

Non-syndromic orofacial clefts in Southern Italy: pattern analysis according to gender, history of maternal smoking, folic acid intake and familial diabetes

Francesco CARINCI^{1,*}, Rosario RULLO², Antonio FARINA³, Danila MORANO⁴, Vincenzo M. FESTA², Nicoletta MAZZARELLA², Daniele DEL VISCOVO², Peter F. CARLS⁵, Alessio BECCHETTI⁶, Fernando GOMBOS²

¹Department of Head and Neck, (Head: Prof. Enrico Granieri), University of Ferrara; ²Dental Clinic, (Head: Prof. Fernando Gombos), Second University of Naples; ³Institute of Histology, (Head: Prof. Paolo Carinci), University of Bologna and Centre of Molecular Genetics, CARISBO Foundation, Bologna; ⁴Department Gynaecology, (Head: Prof. Gioacchino Mollica), School of Medicine, University of Ferrara; ⁵Department of Maxillofacial Surgery, (Head: Fiona Nixon), John Radcliffe Hospital, Oxford, UK; ⁶Department of Surgery, (Head: Prof. Annibale Donini), University of Perugia, Italy

SUMMARY. Background: Genetic studies have demonstrated that non-syndromic clefts of the lip, alveolus and palate have an heterogeneous genetic background, and that environmental factors contribute to the onset of this malformation. Therefore studies on different and homogeneous populations can be useful in detecting potentially related environmental and genetic factors. Purpose: The aim of the present study was to evaluate whether gender, folic acid intake, family history of diabetes and/or smoking during pregnancy were associated with a specific type of cleft in a group of patients affected by non-syndromic clefts, collected from Southern Italy. Material and methods: Data from one hundred and twenty-six patients were evaluated retrospectively. Each cleft was described as composed by separate anatomical entities such as lip, alveolus, primary and secondary palate. None had an isolated alveolar cleft and this was used as internal control. Pattern analysis was used to detect differences in the frequencies of any possible combination of 7 types of clefting stratified according to the studied variables. Data were analysed by comparing observed proportions. Results: Isolated cleft palate as well as right-sided clefts of lip, alveolus and palate were more frequent in females ($p = 0.0014$ and 0.0281 , respectively), while left sided clefts were more frequent in males ($p = 0.0359$). A lack of consumption of folic acid was associated with an higher incidence of clefts of the left lip ($p = 0.018$), while familial diabetes was associated more often with isolated cleft palate ($p = 0.0014$). Conclusions: Gender-related results were comparable with those found in Northern Italy and other countries. Environmentally related results disclosed specific subclasses of clefting associated with lack of folic acid consumption and familial diabetes. © 2005 European Association for Cranio-Maxillofacial Surgery

Keywords: Cleft lip; Cleft palate; Gender; Folic acid; Diabetes; Smoke

INTRODUCTION

Orofacial clefts are congenital malformations characterized by incomplete formation of structures separating the nasal and oral cavities: lip, alveolus, hard and soft palate. It can affect either the right, the left or both sides. If clefts are associated with any further anomaly of the body they are classified as syndromic clefts.

Clefts are among the most common anomalies in man. The average incidence is one to two per 1000 live births (Calzolari et al., 1988; Menegotto and Salzano, 1991; Milan et al., 1994; Shapira et al., 1999; Cooper et al., 2000; Natsume et al., 2000, 2001; Rajabian and Sherkat, 2000).

Epidemiological studies on different populations have demonstrated links between several environmental factors active during pregnancy (i.e. alcohol

consumption, cigarette smoking and intake of anti-convulsants) and an higher risk of having a child with a cleft. In contrast, folic acid has a protective effect (Carinci et al., 2000, 2003).

Since 20% of the patients in different populations have a positive family history for clefting, genetic factors are thought to play an important role in the aetiology of this birth defect. Fogh-Andersen (1942) provided the first population-based evidence that clefts have a strong genetic component. There is evidence that families affected by clefts of the lip, alveolus with or without cleft palate [CL(A)±P] have a different genetic background when compared with families of patients affected by isolated cleft palate only (CPO; Fraser, 1970). Cleft palate patients may be described as CPO, whereas a familial group having CL(A)±P may be termed as CL(P) (Fraser, 1970).

Further genetic studies on human samples have demonstrated that CL(A)±P and CPO have distinct genetic backgrounds and environmental factors leading to these malformations. In CL(A)±P several loci on chromosomes 1, 2, 4, 6, 14, 15, 17, 19 have been identified and in one case also a specific gene (on chromosome 11). In CPO up to now one gene has been identified (on chromosome X) but many more are probably involved (*Carinci et al., 2000, 2003*).

In this retrospective study, the distribution of gender, type of cleft, affected side, folic acid intake, maternal cigarette smoking during pregnancy and family history of diabetes was analysed in a cohort of non-syndromic cleft patients treated consecutively at the Dental Clinic of the Second University of Naples from January 1996 to December 2002.

PATIENTS AND METHODS

One hundred and twenty-six patients affected by non-syndromic clefts were analysed according to gender, affected side and type of cleft. Risk factors like smoking, folic acid consumption, familial history of diabetes were also included in order to evaluate their possible association with a specific pattern of clefting.

The clefts were classified as follows: cleft of the lip (CL), cleft of the alveolus (CA), cleft of the primary palate (CLA), cleft of the secondary palate (CP). CL, CA and CLA can affect the left (L) or (R) side (i.e. cleft of left lip is LCL). No patient had an isolated alveolar cleft and this was used as kind of an 'internal control'.

Univariate analysis was performed by means of 'Test for comparing two proportions' (*Agresti, 1990*).

RESULTS

Table 1 lists the pattern generated according to seven anatomical structures which can be involved in the cleft (i.e. RCL, LCL, RCA, LCA, RCLA, LCLA and CP) stratified for gender, smoking, folic acid and familial diabetes. In this series of data twenty different patterns were found in (Table 1).

Among the cases analysed, isolated cleft palate as well as right cleft lip, alveolus and palate (i.e. patterns CP and RCL+RCA+RCLA+CP) were more frequent in females ($p = 0.0014$ and 0.0281 , respectively), while left side clefts (i.e. pattern LCL+LCA+LCLA+CP) were more frequent in males ($p = 0.0359$).

Regarding environmental factors, smoking and lack of consumption of folic acid tablets during pregnancy were associated with a higher incidence of left cleft lip ($p = 0.018$), whereas familial diabetes was associated with a higher rate of isolated cleft palate ($p = 0.0014$).

DISCUSSION

Epidemiological studies on different populations are of paramount importance for detecting different genetic groups in homogeneous ethnic samples (for example by demonstrating a correlation between phenotype and gender), and for demonstrating the role of environmental factors in different geographical areas (*Calzolari et al., 1988; Menegotto and Salzano, 1991; Milan et al., 1994; Cooper et al., 2000; Natsume et al., 2000, 2001; Rajabian and Sherkat, 2000; Shapira et al., 1999*).

Table 1 – Patterns generated according to 7 anatomical structures potentially affected by the cleft: cleft of the lip (CL), cleft of the alveolus (CA), cleft of the primary palate (CLA), cleft of the secondary palate (CP); R = right, L = left; PC = pattern code; – = variable absent; + = variable present.

No. of cases	PC	Variable							Gender		<i>p</i> -value	Smoking		<i>p</i> -value	Folic acid		<i>p</i> -value	Diabetes		<i>p</i> -value
		R	L	R	L	R	L	CP	Male	Female		No	Yes		No	Yes		No	Yes	
37	1	–	–	–	–	–	–	+	12	25	0.0014	29	7		1	2		12	25	0.0014
15	2	–	+	–	–	–	–	–	10	5		13	1	0.027	25	11	0.018	12	3	
1	3	–	+	–	–	–	–	+	0	1			1		5	9		1		
9	4	–	+	–	+	–	–	–	7	2		5	4		1			4	5	
5	5	–	+	–	+	–	+	–	3	2		4	1		6	3		4	1	
17	6	–	+	–	+	–	+	+	13	4	0.0359	11	6		4	1		13	4	
1	7	–	+	–	+	+	+	+	0	1		1			14	3		1		
2	8	–	+	+	–	+	–	+	2	0		1	1		1			1	1	
6	9	+	–	–	–	–	–	–	4	2		6			2			5	1	
2	10	+	–	+	–	–	–	–	1	1		1	1		3	3		1	1	
2	11	+	–	+	–	+	–	–	2	0		2			2			1	1	
10	12	+	–	+	–	+	–	+	2	8	0.0281	7	3		2			7	3	
1	13	+	–	+	–	+	+	+	1	0		1			9	1		1		
2	14	+	+	–	–	–	–	–	0	2		1	1			1		1	1	
1	15	+	+	–	–	–	–	+	1	0		1				2			1	
1	16	+	+	–	–	+	+	+	1	0			1			1		1		
1	17	+	+	–	+	–	+	+	1	0		1			1			1		
1	18	+	+	+	–	+	–	+	1	0			1			1			1	
1	19	+	+	+	+	–	–	–	0	1		1			1				1	
11	20	+	+	+	+	+	+	+	7	4		8	2		1			8	3	

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