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The relationship between orofacial clefts and consanguineous marriages: A hospital register-based study in Dharwad, South India

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ABSTRACT

Context: Orofacial cleft (OFC) is one of the common craniofacial malformations. The etiology of these OFCs is multifactorial. One of the etiological factors is consanguinity (marriage between blood relatives). There is a lack of literature reporting the number of people affected with OFCs due to consanguinity. **Aims:** The aim of this study is to report the occurrence of OFC and associated factors in relation to consanguinity from a craniofacial hospital specializing in OFCs, head and neck cancer, and trauma management in South India. **Setting and Design:** This was a hospital-based study, retrospective case record analysis. **Methodology:** One thousand two hundred and forty-seven consecutive patients' secondary data records with cleft lip (CL), cleft palate (CP) and cleft lip and palate (CL/P) were collected from January 2007 to July 2009. **Statistics:** Frequency of consanguinity in relation to OFC was analyzed using Chi-square test according to the nature of clefts and selected demographic features such as sex, region, and religion. **Results:** A total of 47.2% patients' parents had consanguineous marriage. Consanguinity was seen in 60.2% of male and 39.7% of female patients. CL/P was noticed in 40.9%, followed by CL (36.7%) and CP (22.2%). Males predominated in all types of clefts proportionally with the study population as compared to females. Statistically, significant association (P = 0.04) was seen with consanguinity and CP. **Conclusion:** Nearly half of the study population had a positive history of consanguinity. Statistically, a significant association was seen between CP and consanguinity. CL/P cases were the most common type identified, followed by CL and CP. Males predominated in all types of clefts. The prevalence of OFC is high, and there is a potential of congenital disabilities from consanguinity. These findings indicate a clear and urgent need for setting up a National Registry of Congenital Anomalies along with craniofacial defects, to monitor these trends and the corresponding need for supportive services.

Key words: Cleft lip, cleft palate, consanguinity, orofacial clefts, South India

INTRODUCTION

Craniofacial congenital disabilities such as cleft lip (CL), cleft palate (CP), and cleft lip and palate (CL/P) grouped under orofacial cleft (OFC) are the most common of all the developmental disorders affecting humans.[1] The incidence and prevalence of OFC vary throughout the world. The epidemiological data on an international perspective are varied, and many countries lack these data.[2] The estimated global prevalence of CL/P is one in every 600 newborn babies.[3] Although there are few studies which describe the prevalence of OFC in India, the most recent data indicate the incidence to be 1.09/1000 live births[4] whereas Mossey and Little[3] reported the prevalence being at 28,600 throughout the country.

The nonsyndromic OFC is a polygenic multifactorial disorder. CL/P is a multifactorial disorder with multiple risk factors such as genetics, environmental causes,

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and cultural factors. The role of genetic factors in the etiology of CL/P is critical and it is associated with 400 different syndromes. In India, consanguineous marriages are not uncommon due to prevailing cultural practices. Consanguinity is an identified factor that increases the risk of transmission of genetic disorders, especially autosomal recessive ones. Consanguinity is a cultural practice which could have an epigenetic role in the development of congenital abnormalities. Hence, along with genetic and environmental factors such as consanguinity which is a cultural factor, it also contributes to CL/P's etiology.[5] A meta-analysis revealed an odds ratio of 1.83 (95% confidence interval, 1.31–2.54) implying the risk of having cleft two times higher in children with consanguineous history.[6] Consanguineous marriages are a common social norm in many societies worldwide where marriages are between close blood-related persons varying from first cousins to uncle-niece relations. About 10.4% of couples in the global population are reported to be related as the second cousins or closer; a similar relationship holds true for the progeny of these couples.[7] Consanguinity is practiced commonly in Arab Countries (50%), South India (10%–50%); China, North India, Latin America, Japan, South Europe (10%) and less common in the United States, Russia, Australia, Parts of Latin America, and Europe (1%).[8]

Bittles and Black[7] have reported that consanguinity is a much wider and more complex issue involving major economic, demographic, and social influences, differential reproductive behavior, and early- and late-onset morbidity and mortality. The influence of consanguinity on the etiology of congenital anomalies is a common observation. Kulkarni and Kurian[9] have reported that consanguinity has a probable deleterious effect on fetal growth and an increased risk of congenital malformations and fetal loss. Several studies have shown significant associations between consanguinity and congenital anomalies.[10-12]

Consanguinity and its effect on OFC have been studied and reported extensively. Some observational studies showing an association between OFC and consanguinity have been reported from arab countries. However, only few studies have been reported from India.[17,18] There is a dearth of recorded data or literature supporting the relation of consanguinity and OFC in India. Therefore, the purpose of this study was to evaluate the relationship between consanguineous marriages and patterns of CL and CP from data collected in a craniofacial hospital in South India. The objectives are to estimate the proportion of different types of OFCs presenting to a tertiary care hospital in South India and to describe the demographic profiles (including gender, region, religion, and consanguinity) in these patients.

METHODOLOGY

A retrospective analysis of a prospectively collected database of all CL/P patients treated in the craniofacial hospital at SDM College of Dental Sciences and Hospital, Dharwad, India. The hospital is a superspecialty tertiary care center of craniofacial abnormalities and rehabilitation. Every OFC case details are entered into a database since 1991. The present study included a retrospective analysis in 2013 of patient records for a 30-month period between January 2007 and July 2009. This tertiary care level hospital is located in the northwestern part of Karnataka of Southern India. The surgical treatment provided here is free of cost under the auspices of the Smile Train India Project. The patient pool is large and attracts patients mostly from North Karnataka and also from the neighboring states of Goa, Maharashtra, and Andhra Pradesh. SDM College of Dental Sciences and Hospital's Institutional Review Board approved this study.

A total of 1247 patient records were audited and used to form the basis of the study. The hospital records included data about demographic details such as age, sex, address (urban/rural), religion, family type (joint/nuclear), parent's education, occupation and monthly income; presence or absence of consanguinity, type of clefts, age of mother at first conception, and any other sibling with OFC and their cleft type. The present study specifically collected data regarding selected demographic features such as sex, region, religion, history of consanguinity, and cleft type. Each patient record was assigned an individual outpatient number, and care was taken not to count the same patient more than once. Patient records/information were anonymized and de-identified before analysis.

A simple descriptive classification was used to record the cleft type. CL was further classified into unilateral and bilateral and CP into partial and complete. CL/P was also classified into unilateral (CL/P U/L) and bilateral.

The information was collected manually and entered into a Microsoft Excel sheet by the investigator. Data were subjected to descriptive statistical analysis using Microsoft Excel and were further analyzed using Version 20 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). The association of OFC with consanguinity, gender, region,

religion and cleft type was analyzed using univariate analysis such as Chi-square test.

RESULTS

Table 1 shows the demographic features. There were 766 males and 481 females, with a male-female ratio of 1.5:1. Clefts were seen more in rural settings (1076, 86.2%) compared to urban (171, 13.7%). Hindu patients (1049, 84.1%) showed the highest rate of OFC. A total of 589 subjects' parents had consanguineous marriage (47.2%). Among the consanguineous group of the study population, a majority were from a rural (508, 86.2%) as compared to an urban setting (81, 13.7%). Among consanguineous progeny, most were Hindus (509, 48.5%), followed by Muslims (76, 40%), Christians (2, 0.33%), and Buddhists and Jains (each one subject). The male-female ratio with consanguinity was 1.5:1. CL/P was most common (511, 40.9%), followed by CL (458, 36.7%) and CP (278, 22.2%). Males predominated in all types of clefts proportionally in the study population compared to females [Table 2]. Unilateral CL (195, 33.1%) was more commonly associated with consanguinity, followed by CL/P U/L (186, 31.5%).

A statistically significant association ($P = 0.04$) was seen with consanguinity and CP [Table 3]. Data related to parent's education and occupation and monthly income were missing in some records. These data were not considered in the present study as they were not related to the aims and objectives. A total of 24 patients had siblings with CL/P. From the total sample, 91 patients' (7.29%) parents gave a family history of CL/P.

DISCUSSION

Consanguineous unions have been practiced since time immemorial. They began as a necessity due to small populations that existed during primitive times and were practiced in most parts of the world until the early 19th century. The merits and demerits of this practice have been a debated topic. Although consanguineous marriages are declining globally, it is still widely practiced in the Middle Eastern countries such as Saudi Arabia, Iran and also in Southern India.[8] There is a wide geographical distribution and variations in consanguineous marriages globally. This marriage system between close biological relations involves many social, cultural, religious, and civil aspects.[7,10,11] The practice of consanguinity within the Indian subcontinent shows similar differences as those observed in other parts of the world. In India, this practice is an accepted method of union between two persons and is accepted culturally, socially, religiously, and also legally particularly in the southern states.

Consanguinity is widely practiced by the Dravidian Hindus and less commonly among the Muslims of South Indian states such as Andhra Pradesh, Karnataka, and Tamil Nadu.[19,20] Bittles *et al*. reported that in Bengaluru and Mysore, two major cities of Karnataka of South India, 21% of Hindu marriages were uncle-niece unions.[21] Although a 1% decline in consanguineous marriages throughout the country was observed from 1960 to the 1990s, there have been no recent data on its prevalence; however, another study found that there was no declining trend in the immigrant Mudaliar community

Table 1: Demographic Profile of the Study Population

Demographic Features		Study Population (%) 1247	Consanguineous (%) 589 (47.2)	Non consanguineous (%) 658
Gender	Males	766 (61.4)	355 (46.3)	411 (53.6)
	Females	481 (38.5)	234 (48.6)	247 (51.3)
Region	Urban	171 (13.7)	81 (47.3)	90 (52.6)
	Rural	1076 (86.2)	508 (47.2)	568 (52.7)
Religion	Hindus	1049 (84.1)	509 (48.5)	540 (51.4)
	Muslims	187 (14.9)	76 (40)	111 (60)
	Christians	6 (0.4)	2 (0.33)	4 (0.6)
	Buddhists	2 (0.1)	1 (0.5)	1 (0.5)
	Jains	3 (0.2)	1 (0.3)	2 (0.6)

Table 2: Distribution of Cleft Deformities by Gender

Gender (*n*)	Cleft Lip (%)		Cleft Palate (%)		Cleft Lip and Palate (%)	
	Unilateral	Bilateral	Partial	Complete	CL/P U/L	CL/P B/L
Male (766)	250 (32.6)	20 (2.6)	94 (12.2)	60 (7.8)	264 (34.4)	78 (10.1)
Female (481)	166 (34.5)	22 (4.5)	79 (16.4)	45 (9.3)	132 (27.4)	37 (7.6)
Total (1247)	416 (33.3)	42 (3.3)	173 (13.8)	105 (8.4)	396 (31.7)	115 (9.2)
Grand Total	458 (36.7)		278 (22.2)		511 (40.9)	

Table 3: Distribution of Cleft Deformities by Consanguinity

Consanguineous (*n*)	Cleft Lip		Cleft Palate*		Cleft Lip and Palate	
	Unilateral	Bilateral	Partial	Complete	CL/P U/L	CL/P B/L
Yes (589)	195 (33.1)	20 (3.3)	96 (16.2)	44 (7.4)	186 (31.5)	48 (8.1)
No (658)	221 (37.5)	22 (3.7)	77 (11.7)	61 (10.3)	210 (31.9)	67 (10.1)
Total (1247)	416 (33.3)	42 (3.3)	173 (13.8)	105 (8.4)	396 (31.7)	115 (9.2)
Grand Total	458 (36.7)		278 (22.2)		511 (40.9)	
	χ^2=0.033		χ^2=6.234		χ^2=1.738	
	P=0.98		*P*=0.04		*P*=0 0.41	

*$P<0.05$

in Kerala, South India.[22] This is in concordance with reports, suggesting the practice of consanguinity among Asian migrants in Europe to be common.[7]

The effects of consanguinity on health and disease have been studied and reviewed extensively. To the best of our knowledge, there are no previous studies reported from India, examining the relationship of consanguinity and the most common craniofacial congenital anomalies, particularly OFC. This study highlights the practice of consanguinity across India but more prevalent in South India, which is widespread throughout the country. The present study was conducted in Dharwad in South India. The craniofacial hospital attracts patients from a radius of 200–300 miles. Since the study's aim was to check the relationship between consanguinity and CL/P from hospital records, the interpretation of the findings is limited to the practice of consanguinity in relation to CL/P, which will also determine the prevalence of consanguinity. Consanguinity was identified during the case history recording and was done usually by the clinician orally. One of the major limitations of the study is that the details related to the degree of the consanguinity were not recorded. This was brought to the notice of the hospital administration, and they decided to include these details in the case history afterward.

In our study, consanguineous marriages were observed among 47.1% of patients' parents, which is less than what was observed by Aljohar *et al*. and Ravichandran *et al*., suggesting a lesser prevalence compared to Arab countries.[5,15,16] On the contrary, consanguineous marriages were seen only in 36% of the study population conducted in the neighboring district of Belgaum of North Karnataka where consanguineous marriages are a common social norm.[23] This could be due to the geographical variation in practice, as well as data availability being secondary and the changing attitudes and behavior toward consanguinity.

This study shows a high prevalence of consanguinity among rural population (86.2%). Studies have reported that consanguinity is commonly practiced by people who are illiterate and from low socioeconomic status and other related factors.[5,10,24] Rural areas show higher rates of illiteracy and low socioeconomic status in India.[25] Despite the several negative consequences of the practice ranging from neonatal mortality to congenital anomalies with genetic mutations, consanguinity also offers certain social advantages seen in rural areas such as ease of enhanced female autonomy, marriage arrangements, more stable marital relationships, lower domestic violence, greater compatibility with in-laws, economic benefits of reduced dowry, lower divorce rates and maintenance of any landholding.

The present study showed a high prevalence of clefts (84.1%) and consanguinity (86.4%) among Hindus. This is in agreement with previous studies suggesting that consanguinity was common in Hindus.[10,22,26] The OFC common in Hindus was again in harmony with results reported by Dvivedi and Dvivedi.[24] The Hindu Code Bill of 1984 and the Hindu Marriage Act of 1955 support the legality of consanguineous marriages in India.[7] The high prevalence rate in the Hindu religion is in proportion to the national population, which is about 80.5% according to 2011 census.[27]

The results of the study also showed a high prevalence of OFC among males. Males predominated in all types of clefts proportionally with the study population compared to females. Aljohar *et al*.[5] reported that CL/P and CL were more common in males and CP in females although Aljohar *et al*. reported that CP was indeed common in males.[15] In contrast, our study found CP to be more common among males as compared to females.[4,5,16]

In the present study, CL/P (40.9%) was seen more than CL and CP, which is consistent with the literature. CL (36.7%) occurring more than CP (22.2%) differs from the literature.[5,16] A statistically significant association ($P = 0.04$) was seen with consanguinity and CP. Similar significant results were reported between consanguinity and OFC,[6,13,15,16,18] whereas

Golalipour *et al*. reported that no significant association was seen between consanguinity and OFC.[28] This significance could indicate the biological plausibility between consanguinity and OFC, particularly CP. This significance is explained by other studies considering factors such as degree of consanguinity,[18] ascertainment,[6] family history of clefts, and intracluster correlation between siblings affected by OFC.[16]

Consanguineous marriages have been debated since Darwinian times. The advent of genetics and its application in medical sciences to diagnose and prevent disease has further broadened our knowledge in understanding effects of this practice on health and disease. Genetically, close biological unions result in expression of autosomal recessive genes which are associated with many congenital anomalies such as childhood deafness, congenital cataracts, heart defects, and craniofacial defects such as OFC.[7,11] Although many studies show statistically significant associations between consanguinity and OFC, they do not prove the etiology of OFC to be consanguinity. Therefore, it necessitates further research to investigate this biological plausibility. Recently, a gene was identified as the causal mutation for CL/P in consanguineous Palestinian families.[29] As theorized, consanguinity could have a genetic effect.[16] Bittles has discussed the relation between consanguinity and genetics and has concluded that in populations where consanguineous marriage is widely practiced, recessive genetic disorders will continue to gain greater prominence in the overall spectrum of ill health.[18]

Since the consanguineous marriage system is characterized by many variations such as region, religion, and caste, it is relevant to the general population. The marriage preferences such as choice of bride/groom, caste preference, and love marriage over arranged marriage all contribute to the increase or decrease of consanguinity. CL/P along with other congenital anomalies has varied etiological risk factors, of which consanguinity is thought be one. The results of this study provide valuable information regarding the prevailing consanguineous marriage system practice and are relevant considering the multiple risk factor etiology for CL and palate deformities. By knowing the prevalence, strategies to prevent and educate masses about the effects of consanguinity should be developed.

India does not have a national registry for congenital anomalies as per the recommendations of World Health Organization. This study helps us to build an evidence base that can be used for approaching the decision-makers for such a need in India focusing on congenital anomalies including craniofacial defects for a collaborative interdisciplinary research on database setup, epidemiology, gene–environment interaction and prevention.[3,19,30-33]

Strengths and limitations

The primary author came across a large number of OFC patients during the graduate residency program which provoked the interest in researching on consanguinity and OFC. This study was conducted using hospital records as opposing to population-based study because of feasibility considerations such as cost and human resource. Since secondary data were collected using hospital records, the question of ascertainment arises. The validity and reliability of the data collected should be considered because the hospital registry-based studies are prone to bias.[30] There is considerable variation in the frequencies of OFC worldwide and comparability of the data is affected by factors such as source of the sample population versus hospital-based studies, method of ascertainment, inclusion–exclusion criteria and sampling fluctuation.[2] The present study's scope was limited to do a cross-sectional descriptive study to describe the relation of consanguinity and CL/P. For this reason, case–control design was not deemed appropriate for our objectives, and thus, control group was not included in this study.

The epidemiological data on OFC and its associated factors is lacking in India.[2] There are no national-level studies conducted to find the prevalence of consanguinity. Therefore, the correlation of observed prevalence in this study to the general population prevalence is not possible.

CONCLUSION

From the present study, it can be concluded that nearly half of the study population was the progeny of a consanguineous union. The number of consanguineous marriages from this study showed the possible magnitude of its effects. There was statistically significant association seen between CP and consanguinity. CL/P was more commonly seen, followed by CL and CP. Males predominated in all types of clefts.

The prevalence of consanguinity and the burden of resulting congenital disabilities identified by this study demonstrate a clear and urgent need for creating a national registry for congenital anomalies, including craniofacial defects. This is based on the recommendations of the World Health Organization to facilitate collaborative, interdisciplinary research using case–control study design by collecting primary data.

Such research will also contribute to a more robust understanding of epidemiology, gene–environment interaction and potential prevention strategies. Finally, strategies to prevent and educate masses about the effects of consanguinity should be developed.

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Conflicts of interest

There are no conflicts of interest.

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