

Epidemiological features of patients with nonsyndromic cleft lip and/or palate in Western Parana

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Abstract

Aim: To describe the clinical, demographic and environmental features associated with NSCL/P (nonsyndromic cleft lip and/or palate) patients born in western Parana state, Brazil. **Methods:** This cross-sectional, observational, retrospective study included 188 patients attended at the Association of Carriers of Cleft Lip and Palate - APOFILAB, Cascavel-Parana, between 2012 and 2014. Information on demographic characteristics, medical and dental histories and life style factors were obtained from records and personal interviews. **Results:** Among the 188 patients, cleft lip and palate (CLP) was the most frequent subtype (55.8%), followed by cleft lip only (CLO, 25.0%) and cleft palate only (CPO, 19.2%). Caucasian males were the most affected, although no differences among types of cleft were observed. The otorhinolaryngologic and respiratory alterations were the most frequent systemic alterations in NSCL/P patients, and more than 80% of the NSCL/P mothers reported no vitamin supplements during the first trimester of pregnancy. **Conclusions:** This study revealed that the prevalence of nonsyndromic oral cleft types in this cohort was quite similar to previously reported prevalence rates. Systemic alterations were identified among 23.4% of the patients and patients with CLP were the most affected. History of maternal exposition to environmental factors related to nonsyndromic oral clefts was frequent and most mothers reported no vitamin supplements during the pregnancy. This study highlights the importance of identifying systemic alterations and risk factors associated with NSCL/P in the Brazilian population for planning comprehensive strategies and integrated actions for the development of preventive programs and treatment.

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Introduction

Nonsyndromic cleft lip and/or palate (NSCL/P) represents the most frequent head and neck congenital malformations in the world^{1,2}. They are traditionally divided in cleft lip only (CLO), cleft lip and palate (CLP) and cleft palate only (CPO). However, as there are similarities in both epidemiologic features and embryologic timing for both CLO and CLP, they are considered variants of the same defect and grouped together to form the group cleft lip with or without cleft palate (CL ± P). The incidence of NSCL/P is approximately 1 in 500-2500 live births and influenced by ethnic and environmental

factors^{3,4}. In Brazil, epidemiological studies demonstrated that the incidence of NSCL/P varies from 1 per 685 to 2800 births^{5,6}. Approximately 70% of CL±P and 50% of CPO are isolated defects and the remaining are related to syndromes including clefts in the clinical spectrum^{7,8}. The etiology of NSCL/P, which involves both genetic and environmental factors, is highly complex and the molecular basis remains largely unknown^{3,9,10}. Epidemiological and experimental data suggest the exposure to tobacco smoke, agrotoxics, alcohol, poor nutrition and drugs as the main environmental factors to the development of oral clefts^{2,11,12}. On the other hand, maternal ingestion of folic acid or multivitamins during early pregnancy can reduce the risk of NSCL/P¹³⁻¹⁵.

NSCL/P results in morphological and functional morbidities associated with nutrition, speech, hearing, psychological and social aspects and imposes a substantial financial burden^{3,16}. Several of the NSCL/P effects may extend into adulthood like an increased risk of cancer¹⁷⁻¹⁹. Previous studies have also shown a high risk of cancer in relatives of patients with NSCL/P^{18,20}. This association has been explained, because cancer and NSCL/P may share similar genetic defects, which may be segregated within family^{21,22}.

The aim of the present study was to report the epidemiological and clinical features of 188 patients with NSCL/P from western Parana state, Brazil, and to evaluate the family background relevant to the disease.

Material and methods

This observational cross-sectional study comprised a population of 188 patients with NSCL/P treated at a reference association in Cascavel-Parana, Brazil. This reference service has a multidisciplinary team of health care specialists, including plastic surgeons, dentists, psychologists, physiotherapists, pediatricians, nutritionists and speech therapist. Patients were enrolled between 2012 and 2014 and all subjects were born in the study area. Experienced professionals evaluated the patients and only those identified with nonsyndromic oral cleft were included in this study. Mothers of NSCL/P patients were interviewed and physical examination of the patients was made to establish the subtype of cleft and involved anatomical structures. The incisive foramen was the reference structure to classify nonsyndromic oral clefts. Clefts were also classified by laterality and extent²³.

Information on demographic characteristics, medical and dental histories and life style factors were obtained from medical records and personal interviews by a trained staff. The variables included gender, age, race/ethnicity, oral cleft type, systemic alterations, mother's exposure to environmental factors, family history and parental consanguinity. Race/ethnicity was established by a multivariate evolution based on skin color in the medial part of the arm, and hair color and texture as previously described²⁴.

All mothers of NSCL/P patients were asked about their habits during pregnancy. They were considered smokers or to consume alcohol during the first trimester of pregnancy if any smoking or alcohol consumption was reported. Maternal passive

smoking was defined as being exposed to the smoke from more than one cigarette per day at home or at the workplace during the first trimester. The same is true for indirect contact with agrotoxics. Positive exposure was considered when the person had environmental contact with agrotoxics or living near places with constant pesticide spraying²⁵. Direct contact with paints, solvents, fuel or laboratory substances were considered as other substances. Mothers who used drugs like antibiotics, anticonvulsants or corticosteroids during the first trimester of pregnancy were classified as positive contact. Data on vitamin supplement intake were also derived from the interview. Women were asked whether they used multivitamins or folic acid supplements during the one-month preconceptional period or first trimester. Written informed consents were obtained from all participants, and the study was carried out with approval of the institutional Human Research Ethics Committee of the University (071/2012).

Statistical analysis was performed using the GraphPad Prism software version 6.01 for Windows with a 5% significance level. Chi-square tests assessed the frequency distributions of clinical, demographic and environmental characteristics with the subtypes of cleft.

Results

A description of study participants is in Table 1. Among the 188 patients, 121 (64.4%) were male, resulting in a male to female 1.8:1 ratio. All types of oral clefts were more frequent in males. The median age of the patients at the first visit was 13 years. Except for a few patients all were classified as Caucasian. Bilateral clefts were significantly more frequent in CLP patients (33.3%) than in CLO patients (4.3%, $p=0.0001$) and clefts with complete extent were significantly more common in CLP compared to CLO and CPO ($p=0.0001$).

Forty-four patients presented diagnosed systemic alterations associated with NSCL/P. Thirty-five patients had only 1 systemic alteration, whilst 9 of the nonsyndromic cleft patients had 2 or more alterations. Otorhinolaryngologic and respiratory alterations were most frequent among NSCL/P patients (Table 2). Palate involvement was essential for otorhinolaryngologic alterations, since patients with CLO did not exhibit any associated alteration in the ears, nose or throat. Allergic bronchitis was the most common associated alteration, more frequent in patients with CLO and CLP (Table 2).

Table 3 depicts the rates of maternal exposure to environmental factors during the first trimester of pregnancy. In general, no significant differences were detected among the NSCL/P groups regarding environmental factors, but the frequency of mothers that did not take vitamin supplements was very high. More than 80% of the mothers reported no vitamin supplements during the first trimester of pregnancy. No mother reported preconceptional use of vitamins or folic acid. According to Table 4, consanguinity and history of miscarriages and stillbirths were not significantly different among the three types of cleft. Similarly, no significant differences were observed regarding presence of orofacial cleft and cancer in the first degree relatives.

Table 1 - Distribution by gender and race and clinical extent of the clefts.

| | Cleft lip n (%) | Cleft lip and palate n (%) | Cleft palate n (%) | p value |
|-----------------------|--------------------|-------------------------------|-----------------------|---------|
| Gender | | | | |
| Male | 30 (63.8) | 69 (65.7) | 22 (61.1) | 0.88 |
| Female | 17 (36.2) | 36 (34.3) | 14 (38.9) | |
| Age | | | | |
| 0-2 years | 2 (4.3) | 7 (6.7) | 0 | 0.08 |
| 2-12 years | 27 (57.5) | 49 (46.7) | 25 (69.4) | |
| 13-20 years | 8 (17.0) | 33 (31.4) | 9 (25.0) | |
| >20 years | 10 (21.2) | 16 (15.2) | 2 (5.6) | |
| Race/ethnicity | | | | |
| Caucasian | 42 (89.4) | 93 (88.6) | 32 (88.8) | 0.98 |
| Non-Caucasian | 5 (10.6) | 12 (11.4) | 4 (11.2) | |
| Cleft side | | | | |
| Unilateral | 45 (95.7) | 70 (66.3) | 0 | 0.0001 |
| Bilateral | 2 (4.3) | 35 (33.3) | 0 | |
| Cleft extent | | | | |
| Incomplete | 25 (53.2) | 18 (17.2) | 18 (50.0) | 0.0001 |
| Complete | 22 (46.8) | 87 (82.8) | 18 (50.0) | |

Table 2 - Distribution of systemic alterations in patients with nonsyndromic cleft lip and/or palate.

| | Cleft lip n (%) | Cleft lip and palate n (%) | Cleft palate n (%) |
|----------------------------|--------------------|-------------------------------|-----------------------|
| Otorhinolaryngology | | | |
| Otitis | 0 | 5 (16.7) | 5 (22.7) |
| Tonsillitis | 0 | 4 (13.3) | 4 (18.2) |
| Allergic rhinitis | 0 | 3 (10.0) | 4 (18.2) |
| Sinusitis | 0 | 0 | 2 (9.1) |
| Pharyngitis | 0 | 1 (3.3) | 0 |
| Respiratory | | | |
| Allergic bronchitis | 3 (27.3) | 7 (23.3) | 3 (13.6) |
| Recurrent pneumonia | 1 (9.1) | 1 (3.3) | 1 (4.5) |
| Cardiovascular | | | |
| Benign heart murmur | 2 (18.2) | 2 (6.7) | 2 (9.1) |
| Dermatologic | | | |
| Allergic dermatitis | 1 (9.1) | 3 (10.0) | 0 |
| Gastrointestinal | | | |
| Reflux | 2 (18.2) | 1 (3.3) | 0 |
| Neurological | | | |
| Seizure | 0 | 2 (6.7) | 0 |
| Ophthalmic | | | |
| Visual deficiency | 0 | 1 (3.3) | 1 (4.5) |
| Musculoskeletal | | | |
| Scoliosis | 1 (9.1) | 0 | 0 |
| Facial | | | |
| Facial asymmetry | 1 (9.1) | 0 | 0 |
| Total | 11 (17.5) | 30 (47.6) | 22 (34.9) |

Discussion

Different studies were conducted worldwide to evaluate NSCL/P distribution, often resulting in varying prevalence rates^{26,27}. However, in most studies, the percentage of patients with CLP is higher compared to that of CLO or CPO²⁸⁻³⁰. Similar results were described in previous studies with Brazilian NSCL/P patients^{29,31}. In the present study, the findings revealed 105 (55.8%) patients with CLP, 47 (25%) with CLO and 36 (19.2%) with CPO. Moreover, in some studies were observed differences in the distribution of NSCL/P between males and females^{28,29}. This study showed that CLO, CLP and CPO prevailed in males. Investigating the epidemiological features of NSCL/P patients treated at the Center for Rehabilitation of Craniofacial Anomalies in Minas Gerais, Brazil, Martelli-Junior et al. (2008) revealed prevalence of CPO in females, whereas males were more affected by other types of cleft³².

Unilateral involvement was more common than bilateral in CLO and CLP patients. However, according to the literature, frequency of bilateral CLP is significantly higher than bilateral CLO^{28,33,34}. In addition, patients with bilateral CLP presented more frequently nasal deformities and nasopharyngeal depths than unilateral CLP^{35,36}. Involvement of the palate in patients with oral cleft is related to facial and airway structures disruption and in an increased risk of sleep and breathing disorders³⁷. In this study, complete CLP was significantly more frequent than complete CLO or CPO.

According to the literature, alterations in NSCL/P patients are complex and beyond the facial structure. Feeding difficulties, speech alterations, recurrent middle ear infections and other difficulties are frequently observed^{3,28}. In this study, 23.4% of oral cleft patients had at least one associated systemic alteration. The highest incidence of systemic alterations was observed in CLP patients. Generally, the most anomalies occur in cases involving the palate rather than the lip and higher rates of hospitalization before age two in children with CP or CLP are reported³⁸. In a study of 5,449 cases from 23 European birth registries, anomalies were found in 20.8% of CLO patients and in 34.0% of CLP patients³⁹, and another study found anomalies in 12.2% of CLO patients, 35.1% with CLP and 36.7% with CPO³⁸. This study confirmed that associated otorhinolaryngologic, respiratory and cardiovascular defects are frequent^{38,40,41}. Children born with cleft palate may need more attention and closer monitoring for a long time.

Many studies have identified a relationship between environmental risk factors and NSCL/P^{2,11,12}. Although cigarette smoking, alcohol consumption (drinking) and exposure to agrototoxics among the mothers were the most common environmental factors, the present results showed no differences among types of cleft. With respect to lack of association between environmental factors of parents and risk for orofacial cleft in this study, in contrast to other studies^{11,42,43}. The current data support the possibility that exposure to risk factors has a different effect on cleft risk among parents, which may reflect a role for genetic susceptibility factors in cleft development^{9,44}. In this study, over two-thirds of mothers did not take vitamin supplements in early pregnancy. Low concentrations of micronutrients increase significantly the risk of orofacial cleft⁴⁵. Recent reports suggest that

Table 3 - Frequency of maternal exposure to environment factors during the first trimester of pregnancy, according to patients with nonsyndromic cleft lip and/or palate.

| | Cleft lip n (%) | Cleft lip and palate n (%) | Cleft palate n (%) | p value |
|-------------------------------------|--------------------|-------------------------------|-----------------------|---------|
| Cigarette smoking | | | | |
| No | 40 (85.1) | 93 (88.6) | 30 (83.3) | 0.67 |
| Yes | 7 (14.9) | 12 (11.4) | 6 (16.7) | |
| Passive smoking | | | | |
| No | 44 (93.6) | 92 (87.6) | 34 (94.4) | 0.33 |
| Yes | 3 (6.4) | 13 (12.4) | 2 (5.6) | |
| Alcohol consumption | | | | |
| No | 43 (91.5) | 99 (94.3) | 33 (91.7) | 0.76 |
| Yes | 4 (8.5) | 6 (5.7) | 3 (8.3) | |
| Illicit drugs | | | | |
| No | 46 (97.9) | 105 (100) | 36 (100) | 0.22 |
| Yes | 1 (2.1) | 0 | 0 | |
| Drugs (medications) | | | | |
| No | 39 (83.0) | 97 (92.4) | 30 (83.3) | 0.14 |
| Yes | 8 (17.0) | 8 (7.6) | 6 (16.7) | |
| Chemicals | | | | |
| Non-exposure | 39 (83.0) | 74 (70.5) | 28 (77.8) | 0.34 |
| Agrotoxics | 1 (2.1) | 12 (11.4) | 4 (11.1) | |
| Environment contact with agrotoxics | 4 (8.5) | 14 (13.3) | 4 (11.1) | |
| Other | 3 (6.4) | 5 (4.8) | 0 | |
| Vitamin supplementation | | | | |
| No | 37 (78.7) | 89 (84.8) | 25 (69.4) | 0.13 |
| Yes | 10 (21.3) | 16 (15.2) | 11 (30.6) | |

Table 4 - Characteristics of parents and relatives of the patients with nonsyndromic cleft lip and/or palate.

| | Cleft lip n (%) | Cleft lip and palate n (%) | Cleft palate n (%) | p value |
|--|--------------------|-------------------------------|-----------------------|---------|
| Consanguinity | | | | |
| No | 45 (95.7) | 100 (95.2) | 34 (94.4) | 0.96 |
| Yes | 2 (4.3) | 5 (4.8) | 2 (5.6) | |
| Miscarriage | | | | |
| No | 43 (91.5) | 98 (93.3) | 35 (97.2) | 0.56 |
| Yes | 4 (8.5) | 7 (6.7) | 1 (2.8) | |
| Stillbirth | | | | |
| No | 45 (95.7) | 102 (97.1) | 36 (100) | 0.48 |
| Yes | 2 (4.3) | 3 (2.9) | 0 | |
| Orofacial cleft in 1st degree relative | | | | |
| No | 37 (78.7) | 80 (76.2) | 28 (77.8) | 0.93 |
| Yes | 10 (21.3) | 25 (23.8) | 8 (22.2) | |
| Cancer in 1st degree relative | | | | |
| No | 30 (63.8) | 74 (70.5) | 20 (55.6) | 0.24 |
| Yes | 17 (36.2) | 31 (29.5) | 16 (44.4) | |

use of vitamins containing folic acid during the early pregnancy may decrease risk of NSCL/P^{46,47}. Additionally, variations on genes related to absorption, transport and metabolism of vitamins may have key roles in NSCL/P predisposition⁴⁸.

Regarding family recurrence, 43 (29%) patients had a family history of NSCL/P among first-degree relatives with little variation among cleft types. This is similar to other studies where a prevalence of oral clefts in other family members was found to range between 18% and 30.5%^{34,49}. Furthermore, the finding that CLO patients were less likely to have a positive family history of oral clefts than patients with CLP and CPO was consistent with Grosen et al. (2010)⁵⁰. Akin marriages are an important factor in the development of a host of genetic anomalies as well as increased risk of oral cleft^{34,51}. The akin relationships observed in the present study (4.9%) were slightly more common than what was observed by Leite and Koifman (2009)⁵². In addition to the congenital anomalies, the consanguinity is also associated with increased risks of low birth weight, preeclampsia, which in turn are risk factors for stillbirth, especially preterm stillbirth⁵¹. In this study, the frequency of miscarriage and stillbirth was of 6% and 2.4% respectively, which are quite similar to average population. This study also revealed that cancer frequency in relatives of patients born with oral clefts ranged from 29.5 to 44.4%. These findings agree with previous studies which suggested that individuals born with NSCL/P have a higher risk for cancer^{18,19,53}. Recent evidences from genetic studies have supported the hypothesis that some genes are simultaneously associated with cancer and craniofacial disorders^{21,22}, but more studies are required to better understand which common mechanisms have a role in both conditions.

In summary, this study observed a CLP prevalence, followed by CLO and CPO. The clefts were more frequent in males than in females. Clefts were more frequent as unilateral and bilateral involvement prevailed in CLP. Complete clefts were significantly more common in CLP compared to CLO and CPO. The most common systemic alterations were in the otorhinolaryngologic system and respiratory tract, and the lack of vitamin supplementation as well as cigarette smoking, alcohol consumption and pesticide exposure were frequent environmental factors. Further studies focusing on specific environmental and genetic factors are required to facilitate health-related policies of resource use as well as oral cleft prevention and care.

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