28 syndrome-associated CTEV feet 12 years of follow-up from a tertiary center	12/17 (75%) with average follow-up of 7 years (4-12) 6/16 have associated muscular skeletal anomalies (hip dysplasia/ knee dislocation) average age at presentation 6.1 weeks (2-17) majority of deformities were severe	Initial correction was achieved in all children with average 6 Ponseti casts (4-9) and tendo-Achilles tenotomy in 21/28 feet (75%) Overall satisfaction was 23/28 (82%) Relapse 4 feet treated with casting 5 feet in 4 children required surgical soft tissue release
Idiopathic CTEV Stone P [48]	New Zealand Follow-up 163 children: more common in Maori, other Polynesian; males	Additional abnormalities in 30.1%: NZ European 43% Maori 21% Polynesian 22% 41% CNS or ND delay	Impact on healthcare planning, counselling, and orthopedic management as additional abnormalities were higher than previously reported
Are idiopathic bilateral clubfeet more severe than unilateral feet? Agarwal A [4]	India retrospective 161 patients bilateral 66 unilateral 95	M F bilateral 49 17 unilateral 76 19	Idiopathic bilateral clubfoot: more severe than unilateral at presentation greater number of casting corrective outcome bilat=unilateral
Systematic Review and Meta-analysis: An Outcome of isolated fetal talipes Di Mascio [43]	25 studies 1567 fetuses	greater anomalies: ultrasound 7.8% MRI 4.0% (after ultrasound) Isolated 7.0% (false negative) abnormal ND 7.6% (95% CI 1.0-19.4%)	Generally isolated talipes has a good prognosis; postnatal examination is required for additional anomalies that may impact prognosis

after an antenatal diagnosis of talipes, for the cohort of 59 complex talipes with associated anomalies: 9 chromosomal; 8 central nervous system; 7 arthrogryposis; 4 hydrops; 4 abdominal wall defects; 3 obstructive uropathy; 2 skeletal dysplasia; 2 sacral agenesis; 1 TTTS; 1 oligohydramnios [36]. The majority of these congenital anomaly associations have a nerve or muscular component that could contribute to the 'secondary or disruptive' talipes outcome.

C. Genomic/Molecular Etiologies (Table 3)

Prenatal diagnostic microarray testing of fetuses with ultrasound identified structural anomalies showed that micro-array aCGH analysis (array comparative genomic hybridization) was a useful diagnostic tool but the anomalies were grouped and not analyzed in individual anomaly diagnostic categories [21]. Skeletal anomalies were present in 74/201 anomalies (35.8%) with yield of copy number variants in 10/74 with multiple anomalies and 4/90 with isolated anomaly cases.

Chau et al. [19] retrospectively analyzed 1510 referred pregnant women, using CMA analysis for prenatal diagnosis, with diagnostic results stratified based on the testing indication. A literature search was used to generate an additional cohort of 22,355 fetuses looking at the fetal characteristics and spectrum of pathogenic CNV's (gains, losses, genomic loci, sizes, mode of inheritance). In total for the two cohorts, there were 23,865 fetuses. Pathogenic CNV were present in 1.6% (375/23,865) with 44 cases involving 2 or more pathogenic CNVs. The results are summarized in Table 2 [19]. While these prenatal diagnosis results were not directed at talipes alone, the fetuses with ultrasound identified abnormalities were the largest invasive diagnostic indication group (4699/23,865) with 4.1% [3.5 to 4.7] (191/4699) having a positive CNV<10 Mb result.

Further detailed genomic analysis by Whole Exome Sequencing (WES) in fetuses with structural abnormalities supported the identification of additional genetic variants that may cause structural abnormalities in fetuses with primary normal testing results using karyotyping and CMA. Fu et al. analyzed a cohort of 3,949 pregnancies with fetal structural abnormalities detected by ultrasound or MRI [22]. Overall, 18.2% of the cohort had an abnormal karyotype (720/3949). Of the fetuses with a normal karyotype, a further 8.2% had a pathogenic CNV (138/1680). WES was used for 196 fetuses with a normal karyotype and CMA, abnormal results being present in 47 cases (24%). In this study, the reported talipes were bilateral and usually were associated with other structural anomalies. The fetal skeletal system malformations were analyzed by karyotype (17/347 - 4.6%), by CMA (7/118 - 5.9%), and by WES (3/10 - 30.0%).

Sadler et al. reviews the genetics of isolated and complex clubfoot [39]. Although there is strong evidence for a genetic basis of isolated clubfoot, much of the heritability remains unexplained. Understanding the spectrum of syndromes that have clubfoot

as a feature enables a better understanding of the underlying pathophysiology of the disorder and directs genetic screening efforts toward certain genes and genetic pathways.

Table 4 summarizes a number of defined genetic syndromes with CTEV as part of the complex anomalies and their inheritance pattern (and new-de novo mutation risk) for genetic causality and recurrence counseling [38-40].

Treatment for CTEV (Considerations/Outcomes)

Machida et al. reported, in a retrospective Japanese cohort, referred to a pediatric center for care with idiopathic congenital clubfoot. Fifty-seven patients, with a total of 84 idiopathic clubfeet, were followed for a minimum of 15 years. The pre-treatment severity of CTEV evaluation tool used the Dimeglio-Benahel classification with defined scoring ranges for benign (0-4), moderate (5-9), severe (10-14), and very severe (15-20) clubfoot. The tool used the anteroposterior radiographs with foot abduction and lateral radiographs with maximum dorsiflexion and plantar flexion for assessment [40,41].

The two main CTEV treatment approaches are non-operative (Ponseti method) and operative techniques. Non-operative manipulation management should be used as the initial approach, regardless of the CTEV severity. The Ponseti approach uses weekly gentle manipulation and followed by application of serial long leg casting every 5 to 7 days. Before the final casting, if the equinus deformity persists, an Achilles tendon percutaneous tenotomy should be considered. The foot is immobilized for 21 days with 60% abduction and maximum dorsiflexion. Following this positional management, the child needs to wear a full-time foot abduction brace (23 h per day for 12 weeks). After this prolonged period of bracing, the brace can be limited to use at night and nap times until the age of 4. The treatment goal for the Ponseti method is to anatomically correct the four basic foot deformities: ankle equinus, hindfoot varus, and forefoot adducts and cavus.

Additional reported non-operative manipulation approaches are the French functional (muscle contracture; using stretching of the medial side of the foot) or physiotherapist method and the Copenhagan method (correcting the adducted deformity first, followed by the cavus, varus, and equinus over 6 weeks) [41].

The definition for the non-operative technique success or failure is based on the AP radiograph in abduction to determine whether the rolling of the calcaneus was corrected. The lateral radiograph in maximum dorsiflexion looks for the Tibio-Calcaneal Angle (TiCA) to be <70 degrees. If the CTEV foot correction was achieved, a Dennis-Brown type orthosis would be considered. If the TiCA was found to be >70 degrees, tenotomy of the Achilles tendon could be performed at 6 to 12 months after birth [41].

Surgical techniques, such as Posteromedial Release (PMR), can be used for uncorrected or relapsed talipes after the initiation of walking [40,41].

Di Mascio et al. [42] used a Systematic Review and Meta-Analysis (SRMA) to evaluate the outcome of isolated fetal talipes [43]. The SRMA conclusions were that fetuses with a prenatal diagnosis of isolated talipes have a good prognosis. Sequential ultrasound assessment is recommended to evaluate additional or later gestational age onset developmental anomalies, especially neuromuscular anomalies, which would increase the long-term developmental risk. The neurodevelopment outcomes of fetuses with isolated talipes is normal in the most cases. The incidence of aneuploidy in isolated talipes cases was reported to be low.

From this SRMA, no difference was identified between unilateral and bilateral talipes for the outcomes explored, but the study was limited by a small number of studies. The small number of cases in each analysis did not allow for a comprehensive assessment of the strength of association between the laterality of the defect and adverse perinatal outcome [42,43].

Matar et al. [43] reviewed a unique cohort of congenital talipes equinovarus that had associated syndromes (amniotic band; chromosomal anomalies; complex syndactyly; Ehler-Danlos syndrome; multiple epiphyseal dysplasia; Larsen syndrome; lissencephaly; sacral agenesis; Towes-Brock syndrome; myotonic dystrophy). The Ponseti method was found to be an effective first-line treatment, in this unique cohort, to achieve functional painless feet but more casting was required with a higher risk of talipes relapse [44]. Gurnett et al. [44] reported that the use of the Ponseti method treatment was successful for both non-idiopathic and idiopathic CTEV etiologies [45].

Table 5 summarizes the published congenital talipes cohorts, from 2000-2019, but the clinical cases and their reported outcomes are limited [4,29,36,37,41-48] Bridgens. Over this period of two decades, the trend for CTEV management has moved to an initial manipulation and serial casting approach with a decrease in primary surgical approaches.

Conclusion

Investigative curiosity is required, following the identification of CTEV in the antenatal or neonatal periods. The prevalence of CTEV is 0.3 to 7.0 per 1000 live births, occurs twice as often in males, and has variable ethnic presentation. Maternal smoking and a family history of CTEV have been identified as risk factors in affected children. The etiologies for complex CTEV have been shown to have multiple fetal environmental, mechanical, external exposure, and genetic/molecular etiologies. Many genetic syndromes have CTEV as a component of the syndrome multiple anomalies. Treatment (evidence; consensus) supports the use of a non-surgical approach (Ponseti method; manipulation, casting, bracing) initially prior to the consideration of surgical techniques.

Best Practice

1. Pre-conception counseling should be considered for women with a history of a child with CTEV (isolated or complex) for CTEV recurrence risk and other genetic risk pregnancy planning discussion. Genetic and maternal smoking factors have been identified by SRMA as risk factors for CTEV.

2. Broad CTEV categories would include idiopathic and non-idiopathic (recurrence risk) etiologies but CTEV has been shown to have multiple etiologies that must be considered.

3. Antenatal ultrasound at 16 to 20 weeks of gestation is recommended but ultrasound screening can be used as early as 13 weeks gestation with 'early' ultrasound expertise providers.

4. Sequential ultrasound (or MRI use) should be considered if CTEV (isolated or complex) is identified.

5. Routine or directed genetic screening/diagnostic testing is recommended but is dependent on the family/maternal CTEV

history or the present pregnancy CTEV (isolated or complex) needs.

6. Pregnancy management and delivery planning need to be individualized based on maternal obstetrical, medical, and surgical history and the present fetal/pregnancy status.

7. A detailed neonatal examination and assessment is recommended within 48 h of birth by pediatrics and pediatric surgery/orthopedics unless a preterm/NICU adverse event is present.

8. Evidence and consensus would support the use of initial non-surgical treatments (Ponseti method; manipulation; casting; bracing) prior to any surgical techniques, for both isolated or complex associated CTEV.

9. Long term pediatric management and follow-up is important for optimization of the CTEV outcomes.

10. Clinical, basic, and developmental research foe CTEV (isolated; complex) is required to better understand the etiological heterogeneity and treatment outcomes of CTEV.

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