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ORIGINAL ARTICLE

Associated anomalies in cases with congenital clubfoot

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Abstract

Congenital clubfoot CTEV is a common congenital anomaly, its etiology is unclear and its pathogenesis is controversial. Cases with CTEV often have other non-CTEV associated congenital anomalies. The purpose of this study was to assess the prevalence and the types of these associated anomalies in a defined population. The associated anomalies in cases with CTEV were collected in all livebirths, stillbirths, and terminations of pregnancy during 29 years in 387,067 consecutive births in the area covered by our population-based registry of congenital malformations. Of the 504 cases with CTEV, representing a prevalence of 13.02 per 10,000, 107 (21.2%) had associated anomalies. There were 31 (6.1%) cases with chromosomal abnormalities, and 21 (4.2%) non-chromosomal recognized dysmorphic conditions including syndromes: 6 arthrogryposis multiplex congenita, 2 22q11.2 microdeletion, and one fetal alcohol syndrome. Fifty-five (10.9%) of the cases had nonsyndromic multiple congenital anomalies (MCA). Anomalies in the cardiovascular, the central nervous, the urinary, the orofacial, and the musculoskeletal systems were the most common other anomalies in the cases with MCA. The anomalies associated with CTEV could be classified into a recognizable malformation syndrome in 52 of the 107 cases (48.6%) with associated anomalies. This study included special strengths: it is population-based, each affected child was examined by a geneticist, all elective terminations were ascertained, and the surveillance for anomalies was continued until 2 years of age. In conclusion the overall prevalence of associated anomalies, one of five cases, emphasizes the need for a screening for other anomalies in cases with CTEV.

KEYWORDS

congenital clubfoot, congenital anomalies, foot malformations, multiple congenital anomalies

1 | INTRODUCTION

Congenital talipes equinovarus (CTEV) also referred to as clubfoot, is the most common congenital abnormality affecting the foot. The CTEV deformity comprises the ankle in the plantar flexed (equinus) position, an inverted (varus) heel and inverted and adducted (varus) midfoot and forefoot. It is immediately recognizable at birth and is of variable severity. It is differentiated clinically from a more easily reduced positional deformity (positional talipes) and isolated metatarsus adductus deformity (Byron-Scott et al. (2005)).

It has been reported that about half the cases of talipes equinovarus have bilateral involvement and that the right leg is more likely to be affected than the left in unilateral cases (Byron-Scott et al., 2005).

CTEV is a common congenital anomaly. The reported prevalence of CTEV ranged from 5.1 (Yi et al., 2013) to 27.2 (Sharon-Weiner et al., 2017) per 10,000 births. However, Yi et al. (2013) did an epidemiological study on congenital clubfoot in China, whereas Sharon-Weiner et al. (2017) ascertained their cases by performing prenatal ultrasound scans in a department of obstetrics and gynecology in Israel.

Non-CTEV congenital anomalies may be associated with CTEV. The musculoskeletal outcome of patients with idiopathic CTEV without associated anomalies is often normal or associated with mild disability (Byron-Scott et al., 2005), whereas the overall prognosis is poor in cases with associated anomalies (Ching, Chung, & Nemechek, 1969). When these associated anomalies of concern are major and serious anomalies they account for increased morbidity and mortality (Byron-Scott et al., 2005).

The reported prevalence of anomalies associated with CTEV at birth varies considerably among diverse studies, between 10.8 (Wang et al., 2019) and 48.5% (Moorthi et al., 2005) as does the proportion and the type of associated anomalies reported (Byron-Scott et al., 2005; Sharon-Weiner et al., 2017, Sreenivas & Nataraj, 2012, Stone, Martis, & Crawford, 2018; Wang et al.,2019). It has also not been established whether CTEV is related to specific types of other congenital defects and there are differences in reports concerning which organ system is most often affected by associated anomalies. For example, Sharon-Weiner et al. (2017) reported that 25% of the patients with CTEV and associated anomalies had ventricular septal defects whereas in the series of Byron-Scott et al. (2005) 56% of the patients with CTEV and associated anomalies also had ventricular septal defects.

Moreover, comparisons between older and more recent studies are difficult because a number of what were formerly regarded as associated anomalies are now recognized to be specific syndromes, associations or sequences. Many studies on CTEV were reported however, most of them were undertaken in tertiary referral centers or in pediatric orthopedic wards. Only four studies on all types of CTEV were performed on populations (Byron-Scott et al., 2005; Jaruratanasirikul et al., 2016; Wang et al., 2019; Yi et al., 2013). The purpose of this investigation was to assess the prevalence of congenital CTEV and the frequency and the type of associated anomalies in a geographically well-defined population.

2 | CASES AND METHODS

Cases for this study came from 387,067 consecutive pregnancies of known outcome recorded by our registry of congenital malformations (Registre des malformations congénitales du Bas-Rhin) previously described (Stoll, 1985). This research project was reviewed and approved by the Ethics Committee of the Medical Faculty of Strasbourg following the World Medical Association Declaration of Helsinki. Informed consent was required for our registry. The newborns of 11 maternity hospitals were examined from January 1, 1979, to December 31, 2007. The region of investigation was the area defined by the "Departement du Bas-Rhin" which includes the urban area of Strasbourg and surrounding rural areas. All newborns including live births and stillbirths of at least 22 weeks of gestation were registered within the first 8 days postpartum, as well as all terminations of pregnancy, regardless of gestational ages. All pregnant women went to a maternity hospital for delivery, no delivery took place at home. The maternity hospital provides facilities for childbirth as well as care for pregnant women and newborn infants. Every case was examined by a clinical geneticist. When a suspected or confirmed case was reported, information was obtained from all available records. Surveillance for anomalies continued until 2 years of age. CTEV was defined as a rigid deformity, not fully passively correctable, with the presence of all of the following: (a) fixed varus of hindfoot; (b) forefoot adductus; (c) tight achilles tendon; and (d) supination posture of foot (Byron-Scott et al., 2005). Cases with ICD-10, code Q66.0 were registered including cases with CTEV secondary to a primary anomaly. Cases of positional talipes equinovarus, talipes calcaneovalgus, metatarsus varus or other foot deformity were excluded from further analysis.

A prenatal ultrasound screening for congenital anomalies in the mid-trimester of pregnancy was a routine part of antenatal care in all maternity hospitals and obstetricians' offices in the region of study. CTEV can be detected prenatally by routine sonography as early as 13 weeks' gestation by transvaginal sonography and at 16 weeks by transabdominal ultrasound (Sharon-Weiner et al., 2017).

Cases with anomalies were subdivided into categories of "isolated," when only CTEV was present, and "associated," when one or more additional non-CTEV major anomalies were recognized. The cases with non-chromosomal syndromic associated anomalies were classified as having either a syndrome, a sequence, an association or a spectrum (Hennekam et al., 2013). The nonsyndromic multiple congenital anomalies (MCA) were sub-classified according to the organ system affected. For each case with associated anomalies, a complete description was obtained, including photographs, radiographs, karyotype and autopsy. However, at the period of the study, chromosomal microarray was not available in our region nor was molecular testing.

A major anomaly was defined as a structural defect of the body and/or organs that impairs viability and requires intervention (Queisser-Luft & Spranger, 2006). Major non-CTEV anomalies within a system were counted as one defect. For example, a case with omphalocele, intestinal atresia and malrotation was counted once as omphalocele (Lowry et al., 2013). For unrelated anomalies, as, for example, polydactyly and spina bifida, these anomalies were counted twice, one in the musculoskeletal system and one in the central nervous system. A case with a Mendelian disorder that includes multiple anomalies, for example, Apert syndrome (MIM #101200), was classified as having a recognizable non-chromosomal condition. Cases with associated minor congenital anomalies such as cryptorchidism were classified as isolated. Intellectual disability was not included because it is difficult to assess in infancy.

For patients with MCA the prevalence of the most commonly associated anomalies was compared with the prevalence of these anomalies in the registry study population.

Prevalence rates were calculated using as denominator 387,067 (total births from 1979 to 2007 including all normal and malformed liveborn infants, stillborns, and prenatally diagnosed affected fetuses that were terminated).

Statistical analysis was obtained via SAS Version 8 (SAS Institute, Inc, Cary, NC). Comparisons were made using the chi-squared test.

3 | RESULTS

The number of cases with CTEV during the study period was 504 resulting in a prevalence at birth of 13.02 per 10,000. Of these

504 cases, 397 (78.8%) had isolated CTEV giving a prevalence of 10.26 per 10,000 births (Table 1) and 107 cases (21.2%) had at least one associated anomaly (Table 2), including chromosomal anomalies, recognized syndromes, and MCA.

There were 434 live births (86.1%), 12 stillbirths (2.4%) and 58 terminations of pregnancy for fetal anomalies (11.5%).

The sex ratio was 1.83 (326 males, 178 females). Unilateral CTEV (265 cases, 52.6%) was more common than bilateral CTEV (239 cases, 47.4%), but this difference did not reach statistical significance. In unilateral cases, 149 (56.2%) were on the right side and 116 (43.8%) on the left side.

In 52 of the 107 cases (48.6%) with associated anomalies, the anomalies could be classified into a recognizable pattern or syndrome. Of the 107 cases with associated anomalies, 31 (6.1%) had a chromosomal anomaly, including 15 trisomy 18, 7 trisomy 21, 3 trisomy 13, and 6 other autosomal anomalies (Tables 1 and 2). Twenty-one (4.2%) had a recognizable non-chromosomal condition including six arthrogryposis multiplex congenita (there were no cases with specific syndromes with arthrogryposis; no other body systems such as the genitourinary, the central nervous, the gastrointestinal, the cardiovascular or the respiratory systems were affected in these cases), two were affected by DiGeorge syndrome (22q11.2 microdeletion), while two showed signs of Fetal Alcohol Spectrum Disorder. There was also one case each of: achondroplasia, Apert syndrome, amniotic band, Coffin-Siris syndrome, Ehlers-Danlos syndrome, Holt-Oram syndrome, Marfan syndrome, osteogenesis imperfecta, Pena-Shokeir syndrome, Pierre Robin sequence and Smith-Lemli-Opitz syndrome. The diagnoses of the syndromes were obtained clinically.

Fifty-five cases (10.9%) were MCA. These 55 patients had 165 anomalies as one patient can have several co-occurring anomalies. A single additional anomaly was found in 63 cases, two anomalies in 27 cases and 3 or more associated anomalies in 17 cases. The anomalies in the cases with two or more associated defects were distributed randomly. Anomalies of the cardiovascular system (n = 51, 30.9%), the central nervous systems (n = 33, 20.0%), the urinary system (n = 28, 16.9%), the orofacial system (n = 22, 13.3%) and the musculoskeletal system (n = 16, 9.7%) were the most common other anomalies in the cases with MCA. The anomalies included in each organ system are shown on Table 2.

Table 3 shows the observed prevalence of the more common associated anomalies compared with the expected prevalence in the population studied obtained by our registry of congenital anomalies as well as the odds ratios and the p-values.

Twenty-one percent (105/504) of the cases of CTEV were diagnosed prenatally. All prenatally diagnosed cases were confirmed postnatally and were included. CTEV was diagnosed prenatally as an isolated anomaly in 43/397 cases (10.8%) and as an associated anomaly in 62/107 cases (57.9%). Chromosomal anomalies were detected prenatally in 26 of the 31 cases (83.8%) with CTEV and chromosomal anomalies. TOPFA (Termination Of Pregnancy for Fetal Anomalies) was performed in 58 pregnancies with fetuses with associated major anomalies diagnosed prenatally. The median gestational age at TOPFA was 19.8 weeks.

TABLE 1 Associated and isolated anomalies in 504 cases with congenital talipes equinovarus ascertained in Northeastern France from 1979 to 2007

	n	%	Prevalence[a]
Associated anomalies			
Recognized entities[b]	21	4.2	0.54
Unrecognized patterns of MCA[c]	55	10.9	1.42
Subtotal	76	15.1	1.96
Chromosomal	31	6.1	0.80
Total associated	107	21.2	2.76
Isolated anomalies	397	78.8	10.26
Total	504	100	13.02

[a]Prevalence per 10,000 births.
[b]Include syndromes, associations, sequences and spectrums.
[c]MCA: multiple congenital anomalies.

4 | DISCUSSION

Only 4 population-based studies, on all types of CTEV, isolated or associated, were reported (Byron-Scott et al., 2005; Jaruratanasirikul et al., 2016; Wang et al., 2019 and Yi et al., 2013). In these studies, the prevalence of CTEV per 10,000 births ranged from 5.1 in China (Yi et al., 2013) to 18.0 in South Australia (Byron-Scott et al., 2005). ICBDSR, an international network of registries of congenital anomalies (ICBDSR, 2013) does not register CTEV. In EUROCAT, a European network of registries of congenital anomalies (EUROCAT, 2015) (http://www.eurocat-network.eu/), the prevalence per 10,000 births of CTEV ranged from 4.4 in Tuscany, Italy, to 16.8 in Wales, UK. In our population-based study we registered a high prevalence of CTEV. This high prevalence could be due to the fact that we included all types of CTEV, whereas many studies, as, for example, Werler et al. (2013), excluded chromosomal anomaly, inherited syndrome, bilateral renal agenesis, Potter syndrome, neural tube defects, amniotic bands and arthrogryposis. Furthermore, Wang et al. (2019) excluded secondary clubfoot associated with neural tube defects, bilateral renal agenesis, Potter sequence, and arthrogryposis. Moreover, the ascertainment of the cases of CTEV was population-based in our study, whereas it was hospital-based in the studies, for example, of Wallander, Hovelius, and Michaelsson (2006), Cardy et al. (2007), and Stone et al., 2018). In the current study, 21.2% of the cases had associated anomalies. The percentage of associated anomalies in the previous reported studies is shown in Table 4. There were large regional differences in the percentage of associated anomalies in CTEV ranging from 10.8 in Europe (Wang et al., 2019) to 48.5 in Texas (Moorthi et al., 2005).

It was difficult to compare the results of our study with previous reports because of methodological differences. For example, in population-based studies, surveillance registries differ in whether ascertainment is active or passive. Other reasons that could explain the different frequencies of additional anomalies may include the time

TABLE 2 Recognizable (chromosomal abnormalities and syndromes) and nonrecognizable (multiple congenital anomalies) conditions in 107 cases with congenital talipes equinovarus and associated anomalies

	N[a]	%[a]
Recognizable conditions		
Chromosomal abnormalities	31	6.1
Trisomy 18	15	48.4
Trisomy 21	7	22.6
Trisomy 13	3	9.7
Other	6	19.4
Nonchromosomal conditions	21	4.2
Arthrogryposis	6	28.6
DiGeorge syndrome	2	9.5
Teratogen (fetal alcohol syndrome)	1	4.8
Other[b]	12	57.1
Non recognizable conditions[c]		
Congenital heart defects	51	30.9
Ventricular septal defect	20	39.2
Coarctation of aorta	1	1.9
Tetralogy of Fallot	1	1.9
Atrial septal defect	2	3.9
Other	27	52.9
Central nervous system	33	20.0
Neural tube defect	9	27.3
Hydrocephaly[d]	8	24.2
Other	16	48.5
Urinary system	28	16.9
Cystic dysplastic kidneys	8	28.6
Ureteral anomalies	10	35.7
Other	10	35.7
Orofacial	20	12.1
Cleft lip and/or palate	7	35.0
Cleft palate	13	65.0
Musculoskeletal	16	9.7
Syndactyly	3	18.7
Spine, rib and sternum	2	12.5
Limb deficiencies	2	12.5
Polydactyly	2	12.5
Other	7	43.7
Genital anomalies	4	2.4
Hypospadias	3	75.0
Other	1	25.0
Digestive system	4	2.4
Esophageal atresia	1	25.0
Intestinal malrotation	3	75.0
Ear, face, and neck	4	2.4
Eye	2	1.2
Cataract	1	50.0
Microphthalmia	1	50.0
Abdominal wall	1	0.6
Omphalocele	1	100.0
Other	2	1.2
	Total	165

[a]Number of cases (*N*) and percentage (%). The percentages for recognizable conditions are the percentages of the total number of cases, the percentages for nonrecognizable conditions are the percentages of the 165 anomalies occurring in 55 cases with multiple congenital anomalies.
[b]Other syndromes including one each: achondroplasia, Apert syndrome, amniotic band, Coffin-Siris syndrome, Ehlers-Danlos syndrome, Holt-Oram syndrome, Marfan syndrome, osteogenesis imperfecta, Pena-Shokeir syndrome, Pierre Robin sequence, Smith-Lemli-Opitz syndrome.
[c]Congenital anomalies by organ system (recognizable conditions excluded).
[d]The hydrocephaly cases did not have spina bifida.

that the surveillance continued after birth and wether all patients were taken into consideration or not, including stillbirths and terminations of pregnancy. For all reports other factors were the differences in clinical definitions and inclusion/exclusion criteria, the length of time after birth that patients were examined, the variability of clinical expression of associated anomalies, the varying proportion of patients diagnosed by objective techniques, the selection of patients, the sources of ascertainment and the size of the sample. In addition to these factors, autopsies were not always performed, there were not always follow-ups, many authors did not report all patients born in a certain geographical area, but, instead, patients referred to a certain health care facility, and there are true population differences and changes in frequency over time (Stoll, Alembik, Dott, & Roth, 2010). Moreover, several authors include the cases with isolated CTEV with the cases with additional non-CTEV major anomalies.

Most studies have found an increased risk of CTEV for the male sex. Relative risks of between 1.6 and 3.7 for males compared with females have been reported (Byron-Scott et al., 2005).

The reported percentages of chromosomal abnormalities in cases with CTEV varied (Table 5), ranging from 4.5 (Wang et al., 2019) to 6.2 (Byron-Scott et al., 2005). In the reported series the most common chromosomal abnormalities were the same as in our study: trisomy 18 and trisomy 21; 112 of 276 cases (40.6%) of CTEV with chromosomal anomalies reported were trisomy 18, with a percentage ranging from 33.3 (Sharon-Weiner et al., 2017) to 41.1 (Wang et al., 2019). Trisomy 21 was also common, with 53 cases of 276 reported cases (19.2%) with a percentage ranging from 16.7 (Byron-Scott et al., 2005) to 19.5 (Wang et al., 2019). Trisomy 13 was less frequent, present in 2 of 276 cases (0.7%) with CTEV and chromosomal abnormalities reported in the literature (Table 5).

Many non-chromosomal syndromes were reported to be associated with CTEV (Byron-Scott et al., 2005; Offerdal, Jebens, Blaas, & Eik-Nes, 2007). In the reported series, the frequency of non-chromosomal recognizable conditions varied considerably (Table 5)

TABLE 3 Prevalence of the anomalies more commonly associated in cases with congenital talipes equinovarus compared with the prevalence of these anomalies in the population studied

	Present study prevalence per 10,000			Population prevalence per 10,000						
	N	Rate	95% CI (majuscules)	N	Rate	95% CI (majuscules)	O/E	OR	CI	*p*
Ventricular septal defect	20	396,8	(244.05; 606.23)	1935	49.99	(47,79; 52,26)	7.94	8.22	(4.97; 12.88)	$3.2.10^{-12}$
Limb reduction deficiencies	2	39.7	(4.81; 142.61)	310	8.01	(7,14; 8,95)	4.96	4.97	(0.60; 18.20)	0.062
Cystic dysplastic kidneys	8	158.73	(68.78; 310.36)	349	9.02	(8.10; 10.01)	17.60	17.87	(7.61; 35.87)	$3.1.10^{-08}$
Cleft lip/palate	7	138.89	(56.02; 284.01)	506	13.07	(11,96; 14,26)	10.63	10.76	(4.28; 22.50)	1.10^{-6}
Spina bifida	9	178.57	(81.97; 336.27)	227	5.86	(5.13; 6.68)	30.47	30.98	(13.91; 60.41)	4.10^{-11}
Hydrocephaly	8	158.73	(68.78; 310.36)	318	8.21	(7.34; 9.17)	19.33	19.61	(8.35; 39.42)	$1.6.10^{-08}$
Hypospadias	3	59.52	(12.23; 172.96)	681	17.6	(16.30; 18.97)	3.38	3.40	(0.70; 10.03)	.061

Abbreviations: CI, confidence interval; O/E, observed/expected; OR, odds ratios; *p*, *p*-values.

ranging from 2.7% (Sharon-Weiner et al., 2017) to 46.3% (Sreenivas & Nataraj, 2012). Among them the most common were arthrogryposis multiplex congenita, with 31 of 219 reported cases (14.2%) with a percentage ranging from 8.5 (Wang et al., 2019) to 100.0 (Sreenivas & Nataraj, 2012); DiGeorge (22q11.2 microdeletion) with 16 of 219 cases (7.3%) with a percentage ranging from 9.2 (Wang et al., 2019) to 9.5 (the present study); and amniotic bands present in 5 of 219 cases (2.3%) with a percentage ranging from 4.8 (the present study) to 8.2 (Byron-Scott et al., 2005). Several hundred genetic syndromic conditions associated with CTEV are listed in the Online Mendelian Inheritance in Man (OMIM) database, including syndromes with identified genes.

Therefore, for individuals with CTEV and any associated malformations, the recommendations of Miller et al. (2010) are advisable. This would involve more detailed genetic tests beyond karyotype such as chromosomal microarray as a first-tier clinical diagnosis test and for some cases further testing: FISH, qPCR, MLPA and single gene tests.

The most common organ system that was affected by additional anomalies in reported cases with CTEV was the central nervous system (257 of 1,086 cases with MCA, 23.7%) (Table 5) followed by the musculoskeletal system (237 anomalies, 21.8%), the cardiovascular system (171 anomalies, 15.7%), the urogenital system (118 anomalies, 10.9%), the gastrointestinal system (72 anomalies, 6.6%), ear, face and neck anomalies (52 anomalies, 4.8%), orofacial anomalies (23 anomalies, 2.1%), and eye anomalies (9 anomalies, 0.8%) (Table 5). In the reported studies (Table 5) the percentage of anomalies of the central nervous system ranged from 11.1% (Sreenivas & Nataraj, 2012) to 83.3% (Stone et al., 2018). There were great variations between the reported studies concerning the anomalies of the organ systems (Table 5). For instance, for the anomalies of the central nervous system, the percentages of reported neural tube defects varied from 16.7 (Stone et al., 2018) to 88.9 (Sreenivas & Nataraj, 2012) and for hydrocephaly from 24.2 (This study) to 35.3 (Wang et al., 2019). For the musculoskeletal system, the percentages of anomalies reported varied from 53.9 (Byron-Scott et al., 2005) to 100 (Sharon-Weiner et al., 2017); for syndactyly from 12.5 (Sreenivas & Nataraj, 2012) to 14.3 (Byron-Scott et al., 2005); for polydactyly from 9.5 (Byron-Scott et al., 2005) to 25.0 (Sreenivas & Nataraj, 2012); for limb deficiencies from 6.2 (Stone et al., 2018) to 22.2 (Byron-Scott et al., 2005); for the cardiovascular system from 10.3% (Byron-Scott et al., 2005) to 31.6% (Wang et al., 2019), and for ventricular septal defect from 25.0% (Sharon-Weiner et al., 2017) to 55.9% (Byron-Scott et al., 2005). The percentage of reported anomalies of the urinary system varied from 7.1 (Sreenivas & Nataraj, 2012) to 33.3 (Sharon-Weiner et al., 2017), for ureteral anomalies from 28.9 (Wang et al., 2019) to 75.3 (Byron-Scott et al., 2005), and for cystic dysplastic kidneys from 42.8 (Sharon-Weiner et al., 2017) to 37.5 (Stone et al., 2018). Few orofacial anomalies were reported in the literature with results varying from 6.1 (Byron-Scott et al., 2005) to 12.7 (Wang et al., 2019) (Table 5).

Children with CTEV have higher incidences of other congenital anomalies than in the general population. In our series, the presence of CTEV increased the risk of ventricular septal defect, cystic dysplastic kidneys, cleft lip/palate, spina bifida, and hydrocephaly with odds ratios of 8.22, 17.87, 10.76, 30.98, and 19.61, respectively.

It is difficult to compare our results with those of other authors since, for example, Byron-Scott et al. (2005) took the total number of cases, including the cases with isolated CTEV as the denominator for the calculation of the percentages of symptom categories.

The higher frequency of additional malformations in this series may be related to the fact that our study was population based, that the ascertainment of cases was complete, that all patients were taken into consideration, including stillborn and terminations of pregnancy, and the surveillance for anomalies was continued until 2 years of age.

In the EUROCAT network (http://www.eurocat-network.eu/), the prenatal detection rates of CTEV ranged from less than 10% in 7 registries to higher than 50% in Paris (57%) and Lausanne (51%). The prenatal diagnosis increased significantly from 20% in 1999–2002 to 29% in 2009–2011.The overall rate of prenatal detection of

TABLE 4 Previous reported studies on congenital talipes equinovarus: prevalence and percentage of associated anomalies

	Moorthi et al.,2005 (Texas)	Byron-Scott et al.,2005 (South Australia)	Wallander et al., 2006 (Sweden)	Cardy et al., 2007 (UK)	Parker et al., 2009 (US)	Kancherla, Romitti, Caspers, Puzhankara, & Morcuende, 2010 (Iowa)	Pavone et al., 2012 (Sicily)	Sreenivas & Nataraj, 2012 (India)	Yi et al., 2013 (China)	Jaruratanasirikul et al., 2016 (Thailand)	Sharon-Weiner et al., 2017 (Israel)	Stone et al., 2018 (New Zealand)	Smythe, Kuper, Macleod, Foster, & Lavy, 2017[a] (databases)	Wang et al., 2019[b] (Europe)	This study
Study years	1996–1999	1986–1996	1995–1996	1993–1997	2001–2005	1997–2005	1991–2004	2010	2001–-2010	2009–2013	2001–2014	1999–2006	1960–2015	1995–2011	1979–2007
Number of births	923,543	20,000/year	198,719	NA	4,744,791	304,308	801,324		8,273,382	186,393	40,320[c]	NA	13,962,989	4,800,000	327,067
Study population	LB	LB, SB, TOP	LB, 44 clinics[d]	LB, Clinics, Talipes registers[d]	LB[d]	LB, SB, TOP[d]	LB	LB, clinic[e]	LB,SB	LB, SB, TOP	Fetuses	LB[f]	LB, SB	LB, SB, TOP	LB, SB, TOP
Total number	1324	388	280	194	6,139	347	827	54	4,233	187	109	163	10,589	5,458	504
Prevalence	14.3	18.0	14.1	NA	12.9	11.4	10.3	NA	5,1	10.0	27.2	NA	7.6	11.3	13.0
Associated number (%)	642 (48.5)	157 (40)	NA	NA	NA	NA	NA	25 (46.3)	NA	NA	33 (30.3)	49	NA	591 (10.8)	107 (21.2)

Abbreviations: LB, live births; NA, not available; SB, stillbirths; TOP, termination of pregnancy for fetal anomaly.

[a]Meta-analysis. Literature review of six databases including 48 studies in 20 low and middle-income countries. Prevalence varied from 5.1 to 20.3 per 10,000 live births.

[b]18 EUROCAT registries of congenital anomalies.

[c]Routine prenatal ultrasound anomaly scans.

[d]Only isolated (idiopathic) cases were studied.

[e]Born out of parental consanguinity marriages.

[f]Retrospective review of all children attending a regional talipes clinic.

TABLE 5 Previous reported studies on congenital talipes equinovarus: recognizable and nonrecognizable conditions (number of cases and percentage)

	(Byron-Scott et al., 2005)	(Sreenivas & Nataraj, 2012)	(Sharon-Weiner et al., 2017)	(Stone et al., 2018)	(Wang et al., 2019)	This study
Number of cases	388[a]	54	109	163	5,458	504
Recognizable conditions						
Chromosomal						
Trisomy 18	9 (37.5)		2 (33.3)		101 (41.1)	15 (48.4)
Trisomy 21	4 (16.7)		1 (16.7)		48 (19.5)	7 (22.6)
Trisomy 13	2 (8.3)					3 (9.7)
Other	9 (37.5)		3 (50.0)		97 (39.4)	6 (19.4)
Total	24 (6.2)		6 (5.5)		246 (4.5)	31 (6.2)
Non chromosomal conditions						
Arthrogryposis[b]	8 (20.0)	5 (100.0)	2 (66.7)	3 (60.0)	13 (8.5)	6 (28.6)
Amniotic bands	4 (10.0)					
Spinal muscular atrophy	2 (5.0)					
22 q11.2 microdeletion					14 (9.2)	2 (9.5)
Other	26 (65.0)		1 (33.3)	2 (40.0)	126 (82.4)	13 (61.9)
Total	40 (10.3)	5 (46.3)	3 (2.7)	5 (3.3)	153 (2.8)	21 (4.2)
Non recognizable conditions						
Musculoskeletal						
Syndactyly	9 (14.3)	1 (12.5)				3 (18.7)
Spine, rib and sternum						2 (12.5)
Polydactyly	6 (9.5)	2 (25.0)				2 (12.5)
LRD	14 (22.2)	1 (12.5)		1 (6.2)		2 (12.5)
Other	34 (53.9)	4 (50.0)	5 (100.0)	15 (93.7)		7 (43.7)
Total	63 (19.0)	8 (28.6)	5 (23.8)	16 (31.4)		16 (9.7)
Congenital heart defects						
VSD	19 (55.9)		1 (25.0)	3 (30.0)	80 (42.8)	20 (39.2)
ASD		3 (60.0)				2 (3.9)
TOF	1 (2.9)					1 (1.9)
CoA	2 (5.9)					1 (1.9)
Other	12 (35.3)	2 (40.0)	3 (75.0)	7 (70.0)	107 (57.2)	27 (52.9)
Total	34 (10.3)	5 (17.8)	4 (19.0)	10 (19.6)	187 (31.6)	51 (30.9)
Urinary system						
Renal agenesis	18 (24.7)					
Ureteral anomalies	55 (75.3)	1 (50.0)	3 (42.8)	3 (37.5)	31 (28.9)	10 (35.7)
Cystic dysplastic kidneys		1 (50.0)	3 (42.8)	3 (37.5)		8 (28.6)
Other			1 (14.3)	2 (25.0)	76 (71.0)	10 (35.7)
Total	73 (22.1)	2 (7.1)	7 (33.3)	8 (15.7)	107(18.1)	28 (16.9)
Genital anomalies						
Hypospadias						3 (75.0)
Other				1 (100.0)		1 (25.0)
Total	21 (6.3)			1 (1.9)		4 (2.4)
Gastrointestinal anomalies						
Esophageal atresia						1 (25.0)
Intestinal malrotation						3 (75.0)
Other				1 (100.0)		
Total	10 (3.0)			1 (1.9)		4 (2.4)

(Continues)

TABLE 5 (Continued)

	(Byron-Scott et al., 2005)	(Sreenivas & Nataraj, 2012)	(Sharon-Weiner et al., 2017)	(Stone et al., 2018)	(Wang et al., 2019)	This study
Central nervous system						
Neural tube defects	34 (70.8)	8 (88.9)	4 (80.0)	2 (16.7)		9 (27.3)
Hydrocephaly					39 (35.5)	8 (24.2)
Microcephaly						2 (6.1)
Other	14 (29.2)	1 (11.1)	1 (20.0)	10(83.3)	71 (64.5)	14 (42.4)
Total	48 (14.5)	9 (32.1)	5 (23.8)	12 (23.5)	110 (18.6)	33 (20.0)
Respiratory system	39 (11.8)					
Eye						
Cataract						1 (50.0)
Microphthalmia						1 (50.0)
Other						
Total						2 (1.2)
Ear, face, and neck				1 (1.9)		4 (2.4)
Cleft lip and/or palate	20 (100.0)					7 (35.0)
Cleft palate		3 (100.0)				13 (65.0)
Total	20 (6.1)	3 (10.7)			75 (12.7)	20 (12.1)
Abdominal wall						
Omphalocele	14 (100.0)					1 (100.0)
Total	14 (4.2)					1 (0.6)
Diaphragmatic hernia	9 (2.7)					
Other				2 (3.9)	112 (18.9)	2 (1.2)
Total	331	28	21	51	591[c]	165

Abbreviations: ASD, atrial septal defect; CoA, coarctation of aorta; LRD, limb deficiencies; TOF, Tetralogy of Fallot; VSD, ventricular septal defect.
[a]The number of cases are under the authors names. For recognizable conditions the percentage after total is the percentage of the total number of cases. For nonrecognizable conditions, the percentage is the percentage of the total number of anomalies.
[b]Arthrogryposis multiplex congenita.
[c]Number of cases, not number of anomalies.

congenital clubfoot was reported to be around 60% in three states of the United States between 2006–2011 (Mahan, Yazdy, Kasser, & Werler, 2014). As in our series, the prenatal detection rate was higher in reported cases associated with other anomalies (Mahan et al., 2014; Offerdal et al., 2007; Seravalli et al., 2015).

In order to evaluate patients and to compare studies, it is necessary to standardize the methods of case classification. Congenital anomalies and associated anomalies must be grouped into meaningful syndromes and conditions. Methods for case classification into isolated, multiple and syndrome categories have been described (Rasmussen et al., 2003). Consideration of these guidelines will lead to more comparable case groups, an important element of carrying out rigourous studies aimed at identifying the etiology of congenital anomalies. However, to design studies that truly aim to identify risk factors and etiologies, cases need to be classified differently, as some isolated cases are now known to have genetic etiologies.

The causes of CTEV include single mutant genes, familial occurrence, known syndromes, chromosome abnormalities, vascular disruption, teratogens and unknown causes. Several theories on the causes of congenital clubfoot have been proposed, although the exact etiology has not been established, including restriction of the uterus in early pregnancy, disturbance of endochondral ossification of the foot, and occurrences which are secondary to neurological abnormalities or a connective tissue disorder (Miedzybrodzka, 2003). Studies have also consistently shown an association between maternal smoking and increased risk of congenital clubfoot (Kancherla et al., 2010; Werler et al., 2015).

A number of other environmental risk factors and medical conditions have been related to the risk of congenital clubfoot in some studies, but not in others, including male gender, Aboriginal race, maternal age, parity, education level, hyperemesis, anemia, maternal alcohol consumption, maternal obesity, medication use in pregnancy and exposure to solvents (Byron-Scott et al., 2005; Cardy, Sharp, Torrance, Hennekam, & Miedzybrodzka, 2011; Hollier, Leveno, Kelly, MCIntire, & Cunningham, 2000; Wang et al., 2019).

A discussion on the molecular basis of CTEV is beyond the scope of this article.

This study has particular strengths including a geographically well-defined population in which all patients were referred to the

Registry of Congenital Malformations (live births, stillbirths, and termination of pregnancies). In addition, each affected child was examined by a clinical geneticist, all elective terminations were ascertained, the surveillance for anomalies was continued until 2 years of age and the registration was active. The potential limitations of the present study include the small number of patients. Other limitations include the fact that microarray and molecular testing were not available during the period under study, our cases with syndromes were clinically diagnosed; and some anomaly groups had very small numbers. Nevertheless, complete ascertainment was achieved and a homogeneous population was studied.

5 | CONCLUSION

In conclusion, the prevalence of CTEV at birth was 13.02 per 10,000 in the population studied and the percentage of cases of CTEV with associated anomalies was 21.2%, one in five cases. These figures were obtained from the study of a well-defined population of close to 400,000 births. The anomalies associated with CTEV represent a large number of different conditions. An anomaly syndrome or pattern was recognizable in 48.6% of the cases of CTEV with associated anomalies. Therefore, cases with CTEV should have a careful multidisciplinary screening. A search for associated congenital anomalies, particularly of the cardiovascular, the central nervous, the urinary, the orofacial, and the musculoskeletal systems is recommended for the cases with CTEV. Genetic counseling may be indicated in many of the cases of CTEV with associated anomalies.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

"n/a"

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