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## Analysis of familial incidence of non-syndromic cleft lip and palate in a Brazilian population

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### Abstract

**Background:** The purpose of this study is to follow the familial incidence of non-syndromic or isolated cleft lip, with or without cleft palate (NSCL/P), and to analyze the relationships between the type of NSCL/P in the affected individual and his/her parent, looking at children in the first grade.

**Material and Methods:** To investigate the familial incidence of NSCL/P we analyzed the records of 185 patients from 2004-2008, retrospectively. Detailed histories were collected regarding the familial incidence of NSCL/P. For the 185 individuals, the relationship between the type of NSCL/P and the sociodemographic and personal characteristics of the affected person and her/his cleft relatives was obtained.

**Results:** The individuals were 42 carriers of CL, 109 with CLP (joined in one group) and 34 with CP ( $p < 0.001$ ). Of the total of participants, 65 (35.13%) presented a positive history of cleft in their families and 120 (64.86%) presented a negative history ( $p < 0.001$ ). There were differences between the cleft groups according to types of cleft and positive familial history ( $p < 0.001$ ). In both groups, the relatives with higher incidence of NSCL/P were cousins, with the same pattern of distribution between the two groups ( $p = 0.175$ ).

**Conclusions:** Most frequently, fissures result from CL/CLP with no familial history. However, CL/CLP was found in familial cases and cousins were the relative type more likely to be affected.

**Key words:** Cleft palate, cleft lip, epidemiology

## Introduction

There is no doubt that the cleft lip and palate (CL/P) field has shown the most progress regarding the understanding of its etiology, including genetic alterations and environment factors, compared with the fields of other complex birth defects (1). The most recent estimates suggest that 3 to 14 genes contribute to CL/P (2). Non-syndromic or isolated cleft lip, with or without cleft palate (NSCL/P), occurs in a wide geographic distribution, with an average birth prevalence of 1:700 (1). We verified the incidence of 1.46 CL/P for each 1.000 life births in the state of Minas Gerais, Brazil (3). Every two minutes, one child is born in the world with cleft: 660 children every day and 235,000 a year. The annual world population is growing by about 1.8 million; therefore, in the future an additional 3,200 cleft children are expected per year (4).

A recent work suggested that there has been a gross underestimation of the consequences of being born with CL/P (1). Individuals born with CL/P have a shorter lifespan, with increased risk for all major causes of death, when compared with individuals born without clefts (5). Contributing to these higher mortality rates are probably psychiatric disorders and cancer. CL/P increases the risk of hospitalization for psychiatric diseases in adults (5). Furthermore, there is an increased occurrence of breast and brain cancer among adult females born with CL/P, and an increased occurrence of primary lung cancer among adult males born with CL/P (6).

Studies carried out so far indicate that there are at least two genetic groups of clefts, each with different risks of manifestation of this malformation: group I, with cleft lip (CL) or cleft lip and palate (CLP), and group II, with isolated cleft palate (CP) (7). In one Brazilian population, we showed the predominance of CLP (52.6%), followed by isolated CL (33.12%) and isolated CP (14.28%) (8). On the other hand, few papers have focused on familial distribution and risk among relatives when NSCL/P is present. The purpose of this study is to follow the familial incidence of NSCL/P in relatives of children in the first grade and to analyze its relationship to the type of CL/P.

## Materials and Methods

To investigate the family incidence of NSCL/P, we studied 185 patients who received treatment during 2004-2008. All registered patients had complete medical documentation. Detailed histories were collected regarding the familial incidence of CL/P using a questionnaire. In this sample (n=185), the relationship between the type of CL/P and the gender of the patient and her/his affected parent was observed. Parents and relatives were sorted into three classes depending on the cleft type: CLP, CL or CP. The incidence of CL/P in parents and

other relatives was determined on the basis of history. All patients were screened for the presence of associated anomalies or syndromes, and only those identified to have NSCL/P were included in this study.

Chi-square and likelihood tests were performed considering 0.05 as statistically significant, and all types of variables were analyzed using their subclassifications. The study protocol was approved by the Ethical Committee in Research at the Dental School. All patients or their familiars were informed about the study's purpose before they consented to participate.

## Results

Among the 185 patients treated during 2004-2008, 100 (54.05%) were male and 85 (45.94%) were female (p=0.270). The ages of these patients were mostly distributed below 10 years-old (50.27%) and 11 to 20 years-old (28.01%). In relation to color of skin, 106 (57.29%) patients were brown, 56 (30.27%) white and 23 (12.43%) were black (p<0.001). The most common types of clefts were CLP (n=109;58.9%), CL (n=42;22.7%) and CP (n=34;18.4%). Of the total number of participants (n=185), 65 (35.13%) presented a positive history of cleft in their families and 120 (64.86%) presented a negative history (p<0.001).

CL and CLP were considered to be one group (7). Of the 151 individuals in this group, 42 of them carriers of CL and 109 of CLP. Of these 151 cleft patients, 86 were male and 65 were female. Of this group, 57 (37.74%) had a positive history of cleft in the family, while 94 (62.25%) presented a negative history of cleft in the family. Of the 42 carriers of CL, 24 were female and 18 male, while of the 109 carriers of CLP, 68 were male and 41 female. In Table 1, the distribution of clefts in the parents of the CL and CLP group can be observed. There were 57 familiars affected, 55 (96.49%) with CLP and 2 (3.5%) with CP. There were differences between the cleft groups according to the type of cleft and whether there was a positive familial history (p<0.001). Even though there were less than 57 people affected with a CL and CLP positive history, it is possible to see a heterogenic distribution.

**Table 1.** Members of CLP and CL family affected.

Member	n	(%)
Mother	2	3.5
Father	3	5.26
Cousins	31	54.37
Uncle	5	8.76
Brothers and Sisters	12	21.05
Daughter and son	4	7.01
<b>Total</b>	<b>57</b>	<b>100</b>

The relatives more likely to be involved were cousins (54.37%) followed by brothers (21.05%). The fathers and mothers represented 8.76%, and furthermore the sons and daughters presented positive histories in only 7.01% of the cases.

In the group of 185 patients with CL/P, 34 (18.37%) showed isolated CP ( $p < 0.001$ ). Of these 34 patients, 8 (23.52%) had a positive history of CLP in the family. When the groups were compared, the frequency of familial reports was not different ( $p = 0.117$ ). Of these 8 individuals affected, 6 (75%) had isolated CP and 2 (25%) had CLP. Table 2 illustrated the members of the family affected. The relatives more involved in the CP group were cousins (62.5%), followed respectively by father and mother (25%) and uncles (12.5%). The likelihood ratio test reveal  $p = 0.175$ , showing no differences between the predominance of cousins in the CL/P and CP groups.

**Table 2.** Members of CP family affected.

Members of family	n	(%)
Mother	1	12.5
Father	1	12.5
Cousins	5	62.5
Uncle	1	12.5
<b>Total</b>	<b>8</b>	<b>100</b>

## Discussion

NSCL/P is considered to be a complex trait with no obvious inheritance mode. Numerous studies on candidate genes have failed to identify either major gene involvement or mutations as exerting a major influence on risk (9). On the other hand, a number of candidate loci that may be involved in the NSCL/P etiology have been identified (1). Moreover, it is becoming clear that complex interactions between genetic and environmental variables cause oral clefts (9). The most recent work on the etiology of CL/P has focused on increased sophistication of clinical descriptions, rather than aiming to study many thousands of people. The creation of subphenotypes based on minor clinical features has been suggested to allow for the identification of 'unaffected' individuals who in fact could be 'carrying' the disease-causing alleles (1). It has been proposed that occult defects of the superior orbicularis oris muscle may represent a subclinical form of cleft of the lip. Comparisons between unaffected cleft relatives and control individuals showed that relatives have twice as many orbicularis oris muscle discontinuities (10).

Different epidemiological studies have been conducted worldwide to evaluate NSCL/P distribution, often resulting in varying prevalence rates (5,11). Recently, in a Brazilian population study, we showed predominance

of CLP (52.6%), followed by isolated CL (33.12%) and isolated CP (14.28%) (8). In most published studies, the percentage of subjects with CLP has been higher compared to that of CL or CP alone, including the Brazilian studies (8,12). Some authors studying a population in Sucre, Bolivia, attributed the highest incidence to CL alone (13). In another analysis performed in Brazil, 126 pediatric patients with NSCL/P but without any additional malformation demonstrated a Caucasian predilection and a 1.3 ratio of male to female. 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%) (3). The findings of the present study reveal that, of the 185 patients with NSCL/P, the prevalence of CLP (58.91%) was significantly higher than that of CL (22.7%) and CP (18.37%). Some authors studying a population in southern Thailand, showed that, of 153 patients affected by CL/P, 55.6% had CLP, 23.5% had CL and 20.9% had CP (14).

Systematic registration of children with a cleft and data on their histories are necessary for the determination of etiopathogenetic internal and environmental factors (15). In our study carried out with CL/P patients treated between 2004-2008 years at this centre, a positive familial history of cleft malformation was found in 35.13% of cases. A study investigating 4557 affected children born in Czechoslovakia over a period of 29 years, registered a positive familial history in 18% of cases (16). In one study comprised of 540 individuals with NSCL/P in Poland, also registered a positive familial history in 18% of cases (16). Data from several centers point to the activity of genetic factors in 20-25% of children with a cleft (16). In another study comprised of 153 individuals with NSCL/P in Thailand, registered a positive familial history in 17.7% of cases (14). In the USA and Western Europe a genetic factor is suspected in about 40% of cases (17). Family clustering in CL/P has been characterized extensively, and epidemiological studies have proposed monogenic models with reduced penetrance, multifactorial models and mixed major gene/multifactorial models to explain its inheritance (18). Evidence suggests that JAG2 and MID1 may play a role in NSCL/P in Italian patients (9). These discrepancies between groups and some centers results from the fact that some of the parents intentionally withheld a positive familial history, some had no knowledge of concealed clefts (abortive forms), and some did not know all of their relatives (15).

The study confirmed the existence of two genetic groups. In the group of 151 patients with CLP or CL, 57 (35.13%) showed a positive history of cleft. For these patients, CP was observed in only 2 (3.5%) of the relatives with the remaining having a positive history of CLP and CL (96.5%). However, in the group of 34 patients

with CP, 8 showed a positive history of cleft. CP was observed in 6 (75%) of the relatives, with the remaining having a positive history of CLP (25%). A genetic distinction of two cleft groups was noted for the first time by Christensen and Fogh-Andersen, who analyzed 703 children with a cleft and 25,000 of their relatives (7). Twin studies also confirmed the distinction of these two clefts groups. Cleft concordance in monozygotic twins is 35% for CL or CLP and 44% for CP, and for dizygotic twins 6.2% and 8.8%, respectively (7). Two different genes are suspected to be responsible for the prevalence of the two genetic groups of clefts. This may be explained by damage to different embryonic structures at different stages of embryo development. CL is the result of hypoplasia of the medial nasal and maxillary process between 4-7 weeks of embryonic life. CP originates later, between 7-12 weeks, as a consequence of hypoplasia of the maxillary palatal process and often coexists with growth retardation of the mandible. A normally growing mandible pulls the tongue forward and down, which creates sufficient space for horizontalization of the palatal plates and is of particular importance in the development of an isolated CP (14,18).

This study presents the relationship between cleft type and first grade patients with CL/P and their affected relatives. In the CL and CLP group, the most affected were cousins (54.37% of the 57 affected). However, there was no statistical difference between the two groups. In the group with CP, 8 members affected 62.5% were cousins, while 25% were parents. All patients were referred to the service without any previous surgical treatment in early childhood (the ideal time for treatment). Referring to management, in adult cases, the sense may be placed on the growing importance of implant-based treatments and telescopic crowns (19).

#### Conclusion

In summary, in this paper, clearly, fissures more frequently result from CL/CLP with no familial history. However, CL/CLP was found more in familial cases and cousins were the relative type more affected. Thus the problem of a genetic factor in CL/P is still open and subject to discussion. Furthermore, thorough studies on family incidence of CL/P are required. The present information may be used in genetic counselling. A more accurate understanding of inheritance mechanisms will enable prediction of this malformation in coming generations. Perhaps there will be a chance of developing cleft prophylaxis.

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