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Risk factors associated with nonsyndromic oral clefts in a Brazilian population: a case-control study

Fatores de risco associados a fissuras orais não sindrômicas numa população brasileira: estudo caso-controle

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Resumo

Introdução: Fissuras do lábio e/ou palato representam as anomalias congênitas mais comuns da face e, em 70% dos casos, tais anomalias congênitas ocorrem de forma não-sindrômica. **Objetivo:** Conduzir um estudo caso-controle para detectar fatores de risco associados às fissuras labiais e/ou palatinas não sindrômicas em um grupo de pacientes brasileiros. **Material e método:** Um questionário foi respondido por 60 mães com filhos apresentando fissuras labiais e/ou palatinas não sindrômicas (grupo caso) e por 51 mães com crianças saudáveis (grupo controle). As seguintes variáveis foram avaliadas: idade materna e paterna, distúrbios maternos, tabagismo e consumo de álcool durante a gravidez, história reprodutiva (aborto espontâneo, gravidez ectópica e natimorto), e uso de medicamentos e de multivitaminas durante a gravidez. Os resultados foram analisados em relação ao risco relativo de cada variável para estimar o *odds ratio,* com intervalo de confiança de 95%, e em seguida as análises bivariada e multivariada foram realizadas. **Resultado:** As análises revelaram que o único fator de risco mais relacionado às fissuras labiais e/ou palatinas não sindrômicas foi a variável história de natimorto, com *odds ratio* = 7,67 (p = 0,05). O uso de drogas lícitas não se correlacionou com as fissuras labiais e/ou palatinas não sindrômicas. **Conclusão:** Dos principais fatores de risco associados às fissuras labiais e/ou palatinas não sindrômicas descritas na literatura, apenas a história de natimorto mostrou significância estatística na população avaliada.

Descritores: Anomalidades congênitas; epidemiologia; embriologia.

Abstract

Background: Cleft lip and/or palate are the most common congenital anomalies of the face. In 70% of cases, such congenital anomalies occur in a nonsyndromic form. **Purpose:** To conduct a case-control study in order to detect possible risk factors for nonsyndromic cleft lip and/or cleft palate in a group of Brazilian patients. **Material and method:** A questionnaire was answered by 60 mothers of children with nonsyndromic cleft lip and/or cleft palate (case group), and by 51 mothers of healthy children (control group). The following variables were assessed: maternal and paternal ages, maternal disorders, smoking and alcohol consumption during pregnancy, reproductive history (miscarriage, ectopic pregnancy and stillbirth), medication and multivitamin usage during pregnancy. The results were analyzed in relation to the relative risk of each variable in order to estimate the odds ratio with a confidence interval of 95%. This was followed by bivariate and multivariate analysis. **Result:** The analyses revealed that the only significantly increased risk factor was a history of stillbirth, with an odds ratio = 7.67 (p = 0.05). The use of licit drugs was not correlated with nonsyndromic oral clefts. **Conclusion:** Of the main risk factors associated with nonsyndromic oral clefts described in the literature, only a history of stillbirth showed a statistical significance in the population studied.

Descriptors: Congenital abnormalities; epidemiology; embryology.

INTRODUCTION

Cleft lip and/or palate (CL/P) are among the most common congenital abnormalities in humans. These abnormalities have a social impact and are an important source of substantial morbidity and mortality worldwide[1,2]. Approximately 70% of CL/P cases are nonsyndromic (NSCL/P), occurring as an isolated condition unassociated with any recognizable anomalies, whereas the remaining 30% are syndromic, presenting in association with deficits or structural abnormalities occurring outside the region of the cleft[3]. CL/P is aetiologically heterogeneous and complex, and this has fundamental implications for understanding the biology of facial development, how environmental risks interact with genetic factors and how we can incorporate known aetiological variables to improve clinical care[2].

The available data indicate that NSCL/P arises in about 1 in 700 live births, with wide variability according to geographic origin, racial and ethnic group, environmental exposure and socioeconomic status[4]. Populations with Asian (2.11 per 1000) and native American (3.6 per 1000) ancestries show the highest prevalence of NSCL/P, and populations from Africa (0.3 per 1000) show the lowest[5]. In Brazil, the prevalence of NSCL/P is 1.46 per 1000 live births[6].

The identification of modifiable risk factors for NSCL/P is the first step toward primary prevention. Risk factors such as maternal exposure to tobacco smoke, alcohol, poor nutrition, viral infection, medicinal drugs, and teratogens in the workplace and at home in early pregnancy, have previously been investigated[2, 7-11]. Further studies should be conducted to investigate the environmental factors involved in the aetiology of NSCL/P to assist in the prevention, treatment and prognosis of this abnormality.

To date, very few studies have evaluated the influence of these environmental factors in the Brazilian NSCL/P population[12]. Therefore, the purpose of this study was to describe and analyze risk factors that might be associated with NSCL/P in a Brazilian population.

MATERIAL AND METHOD

We performed a case-control study at the Center for Rehabilitation of Craniofacial Anomalies to investigate the role of environmental factors in a Brazilian NSCL/P population. From 2009 to 2010, all mothers (n = 60) of children with NSCL/P who came for an appointment or consultation at the hospital were recruited. Fifty-one mothers who had a healthy child of the same age were randomly selected, and served as controls. The control group was recruited from subjects admitted as patients to the School of Dentistry of the same university with conditions unrelated to clefting disorders.

The clefts were classified with reference to the anatomy of the incisive foramen: 1) CL: cleft lip anterior to the incisive foramen, whether unilateral or bilateral; 2) CLP: cleft lip with or without cleft palate, whether unilateral or bilateral; 3) CP: all clefts posterior to the incisive foramen, whether complete or incomplete[13]. The following variables were analyzed based on a questionnaire answered by the children's mothers: maternal and paternal age, maternal health (arterial hypertensive condition, neurological disturbance, sexual diseases, diabetes mellitus, and alcohol abuse during pregnancy), reproductive history (miscarriage, ectopic pregnancy and stillbirth), and use of drugs (antibiotics, anti-inflammatory drugs, antiepileptic drugs, vitamins, hormones and anti-hypertensive drugs). The questionnaire is available upon request. The chi-square test was performed to evaluate the frequency distribution of each variable and for each type of NSCL/P separately. Values of $p \leq 0.05$ were considered significant in this analysis. Written informed consent was obtained from all participants, and the study was carried out with the approval of the Human Research Ethics Committee of the University.

RESULT

Cleft distribution by type and classification is shown in Table 1. The most common types of cleft were CLP (n = 37; 61.6%), CL (n = 18; 30.0%) and CP (n = 5; 8.3%). The general and medical characteristics of mothers distributed in the case and control groups, and comparative statistical features associated with the risk of NSCL/P development are presented in Table 2. Among the 111 participating children, 67 (60.4%) were male and 44 (39.6%) were female (p = 0.27). It was clear that the only significantly increased risk factor was a history of stillbirth, with an OR = 7.67 (p = 0.05). Other factors, such as gender, skin color, hypertensive disease, neurological disturbance, spontaneous abortion, alcohol and drug consumption, presented an increased risk, but this was not statistically significant. Table 3 describes the correlation between licit drugs and nonsyndromic clefts. In this analysis, analgesics, anti-inflammatory drugs, anti-hypertensive drugs, vitamins, contraceptives and anti-epileptic drugs were not statistically associated with the development of NSCL/P, although their use led to a tendency towards this development.

Table 1. Distribution of oral clefts according to type and classification (n = 60)

Type	n	Prevalence (%)
Cleft palate	5	8.3
Complete	2	3.3
Incomplete	3	5
Cleft lip	18	30.0
Unilateral complete	7	11.6
Unilateral incomplete	10	16.6
Bilateral complete	1	1.6
Cleft lip and palate	37	61.6
Unilateral complete	25	41.6
Bilateral complete	12	20
Total	60	100

Table 2. General and medical characteristics of the mothers in both the case and the control groups, and multivariate analysis (n = 111) to assess the risk of NSCL/P* development

Characteristics	Case		Control		Total		OR	IC-95%	p value
	n	%	n	%	n	%			
Gender									
Female	21	35	23	45.1	44	39.6	0.66	0.31-1.41	0.27
Male	39	65	28	54.9	67	60.4			
Color of skin									
Caucasian	22	36.7	17	33.3	39	35.1	0.86	0.39-1.89	0.71
Non Caucasian	38	63.3	34	66.7	72	64.9			
Hypertensive									
No	53	88.3	46	90.2	99	89.2	0.82	0.25-2.77	0.75
Yes	7	11.7	5	9.8	12	10.8			
Neurological disturbance									
No	58	96.7	45	88.2	103	92.8	0.26	0.05-1.34	0.10
Yes	2	3.3	6	11.8	8	7.2			
Spontaneous abortion									
No	53	88.3	44	86.3	97	87.4	0.83	0.27-2.55	0.74
Yes	07	11.7	07	13.7	14	12.6			
Stillbirth									
No	52	86.7	50	98	102	91.9	7.67	0.93-63.44	0.05**
Yes	8	13.3	1	2	9	8.1			
Alcohol consumption									
No	52	86.7	49	96.1	101	91	3.77	0.76-18.63	0.10
Yes	8	13.3	2	3.9	10	9			
Illicit drug consumption									
No	47	78.3	41	80.4	88	35.1	1.13	0.45-2.86	0.79
Yes	13	21.7	10	19.6	23	64.9			

*NSCL/P: nonsyndromic cleft lip and/or cleft palate. **Statistically significant when p = 0.05.

DISCUSSION

NSCL/P is considered a complex trait with no obvious mode of inheritance, and its aetiology has been associated with several modifying genes[2,14]. Identification of new risk factors for NSCL/P development other than known environmental factors would improve recognition of mothers at risk and could be relevant for genetic counseling[2].

Epidemiological studies of NSCL/P have been conducted worldwide, often resulting in varying rates of prevalence[15]. In a Brazilian population study, based on the files of 126 pediatric patients with NSCL/P, a Caucasian predilection was demonstrated with a male-to-female ratio of 1.3. Males were 2.57-fold more affected by CLP than females. CLP with a prevalence of 39.68% and CL with a prevalence of 38.09% were the most common anomalies, followed by CP (22.23%)[16]. Differences in geographic and ethnic distribution may explain some of the variations in prevalence, but not all of them. In European populations, for example, the incidence can range from 1 to 2.21 per 1000 live births, despite similar ethnical and geographical backgrounds[17].

Despite investigation, the etiological factors contributing to these congenital deformities remain unclear[18]. For example, many studies have reported an association between oral cleft development and variables such as maternal health, cigarette smoking and drug use, alcohol consumption, obesity, and folic acid and vitamin deficiencies[18-23]. A multivariate analysis that examined the variables associated with an increased risk for cleft development, performed in the United States, revealed that mothers with diabetes and hypertension associated with pregnancy were at higher risk of bearing offspring with cleft development. Maternal smoking, low birth weight and male

Table 3. Descriptive statistics on drug abuse by mothers in both the case and the control groups, and multivariate analysis (n = 111) to assess the risk of nonsyndromic cleft development

Characteristics	Case		Control		Total		OR	IC-95%	p value**
	n	%	n	%	n	%			
Analgesics									
No	43	71.7	42	82.4	85	76.6	1.85	0.74-4.6	0.18
Yes	17	28.3	9	17.6	26	23.4			
Antimicrobial drugs									
No	56	93.3	43	84.3	99	89.2	0.38	0.11-1.36	0.13
Yes	4	6.7	8	15.7	12	10.8			
Antihypertensive drugs									
No	55	91.7	49	96.1	104	93.7	2.23	0.41-11.99	0.35
Yes	5	8.3	2	3.9	7	6.3			
Vitamins									
No	19	31.7	12	23.5	31	27.9	0.66	0.29-1.55	0.34
Yes	41	68.3	39	76.5	80	72.1			
Contraceptives									
No	55	91.7	49	96.1	104	93.7	2.23	0.41-11.99	0.35
Yes	5	8.3	2	3.9	7	6.3			
Antiepileptic drugs									
No	58	96.7	50	98	108	97.3	1.72	0.15-19.58	0.66
Yes	2	3.3	1	2	3	2.7			

**Statistically significant when p = 0.05.

gender of the babies were also important risk factors. Older, more educated and black mothers all presented a lower risk. The risk associated with tobacco was modest and not unanimous[18]. The evidence linking alcohol consumption to NSCL/P was tenuous when the mother had not been a "binge" drinker (consumption of high doses of alcohol in short periods of time). Likewise, the risk estimates were only minimally influenced after simultaneous adjustment for maternal cigarette smoking, race and ethnicity, education and multivitamin use[24,25]. It has also been proposed that obese mothers are at an overall greater risk for having a child with orofacial clefts associated with other major malformations than with isolated clefts[26]. Despite all these findings, more studies are required in the Brazilian population.

Our study showed that a history of stillbirth can be predictive of NSCL/P development. However, our sample was not large, and our goal was not to focus on secondary characteristics associated with complications during pregnancy. Stillbirth is probably a multifactorial condition with different causes, including possible etiological factors associated with orofacial clefts. Furthermore, previous studies have shown that some geographic locations can be linked to a higher incidence of NSCL/P[1,2]. In our study, although the hospital from which the cases were taken has received patients from different locations in the state of Minas Gerais, the study population was considered homogeneous in terms of exposure to weather conditions, geography and cultural factors, which are similar in all the cities covered by the hospital. These similarities were related in a study published by our group in 2009, when we evaluated the profile of the population treated by the hospital[27]. We would like to add that our group has been investigating other risk factors associated with NSCL/P, such as socioeconomic status, seasonality (submitted for publication), and folic acid metabolism, among others[16,28]. Nonetheless, the present study contains only ancillary data which complements other ongoing research.

Previous studies have also reported that preterm births, premature babies and very low birth weights are important predictive variables[25,29]. Furthermore, perinatal complications, such as breech/malpresentation, hyaline membrane disease in the newborn and mechanical ventilation for 30 or more minutes, were directly associated with NSCL/P development[25].

Similarly, prenatal and perinatal maternal complications that may lead to stillbirths, such as hydramnios or oligohydramnios, eclampsia, placental abruption, amniocentesis, and tocolysis, have been associated with a greater risk of cleft development[25]. A study that addressed the causes of placental abruption in Peru found that this was associated with a history of delivering a stillborn infant (OR: 10.0; 95% CI 4.0-25.2), a pregnancy complicated by

preeclampsia/eclampsia (OR 3.7; 95% CI 2.2-6.3), or a low rate of pregnancy weight gain (<0.15 kg/wk) (OR 2.5; 95% CI 1.3- 4.7)[30]. Indeed, children with a higher birth order are more likely to have CL/P and CP, with the odds ratio increasing the higher the birth order. The same results were obtained when isolated and syndromic cases were combined[31].

Pregnancy planning and periconceptional folic acid supplementation has been shown to have a protective effect against the development of clefts, but the basis of this observation should be explored more deeply[3,10]. This protective effect may reflect the fact that the health status of the mother appears to influence the palate formation in the child, insofar as NSCL/P risk has been shown to increase regardless of gender or cleft type[32]. Indeed, mothers who used multivitamins containing folic acid periconceptionally had a 25-50% reduction in the risk of bearing offspring with NSCL/P, compared to women who did not use such vitamins. However, this association may be explained, not only by folic acid per se, but also by other components of multivitamin supplements or by behavior[20].

CONCLUSION

This study found a history of stillbirth to be a risk factor for NSCL/P in a Brazilian population. This variable is multifactorial and shares predictive factors with conception and preconception difficulty. A larger sample will be able to isolate co-factors and better elucidate the etiology of NSCL/P.

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CONFLICTS OF INTERESTS

The authors declare no conflicts of interests.

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