

Association of Consanguinity, Ethnicity and Addiction with Clubfoot in Pakistan

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ABSTRACT

Objective: To determine the association of clubfoot with consanguinity, ethnicity, lunar eclipse and addictions.

Methods: This observational descriptive case series study was conducted from July 2013 to December 2013. All 200 idiopathic clubfoot patients, who reported at Clubfoot Clinic (CFC) were included in the study. A designed questionnaire was used for asking questions from parents on telephone and during their visit to CFC

Results: Eighty-five (42.5%) patients were born from consanguineous marriage and 115 (57.5%) from non-consanguineous marriage. ($p < 0.001$) 10 out of 115 consanguineous marriage were non-Muslim, who do not marry cousins ($p < 0.001$) Two mothers had a history of smoking during pregnancy, 16 had a habit of chewing Paan (beetle nut & tobacco). None of the mothers had exposure to lunar/solar eclipse.

Conclusion: The Club Foot has a strong association with consanguine marriages, with heterogenic geographical distribution and family history and no association to exposure with lunar eclipse. Association with addiction (cigarette smoking tobacco chewing & paan), could not be identified due to insufficient data.

Key Words: Clubfoot, Consanguinity, Ethnicity, and Addiction

INTRODUCTION

The overall incidence reported for clubfoot is 1-7 in 1000 live births¹. Approximately 80% of them are born in the developing country world². With generally accepted incidences (1-2:1000) the estimated load of clubfoot in Pakistan, where 5.3 million births occur every year^{3,4}, would be 6000-7000 every year i.e 1.4:1000 live births. The Idiopathic Congenital Club Foot (CCF) exhibits male predominance: with male: female ratio of 3.5:1^{5,6} and 46% of these have bilateral deformities⁷.

The incidence of Idiopathic CCF varies in different geo-ethnic groups, influenced by multiple endogenous and exogenous Factors.⁸

The investigators report a strong genetic relationship with significant regional heterogeneity but no seasonal variation^{6,7,8,9}.

Fischgrund⁹ reports 10 times higher incidence in families of affected individuals than the general population. The consanguinity & ethnicity related question, as well occurrence in next siblings is often asked by parents of CCF patients. This study was therefore conducted to know the possible association of parental consanguinity and ethnicity and additions (paan eating and cigarette smoking) with prevalence of the idiopathic CCF deformity.

METHODS

This Clinical Survey was conducted from July 2013 to December 2013. The data evaluated included demographic data of 200 patients with idiopathic clubfoot deformity with age range between 5 days to 3 years. The total population during the study period were who were registered in the International Clubfoot Registry (ICR) from Clubfoot Clinic at JPMC & NMI Hospital Karachi, from November 2011 to December 2013 were included in the study. The study was conducted with approval of Institutional review board JPMC and with informed written consent from the parents of affected children. The research assistants MYB* & MFA* collected data through a purposive designed questionnaire completed with interview from

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the parents attending CFC and from few others who did not attended CCF, on telephone. The questions asked were related to consanguinity, immediate relationship of family members having CCF, mother’s eating habits (beetle nut chewing with tobacco) and cigarette smoking during pregnancy, as well as possible exposure to lunar / solar eclipse. The date was also collected for any associated deformities.

Statistical Analysis

The Data was statistically evaluated through SPSS version 13.0, a statistical package for social sciences. Chi-square test of proportion was employed to determine the association of CCF children born of consanguine marriages and non-consanguine marriages and also to determine the association of CCF children born of non-Muslims who do not marry cousins and non-consanguine marriage in Muslims.

RESULTS

Table1: Demographics and Clinical Variables. (n=200)

Variables	No of patients	%
Male	154	77.0
Female	46	23.0
Bilateral	113	56.5
Unilateral	87	43.5
Right sided	39	45.0
Left sided	48	55.0
Sindhi	73	36.5
Urdu	67	33.5
Pushtoon/Afghani	23	11.5
Punjabi	13	6.5
Blochi	12	6.0
Kachi	12	6.0
Family History	25	12.5
Affected brothers/sisters	4/25	16.0
Mothers	2/25	8.0
Affected 1st and 2nd cousin	19/25	76.0
Smooking during pregnancy	2	1.0
Chewing Paan (Beetle nut & Tobacco)	16	8.0
Relationship with lunar eclipse	Nil	0.0

Out of 200 Idiopathic CCF patients 77% were male and 23% Female, with male: female ratio of 1:3.9 (p=0.001, chi-square=116.6). Majority was of bilateral CCF 113 (56%) and overall majority were with left sided CCF 48 (55%) (p=0.01, chi-square=6.6), refer Table:1.

Eighty-five children (42.5%) were born from consanguineous marriages and 115 (57.5%) children from non-consanguineous marriages (p=0.002, chi-square=9.0). Out of 57.5% non-consanguine relationship, 10% (8.69%) were non-Muslims who do not marry cousins; 6 (3%) from the Hindu community and 4 (2%) from the Christian community (p=0.001, chi-square=275.5). Only two (1%) mothers had a history of smoking during pregnancy, 16 had a habit of chewing Paan including beetle nut with or without tobacco. None of the mothers of affected children had exposure to lunar or solar eclipse (Table: 2).

Table 2: Association with Consanguinity, Family History and Addiction:

CCF Children born of Consanguine Marriage	85/200 (42.5%)
CCF Children born of Non-Consanguine Marriage	115/200 (57.5%)

p=0.002 , chi-square=9.0

CCF Children born of Non-Muslims who do not marry cousins	10/115 (8.69%)
CCF Children born out of Non consanguine marriage in Muslims	105/115 (91.30%)

p=0.001 , chi-square=275.5

The regional, linguistic & ethnic origin revealed 73 patients belonged to the Sindhi community, 12 Baluchi, 67 Urdu speaking, 12 Katchi Memon, 13 Punjabi, 23 to the Pashtoon/Afgani speaking tribes. Percentage wise the incidence among Native of Karachi /Sindh province (Sindhi and Balochi) (42.5%) was almost the same as Urdu and Kachi speaking community (39.5%) Table:3. Two (1%) cases in the study had associated cleft lip, one (0.5%) had torticollis, and two (1%) had congenital knee dislocation. One (0.5%) of them also had DDH but there were no signs of distal arthrogryposis.

DISCUSSION

Hypothetically, etiology of CCF has been attributed to oligo-hydramnios, uterine restriction and arrest of the

normal medial rotation of the foot in lateral foot development^{10,11}. However; Ponseti's¹¹ studies reproduce more logical evidence that CCF is a "Development malformation and influenced by multifactorial genetic, environmental factors", significantly modulated by a genetic mutation¹. These multifactorial factors leads to developmental aberration in limb bud development¹², that is evident as early as 7 week¹¹. The prevalence of Clubfoot is reported lowest in Chinese (0.34 per 1000 per live birth) and highest in Hawaliance and Maoris (7 per 1000). This difference in Clubfoot prevalence across the ethnic populations supports the genetic basis clubfoot pathology¹. Our finding of heterogeneity in multi-ethnic populace living in Karachi does support the findings of Alvarado¹, Zosia¹³, Tachdjian¹², and similar observations made by Wallander⁶. However; we could not find significant difference in occurrence of CCF among natives of Karachi; Sindhi+Balochi v/s Urdu+Katchi speaking. Regarding association of CCF with heritability our finding (Table 2) are nearly similar to Ukoha⁵ and Lochmiller⁷, who significant association CCF with heritability (affected relative), that too varies between populations^{5,7}. Similarly Wynne¹⁴ and Chapman¹⁵ also reports 24% incidence of CCF in Caucasians families compared to 54% in Polynesians. The association of positive family history with CCF in our study was observed in 12.5% patients. And 16% siblings were borne of affected parents having CCF. This incidence is lower than 20%–25% relatives having CCF, as reported by Lochnillar⁷, Wynne¹⁴ and Chapman¹⁵.

The consanguine marriages in our country are very common among Muslim community, because of high consanguinity rates within Muslim populations; the incidence of Congenital Malformations (CM) in Islamic countries is between 10%-45% [16]. In developed countries such as United Kingdom (UK)¹⁷ ratio of CM leading to perinatal mortality is 26%-34%; whereas prevalence of CM is very low (3%) in Denmark¹⁸. This study reveals 42.5% parents of CCF children had marriages with first cousin, double first cousin and half first cousins ($p=0.002$, $\chi^2=9.0$). The ratio of consanguineous marriages in this represented sample (42.5%) is nearly similar to reports from Iran & Turkey (30%-85%)^{16,19,20} and Alper from Antalya Turkey¹⁶ that reports 40.7% consanguineous marriages and very frequent type was between first cousins. The effect of consanguinity has been described as an important factor contributing to increased congenital malformations. A recessive gene has been reported to

influence the incidence of some inherited diseases²⁰. This recessive gene may remain hidden for generations and come to light for the first time in an inbred descendant, who carries two copies of a gene that was present in a single copy in the common ancestor of his/her consanguineous parents²¹. Similarly various other also reports the significant risk of consanguinity in association with clubfoot, the rates reported are 31%-54%^{12,13,21,22,23}. The risk of CCF associated with consanguine marriages in our series is 42.5% versus 57.5% in non-consanguine marriage ($p=0.002$, $\chi^2=9.0$). This is slightly higher than 31% as reported by Sreenivas²² (UK) and Sahin²³. Interestingly, Tayabi²¹ from our neighboring country Iran reports very low such as 0.16% incidence of Clubfoot in consanguine marriages (25%) and 0.25% in non-consanguine marriages (75%)²¹. Sahin O²³ further elaborates that babies born to first-cousin parents had >4 times the risk of idiopathic CTEV and the risk for those born to distant relatives was 2.9 times higher than for children of unrelated parents. Whereas; Kularni²⁴ reports 30 fold increased risk in siblings of affected parents. The incidence of clubfoot in siblings have also been reported that vary from 29% to 32.5%. Tachdjian¹² reports 32.5% incidence in monozygotic twice compared to 29% in dizygotic twins. Ukoha⁵ reports significantly low (0.02%) incidence in monozygotic twins. Whereas; Wyne DR²⁵ reports higher risk for identical twins than for fraternal twins i.e. 33% versus 3%. These all reports favours the role of genetic factor in clubfoot etiology. Regarding laterality in clubfoot and association with etiological factors, literature is silent. However; significant variation has been reported in literature for bilateralism that vary from 46% to 68%^{7,22}. However, our incidence of bilateral involvement (56%) ($p=0.01$, $\chi^2=6.6$) was in accordance to that ratio. Sreenivas²² reports associated congenital malformations with CCF as high as 46.3%, that is very than our findings of 3.5% associated malformations but it was nearly similar to a report from our neighbor Iran, reported by Tayebi²¹.

CONCLUSION

The risk of occurrence of clubfoot is higher with consanguinity, in siblings of affected mothers and in families than in families having no incidence of congenital clubfoot deformity. Percentage wise the incidence among Native of Karachi /Sindh province (Sindhi and Balochi) (42.5%) was almost the same as Urdu and Kachi speaking community (39.5%). The study

does not prove the association to exposure with lunar eclipse. Whereas; its association with addiction (cigarette smoking tobacco chewing & paan), could not be identified due to insufficient data.

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