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Family history and risk factors for cleft lip and palate patients and their associated anomalies

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SUMMARY

Background and aims. Several environmental and genetic issues have been suspected as risk factors for oral clefts; and many studies have been conducted in this regard; however, large socioeconomic impacts of cleft lip and or palate (CL/P) justifies the need for further multifactorial researches. Current study aimed to assess parental risk factors for CL/P and its associated malformations.

Material and Methods. Hospital records of 187 consecutive syndromic and non-syndromic children with cleft lip and or palate (103 boys and 84 girls) with a mean age of 1.7 (SD 2.2) years and 190 consecutive non-cleft children (103 boys and 87 girls) with a mean age of 2.8 (SD 2.2) years formed this study. Parental risk factors and abnormalities and physical problems and anomalies were evaluated in all subjects.

Results. Family history of clefts (OR 7.4; 95% CI), folic acid consumption (OR 7.3; 95% CI) and consanguineous marriage (OR 3.2; 95% CI) were quite strongly associated with increased risk of CL/P. In addition, all congenital abnormalities and physical problems had significantly higher incidence in CL/P patients.

Conclusions. The findings of this study suggest that expecting mothers of consanguineous marriage and families with a history of CL/P should be extra cautious about the occurrence of CL/P.

Key words: family history, risk factors, cleft lip and palate.

INTRODUCTION

Clefts of the lip and/or palate (CL/P) are the most common congenital malformation of the head and neck (1). The overall prevalence rate for live births with cleft lip, cleft palate, or both was 1.39 per 1000 live births (2). Although the incidence varies among different ethnic groups, highest amounts have been reported among Asians (3, 4), and the least amounts have been found amount Afro-Caribbean populations (5). Majority of CL/P patients suffer from feeding difficulties in infancy and speech, hearing and dental problems as they grow older, and life-long social and psychological problems due to the facial deformity. The etiology of cleft lip and palate is multifactorial. Genetic and environmental risk factors have been identified as triggers for syndromic CL/P; however, the etiology of the more common non-syndromic CL/P remains largely unknown (6). Gender, geographical location, nationality, nutritional, tobacco use, use of antiepileptic drugs, alcohol consumption, low birth weight, Pesticides, and contaminated water sources have all been hypothesized as factors increasing the incidence rate of CL/P in newborns (7-11). Figueiredo *et al.* found that maternal family history of clefts as well as having other biological children with a cleft were highly associated with increased risk (12).

Although several environmental and genetic factors have already been identified as risk; however, large socioeconomic impacts of CL/P justify

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the need for further multifactorial researches. The aim of the current study was to evaluate parental risk factors for CL/P and associated malformation in children with CL/P.

MATERIALS AND MATERIALS

This retrospective study was carried out in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki. Informed written consent was obtained from each patient and a parent or guardian.

Study population

Between February, 2010 and December 2014, a hospital-based survey was conducted.

Hospital records of 187 consecutive syndromic and non-syndromic children with cleft lip and or palate patients (103 boys and 84 girls) and 190 consecutive non-cleft children (103 boys and 87 girls) were included in the study. All the patients were selected from a hospital in Tehran and all of the patients were Iranian.

The average age of the cleft patients was 1.7 (SD 2.2) years and the average age of the non-cleft subjects was 2.8 (SD 2.2) years. Both groups' subjects ranged from 1 month to 10 years old. The following variables from the records of the patients and their parents were evaluated for the study: These variables sub-grouped into demographic data, congenital heart disease, ear & eye & pulmonary anomalies, upper and lower limbs anomalies**,** distribution of blood groups and other malformations:

- *Demographic data:* age, gender, birth weight, maternal age, maternal folic acid consumption, consanguineous marriage, history of stillbirth, preterm birth, cleft type, family history of cleft, history of palatal closure, saddle nose, oronasal fistula.
- *Congenital heart disease:* cardiovascular system problems, congenital heart disease, atrial septal defect, ventricular septal defect, pulmonary valvular stenosis, tetralogy of fallot, patent ductus arteriosus.
- *Ear, eye and pulmonary anomalies:* use of ear tube (grommets), conductive hearing loss, middle ear effusion, otitis media, language disability, posteriorly rotated ears, Cholesteatoma, anomaly of the eyes and ears, anophthalmia, microphthalmia, respiratory system problems.
- *Upper and lower limbs anomalies:* malformations of upper limbs, malformations of lower limbs, malformations of vertebral column, mental retardation, fingers and toes problems, nail dystrophy, clinodactyly.
- *Distribution of blood groups and other malformations:* blood groups, blood discrepancy, central nervous System problems, microcephaly, musculoskeletal malformation, affected urogenital system problems, digestive system problems, abdominal wall problems.

Classification of the clefts

The patients were divided into cleft lip (CL), cleft palate (CP), and cleft lip and palate (CLP) based on the location of their clefts. CL and CLP were subdivided into unilateral and bilateral groups. All children had undergone full clinical and paraclinical examinations by a pediatrician, dentist, pediatric cardiologist, oral and maxillofacial surgeon and an otorhinolaryngologist.

Statistical analysis

The Statistical Package for Social Sciences, Version 20 (SPSS Inc. Chicago, Illinois, USA) was used to analyze the data. T-test and Chi-square test were performed to determine the significance of the findings. Statistical significance was set at $P<0.05$.

RESULTS

Of the 187 children, 52 cases (27.9%) had cleft lip only, distributed as following: 41 cases (22%) with unilateral cleft lip and 11 cases (5.9%) with bilateral cleft lip. 56 cases (29.9%) had cleft lip and palate, 45 cases (24%) of which were unilateral and 11 cases (5.9%) were bilateral. The highest number of cleft belonged to cleft palate comprising 79 cases (42.2%) of total patients (Table 1). Of all the cases 103 (55.1%) were male and 84 (44.9%) were female.

The association of the parental risk factors with the occurrence of a cleft lip and/or palate is shown in Table 2. Table 2 depicts that, 33.7% of the cleft

Table 1. Distribution of cleft type

Cleft Type	Male	Female	Total Number	Percentage
Unilateral cleft lip	26	*15*	41	22
Bilateral cleft lip	8	*3*	11	5.9
Unilateral cleft lip and palate	27	*18*	45	24
Bilateral cleft lip and palate	8	*3*	11	5.9
Cleft Palate	34	45	79	42.2
Total	**103**	**84**	**187**	**100**

patients were born from consanguineous marriage. 10.7% of family history of cleft was also seen among the risk factors for CL/P. Family history of clefts (OR 7.4; 95% CI), folic acid consumption (OR 7.3; 95% CI) and consanguineous marriage (OR 3.2; 95% CI) were strongly associated with increased risk of CL/P.

Detailed distribution of abnormalities and physical problems and anomalies can be seen in tables 3 to 7. These table show that all abnormalities and physical problems were strikingly higher in CL/P. As an illustration, 71 of 187 cleft lip and/or palate patients suffered from congenital heart diseases while only 4 of 190 subjects of the control group had heart problems.

Tables 8 and 9 show that 73 (39%) of the patients with oral clefts had A+ blood type, while only 2 patients (1.1%) with the blood type of B- had oral clefts and none of the cleft patients had blood type of AB-. Table 10 shows that RH+ was a factor for cleft lip with or without cleft palate (odds ratio=2.889).

DISCUSSION

This study showed that consanguineous marriage, family history of clefts, folic acid consumption and consanguineous marriage were strongly associated with increased risk of CL/P and also showed that all abnormalities and physical problems were strikingly higher in CL/P. The findings of this study revealed that 38% of cleft lip and/or palate patients suffered from congenital heart disease but only 2% of control groups had congenital heart disease and the majority of CL/P patients are born with congenital abnormalities and physical anomalies. None of the cleft patients had blood type of AB-.

Similarly, Figueiredo *et al.* found that family history of clefts was strongly associated with increased cleft (12). González *et al.* showed that the highest risk for cleft lip and/or palate was associated with variables related to family history background (13). On the contrary Golalipour *et al.* reported that lack of folic acid was not significantly associated with an increased risk of oral cleft in infants (7).

Many children with cleft lip and palate may have a less attractive facial appearance or speech than their peers. A high incidence of teasing over facial appearance is reported among those with cleft lip and palate. Therefore, the treatment of cleft lip and palate is better to start at early ages (14-16).

Shafi *et al.* revealed that there was a significant association between children born of a consanguineous marriage and the risk of associated malformations. The most common of other malformation in cleft patients is congenital heart disease, which accounted for 51% of all associated malformations (17). Sun *et al.* showed that The most common malformation was congenital heart disease, which counted 45.1% of all malformations. Disorders of the central nervous system 14.3% and Skeletal anomalies 13.1% were

Table 2. Association of the parental risk factors with the occurrence of a cleft lip and/or palate

Risk Factor	Number (n=187)	CLEFT		Control		OR	CI (95%)	P value
		Percentage (100%)	Number (n=190)	Percentage (100%)				
Maternal Age (years)	> 21	25	13.4	11	5.8	1.986	0.941-4.191	0.0715†
	21-34*	151	80.7	132	69.5	-	-	-
	>34	11	5.9	47	24.7	0.204	0.101-0.411	0.001†
Consanguineous marriage	Yes*	63	33.7	26	13.7	3.2047	1.911-5.352	0.001†
	No	124	66.3	164	86.3			
Folic acid consumption	Yes*	57	30.5	145	76.3	7.3489	4.653-1.605	0.001†
	No	130	69.5	45	23.7			
History of still birth	Yes	4	2.1	4	2.1	1.0164	0.251-4.125	0.629
	No*	183	97.9	186	97.9			
Preterm birth	Yes	23	12.3	19	10.0	1.262	0.662-2.404	0.478
	No*	164	87.7	171	90.0			
Birth weight (KG)	<2.5	27	14.4	13	6.8	2.352	1.171-4.721	0.016†
	2.5-4*	151	80.8	171	90	-	-	-
	>4	9	4.8	6	3.2	1.698	0.591-4.883	0.325
Family history of cleft	Yes	20	10.7	3	1.6	7.465	2.179-5.573	0.001†
	No*	167	89.3	187	98.4			

* – reference category; † – level of significance P<0.05.

also frequently associated. Echocardiography should be a proposed examination in the evaluation of children with cleft palate before any surgical correction being executed (18). However, Sarkozi *et al.* reported skeletal anomalies were the most common malformations associated with cleft, followed by disorders of the central nervous system and cardiovascular malformations (19) Genisca *et al.* (20). found that heart, limb, and other musculoskeletal defects were the most common anomalies associated with orofacial clefts, and central nervous system defects were also common anomalies in cleft palate in USA.

Venkatesh investigated the prevalence of anomalies in orofacial clefts and found that anomalies were more frequent in patients with cleft lip and palate than in patients with cleft lip alone or patients with cleft palate alone They also reported that the organs most commonly involved with associated anomalies in the order of decreasing incidence are eye, ear, heart, upper limb, lower limb, genitals, mandible, mental retardation, craniofacial clefts, skull, tongue, growth retardation, skin and hair (21).

42.2% of the patients suffering from oral clefts were subjects with blood group A. This finding corresponds with the findings of Chzhan and Khen who found that congenital clefts of the upper lip and palate are most frequent in subjects with blood group A which may be considered as a factor of risk of developing this condition (22). Current study also showed that oral

Table 3. Congenital heart disease and associated problems

	UCL	BCL	UCLP	BCLP	CP	Total cleft (N=187)	Control group (N=190)
Atrial septal defect	11	4	7	0	14	36	3
Ventricular septal defect	1	0	9	0	8	18	1
Patent ductus arteriosus	2	0	4	1	5	12	0
Tetralogy of Fallot	0	0	2	0	3	5	0
Total	**14**	**4**	**22**	**1**	**30**	**71**	**4**

UCL – Unilateral cleft lip; BCL – Bilateral cleft lip; UCLP – Unilateral cleft lip and palate; BCLP – Bilateral cleft palate; CP – Cleft palate.

Table 4. Pulmonary, gastric, and genitourinary problems

	UCL	BCL	UCLP	BCLP	CP	Total cleft (N=187)	Control group (N=190)
Respiratory system problems	1	1	13	1	22	38	4
Pulmonary valvular stenosis	0	0	1	0	0	1	0
Digestive system problems	1	0	6	0	9	16	0
Abdominal wall problems	1	0	5	1	6	13	0
Urogenital system problems	1	0	2	1	4	8	0
Total	**4**	**1**	**27**	**3**	**41**	**76**	**4**

UCL – Unilateral cleft lip; BCL – Bilateral cleft lip; UCLP – Unilateral cleft lip and palate; BCLP – Bilateral cleft palate; CP – Cleft palate.

Table 5. Prevalence of ear, middle ear, and hearing problems

	UCL	BCL	UCLP	BCLP	CP	Total cleft (N=187)	Control group (N=190)
Otitis media	4	1	5	2	27	39	1
Otitis media effusion	4	1	5	2	22	34	1
Conductive hearing loss	2	1	1	2	9	15	0
Use of ear tube (grommets)	4	1	6	2	21	34	0
Posteriorly rotated ears	0	0	2	1	1	4	0
Cholesteatoma	0	1	2	1	0	4	0
Anomaly of the ears	0	0	1	1	3	5	0
Total	**14**	**5**	**22**	**11**	**83**	**135**	**2**

UCL – Unilateral cleft lip; BCL – Bilateral cleft lip; UCLP – Unilateral cleft lip and palate; BCLP – Bilateral cleft palate; CP – Cleft palate.

Table 6. Prevalence of eye anomalies

	UCL	BCL	UCLP	BCLP	CP	Total cleft (N=187)	Control group (N=190)
Anomaly of the eyes	1	0	1	4	5	11	1
Microphthalmia	0	0	0	0	1	1	0
Anophthalmia	0	0	0	1	2	3	0
Total	**1**	**0**	**1**	**5**	**8**	**15**	**1**

UCL – Unilateral cleft lip; BCL – Bilateral cleft lip; UCLP – Unilateral cleft lip and palate; BCLP – Bilateral cleft palate; CP – Cleft palate.

Table 7. Upper and lower limbs anomalies

	UCL	BCL	UCLP	BCLP	CP	Total cleft (N=187)	Control group (N=190)
Malformations of upper limbs	0	0	2	2	7	11	1
Malformations of lower limbs	0	0	0	0	6	6	1
Malformations of vertebral column	0	0	2	2	3	7	0
Fingers and toes problems	1	0	0	0	2	3	0
Clinodactyly	0	0	0	0	0	0	0
Nail dystrophy	0	0	0	0	0	0	0
Total	**1**	**0**	**4**	**4**	**18**	**27**	**2**

UCL – Unilateral cleft lip; BCL – Bilateral cleft lip; UCLP – Unilateral cleft lip and palate; BCLP – Bilateral cleft palate; CP – Cleft palate.

Table 8. Distribution of blood groups in different types of cleft and control group

Phenotype	UCL	BCL	UCLP	BCLP	CP	Total Cleft Patients		Control	
						Number (n=187)	Percentage (100%)	Number (n=190)	Percentage (100%)
A+	19	3	18	3	30	73	39	86	45.3
A-	2	0	1	0	3	6	3.2	11	5.8
B+	6	5	5	2	14	32	17.1	26	13.7
B-	0	0	1	0	1	2	1.1	10	5.3
AB+	1	0	4	1	4	10	5.4	30	15.8
AB-	0	0	0	0	0	0	0	9	4.7
O+	11	3	15	5	24	58	31	12	6.3
O-	2	0	1	0	3	6	3.2	6	3.2
Total	**41**	**11**	**45**	**11**	**79**	**187**	**100**	**190**	**100**

UCL – Unilateral cleft lip; BCL – Bilateral cleft lip; UCLP – Unilateral cleft lip and palate; BCLP – Bilateral cleft palate; CP – Cleft palate.

Table 9. Distribution of blood groups in cleft and non-cleft samples

Phenotype	Total Cleft Patients		Control	
	Number (n=187)	Percentage (100%)	Number (n=190)	Percentage (100%)
A+	73	39	86	45.3
A-	6	3.2	11	5.8
B+	32	17.1	26	13.7
B-	2	1.1	10	5.3
AB+	10	5.4	30	15.8
AB-	0	0	9	4.7
O+	58	31	12	6.3
O-	6	3.2	6	3.2
Total	**187**	**100**	**190**	**100**

UCL – Unilateral cleft lip; BCL – Bilateral cleft lip; UCLP – Unilateral cleft lip and palate; BCLP – Bilateral cleft palate; CP – Cleft palate.

Table 10. Distribution of blood RH in cleft and non-cleft samples

Phenotype	Total Cleft Patients		Control		OR*	CI (95%)	P Value
	Number (n=187)	Percentage (100%)	Number (n=190)	Percentage (100%)			
RH+	173	92.5	154	81.8	2.889	1.501-5.558	0.001
RH-	14	7.5	36	18.2			
Total	**187**	**100**	**190**	**100**			

* – Odds ratio.

clefts were least in AB- and B-subjects. Figueiredo et al found that family history of clefts and advanced maternal age were strongly associated with increased risk (12).

The findings of the current study also correspond with the findings of the study conducted by Figueiredo *et al.* in relation to family history of cleft. However, the currents study showed a higher incidence of CL/P in mothers who were younger than 21 years old. Quite similar to the current study, Acuna-Gonzalez *et al.* (13) also found that the highest risk for CL/P was associated with variables related to family history background and family history of CL/P. Moreover, they reported that prenatal care and vitamin supplement use were protective factors against CL/P. This finding corresponds to the association found in the current study between folic acid consumption and CL/P.

CONCLUSIONS

Consanguineous marriage, family history of clefts, folic acid consumption and consanguineous marriage were strongly associated with increased risk of CL/P. Significantly higher incidence of CL/P was observed among parents with consanguineous marriage and parents with a family history of CL/P. Low consumption of folic acid was also found to be a risk factor. The majority of CL/P patients are born with congenital abnormalities and physical problems and anomalies. Therefore, prenatal screening and genetic tests are strongly recommended in these high risk groups.

CONFLICTS OF INTERESTS

The authors do not have any conflicts of interest.

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