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Risk factors and comorbidities in Brazilian patients with orofacial clefts

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Abstract: Considering that environmental risk factors substantially contribute to the etiology of orofacial clefts and that knowledge about the characteristics and comorbidities associated with oral clefts is fundamental to promoting better quality of life, this study aimed to describe the risk factors, main characteristics, and comorbidities of a group of patients with cleft lip and/or cleft palate (CL/P) from Rio Grande do Norte (RN), Brazil. Data were obtained from 173 patients with CL/P using a form from the Brazilian database on Orofacial Clefts. Most patients were male with cleft lip and palate and had a normal size and weight at birth; presented few neonatal intercurrent events; and had anemia and respiratory and cardiovascular diseases as main associated comorbidities. They also required timely surgical rehabilitation and multidisciplinary care to stimulate their neuropsychomotor development. In addition, a high frequency of familial recurrence and of parental consanguinity was evidenced in the studied population, especially for the cleft lip and cleft palate type. Other relevant findings were the considerable maternal exposure to alcohol, infections, smoking, and hypertension, as well as low supplementation with vitamins and minerals and deliberate consumption of analgesics, antibiotics, and antihypertensives during pregnancy. Characterization of the CL/P patient profile is essential for the planning of health services and integration among the health professionals involved in the diagnosis and treatment of these malformations. Our results reinforce the need for additional research to confirm the association between environmental factors and the development of orofacial clefts.

Keywords: Cleft Lip; Cleft Palate; Comorbidity; Risk Factors; Environmental Exposure.

Introduction

Cleft lip and/or cleft palate (CL/P) is a congenital malformation characterized by the lack of fusion of the upper lip and/or palate, which may be present in isolation or in association with a syndrome.[1] The highest prevalence at birth of CL/P is found in Asian and native American populations (1 in 500 live births), while the lowest prevalence is observed in populations of African descent, with approximately 1 in 2,500 live births.[2]

In Brazil, recent studies have indicated that the mean prevalence of CL/P is 5.86 per 10,000 live births, but these rates can vary across different states.[3] The southern region shows the highest prevalence, whereas the

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Northeast has the lowest one.[3] In recent years, however, there has been an upward trend in the reported CL/P prevalence in the northern and northeastern regions attributed mainly to improved notification to the National Health Information System or, alternatively, to changes in risk factors.[4] In Rio Grande do Norte (RN) state, in the northeastern region, a previous study reported a prevalence of 4.9 per 10,000 live births between 2000 and 2005, remaining within the incidence range of 4.82 to 5.50 per 10,000 live births between the years of 2009 and 2013.[3,4,5]

The etiology of CL/P is attributed to genetic susceptibility and to maternal exposure to environmental risk factors, including smoking, alcohol consumption, medications, and vitamin deficiencies during pregnancy.[2] According to some studies, alcohol consumption can inhibit retinoic acid production, increasing the risk of CL/P.[6,7] Smoking during pregnancy apparently doubles the risk of orofacial cleft in newborns. Moreover, *in vitro* studies have shown that tobacco inhibits palatal fusion and affects cell proliferation, leading to medial edge epithelial cell death.[1] In addition, some drugs such as anticonvulsants with antifolate activity, antihypertensives, and corticosteroids administered during morphogenesis may lead to CL/P through different cellular mechanisms.[8] By contrast, folic acid supplementation, alone or in combination with vitamins and minerals, prevents the development of neural tube defects, and its use from before conception to 12 weeks' gestation is recommended by the World Health Organization (WHO); however, there is no clear evidence of its preventive effect on CL/P.[9]

Family history is also an important factor associated with CL/P development; actually, it has been described as the most important factor in patients with clefts.[10] Familial recurrence is very common among CL/P patients, and their relatives have a high risk compared to the general population, but the risk decreases with increasing genetic distance between relatives.[11] The strong familial aggregation is ascribed to the multifactorial threshold model of inheritance that is characteristic of orofacial clefts, in which the probability of sharing alleles that are identical by descent is constant whether one, a few, or many genes control risk.[12]

In addition to facial deformity, CL/P patients usually present several associated comorbidities such as feeding difficulties, speech problems, dentition defects, dental malocclusion, abnormal facial growth, middle ear infections, and psychological disorders, which can be minimized or prevented through timely surgical treatment and follow-up by a multidisciplinary team.[13] Early identification of these abnormalities and intervention are essential for the appropriate neuropsychomotor development of CL/P patients.

Considering the paucity of data on characteristics associated with the multifactorial nature of CL/P in RN, northeastern Brazil, and the need for early identification of the main CL/P complications for proper monitoring and intervention, the present study aimed to describe the characteristics, main risk factors, and associated comorbidities of a group of CL/P patients from RN, Brazil.

Methodology

Study participants

A total of 173 patients aged 1 month to 21 years presenting with CL/P either as a single entity or in combination with other diseases were recruited from the Pediatrics Unit of the Children's Hospital of the Federal University of Rio Grande do Norte (UFRN), Natal, RN, Brazil, from April 2013 to May 2015. The patients were evaluated and diagnosed by the Orofacial Cleft Multidisciplinary Program, which included a group of pediatricians, radiologists, speech therapists, cardiologists, and geneticists. The CL/P patients were classified into three groups according to Fogh-Andersen: cleft lip and palate (CLP), cleft palate (CP), and cleft lip (CL).[14]

The study, which is an integral part of Brazil's Craniofacial project,[15] was conducted according to the guidelines set by the Research Ethics Committee of the UFRN, in compliance with the Declaration of Helsinki (process number 328.230). An informed consent was obtained from all adult participants and from the parents or legal guardians of underage patients.

Data acquisition

Data were collected through an interview with patients or with their parents or legal guardians using a pre-tested form available on the CranFlow-Brazilian database on Orofacial Clefts.[16] The forms

were applied after routine pediatrician visits by trained pharmacists or undergraduate students in a private room in the Pediatrics Unit. All patients treated at the hospital during the study period were invited to participate, and those who agreed were included in the study. Those patients whose mothers or guardians did not sufficiently answer the questionnaire were excluded from the study (173 out of 180 participants remained). The form included retrospective patient information such as type and severity of cleft, gender, birth weight, birth length, head circumference at birth, neonatal and personal history, and neuropsychomotor development. Data on surgical lip and palate rehabilitation were also assessed. The questionnaire also covered retrospective parent information such as age at conception, educational level, mother's occupation during pregnancy, family history of orofacial clefts, and parental consanguinity. Obstetrical data, alcohol intake, smoking, and illicit drug use at any time during pregnancy, diagnosis of gestational diabetes, and medications used during pregnancy were also retrieved.

Data analysis

The results were presented as absolute numbers (n) and as frequency (%).Weight, length, and head circumference at birth were grouped into lower, middle, or higher according to the WHO child growth standards. Differences between categorical variables were tested by χ^2 analysis or Fisher's exact test. Significance was established at $p < 0.05$. Data were analyzed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

The characteristics of CL/P patients are shown in Table 1. There was a higher prevalence of CLP, followed by CP and CL ($p < 0.001$), regarding the type of cleft. Unilateral clefts prevailed over bilateral ones, and there was a higher frequency of CL/P in male than in female patients ($p = 0.008$). At birth, most patients (70.5%) weighed between 2,500 g and 3,999 g, and body lengths ranged from 46.1 cm to 53.7 cm among boys and 45.4 to 52.9 cm among girls. Most boys had a head circumference at birth between 31.9 cm and 37.0 cm, compared to 31.5 cm to 36.2 cm in girls. Almost 25% of all patients had some neonatal intercurrent event, especially icterus and respiratory distress.

Associated comorbidities or complications were present in 45.7% of the patients (Table 1). The most frequent comorbidities included anemia (16.2%), followed by respiratory diseases such as asthma, rhinitis, cold, and influenza (12.1%); cardiovascular diseases such as patent foramen ovale and ventricular septal defect (9.8%); and neurological diseases such as autism and epilepsy (8.1%).

Eighty-two patients (47.4%) showed appropriate neuropsychomotor development for their age. However, 8.1% showed concomitant motor, speech, and behavioral delay or diagnosis of neuropsychomotor development delay, while 6.9% presented only speech delay. Half of the patients did not attend any supportive therapy. Almost 30% of those who underwent therapy attended speech therapy.

Lip and palate surgical repair outcomes are shown in Table 2. A total of 49 CLP or CP patients had already undergone their first palatoplasty and 67 had already undergone their first cheiloplasty. Most cheiloplasty patients were aged 6 to 12 years (46.9%), while palatoplasty patients were aged 1 to 2 months (53.7%). A high percentage of patients had not undergone any surgery and an even larger percentage exceeded the standard age for both cheiloplasty (72.7%) and palatoplasty (59%).

A higher frequency was found for conception at the ages of 20 to 30 years for both fathers and mothers (46.2% and 54.9%, respectively) (Table 3). Mean paternal age at conception was 29.4 ± 8.3 years, whereas mean maternal age at conception was 26.6 ± 6.5 years (data not shown). There were no differences between the mean maternal ages of syndromic (34.3 ± 6.9) and non-syndromic patients (33.9 ± 8.6) (data not shown).

Most fathers and mothers (27.7% and 39.9%, respectively) had finished high school (Table 3). However, proportionately, mothers had reached higher levels of education than fathers, verified by the higher frequencies of high school and college attendance (39.9% *vs.* 27.7% and 8.1% *vs.* 5.2%, respectively). Mothers were mostly homemakers during the gestational period (51.4%). Parental consanguinity was detected

Table 1. Data on the patients with orofacial clefts.

Variable	n = 173	%	p-value
Type of cleft			
Cleft lip and palate (CLP)	81	46.8	
Cleft palate (CP)	61	35.2	< 0.001
Cleft lip (CL)	31	17.9	
Severity (CLP and CL)			
Unilateral	81	72.3	
Bilateral	30	26.8	< 0.001
Midline	1	0.9	
Gender			
Male	104	60.1	0.008
Female	69	39.9	
Birth weight			
< 2,500 g	26	15.0	
25,00 – 3,999 g	122	70.5	< 0.001
≥ 4,000 g	13	7.5	
Missing data	12	6.9	
Birth length			
Boys			
< 46.1 cm	7	6.7	
46.1 – 53.7 cm	76	73.1	< 0.001
> 53.7 cm	3	2.9	
Missing data	18	17.3	
Girls			
< 45.4 cm	11	15.9	
45.4 – 52.9 cm	41	59.4	< 0.001
> 52.9 cm	6	8.7	
Missing data	11	15.9	
Head circumference at birth			
Boys			
< 31.9 cm	4	3.8	
31.9 – 37.0 cm	54	51.9	< 0.001
> 37.0 cm	1	0.9	
Missing data	45	43.2	
Girls			
< 31.5 cm	5	7.2	
31.5 – 36.2 cm	32	46.4	< 0.001
> 36.2 cm	4	5.8	
Missing data	28	40.6	
Neonatal intercurrent events	43[a]	24.9[a]	
Icterus	25	14.5	
Respiratory distress	23	13.3	
Intubation and mechanical ventilation	9	5.2	
Infections	5	2.9	< 0.001
Other	13	7.5	
None	93	53.8	
Missing data	37	21.4	

Continue

Continuation

Comorbidities	79[b]	45.7[b]	
Anemia	28	16.2	
Respiratory diseases	21	12.1	
Cardiovascular diseases	17	9.8	
Neurological diseases	14	8.1	
Otitis	13	7.5	
Hearing loss	10	5.8	< 0.001
Pneumonia	9	5.2	
Gastrointestinal diseases	6	3.5	
Other	20	11.6	
None	70	40.5	
Missing data	24	13.9	
Neuropsychomotor development			
Normal for age	82	47.4	
Motor, speech and behavioral delays and NPMD[c]	14	8.1	
Speech delay only	12	6.9	
Motor and speech delay	5	2.9	
Motor delay only	4	2.3	< 0.001
Speech and behavior delay	3	1.7	
Behavioral delay only	1	0.6	
Not applicable	27	15.6	
Missing data	25	14.5	
Therapy			
No	87	50.3	
Yes	51	29.5	0.002
Missing data	35	20.2	
Type of therapy			
Speech Therapy	41	23.7	
Physical therapy	8	4.6	
Psychology	5	2.9	< 0.001
Occupational therapy	4	2.3	
Other	4	2.3	
Syndrome			
Nonsyndromic	119	68.8	
Syndromic	47	27.2	< 0.001
Not classified	7	4.0	

[a]Total number of neonatal complications and frequency relative to the whole study group; [b]Total number of comorbidities and frequency relative to the whole study group; [c]NPMD, Neuropsychomotor developmental delay.

in 8.1% of the cases, first cousins being the most common type of kinship. Familial history was found in 39.3% (Table 3).

The obstetric history and birth characteristics of studied patients (Table 4) evidences that most pregnancies were spontaneous (98.3%); Cesarean sections were the most frequent type of birth (41.6%); and most pregnancies reached full term (56.1%). Furthermore, the largest proportion of mothers had one or two pregnancies (31.8% and 32.4%, respectively) with the first child being the most frequently affected by clefts (40.5%). Thirty mothers (17.3%) had at least one miscarriage, and only eight (4.6%) attempted to terminate pregnancy. Prenatal history revealed that 22.5% of the mothers had consumed alcohol during pregnancy, 13.9% had had urinary tract infection, 11.6% had smoked during pregnancy, and 11.0% had been diagnosed with gestational hypertension or preeclampsia. Bleeding and gestational diabetes were also frequently reported. As additional information, two mothers reported direct and daily contact with gases such as ammonia and those obtained from the

Table 2. Data on lip and palate surgical repair.

Variable	n = 173	%	p-value
Age at first surgical repair			
Cheiloplasty			
< 6 months old	18	26.9	0.001
6–12 months old	36	53.7	
13 month–5 years old	13	19.4	
> 5 years old	0	0.0	
Total	67	100	
Palatoplasty			
< 1 year old	6	12.2	< 0.001
1–2 years old	23	46.9	
2–5 years old	16	32.7	
> 5 years old	4	8.2	
Total	49	100	
Delay in surgical repair			
Cheiloplasty			
Waiting for surgery and on time	9	27.3	0.009
Waiting for surgery and delay	24	72.7	
Total	33	100	
Palatoplasty			
Waiting for surgery and on time	32	41.0	0.113
Waiting for surgery and delay	46	59.0	
Total	78	100	

Table 3. Data on parents of orofacial cleft patients.

Variable	n = 173	%	p-value
Paternal age at pregnancy (years)			
< 20	12	6.9	< 0.001
20-30	80	46.2	
31-35	31	17.9	
> 35	28	16.2	
No information	22	12.7	
Maternal age at pregnancy (years)			
< 20	28	16.2	< 0.001
20–30	95	54.9	
31–35	32	18.5	
> 35	18	10.4	
Paternal education level			
Illiterate	9	5.2	< 0.001
Literate	4	2.3	
Elementary School	42	24.3	
Middle School	42	24.3	
High School	48	27.7	
College	9	5.2	
Missing data	19	11.0	
Maternal education level			
Illiterate	2	1.2	< 0.001
Literate	2	1.2	
Elementary School	40	23.1	
Middle School	46	26.6	
High School	69	39.9	
College	14	8.1	
Maternal occupation during pregnancy			
Homemaker	89	51.4	< 0.001
Salesperson	16	9.2	
Housekeeper	15	8.7	
Teacher	9	5.2	
Farmer	7	4.0	
Cook or waitress	7	4.0	
Student	6	3.5	
Industrial worker	5	2.9	
Administrative assistants	3	1.7	
Other	16	9.2	
Parental consanguinity			
No	159	91.9	< 0.001
Yes	14	8.1	
History of familial cleft			
No	105	60.7	0.005
Yes	68	39.3	

evaporation of paint and solvent while working in the industrial sector during the first trimester.

Folic acid and iron supplementation during pregnancy was reported by 24.3% and 21.4% of the mothers, respectively. In addition to these supplements, analgesics (17.3%) such as dipyrone and paracetamol, followed by antibiotics (16.8%) – most notably cephalexin and macrodantin, were taken. The use of antihypertensives (8.7%), especially methyldopa, to treat gestational hypertension was frequently reported. Vitamin supplements, corticosteroids, progesterone, and metoclopramide were also mentioned.

Table 5 shows the risk factors commonly associated with susceptibility to CL/P according to type of cleft. CLP was statistically more frequent in male than in female participants, among whom CP was more

Table 4. Obstetric history and birth characteristics of studied patients.

Variable	n = 173	%	p-value
Conception method			
Spontaneous	170	98.3	< 0.001
Assisted	3	1.7	
Type of Birth			
Vaginal	65	37.6	
Cesarean	72	41.6	0.550
Missing data	36	20.8	
Timing of birth			
Preterm	24	13.9	
Full-term	97	56.1	< 0.001
Post-term	17	9.8	
Missing data	35	20.2	
Number of pregnancies			
1	55	31.8	
2	56	32.4	0.003
3	31	17.9	
> 03	31	17.9	
Birth order			
1st	70	40.5	
2nd	51	29.5	< 0.001
3rd	26	15.0	
> 3rd	26	15.0	
Miscarriage			
No	143	82.7	< 0.001
Yes	30	17.3	
Termination of pregnancy attempts			
No	163	94.2	
Yes	8	4.6	< 0.001
Missing data	2	1.2	
Prenatal history			
Alcohol consumption	39	22.5	
Urinary tract infection	24	13.9	
Smoking	20	11.6	
Hypertension	19	11.0	< 0.001
Bleeding	15	8.7	
Diabetes Mellitus	10	5.8	
Illegal drug use	7	4.0	
Other	30	17.3	
Medications used during pregnancy			
Folic acid	42	24.3	
Iron	37	21.4	
Analgesic	30	17.3	
Antibiotic	29	16.8	
Antihypertensive	15	8.7	
Vitamin supplementation	12	6.9	
Anti-inflammatory	7	4.0	< 0.001
Anti-abortion drug	6	3.5	
Antiemetic	4	2.3	
Hypoglycemic agent	3	1.7	
Other	22	12.7	
None	70	40.5	
Missing data	2	1.2	

Table 5. Risk factors according to cleft types.

Variable	CLP	CP	CL	p-value
Gender				
Male	57 (32.9)	28 (16.2)	19 (11.0)	0.013
Female	24 (13.9)	33 (19.1)	12 (6.9)	
Paternal age at conception				
< 35 years old	55 (31.8)	37 (21.4)	24 (13.9)	0.476
≥ 35 years old	16 (9.2)	15 (8.7)	5 (2.9)	
Maternal age at conception				
< 35 years old	71 (41.0)	53 (30.6)	29 (16.8)	0.611
≥ 35 years old	10 (5.8)	8 (4.6)	2 (1.2)	
Parental consanguinity				
No	71 (41.0)	58 (3.5)	30 (17.3)	0.151
Yes	10 (5.8)	3 (1.7)	1 (0.6)	
Family history				
No	47 (27.2)	44 (25.4)	14 (8.1)	0.035
Yes	34 (19.7)	17 (9.8)	17 (9.8)	
Bleeding during pregnancy				
No	68 (39.3)	58 (33.5)	29 (16.8)	0.028
Yes	12 (6.9)	2 (1.2)	1 (0.6)	
Maternal alcohol consumption				
No	65 (37.6)	45 (26.0)	23 (13.3)	0.657
Yes	16 (9.2)	16 (9.2)	7 (4.0)	
Maternal smoking				
No	73 (42.2)	55 (31.8)	24 (13.9)	0.134
Yes	8 (4.6)	6 (3.5)	6 (6.5)	
Maternal illegal drug use				
No	77 (44.5)	59 (34.1)	29 (16.8)	0.862
Yes	4 (2.3)	2 (1.2)	1 (0.6)	
Gestational diabetes				
No	75 (43.4)	59 (34.1)	28 (16.2)	0.568
Yes	6 (3.5)	2 (1.2)	2 (1.2)	
Folic acid supplementation				
No	63 (36.4)	46 (26.6)	20 (11.6)	0.423
Yes	17 (9.8)	15 (8.7)	10 (5.8)	

CLP: cleft lip and palate; CP: cleft palate; CL: cleft lip .

prevalent (p = 0.013). Family history of clefts (19.7%; p = 0.035) and bleeding episodes during pregnancy (6.9%; p = 0.028) were most often found in the CLP group. There were no statistically significant differences among cleft types with regard to other risk factors.

Discussion

CL/P global prevalence, the need for an integrated long-term multidisciplinary treatment, and economic impact have prompted WHO to consider CL/P a public health problem.[17]

In the present study, aimed at describing the characteristics, comorbidities, and main risk factors

of a group of patients with CL/P from RN, Brazil, we observed a higher prevalence of unilateral CLP followed by CP, and male participants were more affected than female ones. CLP was also more frequent in male participants whereas CP was more frequent in female participants. Most of the assessed patients had normal weight, height, and head circumference at birth and exhibited a low frequency of neonatal intercurrent events. This finding is in agreement with previous reports of higher prevalence of CL/P among male patients and of CLP as the most common type of cleft both in Brazil and worldwide.[18,19] According to the literature, gender differences in the risk for CL/P and CP are explained by the multifactorial threshold model in which the etiology of orofacial clefts is inserted.[12] As in the present study, no evidence of low birth weight and short stature was found in follow-up studies with CL/P children.[20]

A considerable number of associated comorbidities were found in the studied patients, especially anemia, followed by respiratory problems and cardiovascular diseases. These findings are in line with those observed by Dvivedi and Dvivedi,[21] who identified anemia in most of the 4,657 CL/P cases studied in India,[21] and by Nagalo et al.,[22] who found anemia as the most frequent comorbidity in 185 children with CL/P, followed by respiratory infections in Western Africa. The same results were obtained by Kulkarni et al. (2013).[23] Anemia in CL/P patients is attributed mainly to feeding difficulty, while respiratory problems are frequently associated with irritation of the nasal and respiratory cavities by food and saliva, which also predisposes to recurrent infections. The frequency of cardiovascular malformations found by Harry et al.[24] in 10% of CL/Ps cases was similar to that of the present study. Cardiac anomalies are associated with the common development of both palate and heart between 5 and 9 weeks of gestation as part of cardiac and craniofacial development, which relies on complex signaling processes among interdependent embryonic tissues.[24]

Other complications commonly seen in CL/P patients are related to neuropsychomotor development. We observed concomitant motor, speech, and behavioral delay, followed by speech delay only. Moreover, 50% of the assessed children and adolescents did not participate in any supportive therapy, and only 23.7% attended speech therapy. Similar results were found by Feragen et al.[25] in a study with 754 children with CL/P in which 32% had alterations such as developmental delay, attention deficit/hyperactivity disorder, or a specific speech impairment or dyslexia. Despite early cleft repair, some children exhibit "cleft palate speech," characterized by atypical consonant productions, abnormal nasal resonance, abnormal nasal airflow, altered laryngeal voice quality, and nasal or facial grimaces, demonstrating the importance of patient follow-up by a multidisciplinary team.[26]

Lip and palate surgical repair is an important aspect to be considered in the treatment of CL/P patients, but the ideal timing for the repair remains controversial. It has been recommended that cleft lip surgical repair be performed at least 3 months of age – preferably at 4 or 5 months, if possible, and that cleft palate not be corrected after the age of 18 months.[27] At such ages, anesthesia is safer, the repair is more accurate, and malformations are more easily accepted by parents.[28] In the present study, most patients underwent palatoplasty and cheiloplasty at the recommended repair time with a few months' delay. However, there was a long delay among patients who had not undergone surgery yet. This indicates that poor access to surgical treatment and inappropriate management and planning of health services in Brazil are a hindrance, as pointed out previously.[3] Delay in performing the surgery leads to a series of consequences such as difficulty eating, speaking, and listening; psychological problems; stigmatization; social exclusion; and unemployment.[3,29]

By analyzing the characteristics of the parents of children with CL/P in the present study, there was no association between advanced age of mothers and fathers and the occurrence of orofacial clefts. Along the same line, Campos Neves et al.,[6] in a study with 116 orofacial cleft patients from Mato Grosso, Brazil, found 60.34% of the mothers were aged 20 to 34 years and 82.76% of the fathers were aged 20 to 39 years at the onset of pregnancy. Studies performed in Canada, Iran, the Netherlands, and South America did not find an association between advanced maternal age and CL/P or CP.[30] Advanced ages may be related to cumulative changes in gametes throughout life

caused by environmental exposures or chromosomal alterations (lifelong medication use, prevalence of chronic diseases, and socioeconomic factors), as well as low selectivity of the uterus regarding defective embryos and higher placental permeability to teratogenic agents.[31]

Although the etiology of CL/P is still not fully understood, genetic susceptibility has been shown as one of the most important associated causes.[2] Family history of CL/P in the present study corroborates previous findings of high rates of familial recurrence.[1,32] Brito et al.,[32] in a study with 1,042 families from five different locations in Brazil, observed a familial recurrence similar to that observed in the present study, in Barbalha (37%) and in Fortaleza (40%) in the Brazilian state of Ceará. Martelli-Junior et al.[33] found that 35.1% of 185 non-syndromic CL/P patients from Minas Gerais, Brazil, had a positive family history of orofacial clefts. A 30% frequency was found by Figueiredo et al.[34] in a study with 40 CL/P patients from Cuiabá, Brazil. Consistent with Leite and Kofman 's study of a Brazilian sample from Rio de Janeiro, the family history found in the present study was statistically more frequent in CLP cases.[35] Cohort studies indicate that relatives of orofacial cleft patients were at a higher risk than the general population, showing a steep decrease in such risk as the genetic distance between relatives increases.[11]

The parental consanguinity rate found in the present study (8.1%) was close to that found by Brito et al.[32] in Fortaleza, Brazil (11.5%), but it was higher than the 4% reported by Leite and Koifman[35] in Rio de Janeiro, Brazil and the 5% presented by Alvarez et al.[36] in a study with 356 patients from São Paulo, Brazil. The results found here reinforce the inheritable nature of this malformation, probably due to consanguineous marriages typical of the region where the study population is from, and also highlight the importance of genetic counseling for this population.

The prenatal history data presented here concur with those of previous publications: alcohol use and cigarette smoking may be associated with the development of craniofacial malformation.[7] Frequencies of alcohol consumption during pregnancy slightly lower than in the present study (22.5%) were reported by Campos Neves et al.[6] (17.2%) and by Bezerra et al.[37] (15%), both for the Brazilian population. A frequency of smoking higher than that observed in the present study (11.6%) was found by Nilsson et al.[38] in a study of Swedish children with CL/P, in which 23% of the mothers reported cigarette smoking during pregnancy. A 45% frequency of pregnant women who smoked at any time during pregnancy was found by Little et al.[39] in a study with 190 CL/P patients from Scotland and England. These findings make us hypothesize that maternal smoking has different effects on the risk of orofacial clefts.

Previous literature associated the use of drugs (especially phenytoin, phenobarbital, benzodiazepines, and corticosteroids) during pregnancy with CL/P occurrence; however, in the present study, these drugs were administered at low frequencies, and the most common drugs used were folic acid, iron, analgesics, antibiotics, and antihypertensives. Although folic acid was the most widely used drug, considering the whole sample, there was a low percentage of mothers on supplementation with this substance (24.3%). Higher folic acid supplementation during pregnancy was observed by McKinney et al.[40] in a study with 86 CL/P patients from Thailand (35.8%) and by Taghavi et al.[41] in a study with 300 CL/P patients from Iran with frequencies of 93.7% and 80.3% of folic acid and iron intake, respectively. Nevertheless, the effects of folic acid supplementation on orofacial clefts are paradoxical. While in the McKinney et al. (2013)[40] study the use of this supplement did not statistically decrease the risk of having an affected child, the Taghavi et al.[41] study showed a lower risk for orofacial clefts.

The limitations of the present study include the small cohort of patients enrolled, the study design as a descriptive rather than a case-control study, and the collection of data through interviews after the birth of the patients, which is more likely to be associated with decreases in the quality of data and with inaccurate answers due to forgetfulness or unrealistic responses as a result of being overcome with shyness. It is also important to mention that when conclusions about individual-level relationships are inferred from area-level analyses, there is a risk of committing an ecological inference fallacy, which is

one of the disadvantages of ecological studies, as is the case of the present study. However, ecological studies are important as they allow an initial examination of the status and needs of communities, especially of health status.[42]

Conclusions

This study provided an overview of several aspects related to the development and monitoring of CL/P patients, highlighting the risk factors and comorbidities presented by this population in a developing country. Most patients were male with CLP type and born of normal size and weight and presented few neonatal intercurrent events and had or have anemia, respiratory, and cardiovascular diseases as the main associated comorbidities. They also needed timely surgical rehabilitation and multidisciplinary care to stimulate their neuropsychomotor development. Other relevant findings were the considerable maternal exposure to alcohol, infections, smoking, and hypertension, as well as low supplementation of vitamins and minerals and use of analgesics, antibiotics, and antihypertensives during pregnancy. In addition, a high frequency of familial recurrence and mainly of parental consanguinity was evidenced in the studied population, especially in CLP patients. Knowledge of CL/P patient profiles is important to aid professionals with the better management and planning of local health services made available to CL/P patients. Furthermore, our findings reinforce the need for further confirmation of environmental risk factors associated with the development of orofacial clefts.

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