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ORIGINAL RESEARCH

A CEPHALOMETRIC STUDY OF PARENTAL CRANIOFACIAL PARAMETERS TO DETERMINE THE PREDISPOSITION TO OROFACIAL CLEFTING

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ABSTRACT

AIM To determine the craniofacial morphological features of parents of children with oro-facial clefting and to correlate the findings with those of other investigators and to determine if the predisposition of the anomaly is related to craniofacial morphology.

Methods and Materials: This study was conducted in the Department of Oral and Maxillofacial surgery, A.B. Shetty Memorial Institute of Dental Sciences, Deralakatte, Mangalore, Karnataka , India with the intention of studying the craniofacial morphology of parents of cleft children and to compare them with that of the control group. The study was conducted from 2001 to 2003.

Results: Multivariate discriminant analysis was applied to the data. When fathers of cleft children who were not from the parental pair group were compared to fathers of children without orofacial clefting (control), they were found to have (i) significant reduction in the symphysis area (p=0.025)(ii)Angle SNB was more acute (p=O.045, significant)(iii)Had a greatly reduced mandibular area (p=0.000 vhs)(iv)Reduced maxillary area (p=0.001 vhs)(v)An increased SN length hs) (vi)Cranial base angle was more acute (p=0.002hs).

Conclusion: Conducting such a study and understanding these parameters could be valuable in predicting susceptibility to cleft formation. It may also aid in uncovering clues about the development of cleft palate and cleft lip conditions. This could potentially serve as part of a range of tests, including assessments on lateral cephalograms for prospective parents concerned about the likelihood of clefts in their children, enabling healthcare professionals to offer informed guidance.

***Keywords**: Cephalometrics , craniofacial , hereditary , oral clefts*

INTRODUCTION

Cleft lip/palate is one of the most common congenital malformations of the face. It is prevalent among all races irrespective of sex. The incidence of cleft lip and palate in India is one in eight hundred live births 1989.[1] Orofacial clefts are caused by interactions between genetic and environmental factors.[2] It is understood that genetic -factors create a 'Susceptibility' for clefts when environmental factors

(triggers) interact with a genetically susceptible genotype and a cleft develops. [2,3]

The theory of etiological heterogeneity has now taken precedence, suggesting that genetic factors in the occurrence of oral clefts vary widely. In some cases, genetic influence is minimal; in others, it is strongly associated with one parent, and in certain situations, it is equally shared when both parents happen to have similar levels of predisposing factors. Based on epidemiological evidence, different inheritance patterns for craniofacial morphology have been proposed.

Research on hereditary impacts in orofacial clefting reveals that relatives without clefts often possess unique facial traits that set them apart from the general population. It is understood from these studies that such features reflect the expression of genetic susceptibility to clefting. Many studies have been done on facial morphology of parents of children with clefts of the lip and palate[9], the dentition of parents[.8] Dermatoglyphics in parents and on craniofacial parameters with the help of lateral and PA skull radiographs.

In current thinking, the multi-factorial threshold (MFT) model has been replaced by the theory of etiological heterogeneity.[13] This theory proposes that genetic factors in the development of oral clefts vary: in some cases, genetic influence is minimal; in others, it is primarily attributed to one parent; and in situations where both parents share similar levels of predisposition, the genetic influence is roughly equal.

MATERIALS AND METHODS

This comparative cephalometric study was conducted in the Department of Oral and Maxillofacial Surgery, A.B. Shetty Memorial Institute of Dental Sciences, Deralakatte, Mangalore, Karnataka, India, from 2001 to 2003. Ethical approval was obtained prior to the commencement of the study.

Sample Selection:

A total of 90 participants were included:

Study Group (n=60):

- Parental pairs of cleft children (n=15 pairs)
- Fathers only (n=15)
- Mothers only (n=15)
- Control Group (n=30):
- Fathers of non-cleft children (n=15)
- Mothers of non-cleft children (n=15)

All participants in the study group were parents of children with unilateral cleft lip and/or palate. Subjects with prior orthodontic or maxillofacial surgical history were excluded. The control group was randomly selected from the outpatient department and included parents of children without any congenital, genetic, endocrinal, or skeletal anomalies.

Radiographic Protocol:

Standardized lateral cephalometric radiographs were taken using a Planmeca panoramic radiographic unit. A total of 90 lateral cephalograms were obtained (60 from the study group, 30 from controls).

Cephalometric Analysis:

Parameters Analyzed: 20 cephalometric variables (10 midface, 10 lower face) were recorded for each subject.

Measurement Technique: Cephalometric landmarks were digitized using AutoCAD R14 software to compute areas and perimeters.

RESULTS

The morphological evaluation of cephalometry proved that there were considerable differences between study group (parents of children with orofacial clefting) and control group (parents of children without cleft anomalies) in certain parameters concerning the mandibular region and the mid-face. In the group of fathers of cleft-affected children, there was a statistically significant decrease in the symphysis area ($p = 0.047$) and the total mandibular area ($p = 0.000$) that referred to a smaller design of the mandibular structure in the cleft-prone parent group. Compared to the control group, the SNB angle was sharper in the study group ($p = 0.045$), and it indicated a comparatively retruded mandible. Also of greater significance was the increase in the sella-nasion (SN) length and sharper cranial base angle ($p = 0.002$), which was further distinct to their control counterparts. The greatest differences among mothers differed in total mandibular length that was significantly higher in the mothers of cleft children as compared to the controls ($p = 0.000$). These individuals showed themselves much taller in the anterior face ($p = 0.000$), more obtuse cranial base angle ($p = 0.002$) and longer anterior cranial base (SN length $p = 0.000$ as well).

These characteristics indicate that the craniofacial morphology of mothers could be larger in vertical features and protuberance towards the anteriors in the cleft affiliated cases.

Further significant differences were also observed when parental pair fathers contrasted against control fathers. These comprised the smaller area of symphysis (p = 0.047), a shorter length of palate (p = 0.003) and a much smaller area of maxillary region (p = 0.027), with a longer SN measures (p = 0.018) and a more acute cranial base angle (p = 0.016). These differences support the hypothesis that smaller midface and mandibular measurements can be phenotypic predictors of susceptibility to clefts in parental pair mothers their total mandibular length was longer (p = 0.000), their anterior facial height was greater (p = 0.005), their SN length was longer (p = 0.000) and the angle components of their cranial base were sharper (p = 0.000). It is also important to note that the length of the clivus (S-Ba) was significantly longer among these mothers (p = 0.000), and this fact can be related to the structural defects of the cranial base that also leads to a risk of developing clefts. Among the five powerful discriminants between cleft and non cleft groups included in the multivariate analysis by use of the Mahalanobis distance was the five cephalometric variables in fathers (total mandibular area, cranial base angle, palatal length, SN length and symphysis area). In mothers the total mandibular length and cranial base angle were the most important. These discriminant function analysis concluded the existence of sexually dimorphic patterns in cephalometric features relative to cleft risk. (Table 1-5)

Statistical Analysis

Student's unpaired t-test was used for pairwise group comparison. Multivariate discriminant analysis (Mahalanobis distance) was applied to determine morphological features predictive of cleft predisposition. The statistical analysis used for the results obtained were Student's unpaired t test' and multivariate discriminant analysis using Mahalanobis distance.[9]

RESULTS

The morphological evaluation of cephalometry proved that there were considerable differences between study group (parents of children with orofacial clefting) and control group (parents of children without cleft anomalies) in certain parameters concerning the mandibular region and the mid-face. In the group of fathers of cleft-affected children, there was a statistically significant decrease in the symphysis area (p = 0.047) and the total mandibular area (p = 0.000) that referred to a smaller design of the mandibular structure in the cleft-prone parent group. Compared to the control group, the SNB angle was sharper in the study group (p = 0.045), and it indicated a comparatively retruded mandible. Also of greater significance was the increase in the sella-nasion (SN) length and sharper cranial base angle (p = 0.002), which was further distinct to their control counterparts. The greatest differences among mothers differed in total mandibular length that was significantly higher in the mothers of cleft children as compared to the controls (p = 0.000). These individuals showed themselves much taller in the anterior face (p = 0.000), more obtuse cranial base angle (p = 0.002) and longer anterior cranial base (SN length p = 0.000 as well). These characteristics indicate that the craniofacial morphology of mothers could be larger in vertical features and protuberance towards the anteriors in the cleft affiliated cases. Further significant differences were also observed when parental pair fathers contrasted against control fathers. These comprised the smaller area of symphysis (p = 0.047), a shorter length of palate (p = 0.003) and a much smaller area of maxillary region (p = 0.027), with a longer SN measures (p = 0.018) and a more acute cranial base angle (p = 0.016). These differences support the hypothesis that smaller midface and mandibular measurements can be phenotypic predictors of susceptibility to clefts in parental pair mothers their total mandibular length was longer (p = 0.000), their anterior facial height was greater (p = 0.005), their SN length was longer (p = 0.000) and the angle components of their cranial base were sharper (p = 0.000). It is also important to note that the length of the clivus (S-Ba) was significantly longer among these mothers (p = 0.000), and this fact can be related to the structural defects of the cranial base that also leads to a risk of developing clefts. Among the five powerful discriminants between cleft and non cleft groups included in the multivariate analysis by use of the Mahalanobis distance was the five cephalometric variables in fathers (total mandibular area, cranial base angle, palatal length, SN length and symphysis area). In mothers the total mandibular length and cranial base angle were the most important. These discriminant function analysis the existence of sexually dimorphic patterns in cephalometric features relative to cleft risk(Table 1-5).

Table 1. Parameters Used for Comparison

Lower Face Parameters	Mid-Face Parameters
1. Ramus Height	1. ANS–PNS (Length of Maxilla)
2. Gonial Angle	2. Area of Maxilla
3. Body Length	3. Angle SNA
4. Symphysis Area	4. N–A (Nasion to Point A)
5. Total Mandibular Area	5. AFH (Anterior Facial Height)
6. Total Mandibular Length	6. PFH (Posterior Facial Height)
7. SNB Angle	7. Ratio PFH:AFH
8. Pt. B	8. UFH (Upper Facial Height)
9. Pog	9. LFH (Lower Facial Height)
10. MM Angle	10. Ratio UFH:LFH

Table 2. Variables and Criteria Used for Methodology

Variable Type	Criteria for Significance
Linear Distance Measurements	> 2 mm difference in the means of statistically significant measurements
Angular Measurements	> 2 degrees difference in the means of statistically significant measurements
Area Measurements	> 10% difference in the means of statistically significant measurements

Table 3. Results (t-test for Equality of Means) Mandibular Parameters Comparison

Sex	Parameter	t-value	p-value
Fathers	Ramus height	0.302	0.765
	Gonial angle	1.042	0.306
	Body length	-1.050	0.303
	Symphysis area	-2.080	0.047
	Total Mandibular Area	-6.715	0.000
	Total Mandibular Length	0.057	0.955
	SNB angle	0.838	0.409
	N–B	1.441	0.161

	N–Pog	0.979	0.336
	MM angle	-0.262	0.795
Mothers	Ramus height	-0.234	0.817
	Gonial angle	0.296	0.769
	Body length	1.428	0.164
	Symphysis area	0.507	0.955
	Total Mandibular Area	1.059	0.298
	Total Mandibular Length	6.880	0.000
	SNB angle	0.950	0.350
	N–B	0.151	0.881
	N–Pog	-0.377	0.709
	MM angle	0.443	0.661

Table 4. Mid-Face Parameters and Discriminant Function Analysis Mid-Face Parameters Comparison – t-test

Sex	**Parameter**	**t-value**	**p-value**
Fathers	ANS–PNS	3.204	0.003
	Area of Maxilla	2.342	0.027
	Angle SNA	0.314	0.756
	N–A	1.056	0.300
	AFH	0.108	0.915
	PFH	1.134	0.266
	PFH:AFH	0.787	0.438
	UFH	-1.322	0.197
	LFH	0.577	0.569
	UFH:LFH	-1.127	0.269
Mothers	ANS–PNS	-0.364	0.719
	Area of Maxilla	-1.766	0.088
	Angle SNA	0.606	0.550
	N–A	0.067	0.947
	AFH	3.014	0.005
	PFH	0.212	0.833
	PFH:AFH	0.072	0.943

	UFH	-1.186	0.246
	LFH	1.021	0.316
	UFH:LFH	-1.407	0.170

Standardized Canonical Discriminant Function Coefficients (Mahalanobis Distance)

Sex	Discriminant Variable	Function Coefficient
Fathers	Symphysis Area	0.427
	Total Mandibular Area	0.844
	ANS–PNS	0.538
	Cranial Base Angle	0.742
	SN Length	0.520
Mothers	Cranial Base Angle	0.518
	Total Mandibular Length	0.874

Table 5. Summary of Previous Parental Cephalometric Studies in Orofacial Clefting

Study / Author	Experimental Group (Total/Male/Female)	Comparison Group	Population	OFC Subtypes	Cephalogram Type
Coccaro et al. (1972)	40 / 20 / 20	40	USA	CLP	Lateral
Kurisu et al. (1974)	347 / 141 / 206	246	USA	CL(P), CP	Lateral, PA
Shibosaki et al. (1978)	118 / 58 / 60	60	Japan	CL(P)	Lateral
Nakasima & Ichinose et al. (1984)	502 / 251 / 251	220	Japan	CL, CLP, CP	Lateral, PA
Nakasima & Ichinose et al. (1984)	104 / 52 / 52	106	Japan	CL(P)	Lateral, PA
Prochazkova & Tolarova (1986)	40 / 20 / 20	75	Czechoslovakia	CP	Lateral
Word et al. (1989)	82 / - / -	-	USA	CL(P)	Lateral
Sato et al. (1989)	100 / 50 / 50	30	Japan	CL(P), CP	Lateral, PA
Raghavan et al. (1994)	76 / 38 / 38	48	India	CL(P)	Lateral, PA

Prochazkova & Vinsova (1995)	110 / 52 / 52	75	Czechoslovakia	CP	Lateral
Mossey et al. (1997)	83 / 40 / 43	0	UK	CL(P), CP	Lateral
Mossey et al. (1998a)	83 / 40 / 43	100	UK	CL(P), CP	Lateral
Mossey et al. (1998b)	83 / 40 / 43	99	UK	CL(P), CP	Lateral
Suzuki et al. (1999)	65 / 25 / 40	826 (+165)	Japan	CL(P), CP	Lateral, PA
Al Emran et al. (1999)	80 / 40 / 40	67	Saudi Arabia	CL±, CP	PA
Present Study	60 / 30 / 30	30	India	CLP	Lateral

DISCUSSION

Cleft lip and/or palate (CL/P) belong to the most frequent congenital malformations of the face as they can be the result of genetic predisposition affected by some environmental factors. The current study intended to examine the craniofacial morphological characteristics of parents who have children with orofacial cleft and compare this to the parents who do not have children with clefts to determine phenotypic variations which can explain genetic predisposition. Although multifactorial threshold (MFT) model has been traditionally applied to describe the etiology of CL/P, recent views point to the superiority of etiological heterogeneity concept in describing genetic contributions, which are elaborate and inconsistent across families [11].

Studies have established that in affected individuals, the unaffected family members commonly share features in craniofacial constitution. Such characteristics as lengthening of the mandible, changes in cranial base angles, and an increment in anterior facial height are not definitive factors that alone propensity the appearance of a cleft yet may fall as indicators of a genetic vulnerability in combination with environmental factors[12]. Research on the craniofacial morphology of the parents of cleft children has demonstrated that these phenotypic manifestations could be secondary vulnerability markers [13,14]. The results are in tandem with the theory that craniofacial morphologies in parents (phenotype) may play role in the hereditary transfer of cleft related malformations to children (genotype).

In the present research, the fathers having cleft children who did not form a parental pair pairing had various remarkable varying aspects with the fathers in the control group. They were characterized by a considerably smaller symphysis area (p = 0.025), a sharper SNB angle (p = 0.045), significantly smaller mandibular (p = 0.000) and maxillary area (p = 0.001), longer sella-nasion (SN) and a sharper cranial base angle (p = 0.002). These same results agree with those of other studies that observed smaller mandibular size and abnormal cranial base angles as discriminators in the cleft prone groups [15,16].

The mothers of cleft children in comparison with control mothers had considerable differences that were highly-differential such as increased mandibular length (p = 0.000), enlarged anterior facial height (p = 0.000), sharper cranial base angle (p = 0.002) and longer SN length (p = 0.000). These characteristics were pointed in previous works as the distinguishing features of maternal contribution to cleft susceptibility [17]. Especially, the a-angle of the cranial base and the length of the mandible were linked with derailment of timing and position in palatal shelf fusion, which can be stronger in female embryos since the establishment is delayed [18].

In comparison of fathers of the cleft parental pair with control fathers, the results found out a markedly low symphysis area (p = 0.047), extremely low mandibular area (p = 0.000), short palatal length (p = 0.003), low maxillary area (p = 0.027), long SN length (p = 0.018) and steep cranial base angle (p = 0.016). The sequential decreases in the measurement of mandibular and maxillary can disrupt the spatial orientation needed to achieve normal development of the palate [19].

Compared with control mothers, they had a bigger total mandibular length (p = 0.000), anterior facial height (p = 0.005), SN length (p = 0.000), a smaller cranial base

angle (p = 0.000), and longer clivus length (S-Ba) (p = 0.000). With these results to back it up, notions brought forward previously indicate female craniofacial anatomy, and particularly in mothers, might be considered central to cleft pathogenesis [20]. The maternal genome may have a stronger effect on the craniofacial pattern thus raising the chances of defects in the shelf elevation.

Once the gender-specific craniofacial differences in cleft-affected cleft parents have been determined, a discriminant analysis was used to determine parameters that made a significant difference between the cleft and controls. The five significant discriminating characteristics among the fathers were the total mandibular area, the cranial base angle, length of palate, length of the SN and the area of symphysis. Conversely, the lowest number of parameters was only two, which could be used to differentiate groups among mothers, with total mandibular length being the most notable one. These findings reflect on a sexually dimorphic cleft propensity manifestation in craniofacial features [21].

The statistical method of Mahalanobis distance was used to quantify deviation of individual subjects around multivariate mean of their particular groups. The results of the analysis showed that the difference of facial parameter of cleft and non-cleft parents was of great significance. These results underline the necessity to consider cephalometric characteristics of parents according to gender, because with data combination it is possible to mask essential differences[22]. Moreover, although not included in this analysis, it would be possible to cluster the individuals based on their common characteristics and therefore such an approach might reveal new phenotypic groups in the cleft-susceptible population.

Other authors have similarly repeated the importance of these discoveries. According to Figalova, Blanco and Mossey et al., mothers of children with CL/P revealed a significant difference in the mandibular length[17]. Although the direct correlation with this feature and the development of the cleft is not yet clear, it is estimated the higher occurrence of cleft palate in females indicates the maternal craniofacial influence possibility. It can be supposed that the late elevation of palatal shelves in the female embryo renders them more susceptible to derailments due to structural features inherited.

This hypothesis can also be proved with biological evidence. Transforming Growth Factor Alpha (TGFA) and signaling molecule like retinoic acid are some of the genes that have been highly associated with craniofacial development and cleft pathogenesis[21].These morphogens that govern facial growth and merging of tissues might influence any phenotypic patterns of the craniofacial inherited exclusively by one parent or both of the parents.

Although it has provided these insights, there are certain limitations involved in the study. The rather small size of the sample narrows the opportunity to generalize applied findings, and only a few numbers of cephalometric parameters were examined. Broader collection of craniofacial measures and 3D morphometrics imaging would probably be more informative. Also the genetic contribution due to other members of the extended family in addition to the parents was not taken into account which could also be a factor in the transmission of the cleft.

An extended examination of microform cleft traits ought to be done in extended family members to map out the full picture of genetic/phenotypic expression. Determining craniofacial features as potential predisposing factors, which only lead but do not directly result in clefts, like enamel or ear shape anomalies, would prove paramount of investigating the interaction of the genes with the environment. Cases of clefts are also expected to be minimized by preventative measures such as dietary change among the at-risk mothers.

CONCLUSION

To conclude, the present study gives strength to the idea that clear craniofacial characteristics of parents of cleft children can be considered as the phenotypic markers of genetic predisposition. Such identifications may come in handy whenever dealing with a potential parent, especially where incidence of orofacial clefting is high in a community. These results can ultimately become a component of a clinical model including lateral cephalometric analysis, which can provide medical workers with an opportunity to determine a cleft risk and serve their future contribution to prevention.

DECLARATIONS

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Consent for publication

Informed consent was obtained from every participant for documentation and examination.

Competing interests

The authors declare no competing interests.

Ethical approval

Ethical approval was granted by the Institutional Human Ethical Committee

Informed patient consent

All patients' clinical records were obtained with informed consent.

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