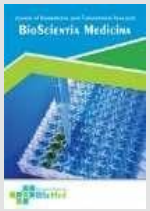
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Talipes Equinovarus (TEV) and VACTERL Associated Anomalies: Narrative Literature Review

Huda Fajar Arianto[1], Faesal A Maodah[2], Yunus Abdul Bari[2]

[1] General Practitioner of Department of Orthopedics, Universitas Airlangga Hospital, Surabaya, Indonesia
[2] Department of Orthopedics, Universitas Airlangga Hospital, Surabaya, Indonesia

ARTICLE INFO

Keywords:
Clubfoot
TEV
Etiopathogenesis
Associated anomalies
VACTERL

***Corresponding author:**
Huda Fajar Arianto

E-mail address:
hafmed89@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v6i7.548

A B S T R A C T

Clubfoot or known as Talipes Equinovarus (TEV), is a common anomaly in world population of newborn. This condition was reported in many studies as isolated anomaly but may come with other associated congenital anomalies. This review aims to further discuss the classification of TEV, its etiopathogenesis and how to diagnosis with all kind of VACTERL associated anomaly together with TEV. Many studies show a range of incidence between 1.1-4.5 per 1000 live birth per year and there is a chance of its condition followed by multiple congenital anomalies. Even though, this anomaly was an idiopathic condition, but still there is multifactorial etiology for its in which revealed through many studies also. Nevertheless, the orthopedic management of TEV with or without other congenital conditions still continue to develop to make a better improvement for the patients.

1. Introduction

Disability in children was known as the impact of the congenital anomalies.[1] Commonly, the word clubfoot, clubfeet, or TEV was represent of certain deformities of ankle and foot at birth.[2] This concept was introduced by Hippocrates on 400 BC.[3] TEV consist of supinated and adducted forefoot, varus heel in subtalar, ankle joint euqinus and the whole foot was medially deviated.[4] Congenital clubfoot is common (incidence of 2 in 1000 live birth), it is bilateral in half of the afflicted children, and affects boys twice as often as girls, which this condition forms in the early weeks of gestational development and may be part of specific syndromes or secondary to neurologic or systemic disease.[1,4]

During 2001 and 2010 in China, there was an epidemiology study through 4233 cases that found the clubfoot prevalence was 4.90 and 5.43 per 10000 live births.[5] A study in Malaysia and Vietnam reported that the incidence of TEV was 4.5 per 1000 live births while 31.5% of it were unilateral with males are more commonly affected with a 2:1 ratio and that 50% are affected bilaterally and the ratio of right to left involvement being 1:2.[6,7] According to the data (low and middle income countries) of TEV in 20 countries over the last 55 years shows an estimated 7-43 new cases of clubfeet per year per million population.[1] In

many cases, clubfoot is often idiopathic and isolated but the prevalence data shows that TEV with other anomalies were between 10.8 and 48.5% as does the proportion and the type of associated anomalies reported.[8] A postnatal and autopsy study of 44 fetus with TEV, found that 19 fetuses (43.3%) was isolated TEV and complex TEV in 25 fetuses (56.8%), in which complex TEV the associated abnormalities consist of CNS involvement in 13/25 (52.0%); musculoskeletal defect in 7/25 (28.0%); thoracic abnormalities in 3/25 (12.0%); and one case of each tumour and hydrops fetalis.[9] This review aimed to discuss the mechanism of CTEV, the following VACTERL associated anomalies (costo-vertebral segmentation and neural defects, anal atresia, cardiac malformation, trachea-esophageal fistula/atresia and orofacial defect, renal and urinary system anomalies, limb anomalies) together with CTEV and the orthopaedic managements in CTEV patients.

Classification of CTEV

Based on the causes and patient response to therapy, clubfoot was grouped into: postural, idiopathic, neurogenic, and syndromic. Stretching and casting usually could correct the postural. The 'true' clubfoot was idiopathic, in which divided into various severity level. It was a neurogenic clubfoot if neurological conditions involved. Syndromic usually involving complex anomalies which accompanying the clubfoot.[10]

Table 1. Grade in Dimeglio Clubfoot Classification[11]

Grade	Type	Score	Reducibility
I	Benign	<5	>90°, reducible
II	Moderate	5 to 10	>50°, reducible, partially stiff
III	Severe	10 to 15	<50°, stiff, partially reducible
IV	Very Severe	15 to 20	<10°, rigid

Dimeglio et al. classification system and the Pirani score was two of the most used in order to assess the severity.[12,13] The Dimeglio classification was introduced in 1995, it categorized into: grade I – grade IV (table 1). To measure the severity, he used the sagittal and horizontal plane parameters (figure 1): Sagittal plane – 1) evaluation of equinus; 2) evaluation of varus; and horizontal plane – 3) evaluation of derotation; 4) evaluation of forefoot adduction relative to the hindfoot.[10]

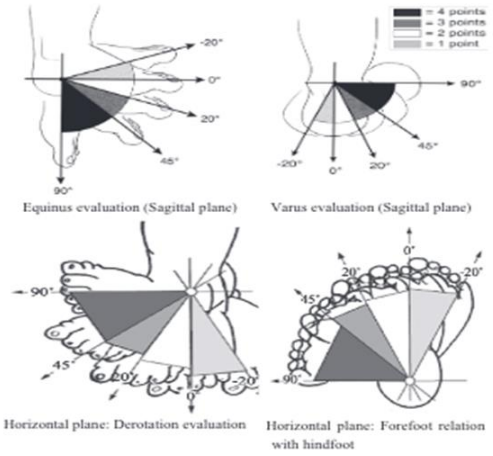


Figure 1. Dimeglio et al. clubfoot classification system[10]

This system can be used only when correction formed after gentle reduction forced was apply to the affected foot, and the stiffest had a maximum score of 16. If there is a gravity sign (plantar crease, medial crease, cavus retraction and fibrous musculature), 1 points should be added for each sign.[11]

Table 2. Pirani clubfoot classification[11]

Variable	Score
Hindfoot score	0 to 3
Posterior crease	0, 0.5, 1
Empty heel	0, 0.5, 1
Rigid equinus	0, 0.5, 1
Midfoot score	0 to 3
Curvature of the lateral border	0, 0.5, 1
Medial crease	0, 0.5, 1
Talar head reducibility	0, 0.5, 1
Total score	0 to 6

Pirani scoring system (table 2), is a simple yet reliable tool to determine the severity, and Ponseti method therapy progress. Six clinical contracture signs were assessed (fig.2), three signs in midfoot and three signs in hindfoot. Every single contracture had value from 0 to 1, where 0 represent no deformity, 0.5 was moderate, and 1 was severe.[10,12]

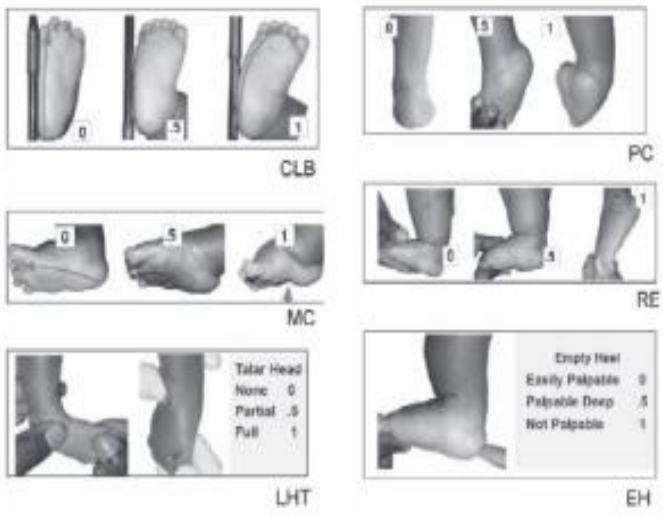


Figure 2. Pirani scoring system[10]

Etiopathogenesis

Around the fourth week of pregnancy, the limbs buds begin to appear. Three weeks after, the finger and toe rays were developed and it will grow into separated digits. As it continues to grow, the upper will rotates outward, and the lower will rotates inward. The rotation made future elbow and knee being rotated by 180 degrees with respect to each other. CTEV deformity primarily formed by this rotation process.[14]

Multiple theories have been put forward to explain its etiology. Including vascular deficiencies, environmental factors, in utero positioning and mechanical factors inside, abnormal muscle insertions, and genetic factors. There are several risk factors such as previous occurrence in the ancestors, maternal condition (smoking, intake of SSRI, obesity

and gestational diabetes), and procedure performed during pregnancy.[15–17] First degree relatives and monozygotic twins (33%) tend to be more affected according to family studies. HOX, STS, PITX1, TBX4, RBM10 protein presumed to be the major causes of isolated and non-isolated clubfoot. Genetic defects in any of the component of these pathways lead to limb defects.[18] Studies also found that vascular defect of anterior peroneal and tibial arteries lead to depletion of muscle volume development mainly caused by PITX1 mutations.[17,19]

SSRI (selective serotonin reuptake inhibitors) was frequently used as antidepressants in pregnant woman. In which, it has been suspected that this drugs action could reduce uterine blood flow resulting to vessels disruption of the fetus in animal models. Early amniocentesis procedure had been identified as increasing factor of clubfoot. This action can cause an amniotic fluid leakage and injury to the fetus, in which the leakage could decreasing limb mobility.[17] Vessel disruption caused by fetal hypoxia and growing restriction of limb caused by cigarette chemical was two main reasons of the limb defect. When a pregnant women inhales the cigarette smoke, it could decreasing 15-20% of intervillous blood flow lead to fetal hypoxia and the toxic substance of nicotine and CO which has antimitotic and antimetabolic characteristic could disturb limb development.[20]

Diagnosis

Foot impairment was clearly seen at birth; it turn and twisted inwards so that in the worst case the sole faces posteromedially and it is rarely difficult to identify a true clubfoot in a newborn.[21,22] The child should be assessed soon after birth by an orthopedic surgeon or physiotherapist with training in clubfoot management, to use a standardized, systematic approach including 'head to toe' examination to exclude any associated abnormalities.[23] The radiographs might ensure the clubfoot deformities correction or identify the residual deformity area who has been undergoing serial manipulation and casting. Furthermore, the imaging could confirm the adequacy of correction of the deformities intraoperatively.[24]

In the past decade, USG has help to increase the number of clubfeet that diagnosed prenatally. Many retrospective studies conclude that fetal anomaly ultrasound screening diagnosis of CTEV has a good positive predictive value. The transvaginal ultrasound can be used to identify defect of musculoskeletal earlier than 14th to 16th week of pregnancy, but after 16th week transabdominal more considered suitable for it because the fetus displacement with the progress of the pregnancy. However, late onset development can still occur, therefore the scans performed around 20th-24th week seems to be the most reliable to confirm or exclude clubfoot diagnosis.[25–27]

VACTERL associated anomalies

There is 67% cases of TEV cases in which concurrent with birth deformity, syndromes and many other congenital anomalies.[9] In 2019, study in Paris stated that among 504 cases with CTEV, 397 had isolated CTEV and 107 cases had at least one associated anomaly.[8] This concurrent anomalies can be group into VACTERL:[28] 1. Costovertebral segmentation and neural defects; France genetic study stated that the most common organ system that was affected by additional anomalies in reported cases with TEV was the central nervous system.[8] MRI study to 25 fetus, found that central nervous system/spinal cord abnormalities were diagnoses in 13/25 fetus with TEV. It includes Chiari II malformation, myelomeningocele, tethered cord syndromes (TCS) and hydrocephaly.[9] The location of the myelomeningocele ranged from the thoracic to sacral levels but predominantly involved the lumbosacral spine.[29] A single and fatal case of spina bifida and severe congenital bilateral TEV in one twin of monoamniotic pair which diagnoses postnatally shows that early prenatal diagnoses and appropriate counseling of parents are very important because a better outcome was difficult to secure even with a prompt referral in this case.[30] Furthermore, the clinicians should be aware of underlying TCS or other anomalies, because a study found that a lower

recurrence rate when TCS was identified/treated before completion of Ponseti casting.[31] 2. Anal atresia/stenosis including digestive system defect; Twelve pregnancies with 12 affected fetuses in Germany healthy and non-consanguineous couple, were examined for omphalocele-exstrophy-imperforate anus and spinal defects (OEIS) complex. There are 9 out of 12 fetuses with omphalocele and anal atresia, in which 4 out of 9 babies with omphalocele and anal atresia were combine with clubfeet.[32] During 1984 to 1996 in Africa, 11 babies was observed with Eagle-Barret syndrome (also known as prune belly syndrome) which had triad including absent or hypoplastic of abdominal wall, cryptorchidism and renal defect, 5 of the babies also had clubfoot as associated defect.[33] Althought it was very rare, but in 2018, single baby with Robinow Syndrome in Philadelphia was reported had imperforated anus and clubfeet, which diagnosed postnatally.[34] 3. Cardiac malformation; There was a TARP syndrome, in which consist of talipesequinovarus, atrial septal defect, Robin sequence and persistent left superior vena cava where caused by mutations in the RBM10 gene.[35] Several cases reported that, the patient had physical findings in common but more patients are identified through genetic testing. The TARP syndrome acronym was widened into more complex cardiac lesions, distal limb defect in combine with TEV, disfunction of nervous system and renal abnormalities.[36] Patient with TARP may survive even with severe developmental delay and they need an intensive care. The physician should considered this condition together with the parents in genetic counseling and clinical follow up.[37] 4. Trachea-esophageal fistula/atresia and orofacial defect; The MRI study involving 25 fetus has found that it was helpful in revealing the complex abnormalities associated TEV such as dysmorphic facial features.[9] At least 13 population had a cleft palate and 7 population had cleft lip and/or palate from 55 subject of France population study in 1979 until 2007.[8] Sub-saharan African cohort study said, the possible varying genetic act as causes the orofacial cleft and TEV could occur in some individuals.[38] 5. Renal and urinary system anomalies; The presence of renal and urinary system anomalies in combine with TEV was quite rare, it was in the fourth place of the most common affected organ according to the large population study in France.[8] Most of them was a complex syndrome such as cystic dysplasia of kidney, multiple vas deferens with polyorchidism in 11-year boy including a left polydactyly clubfoot, and also some lethal case was reported in siblings back then in 1978 who came from nonconsanguineous father and mother.[8,39,40] This underlined the importance of prenatal screening and diagnosis of several congenital malformation nowadays. 6. Limb anomalies; The second most common affected organ system was musculoskeletal system, it could be in form of syndrome like Ehlers-Danlos Syndrome, Apert Syndrome with complex syndactyly, Marfan Syndrome with elongated arm and finger or in form of single anomalies like developmental dysplasia of the hip, osteogenesis imperfecta, limb deficiencies also nerve impairment.[8,28,41–43] United Kingdom 6.5 years study, stated that prenatal ultrasound screening was important because this study found 119 cases of idiopathic TEV with hip dysplasia. It found in 81 boys and 38 girls, 62 cases were bilateral, and 97 cases included in grade I (Graf classification).[43] Even it was very rare, but TEV with osteogenesis imperfecta (OI) type IV was reported in 2016, found in 2 weeks old infant where his mother suffering the same disease, and underwent surgery correction also maintain with bilateral spica cast-like brace.[41] In addition, several incidence involving tibial hypo/aplasia and peroneal nerve palsy was reported. It is critical to perform the screening of peroneal nerve palsy in TEV before the patient undergo the TEV treatment, in order to avoid future problem between clinician and the parents.[28,42]

Table 3. TEV cases with VACTERL associated anomalies

No	Researchers	∑ of Subject	Year	∑ of Subject Fit Into One of The Following Criteria							
				Unilateral TEV	Bilateral TEV	Costo-vertebral segmentation and neural defects	Anal atresia/stenosis including digestive system defect	Cardiac Defect	Trachea-esophageal fistula/atresia and orofacial defect	Renal and Urinary Anomalies	Others Limb Anomalies
1	Claude Stoll et all.[8]	504	2020	52,58%	47,42%	20%	12.1%	30.9% including TOF, VSD and ASD	2.4%	16.9%	9.7% including polydactyly and syndactyly
2	Ursula Nemec et all.[9]	25	2012	20%	80%	52%	-	3%	-	-	7%
3	Marco Castori et all.[28]	1	2008	+	-	+ (hypoplastic ribs, butterfly vertebrae)	+	+ (dextrocardia, PDA)	+	+ (left renal agenesis)	+ (left club hand, absent thumb etc.)
4	Sabah Servaes et all.[29]	7	2010	14,3%	85,7%	100% (myelomeningocele)	Not Observed				
5	Benjamin Momo Kadia et all.[30]	1	2017	-	+	+ (spina bifida cystica)	Not Observed Due to Death				
6	Trevor Jackson et all.[31]	24	2017	50%	50%	+ (tethered cord syndrome)	Not Observed				
7	Michael Rudolf Mallman et all.[32]	12	2016	33,3% of unspecified unilateral or bilateral TEV		100% (spina bifida, shortened Spina)	58,3% of anal atresia and imperforate anus, 75% of omphalocele	-	-	100% of bladder exstrophy	-
8	M.H. Aliyu et all.[33]	11	2003	45% of unspecified unilateral or bilateral TEV		-	27% (imperforate anus)	-	36% (potter facies)	-	18% (arthrogryposis)
9	Chaya N. Murali et all.[34]	1	2018	-	+	-	+ (imperforate anus and omphalocele)	+ (hypoplastic left heart syndrome)	+ (choanal atresia and facial dysmorphology)	-	+ (duplicated distal phalanx)
10	Hernan Manotas et all.[35]	1	2021	Unspecified		-	-	+ (persistent left superior vena cava)	+ (optic nerve atrophy)	+ (horse shoe kidney)	-
11	Kathrine E. Kaeppler et all.[36]	1	2018	-	+	+ (tethered spinal cord)	+ (imperforate anus, sacral dimple)	+ (ASD)	+ (micrognathia)	+ (hydronephrosis)	+ (syndactyly)
12	Marcello Niceta et all.[37]	1	2019	-	+	+ (scoliosis, hypoplasia corpus callosum)	-	+ (ASD)	+ (microcephalic, asymmetric skull)	-	+ (syndactyly)
13	Lord J.J. Gowans et all.[38]	6	2021	66,67%	33,33%	Not Observed			+ (cleft lip and or palate)	+ (micropenis, cryptorchidism)	+ (weak muscle tone, syndactyly)
14	Marah Mansour et all.[39]	1	2022	+	-	-	-	-	-	+ (polyorchidism, left kidney dysgenesis)	+ (polydactyly)
15	Schinzel and Gideon.[40]	2	1978	+	-	+ (tetraplegia)	-	+ (ASD)	+ (protruding forehead, saddle nose)	+ (hydronephrosis, hydroureter)	+ (tibial and fibula bowing)
16	Pietro Persiani et all.[41]	1	2016	-	+	-	-	-	-	-	+ (osteogenesis imperfecta type IV)
17	Kwan Soon Song et all.[42]	6	2008	100%	-	-	+ (imperforate anus)	-	-	-	100% (peroneal nerve palsy)
18	D.C. Perry et all.[43]	119	2010	47,9%	52,1%	Not Observed					5.9% (DDH)

2.Conclusion

TEV is an ankle or foot deformities including forefoot adduction and supination through the midtarsal joint, heel varus through the subtalar joints, equinus through the ankle joint, and medial deviation of the whole foot in relation to the knee. It could be isolated or with complex associated anomalies that can be grouped into VACTERL mnemonics. The physicians should aware of these conditions, and carefully examine the patient from head to toe in terms of giving the best treatment for the patients.

3.References

1. Smythe T, Kuper H, Macleod D, Foster A, Lavy C. Birth prevalence of congenital talipes equinovarus in low-and middle-income countries: a systematic review and meta-analysis. Trop Med Int Heal. 2016; 22(3): 269–85.
2. Kyzer SP, Stark SL. Congenital idiopathic clubfoot deformities. AORN J. 1995; 61(3): 492–506; quiz 508.
3. Laloan RJ, Lengkong AC. Congenital Talipes Equinovarus (CTEV). E-Clinic. 2020; 8(2): 211–21.
4. Salter RB. Textbook of disorders and injuries of the musculoskeletal system: An introduction to orthopaedics, fractures, and joint injuries, rheumatology, metabolic bone disease, and rehabilitation. Lippincott Williams & Wilkins; 1999.
5. Yi L, Zhou GX, Dai L, Li KS, Zhu J, Wang YP. An descriptive epidemiological study on congenital clubfoot in China during 2001 to 2010. J Sichuan Univ (Medical Sci Ed). 2013; 44(4): 606–9.
6. Boo NY, Ong LC. Congenital talipes in Malaysian neonates: incidence, pattern and associated factors. Singapore Med J. 1990; 31(6): 539–42.
7. Mcconnell L, Cosma D, Vasilescu D, Morcuende J. Descriptive epidemiology of clubfoot in Romania: A clinic-based study. Eur Rev Med Pharmacol Sci. 2016; 20(2): 220–4.
8. Stoll C, Alembick Y, Dott B, Roth MP. Associated anomalies in cases with congenital clubfoot. Am J Med Genet Part A. 2020; 182(9): 2027–36.
9. Nemec U, Nemec SF, Kasprian G, Brugger PC, Bettelheim D, et al. Clubfeet and associated abnormalities on fetal magnetic resonance imaging. Prenat Diagn. 2012; 32(9): 822–8.
10. Balasankar G, Luximon A, Al-Jumaily A. Current conservative management and classification of club foot: A review. J Pediatr Rehabil Med. 2016; 9(4): 257–64.
11. Cosma D, Vasilescu DE. A Clinical Evaluation of the Pirani and Dimeglio Idiopathic Clubfoot Classifications. J Foot Ankle Surg. 2015; 54(4): 582–5.
12. Canavese F, Dimeglio A. Clinical examination and classification systems of congenital clubfoot: a narrative review. Ann Transl Med. 2021; 9(13): 1097.
13. Chu A, Labar AS, Sala DA, Van Bosse HJP, Lehman WB. Clubfoot classification: Correlation with ponseti cast treatment. J Pediatr Orthop. 2010; 30(7): 695–9.
14. Barry M. Prenatal assessment of foot deformity. Early Hum Dev. 2005; 81(10): 793–6.
15. Kumari P. Congenital Clubfoot: A Comprehensive Review. Orthop Rheumatol Open Access J. 2017; 8(1).
16. Dobbs MB, Gurnett CA. Update on clubfoot: Etiology and treatment. Clin Orthop Relat Res. 2009;467(5):1146–53.
17. Chen C, Kaushal N, Scher DM, Doyle SM, Blanco JS, Dodwell ER. Clubfoot Etiology: A Meta-Analysis and Systematic Review of Observational and Randomized Trials. J Pediatr Orthop. 2018; 38(8): e462–9.
18. Basit S, Khoshhal KI. Genetics of clubfoot; recent progress and future perspectives. Eur J Med Genet. 2018; 61(2): 107–13.

19. Bacino CA, Hecht JT. Etiopathogenesis of equinovarus foot malformations. Eur J Med Genet. 2014; 57(8): 473–9.
20. Dickinson KC, Meyer RE, Kotch J. Maternal Smoking and the Risk for Clubfoot in Infants. Birth Defects Res Part A - Clin Mol Teratol. 2008; 82(2): 86–91.
21. Solomon L, Warwick D, Nayagam S. Apley's system of orthopaedics and fractures. CRC press; 2010.
22. Herring JA. Tachdjian's Pediatric Orthopaedics: From the Texas Scottish Rite Hospital for Children E-Book. Elsevier Health Sciences; 2020.
23. Colaço HB, Patel S, Lee MH, Shaw OM. Congenital clubfoot: A review. Br J Hosp Med. 2010; 71(4): 200–5.
24. Eastwood DM. Lovell and Winter's Pediatric Orthopaedics. 7th ed. Weinstein SL, Flynn JM, editors. Philadelphia: Wolters Kluwer; 2007; 89-B: 424–424.
25. Yau A, Doyle SM. Clubfoot for the primary care physician: Frequently asked questions. Curr Opin Pediatr. 2020; 32(1):100–6.
26. Pullinger M, Southorn T, Easton V, Hutchinson R, Smith RP, Sanghrajka AP. An evaluation of prenatal ultrasound screening for CTEV. Bone Joint J. 2014 J; 96-B(7): 984–8.
27. Faldini C, Fenga D, Sanzarello I, Nanni M, Traina F, Rosa MAA. Prenatal diagnosis of clubfoot: a review of current available methodology. Folia Med (Plovdiv). 2017; 59(3): 247–53.
28. Castori M, Rinaldi R, Cappellacci S, Grammatico P. Tibial developmental field defect is the most common lower limb malformation pattern in VACTERL association. Am J Med Genet Part A. 2008; 146(10): 1259–66.
29. Servaes S, Hernandez A, Gonzalez L, Victoria T, Johnson M, et al. Fetal MRI of clubfoot associated with myelomeningocele. Pediatr Radiol. 2010; 40(12): 1874–9.
30. Kadia BM, Aroke D, Tianyi FL, Bechem NN, Dimala CA. Spina bifida cystica and severe congenital bilateral talipes equinovarus in one twin of a monoamniotic pair: A case report. BMC Res Notes. 2017; 10(1): 771.
31. Jackson T, Jones A, Miller N, Georgopoulos G. Clubfoot and tethered cord syndrome: results of treatment with the Ponseti method. J Pediatr Orthop. 2019; 39(6): 318–21.
32. Mallmann MR, Reutter H, Müller AM, Geipel A, Berg C, et al. Omphalocele-exstrophy-imperforate anus-spinal defects complex: associated malformations in 12 new cases. Fetal Diagn Ther. 2017; 41(1): 66–70.
33. Aliyu M, Salihu H, Kouam L. Eagle-Barret syndrome: occurence and outcomes. East Afr Med J. 2003; 80(11): 595–7.
34. Murali CN, Keena B, Zackai EH. Robinow syndrome: A diagnosis at the fingertips. Clin Dysmorphol. 2018; 27(4): 135–7.
35. Manotas H, Payan-Gomez C, Roa MF, Piñeros JG. TARP syndrome associated with renal malformation and optic nerve atrophy. BMJ Case Rep. 2021; 14(5).
36. Kaeppler KE, Stetson RC, Lanpher BC, Collura CA. Infant male with TARP syndrome: Review of clinical features, prognosis, and commonalities with previously reported patients. Am J Med Genet Part A. 2018; 176(12): 2911–4.
37. Niceta M, Barresi S, Pantaleoni F, Capolino R, Dentici ML, et al. TARP syndrome: Long-term survival, anatomic patterns of congenital heart defects, differential diagnosis and pathogenetic considerations. Eur J Med Genet. 2019;62(6).
38. Gowans LJJ, Al Dhaheri N, Li M, Busch T, Obiri-Yeboah S, et al. Co-occurrence of orofacial clefts and clubfoot phenotypes in a sub-Saharan African cohort: Whole-exome sequencing implicates multiple syndromes and genes. Mol Genet Genomic Med. 2021;

9(4).

39. Mansour M, Ismail MA, Dashan MA, Kheat A, Alsuliman T, Alrebdawi K. Multiple vas deferens with polyorchidism and many congenital malformations in a symptomatic 11-year-old male patient: a rare case report. BMC Urol. 2022; 22(1).
40. Schinzel A, Giedion A. A syndrome of severe midface retraction, multiple skull anomalies, clubfeet, and cardiac and renal malformations in sibs. Am J Med Gen. 1978;1.
41. Persiani P, Ranaldi FM, Martini L, Zambrano A, Celli M, et al. Osteogenesis imperfecta and clubfoot - A rare combination: Case report and review of the literature. Med (United States). 2016; 95(31).
42. Song KS, Kang CH, Min BW, Bae GC, Cho CH, et al. Congenital clubfoot with concomitant peroneal nerve palsy in children. J Pediatr Orthop Part B. 2008;17(2): 85–9.
43. Perry DC, Tawfiq SM, Roche A, Shariff R, Garg NK, et al. The association between clubfoot and developmental dysplasia of the hip. J Bone Jt Surg - Ser B. 2010; 92 B(11): 1586–8.