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Original Article

The chromosomal abnormalities associated defects and outcomes of fetuses diagnosed prenatally with clubfoot

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Abstract

Aim: To assess associated findings, chromosomal abnormalities and outcomes of the pregnancies diagnosed with fetal clubfoot.
Materials and Methods: Ultrasonographic characteristics, pregnancy work-up and fetal outcomes of the pregnancies diagnosed with fetal clubfoot between January 2015 and October 2019 were evaluated retrospectively. Clubfoot was considered as complex or isolated depending on the presence or absence of additional structural abnormalities. The results of cases, which grouped according to the presence of additional abnormalities and laterality, were compared.
Results: A total data of 46 pregnancies diagnosed with fetal clubfoot during the study period were included. The most associated abnormality with clubfoot was central nervous system (CNS) anomalies. Nineteen (41%) of fetuses were considered complex, and 27 (59%) were considered isolated. The ratio of the cases with poor outcomes was higher in the complex group than in the isolated group and was 15 (79%) and 1(3%) respectively (p=0.000 for bilateral group and p=0.013 for unilateral group). There were 7 (36%) cases with a chromosomal abnormality in the complex group and 1(4%) case in the isolated group. The deformity was unilateral in 16 (35%) and bilateral in 30 (65%) cases. The rate of poor outcomes was not different in cases with bilateral and unilateral clubfoot deformity (p=0.356).
Conclusion: The prognosis of the fetuses diagnosed with clubfoot mostly depends on associated abnormalities. Therefore a careful evaluation of these fetuses must be performed even if karyotyping is normal. The laterality did not have any impact on the prognosis of cases with clubfoot.

Keywords: Clubfoot; congenital talipes eqinovarus; prenatal diagnosis; ultrasonography

INTRODUCTION

Clubfoot (Talipes eqinovarus) is one of the most common congenital musculoskeletal system malformations. The prevalence of clubfoot is 1-3 per 1000 live births and it occurs with a 2:1 male to female ratio (1). İn this anomaly the ankle joint affected which is caused by the underdevelopment of soft tissue on the medial side, calf, and peroneal muscles and result in that the foot being fixed in supination, varus and adduction positions (2). The treatment of clubfoot varies and depends on its severity and ranges from mild cases that resolve only with manipulations of talo-calcaneo-navicular joint to requiring multiple surgeries with disability persisting into later life.

The diagnosis of the clubfoot is mostly possible by ultrasonography (3). The detection rate of ultrasonography has been increased during the last decade and depends on the quality of device, the ultrasonographer's skills and experiences, gestational age at the time of ultrasonography, fetal positions, maternal obesity or oligohydramnios (3, 4). The clubfoot is categorized as unilateral or bilateral which depend on the presence of the anomaly in one or both foot (5,6). Additional anomalies and aneuploidy frequently accompany with this abnormality (7). Most authors are also classified the club foot as isolated if there is no additional structural abnormality and as complex if at least one additional structural abnormality. Accompanied structural abnormalities have mostly determines the prognosis because additional anomalies have a significant impact on the prognosis. There have been numerous malformations associated with clubfeet such as hydrocephalus, micrognathia, cleft lip and palate, heart defect, myelomeningocele, diaphragmatic hernia, renal agenesis, hydrops, sacral agenesis and olygohydraminosis (8,9). Prenatal counselling to parents diagnosed with fetal clubfoot and additional anomalies is of great importance because it allows parents to know treatment, prognosis,

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and other decision-making processes (10,11). Despite the fact that most authors recommend prenatal karyotyping for clubfoot with additional anomalies, for isolated unilateral and bilateral clubfoot remain controversial (12). The most common chromosomal abnormalities related to club foot are trisomy 13, trisomy 18 and triploidy on karyotyping.

The aim of this study was to investigate the chromosomal findings, associated anomalies, and outcomes of pregnancies diagnosed with clubfoot.

MATERIALS and METHODS

This is a retrospective study conducted in a tertiary referral centre where about 13,000 routine prenatal ultrasound scans were performed on women at 14-16 weeks or 18-22 weeks of gestation per year. The local ethics committee approved the study (Ethical committee approval date and number 21.04.2020-06/03). For the study, we retrieved the data of fetuses diagnosed with clubfoot between January 2015 and October 2019 from computer database and patients' files. When obtaining data was incomplete we contacted the parents by telephone to obtain the required information. The cases diagnosed with or suspected for fetal clubfoot a second-degree ultrasonographic examination was performed where at least two senior perinatologists were available. A clubfoot was diagnosed when the long bones (ie, tibia and fibula) of the lower leg were observed in the same plane of the plantar face of the fetal foot throughout the entire examination (13). Once a fetus diagnosed with clubfoot detailed ultrasonographic evaluations were performed for additional fetal structural anomalies. Accordingly, the clubfoot was classified as complex if additional fetal structural anomalies were present and as isolated when no additional anomalies were detected. Also classified as bilateral and unilateral depend on whether the presence of clubfoot in both feet and one foot.

Prenatal screening for chromosomal abnormalities was recommended to all patients in the complex group and also patients in the isolated group unless a family history of isolated clubfoot existed. We included the patients whose diagnosis remained unchanged throughout the entire follow up in repeated US examinations. The termination of pregnancy (TOP), chrosomal abnormality, neonatal death, and genetic syndrome diagnosed at birth was considered as the poor outcome.

The posthoc power calculation was performed due to limited sample size. A sample size of 46 achieves 100% power to detect an effect size (W) of 0.7779 using a 1 degree of freedom Chi-Square Test with a significance level (alpha) of 0.05000.

The data were completed by transferring to IBM SPSS Statistics 23 program. For evaluating the data, frequency distribution (number, percentage) for categorical variables and descriptive statistics (mean, standard deviation) for numerical variables were given. Chi-square test was used to examine the relationship between two categorical variables. P <0.05 was considered significant.

RESULTS

The data of 45 singletons and one twin pregnancies which club foot diagnosed in one fetus were included in this study. The diagnosis of clubfoot for all fetuses who were examined after bird or TOP was confirmed postnatally and none of them was defined as positional (ie, reversible positioning of the foot). The clubfoot occurred bilaterally in 30 fetuses and unilaterally in 16. The study follow diagram was given in Figure 1. No cases of complex clubfoot were misclassified, however, two fetuses who classified as isolated were associated with other anomaly and classified as complex clubfoot retrospectively. İn 5 complex clubfoot cases additional structural anomalies which could not be detected in the prenatal period were found after TOP. The descriptive characteristics of the study group was summarized in Table 1.

Table 1. Descriptive analysis of the study group

Characteristic	No of cases
General	
Maternal age at diagnosis (mean ±SD)	29.5±6.03
Gravidity (mean±SD)	2.78±1.44
Parity (mean±SD)	1.15±0.94
Family history	
Parent with clubfoot n (%)	1(2.2%)
Sibling with clubfoot n (%)	5(11%)
Pregnancy	
Gestational week at diagnosis (mean ±SD)	23.2±5.4
Type of clubfoot	
Isolated	
Unilateral	11
Bilateral	16
Complex	
Unilateral	5
Bilateral	14
Stillborn	
IPFD	1
IUFD	6
TOP	10
Live born	
Verified Club foot after birth (live born only)	22
Verified additional anomalies after birth	7
Birth	
Singleton pregnancies	28
Twin pregnancies	1
Treatment	
Non-surgical treatment	11
Surgical treatment	10
No treatment	1

IPFD: Intrapartum fetal death, IUFD: Intrauterin fetal death, TOP:Termination of the pregnancy

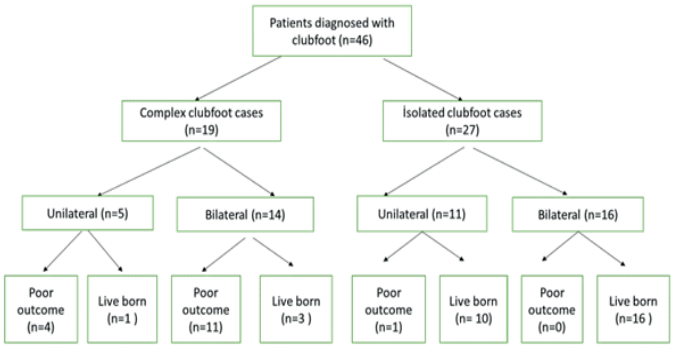

Figure 1. Study flow diagram

Most of the parents included in the study declined karyotyping and postmortem pathologic examination. Among 46 fetuses diagnosed with clubfoot, only 14 sets of parents accepted invasive prenatal testing for karyotyping and 11 of them were in a complex group. The rate of chromosomal abnormality associated with a club foot in complex cases who accepted karyotyping was 63% (7/11 cases) and in isolated were 33% (1/3). Although the rate of chromosomal abnormality in the complex group nearly two times higher than in isolated statistical significance could not be reached due to the small number of cases performed karyotyping. İn the complex group the poor outcomes were significantly higher than the isolated group (p=0.000 for bilateral group and p=0.013 for unilateral group) (Table 2. and Table 3.).

Table 2. Rates of Chromosomal Abnormalities and Overall Poor Outcome in a Cohort Study of 46 Cases of Prenatally Diagnosed Clubfoot Classified as Complex or Isolated and as Unilateral or Bilatera

Laterality	Characteristic	Complex Clubfoot	Isolated Clubfoot	Total	P value
Bilateral	No of. cases	14	16	30	
	Karyotyping performed n(%)	6 (43)	1 (6)	7 (23)	1.000
	Abnormal karyotype dedected n(%)	4 (29)	0 (0)	4 (13)	
	Corrected rate of chromosomal abnormalities, n (%)	2 (14)	1 (6)	3 (10)	
	Poor outcome, n (%)	11 (78)	0 (0)	11 (37)	0.000
Unilateral	No of. cases	5	11	16	
	Karyotyping performed n(%)	5 (100)	2 (18)	7(44)	1.000
	Abnormal karyotype dedected n(%)	3 (60)	1 (9)	4 (25)	
	Corrected rate of chromosomal abnormalities, n (%)	2 (40)	1 (9)	3 (18)	
	Poor outcome, n (%)	4 (80)	1 (9)	5 (30)	0.013
Total	No of. cases	19	27	46	
	Karyotyping performed n(%)	11 (47)	3 (11)	14 (30)	1.000
	Abnormal karyotype dedected n(%)	7 (36)	1 (4)	8 (17)	
	Corrected rate of chromosomal abnormalities, n (%)	4 (21)	2 (7)	6 (13)	
	Poor outcome, n (%)	15 (79)	1 (3)	16 (35)	0.000

Table 3. Rate and Description of Chromosomal Abnormalities Identified in 46 Fetuses with Prenatally Diagnosed Clubfoot Classified as Complex or Isolated and as Unilateral or Bilateral

Laterality	Complex-Clubfoot Group	Isolated-Clubfoot Group
Unilateral	3	1
Chromosomal abnormalities identified	1(47xx+13)	1(47,xxy)
	1(47xy+18)	
	1(Triploidy)	
Bilateral	4	0
Chromosomal abnormalities identified	1(47xy+18)	
	1(47xx+18)	
	1(47xx+13)	
	1(del 7q[35])	

In the isolated group (n=27) the prognosis was poor only in a fetus who have chromosomal abnormality (47, xxy) and terminated in 15 weeks of gestation on parents request.

İn the complex clubfoot group the outcome was considered as good in only 4 of 19 cases.

Case 1: The fetus has unilateral clubfoot with mild lateral ventriculomegaly (left:11 mm, right:11,5 mm) and clutch hand. The karyotyping of this case was reported as normal.

Case 2-3-4: Fetus 1; have outlet type ventricular septal defect, fetus 2; have cleft lip and palate and fetus 3; have muscular type ventricular septal defect, additionally. All three fetuses were bilateral clubfoot and the parents of all declined karyotyping. The surgical treatment for clubfoot was performed for all in six months.

The most common anomalies accompanied with clubfoot were the central nervous system. İn Table 4. Showed the anomalies accompanied with clubfoot.

Concerning laterality, there was no difference in respect to chromosomal or poor outcome between unilateral and bilateral groups (p=0.714 and p=0.356 respectively) (Table 5).

Table 4. Associated abnormalities in the Complex group- by Laterality

Laterality	Bilateral	Unilateral
Type of the abnormality	Hydrops fetalis(n=2)	Hydrocephalus and lumbosacral spina bifida (n=2)
	Thoracic hypoplasia	Hydrocephalus
	Diaphragmatic hernia	Cardiac anomaly and bilateral clunch hand
	Hydrocephalus and lumbosacral ntd	
	Agenesis of corpus callosum and hypertelorism	
	Exencephaly	
	Agenesis of corpus callosum and trekeaesophageal fistula	
	Holoprosencephaly	
	Clutch hand+VSD	
	Hydrocephalus, spina bifida and cleft palate and lip	

Table 5. Comparison of Chromosomal Abnormality Rates and Poor Outcomes, by Clubfoot Laterality (n= 46 Cases)

Laterality of Clubfoot	Associated Findings	Chromosomal Abnormalities	p Value	p Value	Overall poor outcome	p Value	p Value
Unilateral	Isolated	1	1.000		1	0.013	
	Complex	3			4		
	Total	4		0.356	5		0.713
Bilateral	Isolated	0	1.000		0	0.009	
	Complex	4			11		
	Total	4			11		

P<0.05 considered as significat

DISCUSSION

In this retrospective study, we sought to the outcomes of pregnancies diagnosed prenatally with clubfoot and factors affecting prognosis such as laterality of the deformity and presence of the associated abnormalities. Also, we compared the proportion of the poor outcomes for each type of clubfoot (ie. Isolated and complex concerning laterality). The study results indicate that regardless of the laterality having an additional congenital abnormality (complex clubfoot) a major determining factor on prognosis.

Previous studies reported the incidence of clubfoot as 0.1-0.3% in an unselected population. Due to our database included referred cases we cannot determine the prevalence of the clubfoot. This may explain a higher rate of associated abnormalities which is classified as complex. The rate of complex clubfoot was 41% which is higher than in previous studies (14). Similarly, Senego et al. conducted a study on selected cases due to referred patients found the complex clubfoot ratio as 37% (15). Weiner et al. conducted a study on the unselected population which evaluated 109 fetuses with clubfoot of whom 77 cases were singleton, found the rate of complex clubfoot 18% (14).

Perhus et al. (16) demonstrated that the familial clubfoot rate was between 12% and 20%. İn another study conducted by Wynne-Davies showed that recurrence risk for siblings with normal parents varies in respect to the sex of affected sibling and found risk 2% for affected female siblings and 5% for affected male siblings (17). Our findings were consistent with the literature; there were 5 (11%) parents with a history of affected sibling and a mother with a history of clubfoot. The karyotyping was not offered to parents with isolated fetal clubfoot with a family history in light of literature (16,17).

Similar to most studies (14,15,18), our results showed that the presence or absence of the associated abnormalities is the most determining factor on prognosis and chromosomal abnormality. We detected chromosomal abnormality 1 in 27 in the isolated group versus 7 in17 cases in the complex group. The detected chromosomal abnormalities in the complex group are trisomy 18 (n=3), trisomy 13 (n=2), triploidy (n=1) and 7q-35 (n=1), which are mostly lethal. In the isolated group a fetus diagnosed with 47, xxy) chromosomal abnormality. Therefore, consistent with previous studies, our study showed that for patients diagnosed with clubfoot if detailed ultrasonography eliminated other defects karyotyping is not mandatory. The presence of the clubfoot does not seem to a part finding of Down syndrome showed this study is similar to previous studies (14,15,18).

When associated anomalies are observed, as shown in our study and previous studies (14,15,19), the rate of the poor outcome is considerably increased. Weiner et al. (19) found that the rates of poor outcomes increased from 3.94% to 63.6% with associated anomalies. Therefore, we and many authors recommend a carefully ultrasonographic evaluation for cases diagnosed with a clubfoot. Moreover, detecting associated anomalies, especially for parents who want to continue the pregnancy, gives the chance to consult the parents for detailed prognosis and take measures for possible emergencies such as diaphragmatic hernia that warrant urgent interventions right after delivery.

CNS abnormalities are the most common associated abnormality with clubfoot in our study and previous study. Other associated abnormalities are hydrops, cardiac abnormalities, diaphragmatic hernia, cleft lip and palate, cystic hygroma, clutch hand and amniotic fluid abnormalities.

There was no statistically significant difference between unilateral and bilateral groups with respect to poor outcomes in this study (p>0,05). Although the most of recent studies concluded similar result with us (12,15,19), the study conducted in 2002, by Bakalis et al. (20), reported that the ratio of the poor outcomes was higher in the bilateral group than the unilateral group. We are in the opinions that, like recent studies, the laterality have no impact on prognosis in cases with clubfoot. But the prospective studies with larger cases are needed.

We observed that the diagnostic performance of prenatal diagnosis via ultrasonography for the clubfoot is satisfactory. There is no false-positive diagnosis in 46 fetuses diagnosed with clubfoot. This may have resulted from that all patients diagnosed or suspected with fetal clubfoot were evaluated by two experienced perinatologists. İf any suspicions were raised from diagnostic accuracy, they repeated ultrasonographic examination for several time. But because of the nature of the study the exact false-negative ratio could not determine. İn the literature the false-positive diagnosis rate reported 0% to 40% (14,19). Also, the rate of diagnostic accuracy found to be higher for cases with the bilateral club foot. İn a study reviewed 87 affected cases, the rate of misdiagnosis in the unilateral group was 29% and in the bilateral group was 7% (18).

The strengths of this study are that it included the quality of the imaging was uniform throughout the years of the study.

LIMITATIONS

Limitations are that club foot was confirmed postnatally by different physicians, the rate of the karyotyping was low, not have pathologic examination data and derived from the retrospective nature of the study including potential selection bias due to lost to follow-up.

CONCLUSION

For pregnancies detected with fetal clubfoot, even if an invasive prenatal test is normal, a detailed fetal US examination must be performed. The prognosis of the pregnancies with fetal clubfoot mostly depends on the presence of the additional anomalies. The laterality has no significant effect on prognosis.

Competing Interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical Approval: The local ethics committee of Etlik Zubeyde Hanim womans' Health Training and Research Hospital approved the study (Ethical committee approval date and number 21.04.2020-06/03.

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