

Oral Clefts and Consanguinity: A Report from Karachi, Pakistan

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ABSTRACT

Objective: To evaluate the occurrence of the risk of offspring having cleft lip and palate in consanguineous marriages

Methodology: This is a cross sectional study which was done for a period of six months from March 2022 to November 2022 at Al-Mustafa Hospital, Karachi. All patients without any syndromes and medically fit were included and respondents were interviewed using a questionnaire.

Results: A total of 278 patients with 129 (46.4%) females and 149 (53.6%) males were included. Fifty one (18.3%) patients had isolated cleft lip, 162 (58.3%) patients had complete cleft, and 65 (23.4%) patients had isolated cleft palate. Total 158 (56.8%) parents of children had consanguineous marriages, of which 83 (29.9%) were married to paternal side and 76 (27.3%) were married to the maternal side. History of parental cleft was seen in 9 (3.2%) patients. Among risk factors, 8 (2.9%) mothers had radiation exposure during pregnancy and 8 (2.9%) and 2 (0.7%) had habits of huqqa and smoking respectively. Seven (2.5 %) patients were twins and one was born with cleft either isolated or complete and other without any anomaly.

Conclusion: Nearly half of the study population in this study had consanguineous marriages. Strategies should be developed to educate people about association of orofacial clefts with consanguinity along with risk factors.

Key Words: Consanguinity, cleft lip, cleft palate, non-syndromic

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INTRODUCTION

Non-syndromic cleft lip and palate (NSCLP) are among the commonest craniofacial anomalies, with varying incidence reported across the world. Published reports suggest an incidence rate ranging from 1 in every 500 to 2,000 live births¹.

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Pathologically, cleft lip and palate result from the failed fusion of nasal and maxillary prominences during the first 6-8 weeks. Although the reasons for this failed fusion remain unknown, several genetic and environmental factors have been associated with the pathogenesis of cleft lip and palate². Environmental factors include advanced maternal age, as well as the use of teratogenic drugs (eg. phenytoin, retinoid, diazepam, and steroids). Other factors include alcohol consumption and smoking during pregnancy³. Genetic factors linked to NSCLP include aberrations in various genes, including TGF- β -3 (Transforming Growth Factor beta 3), MSX-1 (Msh home box 1), IRF-6 (Interferon regulatory factor 6), FGF (Fibroblast growth factor), and PVRL-1 (Poliovirus receptor related-1)^{4,5}.

A significant risk factor for recessive diseases is consanguinity, with higher frequency of congenital conditions observed in children born to first degree consanguineous parents compared to those of non-consanguineous parents^{6,7}. Similarly, studies from some countries have observed an association between consanguinity and cleft lip and palate⁸.

The primary objective of our study was to explore the history of first-degree consanguinity in a cohort of

children with non-syndromic cleft lip and palate presenting at an established cleft surgery center in Karachi, Pakistan. Furthermore, we describe the patterns of NSCLP, gender distribution, and familial prevalence of CLP observed among this cohort.

METHODOLOGY

We conducted a descriptive cross sectional study from March 2022 through November 2022 at the Cleft Center at Al-Mustafa Hospital in Karachi, Pakistan after approval from IRB (ref: AWS/2023/210). All the patients presenting with cleft lip and palate were included in the study. Patients with self-reported syndromes, or physical exam findings consistent with clearly defined syndromes were excluded. A detailed questionnaire was developed as our data collection tool, and included variables such as age, gender, presence or absence of consanguinity, type of NSCLP, paternal and maternal age at time of birth, history of maternal tobacco consumption, and radiation exposure during pregnancy.

For the purpose of our study, history of consanguinity was considered positive only if the parents were first degree cousins. Due to the low literacy rate in Pakistan, and the medical knowledge necessary to identify type of NSCLP, we opted against a self-administered questionnaire, and a physician in the outpatient clinic setting administered it.

The non-probability convenience sampling method was adopted in the study. Data collected via the questionnaires was archived and analyzed for descriptive statistics using Statistical Package for Social Sciences version 20. Mean was calculated for quantitative variable e.g. age while frequency and percentages was calculated for qualitative variables e.g. gender, type of cleft, paternal / maternal consanguinity and risk factors associated with cleft. The association of cleft lip and palate with consanguineous marriage was calculated with application of Chi-Square Test. P-value of <0.05 was considered significant.

A total of 278 patients who fulfilled the inclusion criteria were included in the study. Mean age of patients was 9.74 months ± SD 7.7, minimum of 3 months and maximum of 36 months (Table 1).

Consanguinity was reported in (n=158, 56.8%) with a slight predominance of paternal consanguinity (n=83, 52.5%) vs maternal consanguinity (n=76, 47.5%). The association of consanguinity and oro-facial cleft was assessed using Chi-Square test which showed a significant association of cousin marriage and presence of cleft lip and palate, p-value <0.05 (Table 2).

Table 1: Gender and Type of Cleft Distribution

		Frequency	Percentage
Gender	Male	149	53.6
	Female	129	46.4
Type of Cleft	Cleft lip	51	18.3
	Cleft palate	65	23.4
	Complete cleft	162	58.3

Table 2: Association of Consanguinity and Cleft

		Type of Cleft				p-Value
		Cleft Lip	Cleft Palate	Complete Cleft	Total	
First Degree Consanguinity	Present	45 (28.4%)	28 (17.7%)	85 (53.7%)	158 (100%)	0.012
	Absent	6 (5%)	37 (30.8%)	77 (64.1%)	120 (100%)	
Total		51 (18.3%)	65 (23.4%)	162 (58.3%)	278 (100%)	

We found a low prevalence of cleft lip and palate among parents of patients with NSCLP (n=9, 3.2%), but overall family history of cleft lip and palate was high (n=41, 14.7%) after including other relatives such as siblings, aunts, uncles, cousins, etc. A small number of patients with NSCLP reported history of maternal radiation exposure (n=8, 2.9%) and tobacco consumption during pregnancy (n=10, 3.6%) (Table 3).

Table 3: Characteristics of Patient Cohort (n=278)

Other Factors	Frequency	Percentage
Parental Consanguinity		
Present	158	56.8
Absent	120	43.2
Type of Consanguinity		
Maternal	76	27.3
Paternal	83	29.9
Parental History of Facial Clefts		
Present	9	3.2
Absent	269	96.8
Family Members with Facial Clefts		
Present	41	14.7
Absent	237	85.3
Risk Factors of Facial clefts		
Radiation Exposure	8	2.9
Tobacco Exposure	10	3.6

We also identified seven twin siblings in our cohort (2.5%). An interesting finding in all the twin pairs was that only one child out of the twins was born with cleft lip or palate.

DISCUSSION

Orofacial clefts are among the commonest congenital defects in the world, with incidence rates as high as 1 in 2000 live born children⁹. Moreover, in developing countries such as Pakistan, the incidence is significantly higher, reaching up to 1 in 500 live born children¹⁰. There are significant resources in the developed world to promptly diagnose and manage children with the congenital defect of cleft lip and palate, and multidisciplinary team approach is adopted for surgical repair, speech, hearing, and nutritional optimization. Unfortunately, similar resources are usually lacking in most developing countries, and identification and prevention of risk factors associated with orofacial clefts offer a more pragmatic strategy in these settings.

Previously published literature from Karachi, Pakistan has found the prevalence of first-degree consanguineous marriages to be around 25%¹¹. However, our cohort of children with NSCLP had a significantly higher background of first-degree parental consanguinity at approximately 57%. Although we did not design our study as a case-control, which is a limitation of our study, but comparing our data with published data on consanguinity from the same geographical area in Pakistan¹¹ suggests that first-degree consanguineous marriages are associated with a higher risk of NSCLP.

Various studies across the world have demonstrated a strong association between NSCLP and consanguinity. Interestingly, a study from Saudi Arabia in 2012, found the background of consanguinity among patients with NSCLP to be equal to ours: 56.8%¹². However, their estimate included parents with first and second-degree consanguinity, whereas we only assessed for first-degree consanguinity. This suggests that the prevalence of parental consanguinity in our cohort might have been higher if we had included second-degree consanguinity.

The only population-based epidemiological study on CLP in Pakistan was conducted in the Northern Areas of Pakistan, and utilized a provincial birth registry from documented health facilities¹⁰. Compared to our data, this large-scale study found a relatively lower prevalence of first or second-degree parental consanguinity among children with CLP, approximately 32%. Our study from Karachi, Pakistan found the prevalence to be as high as 57%, whereas another hospital-based study conducted in Lahore, Pakistan found 63% of children with CLP had parents with consanguineous marriage¹³. We feel that the lower prevalence recorded by Elahi et al is likely due to limitations of birth registries in Pakistan, as up to 74%

of births may take place outside of health facilities, and are therefore not documented in birth registries¹⁴.

Consistent with previous studies, our study found males were predominantly afflicted with complete cleft of lip and palate and also isolated cleft lip, while females were predominantly afflicted with isolated cleft of palate⁹. We also identified that 2.5% of our patients were twins, and this is the first study, to the best of our knowledge, from Pakistan to identify twinning among patients with NSCLP.

Tobacco consumption among females in Pakistan is relatively high, and most pregnancies are unplanned due to the low rates of family planning¹⁵. However, when evaluating risk factors for NSCLP, we found only 2.9% of patients had a history of maternal radiation exposure during pregnancy, and only 3.6% had a history of maternal tobacco use during pregnancy. Tobacco use among women is associated with significant social stigma in Pakistan, and the low rates in our study are likely a limitation of the self-reported nature of our project, thereby leading to under-reporting¹⁵.

In summary, we demonstrate a high prevalence of parental consanguinity leading to NSCLP in Pakistan. Although several national and international organizations are devoting significant resources to provide medical and surgical services for children afflicted with NSCLP, there is virtually no effort to prevent NSCLP.

In our opinion, a dire need for educational efforts exists at the population level to highlight the negative outcomes associated with consanguineous marriages. We propose that the government implement a mandatory premarital screening programme to detect carrier couples with recessive diseases, and counsel all couples against consanguineous marriages. Although there is mixed data regarding the utility of these measures in conservative societies where consanguineous marriages are a deep rooted tradition, similar programmes have been implemented successfully in many Arab countries that are identical to Pakistan from a cultural and religious standpoint^{16,17}. We feel these measures would be a reasonable first step to reduce the burden of NSCLP in Pakistan and would also produce the added benefit of decreasing other recessive disorders.

CONCLUSION

From this study, it can be concluded that consanguineous marriages can be considered as one of the risk factors that can result in the occurrence of non-syndromic congenital cleft lip and palate. This study also enables us to design strategies for counselling regarding the most common craniofacial anomaly.

Conflict of interest: Authors declare that there is no conflict of interest.

Authors' Contributions: SK is the principal author who conceived the idea and penned the manuscript; TA provided valuable assistance in drafting the manuscript; FAG contributed to data collection efforts; MAG, ZZ, and DH conducted thorough final reviews of the manuscript and provided critical feedback on the final version.

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