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Risk factors for orofacial clefts: case-control study in non-syndromic individuals in Rio de Janeiro, Brazil.

Fatores de risco para fissura orofacial: Estudo caso-controle em indivíduos não sindrômicos no Rio de Janeiro, Brasil.

Leonardo dos Santos Antunes[1]
Erika Calvano Kuchler[1]
Patrícia Nivoloni Tannure[2]
Luise Gomes da Motta[3]
Marcelo de Castro Costa[2]
Jose Mauro Granjeiro[1]
Beni Olej[1]

1 - Programa de Pós-graduação em Ciências Médicas da Universidade Federal Fluminense, Niterói, Rio de Janeiro, Brasil,
2 - Faculdade de Odontologia da Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brasil,
3 - Faculdade de Odontologia da Universidade Federal Fluminense, Niterói, Rio de Janeiro, Brasil.

Correspondência:
Leonardo dos Santos Antunes
Endereço: Rua Dr. Silvio Henrique Braune, 22 Nova Friburgo, RJ, CEP - 28625-650
Telefone: (22)25287166 (21)88911919
Email: lsantunes@terra.com.br

ABSTRACT

Orofacial clefts (OFC) are common congenital malformations that affect family quality of life. The identification of risk factors involved with OFC would contribute to the implementation of public health programs. A hospital based case–control study was conducted with non-syndromic OFC cases (n=150) and unaffected controls (n=150) in Rio de Janeiro, Brazil, to identify the association of OFC with risk factors. The relation of gender, ethnicity, systemic history of relatives, family history of oral clefts, alcohol, tobacco use and passive maternal tabagism during pregnancy and the mother's residence were evaluated. Differences between orofacial cleft cases and controls and between types of orofacial clefts were analyzed. According to the study, the main associations relating to OFCs were a positive family history of OFC (OR: 20.34, 95% CI: 5.86-84.42; p=0.000), alcohol use during pregnancy (OR: 3.75, 95% CI: 1.62-8.92; p=0.001), tobacco use during pregnancy (OR: 3.65, 95% CI: 1.82-7.44; p=0.000) and mother's residence (rural) (OR: 2.41, 95% CI: 1.04-5.69; p=0.025). Also a family of OFC individuals presented a higher risk for renal diseases (OR: 2.99, 95% CI: 0.84-11.64; p=0.058). The study concluded that exposure to some environmental risk factors during pregnancy increase the risk for OFC.

KEYWORDS: Risk factors; Cleft lip; Cleft palate

RESUMO

Fissuras orofaciais (OFC) são malformações congênitas comuns que afetam a qualidade de vida da família. A identificação de fatores de risco envolvidos com a OFC contribuiria para a implementação de programas de saúde pública. Foi conduzido um estudo caso-controle em um hospital de referência com casos não sindrômicos de OFC (n = 150) e controles não afetados (n = 150), no Rio de Janeiro, Brasil, para identificar a possível associação da OFC com fatores de risco. A relação de gênero, etnia, história sistêmica de parentes, história familiar de fenda orofaciais, álcool, tabaco e tabagismo passivo pela mãe durante a gravidez e localização da residência da mãe foram avaliadas. As diferenças entre os casos de fendas orofaciais e controles e entre os tipos de fendas orofaciais foram analisados. Como principais associações obtiveram a história familiar positiva de OFC (OR: 20,34, 95% CI: 5,86-84,42, p = 0,000), uso de álcool durante a gravidez (OR: 3,75, IC 95%: 1,62-8,92, p = 0,001), uso de tabaco durante a gravidez (OR: 3,65, 95% CI: 1,82-7,44, p = 0,000) e a localização da residência da mãe (rural) (OR: 2,41, IC 95%: 1,04-5,69, p = 0,025). Familiares de indivíduos com OFC apresentaram maior risco para as doenças renais (OR: 2,99, IC 95%: 0,84-11,64, p = 0,058). A exposição a determinados fatores ambientais durante a gravidez aumentaram o risco de OFC.

PALAVRAS-CHAVE: Fatores de Risco; Fenda Labial; Fenda palatina

INTRODUCTION

Orofacial clefts (OFC), including cleft lip (CL), cleft lip with cleft palate (CLP), and cleft palate alone (CP), comprise a range of disorders affecting the lips and oral cavity[1]. Overall, available findings indicate that OFC occur in approximately 1 out of every 700 live births, with ethnic and geographic variations[2]. In addition, infants with OFC have an impaired ability to feed, resulting in nutritional problems and weight gain in the first weeks of life[3]. Affected individuals require surgical, nutritional, dental, speech, medical and behavioral interventions from infancy to adulthood. Thus, in addition to the burden on families, OFCs represent an important cost for public health and related services[4]. Although these severe birth defects are relatively common[5], their exact etiology remains unclear[6]. These defects are thought to be multifactorial with an interaction between genetic and environmental factors[7].

Epidemiological and experimental data suggest that a number of potential environmental risk factors may be important for the origin of OFC during pregnancy, including tobacco smoking[6,8], medicinal drugs[9], agricultural chemicals[10] and alcohol[8,11]. During pregnancy the mother is the environment of the child, so maternal exposures together with genetic vulnerabilities of the mother and/or child are of interest in OFC research[9].

Individuals born with OFC have a shorter lifespan, with increased risk for all major causes of death[12]. In addition, previous works also demonstrated that relatives of individuals born with OFC have an increased risk for cancer[13,14].

Although several studies on the family history of OFC individuals have been published, very few works have evaluated the potential association with systemic diseases of the family. Systemic diseases, mainly the chronic ones, have a strongly impact on the public health system. Preventive strategies would help to minimize their effect on citizen's health and government's budget. Therefore, the aim of the present work is to study the association of OFC with risk factors in a Brazilian population.

MATERIALS AND METHODS

Ethical approval was obtained from the Human Ethics Committee at the Federal Fluminense University, Brazil (approval # 248/09). Informed consent was obtained from all participating individuals or parents/legal guardians.

The OFC group consisted of 150 individuals receiving assistance at a Center for Treatment of Craniofacial Anomalies (CTAC) in the city of Rio de Janeiro, Brazil. Cases were assigned according to the International Classification of Diseases, Ninth Revision (ICD-9). Individuals with syndromes and clefts of known origin (amniotic bands, Potter sequence, fetal alcohol syndrome or chromosomal anomalies) were excluded. To further reduce possible etiological heterogeneity, we excluded those clefts with additional unspecified multiple malformations.

The control group set up at the same time consisted of individuals with no congenital malformations. Controls (n=150) were randomly selected among patients at the School of Dentistry of the Federal University of Rio de Janeiro. Individuals born with OFC were examined clinically and their medical records were consulted to confirm the cleft type (CL, CP or CLP). Two dentists conducted the interviews with the individuals or their parents using a structured questionnaire for both cleft and non-cleft groups.

The present study evaluated whether the following variables were or not risk factors for isolated craniofacial malformations: gender, ethnicity, history of systemic diseases of relatives (first degree: father, mother and siblings of index), positive family history of OFC (first, second and third-degree relatives in addition to index), alcohol, tobacco use and passive maternal tabagism during pregnancy and the mother's residence.

All of the data management and statistic analyses were performed using the Statistical Package for the Social Sciences (SPSS – 16.0). Quantitative variables were compared using Chi square test or Fisher exact test with a confidence interval of 95%. A *P*-value of <0.05 was used for the analyses. Qualitative variables were analyzed using odds ratio with a confidence interval of 95%. OR measures the association between a potential risk factor and case/control status with the null hypothesis being OR: 1.

RESULTS

Of the 300 individuals included in this study, 150 were case group and 150 were control group. The distribution of socio-demographic aspects, medical history and maternal habits during pregnancy are summarized in Table 1. The monthly family income of the majority of individuals in both groups varied from less than 1 to 3 times the minimum wage, equivalent to US$ 210–630. The univariate analysis showed that ethnicity, family history of cleft, alcohol use during pregnancy, tobacco smoking during pregnancy and the mother's residence were associated significantly with OFC (Table 1).

Regarding the OFC group, no statistical differences were observed between cleft lip with or without cleft palate (CL±P) and CP in alcohol (p=0.333) and tobacco (p=0.542) experience during pregnancy nor in the mother's residence (p=0.217). A CL±P was more common in males whereas CP was more common in females (p=0.020) (Table 2). Tobacco use during pregnancy was more frequently in CLP than in CL individuals (p=0.06).

Family of CL±P individuals presented a higher risk for renal diseases than control group (p=0.058) (OR: 2.99, 95% CI: 0.84-11.64).

DISCUSSION

Our study evaluated the family history of individuals with OFC, which could be an important tool to find new clinical markers that may indicate higher risk for specific diseases, and could be a potential tool for screening and prevention of OFC and associated diseases. Provide support for informed decision is very important to help health managers to conduct a health care system.

There is a great variation in the incidence of OFC among ethnic groups according to the literature[2]. In our study we found an association between Caucasians and OFC. It is important to emphasize that South America is a tri-hybrid of native Indians, European descendents and Africans descendents. In Rio de Janeiro, individuals with African ancestry comprise about 40% of the population, while those with native Indian ancestry not more than 2%[15].

It is generally accepted that tobacco smoking during pregnancy increases the risk of intrauterine growth retardation, prematurity, perinatal mortality, and spontaneous abortion[16]. Our study demonstrated that tobacco use during pregnancy was significantly associated with a risk of having a child with OFC, which is in agreement with other authors[6,10]. The evidence regarding an association between maternal tobacco smoking and OFC was also confirmed by Little et al. (2004). The tobacco effect was also observed for both isolated and multiple clefts and was stronger and more consistent for CL±P than CP. A woman has approximately a 30% increased risk of having a child with CL±P and a 20% increased risk of having one with CP if she smokes during pregnancy. Our findings indicate that tobacco use during pregnancy was borderline more frequent in CLP than in CL patients, suggesting an association between tobacco and the most severe form of this condition.

Results for alcohol intake during pregnancy are much more diverse, possibly because alcohol intake during pregnancy varies substantially over time and between populations[17]. Although several studies have suggested an association between alcohol use during the pregnancy and OFC[8,10,11], as our study, others, studies did not found this association[18,19]. According to Mossey et al. (2009), social and dietary contexts of alcohol consumption are varied and complex and can include modifying or confounding effects, of nutrition, smoking or drug use.

Concerning the association between the mother's residence and risk of OFC, our results are similar to previous reports, in which the mothers of case patients were more likely to live in rural areas than in urban areas (9.3% vs 4.1 %)[10].

Positive family history of OFC increased the risk of CL±P and CP, being consistent with previous studies[8]. OFC tends to occur in families and the inheritance is not usually Mendelian[20,21]. In this study, we found interesting results never previously reported as far as we know: relatives of CL±P individuals presented a higher risk for renal diseases. Other studies have also observed that individuals born with OFC have a high risk for certain diseases[22], such as psychiatric disorders and cancer[12]. It is possible that the sample size and the young population may have influenced our results. Further investigations with larger sample sizes and in other populations are needed to confirm or not this association.

In summary, our results support the hypothesis that the exposures of some environmental risk factors during pregnancy increase the risk for OFC, however the role of gene-environmental interaction may be investigated in this population. Some genes, such as Transforming Grow Factor, could interact with smoking during palatal development leading to OFC[23]. This gene may also be involved in chronic renal disease in later years of life[24]. This observation suggests that, in some instances, medical diseases in adulthood may share a similar genetic background of OFC

CONCLUSION

The exposure of some environmental risk factors during pregnancy increases the risk for OFC. In addition, this study demonstrats that relatives of CL±P individuals present a higher risk for renal diseases. This observation may suggest that a family health history assessment could be a potentially tool for reducing the societal impact of OFC and associated diseases.

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Table 1. Distribution of socio-demographic aspects, family medical history and maternal habit variables during pregnancy for oral cleft cases and controls.

	Cases (%)	Controls (%)	OR (95%IC)	P-value
Mean age patient (SD)	16.88 (11.30)	15.65(12.15)	-	-
Gender (%)				
Female	70 (46.7)	67 (44.7)	1.08 (0.67-1.75)	0.728
Male	80 (53.3)	83 (55.3)		
Ethnicity (%)				
Caucasian	117 (78)	97 (64.7)	1.94 (1.13-3.34)	
Black	15 (10)	21 (14)	0.68 (0.32-1.46)	0.034*
Mixed	18 (12)	32 (21.3)	0.50 (0.26-0.98)	
Family medical history (%)				
Diabetes	10 (6.7)	8 (5.3)	1.27 (0.45-3.64)	0.627
Hypertension	31 (20.7)	34 (22.7)	0.89 (0.49-1.60)	0.674
Heart disease	17 (11.3)	10 (6.7)	1.79 (0.74-4.37)	0.158
Renal disease	10 (6.7)	4 (2.7)	2.61 (0.73-10.12)	0.101
Liver disease	2 (1.3)	2 (1.3)	1.00 (0.10-10.07)	1.000
Family history of cleft (%)				
Yes	44 (29.3)	3 (2)	20.34 (5.86-84.42)	0.000*
No	106 (70.7)	147 (98)		
Alcohol use during pregnancy (%)				
Yes	29 (19.3)	9 (6)	3.75 (1.62-8.92)	0.001*
No	121 (80.7)	141 (94)		
Tobacco use during pregnancy (%)				
Yes	41 (27.3)	14 (9.3)	3.65 (1.82-7.44)	0.000*
No	109 (72.7)	136 (90.7)		
Passive maternal tabagism during pregnancy (%)				
Yes	44 (29.3)	32 (21.3)	1.53 (0.88-2.68)	0.111
No	106 (70.7)	118 (78.7)		
Mother's residence (rural) *(%)*				
Yes	22 (14.7)	10 (6.7)	2.41 (1.04-5.69)	0.025*
No	128 (85.3)	140 (93.3)		

Note: □□□or Fisher exact test; * indicates statistical significance

Table 2. Distribution of socio-demographic aspects, family medical history and maternal habit variables during pregnancy according to each type of oral cleft.

Risk Factors	Cleft type		P-value*
	CL±P (n=132)	CP (n=18)	
Gender (%)			
Female	57 (43.2)	13 (72.2)	0.020*
Male	75 (56.8)	5 (27.8)	
Family medical history (%)			
Diabetes	8 (6.1)	2 (11.1)	0.342
Hypertension	26 (19.7)	5 (27.8)	0.427
Heart disease	15 (11.4)	2 (11.1)	0.667
Renal disease	10 (7.6)	0 (0)	0.266
Liver disease	2 (1.5)	0 (0)	0.773
Epilepsy	5 (3.8)	0 (0)	0.522
Family history of cleft (%)			
Yes	40 (30.3)	4 (22.2)	0.479
No	92 (69.7)	14 (77.8)	
Alcohol use during pregnancy (%)			
Yes	24 (18.2)	5(27.8)	0.333
No	108 (81.8)	13 (72.2)	
Tobacco use during pregnancy (%)			
Yes	35 (26.5)	6(33.3)	0.542
No	97 (73.5)	12 (66.7)	
Passive maternal tabagism during pregnancy (%)			
Yes	36 (27.3)	8 (44.4)	0.133
No	96 (72.7)	10 (55.6)	
Mother's residence (rural) (%)			
Yes	21(15.9)	1 (5.6)	0.217
No	111 (84.1)	17 (94.4)	

Note: ☐☐ / Fisher exact test; * indicates statistical significance; CL±P Cleft lip with or without cleft palate; CP: cleft palate