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The Craniofacial Morphology of the Parents of Children with Cleft Lip and/or Palate: A Review of Cephalometric Studies

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SUMMARY

Objective: To review the cephalometric studies investigating the craniofacial morphology of the parents of children with cleft lip and/ or palate (CL(P)).

Methods: A review of the literature has been conducted using MedLine sources dated 1970-2005. The Cleft Palate - Craniofacial Journal has been searched manually. The reference lists of all previous publications were consulted to identify any publications, not already identified using the electronic search.

Results: 21 similar cephalometric studies investigating the parental craniofacial morphology in orofacial clefts were identified.

Conclusions: The craniofacial morphology of the parents of children with cleft lip and/ or palate CL(P) is different in comparison to the non- cleft population. There is a lack of consistency in study designs and results to accurately characterize the parents of children with CL(P). The craniofacial morphology of the parents of children with CL(P) differs from the parents of children with isolated cleft palate (CP), there is insufficient information to precisely localize these differences.

Key words: cleft lip and/ or palate; parents; craniofacial morphology, cephalogram.

INTRODUCTION

Cleft lip and palate is a worldwide health care problem. They occur among all ethnic groups with an incidence that varies by race and nationality. Asians are at higher risk than Caucasians or Blacks (21). Orofacial clefts (OFC) show considerable geographical variation in life birth prevalence, from approximately 1/ 500 in Mongoloid populations to 1/ 2000 in Afro-American populations. (28)

A cleft lip and / or palate is multifactorial in origin. Some clefts are caused by single mutant genes, some are due to chromosomal aberrations, and some are caused by specific environmental agents; the great majority of cleft lips and/ or palates(CL(P)) and isolated cleft palates (CP) are anomalies with a genetic predisposition and a contributory environmental component (10; 14; 17; 20; 21 and others). There is a greater environmental component involved in the aetiology of non- syndromic isolated CP (12; 23).

CL(P) and CP are caused by primary defects in the fusion of craniofacial processes that form the primary and secondary palate respectively, but differ in respect to timing. Primary palate fusion takes place at about the fifth week of embryonic life by a highly regulated process of mesenchymal proliferation and epithelial breakdown in three facial prominences, the medial nasal, lateral nasal, and maxillary prominences, whereas elevation and fusion of the secondary palate occurs at about eight weeks of gestation. Furthermore, epidemiological and family studies indicate that CL(P) and CP are separate clinical entities and for both polygenetic multifactorial aetiology has been proposed (6; 12).

It is recognized that the craniofacial form of individuals with orofacial clefts is different in comparison with unaffected people, and that craniofacial form is influenced by hereditary factors. Thus it could be assumed that the craniofacial morphology of the biological parents of children with CL(P) could be different to the general population.

Several craniofacial studies show that not only subjects with cleft lip and or palate but also their parents are characterized by distinct craniofacial features. Initial studies to test this assumption were based on the experimental investigation by Trasler (1968) in mices, which demonstrated that the shape of the embryonic face could be a predisposing factor to clefting. Fraser and Pashyayan (1970) investigated a number of craniofacial features that appeared to be predisposing to cleft lip in humans. Other studies by various groups followed (Coccaro et al., 1972; Kurisu et al., 1974; Nakasima and Ichinose, 1983; Prochazkova and Tolarova, 1986; Sato, 1989; Ward et al., 1989; Raghavan et al., 1994; Mossey et al., 1998; Suzuki et al., 1999; McIntyre et al., 2002; Perkiomati et al., 2003; Yoon et al., 2004).

Objective

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METHODS

A review of the literature has been conducted using MedLine sources dated 1970- 2005. The Cleft Palate – Craniofacial Journal has been searched manually. The reference lists of all previous publications were consulted to identify any publications, not already identified using the electronic search.

RESULTS AND DISCUSSION

Comparison of the parents cephalometric studies

Tables 1, 2 and 3 summarizes the data from 21 studies, all of which compare parental groups with local population controls.

Studies on the craniofacial morphology of the non cleft parents of children with CL(P) have always reported differences that distinguish the general population. The data from the tables showed that parents of children with CL(P) had no common characteristic features. This encouraged further investigation into the question of heritability and genetic susceptibility to clefting.

Differences in the results of these studies can be explained by:

- differences in used methodology among the studies;
- etnic and geographic variability in (a) the
- craniofacial morphology, (b) the incidence of OFC, and (c) the ratio of CL(P) to CP;
- the aetiologic heterogeneity in orofacial clefting;
- lack of male- and female-specific analyses.

Are the differences in the parental craniofacial morphology dependent on the CLP subtype possessed by their offspring?

Mossey et al (1997) found that there were no significant differences in the craniofacial morphology between the parents of children with CL and CLP, but differences were found between the CL(P) and CP groups. The most significant of these were in mandibular length, ramus length, mandibular area, and cranial area, these being greater for CP. Stepwise discriminant analysis showed that the one single parameter that discriminated best was the mandibular ramus length, that being an accurate predictor in 71.4% of CP and in 62.5% of CL(P) cases. Maternal and paternal differences in craniofacial morphology were detected. Separate analysis of fathers and mothers showed that ramus length and cranial height together reliably distinguished between mothers in 75% of CP and 80% of CL(P) cases (14).

Another study of Mossey et al (1998) showed that the fathers of children with orofacial clefts have significantly smaller mandibular, symphyseal, and maxillary areas on lateral cephalograms and reduction in palatal length. In addition, the cranial base angle was more acute and although the cross sectional area of the cranium was smaller in the fathers compared to the control males the occipital subtenuce was larger. Using stepwise discriminant analysis, 83.3% of fathers were correctly classified as being at risk for having a children with orofacial clefting. The mothers had larger anterior facial height and total facial length, also the anterior cranial base and the clivus length were larger than in the control females. As in the paternal group, reduced cross sectional area of the cranium and increase in the occipital subtenuce length was observed. Using these parameters in a stepwise discriminant analysis, 95.1% of mothers were correctly classified as being at risk for having a children with orofacial clefting (12).

Suzuki et al (1999) identified the features that classified the parents in comparison to the control group: a larger inter orbital distance, larger nasal cavity width and larger interconoid distance relative to the maximum head width, and shorter mandibular length relative to the anterior cranial base length. This correctly classified the pooled experimental and control subjects in 67.9% of cases and on the pooled test group in 61.8% (24).

Yoon et al found that the side of parental nasal asymmetry was significantly associated with the side of the cleft in their children. For the majority of parents with children suffering from a left cleft, nasal width was larger on the left, compare with the right side and inversely. The results suggest that unilaterally increased nasomaxillary width in parents may play a key role in the development of ipsilateral palatal clefting in their offspring, therefore underscoring the importance of craniofacial form as a genetic etiologic factor in the genesis of clefting (27).

McInture and Mossey (2002) investigated asymmetry of the parental craniofacial skeleton and detected size

Table 1. General information about studies

No	Studies	Year	Population	Color code
1.	Fraser and Pashayan (5; 6)	1970	Canadian population	Red
2.	Coccaro et al (4)	1972	American population	Blue
3.	Kurisu et al. (7)	1974	American population	Blue
4.	Shibasaki and Ohtsuka (23)	1978	Japanese population	Yellow
5.	Nakasima and Ichinose (15; 16)	1983	Japanese population	Yellow
6.	Prochazkova and Tolarova	1986	Czech population	Braun
7.	Sato (22)	1989	Japanese population	Yellow
8.	Ward et al (26)	1989	American population	Blue
9.	Blanco et al (2)	1992	Chinese population	Light blue
10.	Raghaven et al (21)	1994	Indian population	Green
11.	Prochazkova and Vinsova (18)	1995	Czech population	Braun
12.	Mossey et al (12; 13; 14)	1998	Scotch population	Grey
13.	AlEmran et al	1999	Saudi Arabia population	Violet
14.	Suzuki et al (24; 25)	1999	Japanese population	Yellow
15.	Perkiomati et al (17)	2003	Costa Rican population (European origin)	Pink
16.	Yoon et al (27; 28)	2004	Costa Rican population (European origin)	Pink

Table 2. Comparison of most investigated cephalometric features in the lateral cephalograms of parents of children with CL(P)

Studies:	1	2	3	4	5	6	7	8	9	10 CLP	11 CP	12	14	15
Cranium														
Length					↓				↓		↓			↓F
Area					↓							↓		
Cranial base														
S – N						↑					↑	↑F	↑	↓
S – Ba												↑F		
N – Ba													↑	
N – S – Ba		↓		↑	↑			↓		↑		↓M		
S – Ar – Go										↓	↑M			
Facial														
TFH	↑					↑	↑		↓	↓	↑	↑F		
ANB	↓	↓	↓	↓		↑		↓						
MMPA											↑			
Maxilla														
UFH		↓		↓	↓		↑		↓	↓				
ANS – PNS		↓			↓	↑		↑		↑	↑M	↓M		↓
PFH					↓	↑F		↓						
SNA	↓									↑				
Mandible														
LFH					↓	↑M	↑	↑			↑M			
Gonial ∠			↓	↓		↑				↑				
Ramus					↑						↑M	↑F		
Body						↓								
SNB														

Table 3. Comparison of most investigated cephalometric features in the posteroanterior cephalograms of parents of children with CL(P).

	10 CLP	11 CP	12	13	14	16
Max head width (E – E")	↓	↑M	↓F	↓F		↓F
Interorbital width (O – O")		↓			↑	↑M
Byzigomatico- frontal suture (FT – FT")	↓					
Intercoronoid process distance (CP – CP")					↑	
Nasal width (NC – NC')	↑		↑M	↑M	↑	↑M
Alveolar width (MX – MX")	↓		↓	↓M		↑M
Bizigomatic width (ZY – ZY")	↓		↓F	↓F		
Bigonial width (Go – Go")	↓		↓F	↓F		
O / O" to Midline			≠M	≠M		
NC / NC" to Midline						≠
MX / MX" to Midline			≠M	≠M		
Facial width in relation TFH						↑

Keys:
CP – the study that was examine the parents of children with cleft palate (the others examined the parents of children with cleft lip and/ or palate).
CLP – the study that was examine the parents of children with cleft lip and palate
↑ – increased
↓ – reduced
≠ – asymmetry
F – females only
M – males only

Major linear and angular cephalometric measurements used to evaluate differences between the parents of children with CL(P) and control group:

Lines:

Se – N	Anterior cranial base
Se – Ba	Posterior cranial base
ANS – PNS	Palatal length
Ar – Go	Mandible ramus height
Go – Pog	Mandibular body length
N – Me	Total facial height (TFH)
N – ANS	Upper facial height (UFH)
ANS- Me	Lower facial height (LFH)
S – Go	Posterior facial height (PFH)

Angles:

<N – S – Ba	Cranial base flexure
<Ar – Go – Me	Gonial angle
<MP – PP	The angle between mandibular plane and palatal plane
<SNA	Maxilla position relative to cranial base
<SNB	Mandible position relative to cranial base
<ANB	Facial convexity angle

asymmetry characterized by a wider left side of the face and a shorter vertical dimension on the right side (directional asymmetry). The shape asymmetry was detected, as well. The results suggest that craniofacial skeletal asymmetry could be of considerable relevance in the left-side predilection of OFC (11).

Perkiomaki et al (2003) assessed relationships of distinct craniofacial features among family members with CLP and found out significant associations between unaffected mothers and their daughters with CLP in shortened anterior cranial base length, palatal plane length as well as hyperdivergent angle of anterior cranial base and palatal plane. Unaffected fathers had singnificant association in palatal length (shortened)with their sons with CLP. There was no significant association of the distinct craniofacial measurements between mothers and their unaffected daughters or between fathers and their unaffected sons. However, mothers also had significant association in hyperdivergent angle of anterior cranial base and palatal plane with their affected and unaffected sons (17).

Mossey et al (1998) studied the relevance between the genetic and morphometric factors predispose to orofacial clefting. Parents of children with CL(P) and CP showed an increased frequency of the TGFa/ TaqI C2 allele relative to the comparison group. Also the TGFa/ BamHI A1 allele was more prevalent in the CP parents. According to them using stepwise logistic regression analysis the TGFa/ TaqI C2 polymorphism provides the best model for liability to orofacial clefting. To determine the type of clefting a model involving interaction between the parental TGFa/ BamHI and TGF/ RsaI genotypes showed the best fit. Using genotype only to predict the clefting defect in the children according to parental genotype, 68.3% could be correctly classified. By adding the information about the craniofacial measurements of the parents, 76% of CP and 94% of CL/P parents could be correctly classified (12).

Congenital abnormalities are the greatest concern for people who are considering having a child. The recognition of risk indicators is important for assessing populations or groups to identify individuals at risk for producing a child with a cleft. That may be valuable for genetic counseling, but further studies into the validity and specificity of the cephalometric data for particular individuals are required, and the question of whether or the cephalometric criteria differ between different groups of population needs to be clarified. It is suggested that more precise results could be able to get using the techniques which can measure shape and area differences.

Additional studies are needed to determine whether or not similar morphometric features can be identified among parents of familial CL/P cases and to determine if (and how) such features segregate among siblings of affected individuals. Similarly, parents and siblings of children with isolated cleft palate need to be investigated. Such studies should help to sort out the inheritance pattern of relevant cephalometric features and to determine if such features are useful in identifying individuals with increased predisposition to have child with a cleft. Much larger samples, preferable obtained trough multicentre collaboration, are required for meaningful and statistically powerful analysis even when these are subdivided for analysis into cleft type and gender.

Future research into the etiology of cleft lip and/or palate will require an interdisciplinary approach between clinicians, cleft teams, and molecular geneticists. Research is required to explore the association between phenotype (i.e. craniofacial shape) and genotype.

CONCLUSION

- The craniofacial morphology of the parents of children with CL(P) is different in comparison to the non-cleft population
- There is insufficient consistency in study design and results to accurately localize the features that characterize the parents of children with OFC.
- Although there is evidence that the craniofacial morphology of the parents of children CL(P) differs to the craniofacial morphology of the parents of children with CP, there is insufficient information to be able to precisely localize these differences.
- There are methodological differences between the various studies, causing major problems to compare the results.

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