Original Article

Factors Predisposing to Development of Cleft Lip and Palate A Case Control Study

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Objective: To determine the predisposing risk factors of cleft lip and palate among children in a tertiary care hospital.

Methods: This case control study was conducted at The Children Hospital and Institute of Child Health Lahore and included 55 cases and 55 controls. Data was collected using a structured questionnaire. SPSS 20.0 software was used for data entry and analysis. Analysis included frequency distributions and proportions for categorical variables and calculating odds ratios (unadjusted and adjusted) for association between various risk factors and cleft lip. Regression modeling was done to point out the main contributing factors.

Results: A total of 55 cases and 55 controls were included in the study with mean age of 8.25 months. Maternal illness, cousin marriage, female gender of the child and absence of supplementation of multivitamins and folic acid during pregnancy were significant risk factors for the development of cleft lip and palate.

Conclusions: Maternal illness, cousin marriage, female gender of the child and lack of multi-vitamin and folic acid supplementation during pregnancy were found to have significant association with the development of cleft lip and palate. In this regard, it is recommended to improve the status of health education of prospective parents as well as society at large to curtail the modifiable risk factors viz. cousin marriage and absence of supplementation of multi-vitamins and folic acid during pregnancy. Better setup for community antenatal care provided by the concerned authorities may help control the problem.

Keywords: congenital abnormalities, cleft lip, cleft palate.

Introduction

Childbearing is one of the fundamentally imperative physiological properties of life, especially in the case of human beings. The locus of technical knowledge in the fields of gynaecology, obstetrics and paediatrics is to ensure the birth of healthy and defect free offspring. The largest asset of a country is its new generation of healthful, diligent, brilliant, and mindful youngsters. Congenital abnormalities appearing in the children is a major reason resulting in the nullification of this precious asset rendering it inefficient and leading to great losses in the human capital. Cleft lip and palate with a measured worldwide incidence of 1 in every 700 live births, is one of these malformations.[1,2]

Cleft lip and palate are the commonest birth anomalies due to the abnormal facial growth in the foetal life.[3] Cleft lip which may co-exist with or can be in the absence of cleft palate (CP), is amongst the commonest of the various malformations observed in the infants. Asians are at higher risk for facial clefts, followed by Caucasians and African Americans.[4,5] In Iran, its prevalence varies from 0.93 to 1.03 per 1,000 live births.[6]

Every year, five thousand new-borns suffer from cleft lip and palate in United States of America.[7,8] Cleft lip alone or a cleft lip concomitant with a cleft palate is classified as cranio-facial birth abnormality and requires several forms of surgery and additional complicated surgical interventions.[9] The cleft in its nature can be unilateral, bilateral, complete or partially complete. The predisposing factors of cleft lip and cleft palate may be ascertained by genome of the parents and can be determined from the phenotyping of both the parents.[10]

Most of these defects occur due to genetic influence;about 20% of them are generated as a result of environmental factors and teratogens in the embryo development which are mostly responsive to prevention. Common factors are cousin marriages, medication during pregnancy, weather fluctuations, alcohol use, active and passive smoking, obesity in mother, and hereditary influencers like race and ethnicity etc.[1,7,11,12,13] Various studies have demonstrated that seventy per cent of cleft lip and or cleft palate (CL/P) cases are non-syndromic and the residual thirty per cent are tied to structural aberrations except those in the cleft area.[14] During the 4th to 9th week of

Gestation, the most vital developmental changes occur in the face. Till the 8th week, the facies are completely developed except the palate region, which is not completely developed for another 3 weeks. Major challenge for a new-born with cleft lip and palate is the articulation and formation of normal speech.[15] These abnormalities arise in the syndromic and non-syndromic types and the diagnosis of its associated risk factors is also quite complex.[16] Feeding is another issue for the parents of such children. There is impairment of functions like sucking, swallowing and deglutition.[17] The children having cleft lip and cleft palate or both CL/P are prone to several dental problems i.e., pertaining to the number of teeth, their form, dimensions, development, and root laying, in numbers greater than those in the non-affected population.[18] The face is made by fusion of 5 distinct prominences (including the twin maxillary, mandibular and the one nasofrontal prominences). Facial clefts are believed to be a consequence of abnormal fusion and further consequent obliteration of the grooves amongst the facial prominences. There is a lack of knowledge of factors predisposing to cleft lip and palate in children in developing countries and researches on this topic from Pakistan are scarce. We therefore planned this study with the aim to determine the pre-disposing environmental and genetic risk factors for cleft lip and palate in children, their association with various congenital abnormalities and co-existence of associated risk factors in such patients. The importance of identification of risk factors lies in the fact that by controlling the risk factors, we may decrease the oro-facial anomalies and help reduce the burden of problems associated with it. Prevention is the ultimate objective for clefts of the lip and the palate and a prerequisite of this aim is to determine preventable risk factors of these disorders.

Methods

It was a case-control study conducted at Children's Hospital & Institute of Child Health Lahore. Children with congenital cleft lip and cleft palate were included as cases from outpatient and in-patient departments of paediatric medicine, plastic surgery and paediatric surgery, while children without congenital cleft lip and cleft palate were enrolled as controls from the routine OPD and vaccination center. Duration of study was three months (Oct-Dec, 2017). Sample size was calculated to be 55 cases and 55 controls using Open-epi statistical calculator with 95% CI, power of study 80% and a case to control ratio of 1:1. All those children from birth to any age having congenital cleft lip or cleft palate who visited The Children's Hospital Lahore, Surgery or Plastic Surgery, Out-patient department or were admitted in these wards for surgical treatment were included in the study as cases. Children without cleft lip or palate visiting the outpatient department with minor ailments or for routine vaccination purposes were included as controls. Children having traumatic cleft lip or palate were excluded. All the mothers were interviewed using pre-designed and pre-tested questionnaire. Permission from hospital Institutional Review Board and the Heads of relevant departments (Paediatric Plastic Surgery and Paediatric General Surgery) and verbal consent from the mothers were obtained. Privacy and confidentiality of the participants was maintained. Information about socio-demographic characteristics and risk factors of cleft lip/palate was noted. Clinical examination was done for syndromic facies, and any other associated congenital anomaly like talipesequinovarus or presence of congenital heart defects. The presence of congenital cleft lip or cleft palate in siblings or any other relative, and number of children (first born or having elder siblings) in the family were noted in the history. History related to maternal age, father's age, previous abortions, still births, duration of conception after marriage if first born and consanguinity was also taken along with history of multivitamin and folic acid supplementation during pregnancy. Same history and examination was done for controls without having oral clefts. The data was analyzed using Statistical Package for Social Sciences (SPSS) version 23 software.

Results

The findings of the study are summarized in the tables below. **Table-1** summarizes the Sociodemographic characteristics of the families of cases and controls. **Table-2** summarizes the information pertaining to the children included in the study as cases and controls. **Table-3** comments on the frequency of congenital defects including those other than cleft lip/ palate as well. **Table-4** presents the risk factors of cleft lip/ palate as studied among cases and controls. **Table-4** shows the multivariate analysis (regression modeling) used to point out various risk factors contributing towards the cleft lip/palate. **Table 5** shows the reduced model of the same data as used in the above model. After applying the reduced model (Backward: LR) on the Regression model **(Table 6)** the female sex of the

Table-1: Socio-demographic characteristics of the family.

Variables		Cases		Controls	
		N	%	N	%
Mother's age	<20 years	03	5.5	03	5.45
	20-29 years	39	70.90	38	69.1
	30-40 years	13	23.6	14	25.5
Mother's age at tieme of birth	=20 years	29	51.8	27	48.2
	> 20 years	26	48.1	28	51.9
Father's age	< 25 yreas	05	9.1	03	5.5
	25-29 years	17	30.9	17	30.9
	30-34 years	17	30.9	21	38.2
	35-40 yrears	11	20.0	10	18.2
	>40 years	05	9.1	04	7.2
Father's education	Illiterate	24	43.6	27	49.1
	Literate	31	56.4	28	50.9
Father's income	Less than Rs. 15000/-	64	65.5	29	52.7
	> 15000/-	19	34.5	26	47.3
Area of Residence	Rural	34	61.8	27	49.1
	Urban	21	38.2	28	50.9

Table-2: Summarizes the information pertaining to the children included in the study as cases and controls.

Variables		Cases		Controls	
		N	%	N	%
Age (months)	Birth to 12 months	47	85.5	44	80.0
	Above 12 months	08	14.5	11	20.0
Sex	Male	27	49.1	41	74.5
	Female	28	50.9	14	25.5
Nutritional status	Under wight	28	50.9	31	56.4
	Normal	27	49.1	20	36.4
Birth order	1-2	32	58.2	31	56.4
	3-4	12	21.8	14	25.4
	5-6	10	18.2	09	16.4
	>6	01	1.8	01	1.8
Any other child having cleft lip and palate	Yes	01	1.8	0	0
	No	54	98.2	55	100

Table-3: Comments on the frequency of congenital defects including those other than cleft lip/palate as well.

Variables		Cases		Controls	
		N	%	N	%
Children suffering cleft lip only	Yes	10	18.2	0	0
	No	45	81.8	55	100

Children suffering from cleft plate only	Yes	23	41.8	0	0
	No	32	58.2	55	100
Children suffering from both cleft lip and palate	Yes	21	38.2	0	0
	No	34	61.8	55	100
Children suffering from any syndrome	Yes	01	1.8	0	0
	No	54	98.2	55	100
Children suffering from congenital heart disease	Yes	02	3.6	8	15.5
	No	53	96.4	47	84.5

Table-4: Shows the multivariate analysis (regression modeling) used to point out various risk factors contributing towards the cleft lip/ palate.

Factor	Crude odds ratio OR (95%CI)	P-value	Adjusted odds ration OR (95CI)	P-value
Female sex of the child	3.037(1.358-6.791)	0.001	4.231(1.620-11.048)	0.003
Cousin marriage	3.316(1.518-7.244)	0.004	3.907(1.592-9.591)	0.003
Father's income	1.552(0.731-3.296)	0.252	1.000(1.00-1.00)	0.173
History of passive smoking	1.0(0439-2.277)	1.00	0.760(0.282-2.209)	0.653
History of Abortion	1.7(0.520-50574)	0.556	1.598(0.401-6.369)	0.506
Anaemia in pregnancy	0.92(0.427-2.00)	0.844	0.976(0.349-2.728)	0.963
Maternal illness	2.57(0.955-6.923)	0.057	2.817(0.217-36.608)	0.429
History of medication	2.289 (0.916-5.710)	0.073	0.8 (0.069-9.301)	0.859
Lack of multivitamin & folic acid supplementation	2.299 (1.05-4.96)	0.034	2.888(1.149-7.259)	0.024

Table-5: Final logistic regression model: risk factors for cleft lip/ palate .

Variables	ß	P-value	Odds Ration	95% C.I for OR Lower	Upper
Children suffering cleft lip only	-1.422	0.002	0.241	0.097	0.602
Children suffering from cleft plate only	1.388	0.002	4.005	1.663	9.646
Children suffering from both cleft lip and palate	0.974	0.083	2.648	0.880	7.969
Children suffering from any syndrome	1.074	0.018	2.927	1.202	7.124

child, cousin marriage, maternal illness and lack of multivitamin and folic acid supplementation were found to be the significant contributory factors towards development of cleft lip/palate in the study population.

Discussion

Many congenital anomalies affect children at the time of their birth. Cleft lip and palate are amongst the most prevalent forms of congenital birth abnormalities in this regard. They have a multifactorial causation with a primarily genetic origin with influencing factors like socioeconomic status, race, origin, ethnicity and environmental factors.[3,5,7] The present case control study was undertaken to explore the factors pre-disposing to cleft lip and palate among children presenting to the Children Hospital, Lahore, a tertiary care setting. A total of 110 children were studied which were divided into case and control groups consisting of 55 children each. The mean age of children included in the study was 11.39±23.12months. This is similar to studies done in Singapore and India.[19-21] This is attributable mainly to the fact that Children Hospital and Institute of Child Health, Lahore (CHICH) is a tertiary care hospital located in the heart of Lahore catering to the specialized paediatric healthcare needs; therefore patients report earlier for treatment and

diagnosis. In the study, majority (61.8%) of the fathers were between 25-29 years, mean age being 31.47±6.27years. Similarly, in case of mothers, majority (68.2%) were between 20-29 years, mean age being 26.52±6.05years. In a similar study by Ahmad, R et al, majority of the mothers (49.38%) were between 25-34 years.[22] The current study showed that cleft palate alone (41%) is the most common defect followed by cleft lip & palate (38%) and cleft lip alone (18%). These results are similar to a study done in Iran.[21] Studies done in other countries have contrasting results where cleft lip is more common. Factors predisposing to cleft lip and palate identified in this case control study, were cousin marriage, female gender of the baby, maternal illness and lack of multivitamin and folic acid supplementation during pregnancy. In a local study on the link between consanguinity and congenital birth defects conducted at Holy Family Hospital, Rawalpindi, out of 176 pregnant or recently delivered women studied, 78 cases were women with neonates having congenital birth defects and there were 78 matched controls with normal healthy neonates. The results of the study demonstrated that upon comparing consanguinity in cases and controls, it increased the risk of congenital defects by two-fold, (OR 2.23, 95% CI 1.16- 4.27 and p-value 0.01). This is quite similar to the findings of our study where cousin marriage increased the risk of cleft palate by nearly 4 times (AOR 3.907, 95% CI 1.592-9.591, p-value 0.003). Consanguinity and cousin marriage is a widely studied phenomenon especially in the Pakistani societal setup and the results of various studies regarding congenital birth defects are similar. These findings prompt for a further research into the genetic mechanisms responsible for generation of birth defects as a result of consanguinity.[11,21,] Similar results are observed in studies done in other parts of the world also.[23,25]

Another study on the pattern of cleft lip and palate in the Northern area of Pakistan shows that among the 61.6% of cases, there was history of consanguineous relationship which is quite similar with the findings of our study. However, this study showed that these deformities affected males more frequently than the females. Our study shows that females primarily suffered from isolated cleft palate. Our study implicates female gender as a pre-disposing factor for the development of cleft abnormalities. Lack of multi-vitamin and folic acid supplementation was found in the current study as a significant pre-disposing factor for the etiology of cleft lip and palate. This finding is consistent with the findings of a national level and population-based case-control study in Norway which showed that least risk of cleft lip was evidenced in females who consumed folate-rich diets and also had folic acid and multivitamin supplementation (AOR 0.36; 95% CI, 0.170.77).[26] One limitation of our study was the exact history of multivitamin intake which was purely reproduced on recall, in contrast to the study in Norway, where strong antenatal programs coupled with improved educational and awareness status of women warrant reliable information regarding their status of multi-vitamin intake. Moreover, our study also lacked differentiation between multivitamin and folic acid supplementation as most of our patients remembered both as one and the same thing.

In a similar study but with different socio-demographic and geographical considerations (Mexico), Acuña-González et al,[27] ina multivariate analysis identified the risk factors described as follows: belonging to the lower socioeconomic strata, having birth in the southern areas of the Campeche state; home-delivery or natality in a government hospital; having past non-syndromic cleft lip in addition to or without cleft palate instances in the father's or mother's immediate family, having a brother or sister with non-syndromic cleft lip along with or without cleft palate, and a history of infections occurring in the pregnancy. In this study, prenatal care consisting of vitamins and folic-acid supplementation was implicated as a protective element for non-syndromic cleft lip with or without cleft palate (OR 0.29) which is consistent with the findings of the current study.[26,27] This implies that regardless of the socio-demographic and geographical characteristics, multi-vitamin and folic acid supplementation is an essential protective measure against birth abnormalities and pregnant women cannot rely solely on their diet for a healthy child-bearing process.

Conclusion

There is a substantial burden of cleft lip and palate in the developing countries like Pakistan. These abnormalities not only pose a health risk for the children but also an important public health issue. The current study shows that most of the subjects were female and up to 12 months of age. Majority of the children were underweight. Similarly, most of the children were residents of rural areas and in an overwhelming majority, didn't have a sibling with cleft abnormalities. The study found significant association

of cleft lip and palate with cousin marriage or consanguinity, female gender of the child, maternal illness and lack of multi-vitamin and folic acid supplementation during pregnancy. Father's income, history of passive smoking by mother, history of abortions or anaemia in pregnancy did not show any significant association with development of cleft lip and palate.

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