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Distribution of Associated Anomalies in Cleft Lip and Palate in Pakistani Population

[1]Muhammad Abrar, [2*]Samyyia Abrarm [3]Zobia Ahsan, [4]Sheeza Nighat

Article Details

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Muhammad Abrar
Department of Biological Sciences, The Superior University, Lahore, Pakistan
Samyyia Abrar
Assistant Professor, Department of Biological Sciences, The Superior University, Lahore. Corresponding Author Email: Sammiya.abrar@superior.edu.pk
Zobia Ahsan
Department of Biological Sciences, The Superior University, Lahore, Pakistan
Sheeza Nighat
Department of Biological Sciences, The Superior University, Lahore, Pakistan .

ABSTRACT

Objective: A cross-sectional study design was used to estimate frequency of non-identical anomalies with cleft lip and palate (CLP). Prevalence of disease in Pakistani population. Analysis with similar disorders. Methodology: A cross-sectional study design was used to estimate frequency of non-identical anomalies with cleft lip and palate (CLP). The duration of study was from January 2022 to January 2023. The sample size was 100. Data was analyzed by using SPSS version 16. A p-value less than 00.5 were considered significant. Results: In this study a total of 100 patients were recruited from different hospitals of Lahore. All of them were examined physically and classified in different categories including Cleft Palate Only, Cleft Lip and Palate. Out of these 100 patients 55(55%) were males and 45(45%) were females. 11 (11%) of them were having Cleft Lip only, 18(18%) Cleft Palate only, and 71(71%) having Cleft Lip and Palate. Conclusion: The prevalence of the associated anomalies is high in those patients who have family history of cleft lip and palate. In this study we get to know that the males (55%) are more affected than females (45%). There is a very high prevalence of tooth agenesis in cleft patients as compared to other anomalies. Complete cleft lip and palate is more present in males as compared to females. Consanguinity is the major reason for this disorder. In this study we also get to know that in our data there is high prevalence of cousin marriages in Pakistani population.

INTRODUCTION

Disruptions of normal facial structure recognized as cleft of lip and palate (CLP). In developed countries it's not a major cause of mortality. For families it is a substantial financial risk with a concomitant societal burden. Morbidity to effected children caused by CLP [1]. Feeding speaking hearing and social integration are the experience faced by individuals with CLP. By surgery dental treatment speech therapy psychosocial intervention these experiences can be corrected. For understanding the biology of facial development critical implications can performed. Etiology of the CLP is heterogeneous. The implications include how genetic factors interact with environmental risk and how we can improve clinical care to known etiologic variables. Recent association studies and successes in genome wide linkage prove the association of CLP with novel loci [2]. Etiologic variants at these novel loci to understand the developmental disturbances which cause CLP are difficult to identify by researchers. Prevention, treatment and prognosis for individual with these conditions are improved by the help of this knowledge. A disruption of tissue planes above the lip is the common forms of CLP and extending into nares and the palate. On both genetic and embryologic grounds, the interior structures i.e. lip and primary palate could be separated. These interior structures involving clefts are noted by Fogh Andersen and Fra Ser [3]. Craniofacial complex are affected by many disruption, upper lip or palate are involved as majority. Isolated and entities with no other structure abnormalities or apparent cognitive are approximately 70% of cases of CLP. In embryological development the defects are arise early. The etiology of both environmental and genetic contributions is complex. The etiologic factors are difficult to identify.

The non-syndromic CLP causes are combination of candidate gene and epidemiology. There have been major advances with the advent of genomics era in the identification of causative genetic mutations. There has been less progress to understanding of genetic etiology of non-syndromic CLP due to lack of genomic tools and necessity for very large data sets. Over understanding of non-syndromic CLP has increased by development of innovative approaches to phenotyping and powerful genomic tolls. With wide variability across racial, geographic origin and ethnic groups CLP affects approximately 1/700 live births as well as socioeconomic status and environmental exposures [4]. Highest reported birth prevalence rates present in Asians populations often as high as 1/500. The prevalence rates about 1/1000 among European derived populations. The lowest prevalence rate about 1/2500 among African derived populations. Across different populations these observations suggest the contribution of susceptibility genes of individuals. By sex the frequency of CLP is differ. For cleft involving the lip ratio for male to female is 2:1. For cleft of palate only male to female ratio is approximately 1:2. Among unilateral cleft lip cases of left to right sided ratio is 2:1. Without cleft palate or cleft lip with and cleft palate only are divided by CLP in historical perspective [5]. Cleft lip only may have unique etiologic feature suggested by recent epidemiologic data which include some individual with cleft palate only and show strong genetic associations and show evidence of subclinical cleft lip [6]. About 50% cases of cleft palate and approximately 70% of all cases of CLP are considered to be non-syndromic. Wide ranges of malformation syndrome are composed by remaining cases which include approximately 500 mendelian syndrome. For genetic analysis these syndromic forms are more tractable. Compelling evidence for a genetic component to non-syndromic is provided by twin studies and familial clustering. Clear cut Mendelian inheritances are showed by few pedigrees and most cases are appeared as sporadic. By environmental factors CLP is influenced [7]. Environmental covariates are interacted with small induvial of genetic risk factors that is favored with multi factorial model of inheritance. Genetic analysis of non-syndromic forms of CLP is complicated by these

combined factors. Epidemiology and etiology of any congenital malformation are understood by accurate phenotype, the reason is that when heterogeneous groups are treated as a single entity it effects of the power of detection. The range of phenotypic expression are showed by clefts of lip and palate, we can say it as qualitative traits. Important information can be losing by dividing CLP in this simplistic way. Genome wide linkages are observed by different patterns, careful attentions to phenotypes are suggested by it and it play as an important tool in our understanding of genetic heterogeneity. The spectrum includes a variety of subclinical phenotypic feature and show more complexity observe in an individual with CLP [8].

Minor structure variants are included in subclinical phenotype which detect of orbicularis oris muscle, dental anomalies, 3d facial image measurement, brain variant by surrogate measures. Less exploration is showed by palatal sub phenotype but also include sub mucous cleft palate, bifid uvula. For both human and mouse models it is beneficial as better understanding of palatal sub divisions by phenotypes and pathways. Particular promise is showed by defects of orbicularis oris muscle. Its for contributing to clinical risk assessment and for variants of genetics. By using high resolution ultrasound of upper lip, the orbicularis oris defects can be assessed. Opportunities for translational research relevant for clinical genetics serve as science and patients with clinical care lead by subclinical phenotyping. Linkage analysis, smaller or multiplex families or analysis of affected pairs of relatives are included in genetic approaches to non-syndromic CLP. Candidate genes or genome wide strategies or applied in these methods. Advantages and disadvantages or include in every approaches. Disease with genetic architecture are depend on these approaches, this include technology and economics realities. Cleft lip with or without cleft palates are more focused then isolated cleft palate. This gap is needed to be address in future. Since Ardinger and colleagues, the core of cleft research was candidate gene [9]. In risk for non-syndromic CLP role of TGFA variants are suggested by Ardinger and colleagues. Developmental analysis and gene expression in model organisms are helped in identification of candidate genes. For the association the first identification of candidate genes are performed in mouse and provide biological plausibility. In this approach extrapolation can be proved as a useful adjunct in the study of syndromic forms of CLP. In many complex disorders the candidate gene is study. For the identification and confirmation of CLP loci its productive rout of analysis of chromosomal anomalies. Recently analysis of chromosomal anomalies and candidate gene-based association reviewed in detail. There are many attempts to identified regions of genome with the use of linkage analysis which carry a gene which control CLP pathogenicity. For the identification of specific variants there have been thousands of sequencing studies of candidate genes are performed which have association of statics with clefting. For mutations in MSX1, FGF8, FGFR1 and BMP4 the best current evidence has been reported [10].

In identifying causative genetic variants whole exome sequences has been successful for miller syndrome, mendelian traits and kabuki syndrome. Major advances are provided by GDA studies in over understanding of pathways and genes. In the etiology of CLP it plays an important role. Using the case-controlled design for CLP there are three GDA studies are published. Cleft palate is excluded by the studies which are based on heterogenic etiology. Impact of IRF6 is confirmed by Birnbaum and colleagues. On chromosome a new region 8q24 identified in candidate gene studies. In European case control sample, it has greeted association. Gene dessert region on chromosome 8q24 are independently confirmed by Grant and colleagues. Association between European American controls and cases in CLP is extremely strong. Chromosome 8q24 and 10q25 replication are fined by GENEVA Cleft consortium study. Among case parent trios of European ancestry, the level of statistical evidence with in

chromosome 8q24 is much stronger than consortium study. IRF6 markers in trios of Asian ancestry the evidence for association and linkage extremely strong. Two new loci ABCA4 and MAFB are identified by GENEVA study which is not associated with CLP [11]. From multiple populations using independent families the population difference and signals were replicated. Multiple genetic variants risk of CLP is suggested by these observations but by the help of polymorphic markers some of genes are different tags. Among parents of European ancestry, the rate of heterozygosity showed by 8q24 chromosome are higher as compared to ancestry of Asian. Asian trios are less informative as compare to European ancestry according to these studies. In different populations the genetic variants are difficult to identify. Through polymorphic markers in most populations are helped to identify causal genetic variants. Other chromosomes ABCA4, MAFB, 8Q24 are more specific population and they show variable markers or heterogenic allelic. Different background haplotypes carried multiple mutations are known to be true allelic heterogeneity. By association studies the identification of casual genes are more difficult. Multiple rare alleles' mixtures in a single causal gene on common haplotypes are noted by Dickson and colleagues. The casual gene is involved in heterogeneous and complex disorders like CLP [12].

MATERIALS AND METHODS

A one-year cross-sectional study was conducted at the tertiary care hospital of Lahore, Pakistan. The data of cleft lip and palate patients were collected from CLAP General Hospital Lahore. The duration of study was from January 2022 to January 2023.

SAMPLE COLLECTION:

This study employed a cross-sectional design to assess the prevalence and distribution of non-identical anomalies in individuals diagnosed with cleft lip and/or palate (CLP). The research was carried out over a one-year period, beginning in January 2022 and concluding in January 2023. A total of 100 patients were selected as part of the study population. Participants were included based on a confirmed diagnosis of CLP, ensuring that the sample specifically represented this congenital condition. Individuals presenting with other medical conditions or congenital anomalies unrelated to CLP were excluded to maintain the specificity and integrity of the analysis. Data collection involved clinical examination and documentation of associated anomalies, followed by statistical evaluation.

STATISTICAL ANALYSIS

All data were entered and analyzed using the Statistical Package for the Social Sciences (SPSS), version 16. Descriptive statistics were used to summarize the demographic and clinical characteristics of the participants, while inferential statistics, including the Chi-square test, were applied to determine the significance of observed associations. A p-value of less than 0.05 was considered statistically significant, indicating a meaningful relationship between variables under investigation.

RESULTS

PHYSICAL EXAMINATION AND RESULTS

In this study a total of 100 patients were recruited from different hospitals of Lahore. All of them were examined physically and classified in different categories including Cleft Palate Only, Cleft Lip and Palate. Out of these 100 patients 55(55%) were males and 45(45%) were females. 11 (11%) of them were having Cleft Lip only, 18(18%) Cleft Palate only, and 71(71%) having Cleft Lip and Palate. Each and every patient was examined physically for presence of cleft in palate or lip, chin size and tongue size, skin color and many other factors as included in questionnaire.

TABLE 3:2: THE BASELINE FREQUENCIES OF GENDER, TYPE OF OROFACIAL CLEFT, AGE GROUP, AND ASSOCIATED ANOMALIES.

GENDER-BASED COMPARISON

The most commonly found type of cleft was cleft lip and palate (71%) and the least found was isolated cleft lip (11%). Most of the patients were in the age range of 0-12 years (88%) while the other patients were placed into the >50 years (1%). Different anomalies were found in 16 % of the patients. Table 3.2 shows the details of the below-mentioned data.

PREVALENCE OF ASSOCIATED ANOMALIES

Out of 100 patients 16 (16%) patients had an associated anomaly, of whom 10 were male and 6 were female. There was no significant relationship between gender and associated anomalies. The most common associated anomaly among cleft patients was a tooth agenesis, in 16% of cleft patients. There was no significant relationship between cleft disease and associated anomalies.

Variable		N (%)
Gender	Male	55 (55%)
	Female	45 (45%)
Type of Cleft	Lip	11 (11%)
	Palate	18 (18%)
	Lip and palate	71 (71%)
Age (months)	0-12	88 (88%)
	13-25	11 (11%)
	26-50	1 (1%)
Associated anomalies	Yes	16 (16%)
	No	84 (84%)

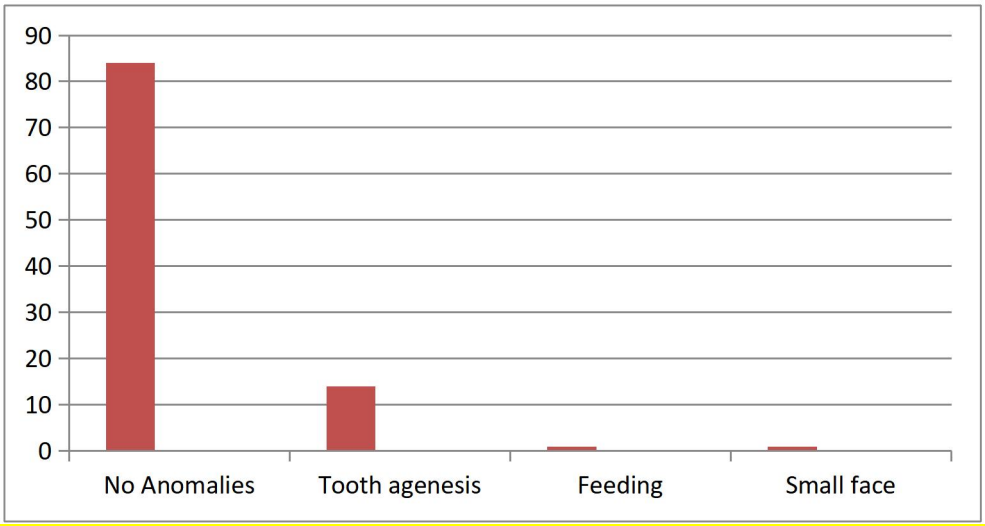

TABLE: 3:3 PREVALENCE OF ASSOCIATED ANOMALIES AMONG CLEFT LIP AND PALATE PATIENTS. (N = 100)

TYPES OF DISORDERS

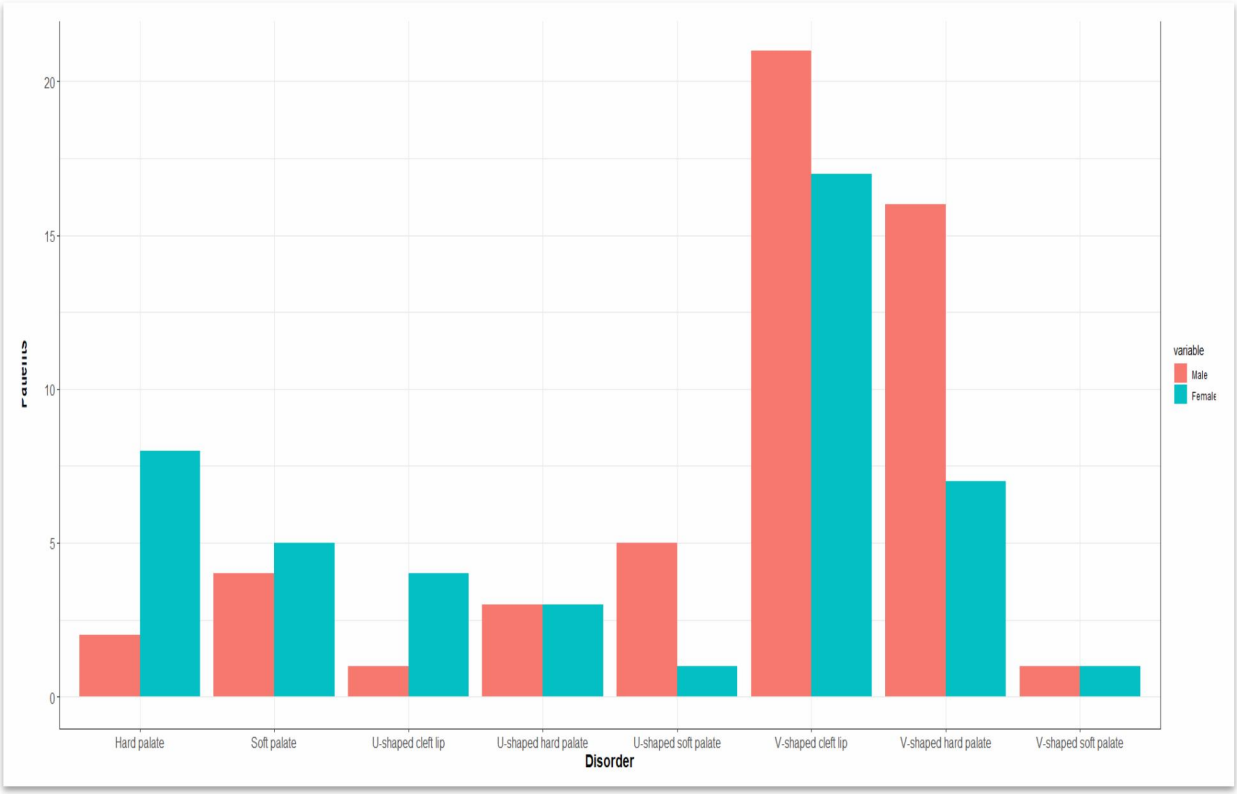

TABLE *3.3*: THE BASELINE FREQUENCIES OF GENDER, TYPE OF DISORDER.

DISCUSSION

This study found that consanguineous marriage, a family history of clefts, and folic acid usage were all highly associated with an elevated risk of CLP, as were all anomalies and physical difficulties. According to the findings of this study, 14 (14%) of cleft lip and palate patients had tooth agenesis, and the majority of CLP patients are born with physical defects. None of the cleft patients had the blood type-AB.

Similarly, (Figueiredo et al.) discovered that a cleft family history was substantially related with increased cleft (13). (González et al.) discovered that the largest risk for cleft lip and/or palate was associated with family history background variables (14). On the contrary, (Golalipour et al.) found that folic acid deficiency was not connected with an increased risk of oral cleft in babies (15). Many children with cleft lip and palate may have less appealing facial features or speaking than their classmates. Teasing about one's facial appearance is common among persons with cleft lip and palate (CLP). As a result, it is preferable to begin treatment for cleft lip and palate at a young age (16). (Shafi et al.) indicated a substantial link between children born from a consanguineous marriage and the probability of related abnormalities.

In the current study, seventy patients with cleft lip and palate were discovered, with 42% males and 27% females. Cleft lip and palate had a higher rate of 100 participants recruited in our study than cleft lip and palate. In our study, 71 (71%) cases of cleft lip and palate, 18 (18%) cases of cleft palate, and 11 (11%) cases of cleft lip only were reported. In contrast to (Cooper et al.), our community has a larger percentage of cleft lip and palate, as evidenced by the data. Tooth agenesis is the most obvious dental defect in humans. When compared to the general population, the frequency of tooth agenesis (both inside and outside the cleft region) is significantly higher in people with clefts (17). This is supported by our research.

The prevalence of dental agenesis in the cleft population is 14 (14%). In 2019, a cross-sectional descriptive study of 601 orthodontic patients at Tribhuvan University Teaching Hospital and Dental Villa-Orthodontic Centre and Specialty Dental Clinic in Kathmandu, Nepal revealed that the prevalence of dental agenesis in the general population was 7.48%, excluding the third molar (18).

Scientific research supports the significant occurrence of dental agenesis among dental malformations in the cleft population. In the Jordanian population, Al Jamal et al found that 66.7% of CL/P samples had missing teeth(19). The most prevalent dental defect in a research by Al Kharboush et al was hypodontia, which occurred in 123 (66.8%) of Saudi cleft lip and palate patients (20). Similarly, (Reina Colombo et al) (21) found 93% dental agenesis in Colombo cleft patients and 47.5% dental agenesis in the Brazilian population, which were the most common anomalies among cleft lip and palate patients in their respective investigations. The percentage of dental agenesis varies greatly in these studies, including ours.

Previous research has found a sexual dimorphism in oral clefts: CL/P is more common in males, and severe variants are more common in males (22). This study supports this assertion because we had more male patients who had a higher proportion of dental anomalies than females. There were also discrepancies in the correlations of dental abnormalities with cleft type. All dental anomalies were more common in patients with complete clefts than in patients with incomplete clefts.

The absence of fusion between the maxillary and medial nasal processes, which resulted in the CL/P, may be a contributing reason to the numerous lateral incisor abnormalities. Published research on dental anomalies in CLP patients has revealed that the maxillary permanent lateral incisors are the most vulnerable teeth in the area of the cleft (23). Our research backs up this

assertion. Maxillary laterals were the most commonly missing teeth in our cleft populations, with the highest prevalence.

Our study provides a thorough and complete description of dental anomalies found in a sample of cleft lip and palate patients; however, a much larger multi-center sample may be required to determine the relationship of each dental anomaly with cleft type and literality of cleft.

CONCLUSION

The prevalence of the associated anomalies is high in those patients who have family history of cleft lip and palate. In this study we get to know that the males (55%) are more affected than females (45%). There is a very high prevalence of tooth agenesis in cleft patients as compared to other anomalies. Complete cleft lip and palate is more present in males as compared to females. Consanguinity is the major reason for this disorder. In this study we also get to know that in our data there is high prevalence of cousin marriages in Pakistani population.

DECLARATION

This study is the part of Muhammad Abrar's BS thesis.

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AVAILABILITY OF DATA AND MATERIALS

The data sets analyzed during the current study are available from the corresponding author.

AUTHORS' CONTRIBUTIONS

SA: designed the study, designed the analysis, NA: Data collection and Manuscript write-up.

COMPETING INTERESTS

The authors declare that they have no competing interests.

CONSENT FOR PUBLICATION

Not applicable

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

None Required

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