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Prevalence of cleft lip and palate and associated factors in Brazil's Midwest: a single-center study

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Abstract: The aim of this study was to evaluate the prevalence of cleft lip and/or palate (CL/P) and associated factors in patients treated at a referral service in Brazil's Midwest. Data were obtained from medical records on file between 2010 and 2017 for this epidemiologic and associational study. A descriptive analysis of the sociodemographic and clinical data was carried out, after which the data were analyzed using the chi-square test and Poisson regression with robust variance. A total of 1,696 medical records were eligible. The requests for rehabilitation were mainly for children in the early years of life, and were mostly for patients from low-income families in the state of Goiás. CL/P was more prevalent in its most severe morphological representation (cleft lip and palate), and the most frequently affected side was the left. Syndromic cleft was present in 4.1% of the cases, and the Pierre Robin sequence and Apert syndrome appeared more frequently. Adjusted multivariate Poisson regression showed an association between cleft palate and the presence of syndromes, since the prevalence was 2.33 times higher in this case than that of no syndrome. Cleft lip and palate were associated with males, whereas cleft palate was associated with females. This study highlights the importance of collecting and analyzing epidemiological data, managing health service planning, and allocating funds to assist cleft patients.

Keywords: Cleft Lip; Cleft Palate; Epidemology.

Introduction

Cleft lip and/or palate (CL/P) is the most prevalent congenital anomaly affecting the human face. It usually involves the lip, alveolar process, teeth and/or palate, with several degrees of severity.[1,2] Hence, some of the basic functions of individuals with CL/P may be affected, such as chewing, phonation, breathing and hearing. These people may also suffer a psychosocial impact and experience systemic health risks.[3,4]

CL/P is related to genetic and environmental risk factors, which characterize a multifactorial etiology.[5,6,7] The etiology and pathogenesis of CL/P have not yet been fully explained, owing to the complexity and diversity of the molecular mechanisms involved in embryogenesis.[6] It is estimated that the CL/P prevalence in low- and middle-income countries

is 1 in 730 children born[1], but too few populational surveys have been conducted in Brazil to confirm this figure.[8,9,10,11,12,13]

Several CL/P classification systems based on morphological and genetic aspects have been proposed.[6,9] The Spina et al.[14] classification commonly adopted in Brazil uses the incisive foramen as the anatomical reference. CL/P can appear in its isolated (or nonsyndromic) form when not associated with another physical and/or developmental anomaly, or in a combined form when associated with another congenital anomaly or syndrome.[6,15] It is estimated that nonsyndromic fissures are more prevalent (70.8%) than syndromic fissures (29.2%).[16]

Rehabilitation is always long-term, integrated and multidisciplinary, involving dentists, plastic surgeons, pediatricians, otorhinolaryngologists, psychologists and speech therapists.[17] Therefore, CL/P entails long, complex rehabilitation treatment that requires high monetary costs and highly complex care centers.

According to previous epidemiological studies, treatment charges range according to geographic distribution, ethnicity and methodology, without any absolute consensus.[11,18,19,20,21,22,23,24,25,26,27] In Brazil, there are thirty centers licenced by the Ministry of Health to treat CL/P. They are distributed according to the Brazilian regions: Southeast (n = 12), South (n = 8), Northeast (n = 5), Midwest (n =4), and North (n = 1). The Center for Rehabilitation of Cleft Lip/Palate, called CERFIS, is a public institution that is established under the National Health Service (SUS), and that operates out of the Hospital Estadual Materno-Infantil Dr. Jurandir do Nascimento, in Goiânia, state of Goiás. It is recognized as a referral service for the rehabilitation of subjects with orofacial clefts in the Midwest, since 1990. However, no study has yet been published on CERFIS patients. Thus, the aim of the present study was to evaluate the prevalence of CL/P patients treated at CERFIS, and associated factors.

Methodology

The study design was retrospective, cross-sectional and single-center, following STROBE guidelines.[28] The research protocol was approved by the Institutional Ethics Committee at the Federal University of Goiás, and the Hospital Estadual Materno-Infantil Dr. Jurandir do Nascimento, in compliance with national ethics regulations and the Declaration of Helsinki. The study sample consisted of medical records on file at CERFIS. The inclusion criteria stipulated patients with CL/P, whether syndromic or nonsyndromic, treated between January 2010 and February 2017. Medical records that had no established diagnosis of CL/P type, or that were materially damaged or illegible were excluded from the study.

Initially, two researchers (CF-P, LANB) were trained and calibrated by piloting 100 randomly selected medical records. The agreement resulted in "almost perfect" interexaminer agreement (kappa = 0.95). The data covered sociodemographic factors (sex, age, place of birth, residence, occupation, family income, family cases of CL/P and pregnancy complications) and clinical factors (CL/P type, presence of syndrome, major or minor associated defects, and treatments performed at CERFIS). Minor defects comprise morphological abnormalities with no significant aesthetic or functional damage, whereas major defects include microcephaly, microtia, syndactyly, hydrocephalus, and others that do not fit into the category of minor defects.[29] The clefts were classified according to the types described in the Spina et al.[14] classification, modified and updated by Silva Filho et al.[30] as cleft lip, cleft palate, cleft lip and palate or rare cleft, and sub-classified as complete or incomplete, and unilateral (right or left side), bilateral or median. Although the submucous cleft belongs to the CP group, it was quantified separately in the present study.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences PC version 22.0 (SPSS, Chicago, USA), and included frequency distribution and association tests. Associations between cleft type and the independent variables (sociodemographic and clinical factors) were determined using the chi-square test. All independent variables associated with the cleft type and with a *p*-value of less than or equal to 0.20 in the chi-square test were incorporated into the Poisson regression with robust variance, an option used to estimate the prevalence ratio (PR) in

cross-sectional studies, when the dependent variable is binary[31]. The magnitude of the association of each factor was assessed using both nonadjusted and adjusted prevalence ratios, respective confidence intervals (95%CI), and p-values (Wald test). Explanatory variables with a p-value of less than or equal to 0.20 in the bivariate analysis and those with theoretical relevance (irrespective of the p-value) were incorporated into the model. Variables were included one by one, and only those with a significance level of $p < 0.05$ were maintained in the final model. The significance level was set at 5%.

Results

A total of 3,594 medical records were on file at CERFIS, 1,803 of which referred to the treatment period from January 2010 to February 2017. In all, 107 medical records were excluded from the study, because they did not indicate the cleft type classification, leaving a total of 1,696 medical records that were analyzed.

Table 1 describes the sample characteristics, according to sociodemographic and clinical factors. Nonsyndromic CL/P was the most prevalent type of cleft, although the Pierre Robin sequence and the Apert syndrome were the most common combinations found in syndromic patients (Table 2). In terms of cleft type, the most severe morphological representation—cleft lip and palate (CLP)—was the most prevalent, and the left was the most frequently affected side (Table 3). Rare clefts were a minority, totaling 2% of the cases (Table 3).

In the adjusted multivariate regression, CLP prevalence was 26% (PR = 1.26; 95%CI: 1.14–1.40) higher in males than in females. Otherwise, cleft palate (CP) was more prevalent in females. There was an association between CP and the presence of a syndrome, in which case the prevalence was 2.33 times (PR = 2.33; 95%CI: 1.92–2.82) higher than when there was no syndrome. Cleft lip (CL) and CLP were more prevalent in nonsyndromic patients. The rare cleft group did not yield any significant results in the chi-square test, and only sex presented a $p < 0.20$ in the bivariate analysis. Consequently, a multivariate analysis could not be performed (Table 4).

Discussion

This is the most significant study on CL/P and associated factors in patients in Goiás and surrounding states. A total of 1,696 medical records registered at a referral center between 2010 and 2017 were evaluated. Two other studies were undertaken in the Midwest prior to this study.[19,25] However, they were restricted to two states, and the sample was limited. The first study was carried out in the state of Mato Grosso do Sul, and data were collected from the Craniofacial Anomaly Rehabilitation Hospital, in Bauru, São Paulo, for patients living in the state of Mato Grosso do Sul (n = 271), between 2003 and 2007.[25] The second study evaluated patients at a university hospital in Cuiabá, Mato Grosso (n = 313) between 2004 and 2007, and focused on the epidemiological profile without analyzing the associated factors.[19] Therefore, the present study is the most recent in-depth study conducted in the Brazilian Midwest, which used the multivariate model to test the association between exposure (risk factors) and outcome (cleft type).

As in other Brazilian studies, the highest frequency of cleft types was that of CLP, followed by CP, CL and, lastly, rare clefts.[20,22,23,24] The study found a greater likelihood of the bilateral type of CL and CLP occurring on the left side. The literature is in agreement on this point, and on the likelihood of a genetic influence.[5,12,24]

Complete CP—considered more severe than incomplete CP—was the most frequent subtype found in all the cases evaluated. Cymrot et al.[23] evaluated 551 children in a referral hospital in the Northeastern, and found that 128 of 130 cases of CP were the complete type. However, other Brazilian studies have reported a higher frequency of incomplete CP.[12,24] The hypothesis for a higher prevalence of complete CP can be explained by greater severity being related to a higher demand for treatment.

In terms of syndromic clefts, 70 patients (4.1%) were detected in the present study. Poisson regression results indicated that CL and CLP were associated with nonsyndromic CP, whereas the prevalence of syndromic CP was 2.33 times higher than nonsyndromic CP. Other studies also corroborated the

Table 1. Clinical characteristics of the sample (n= 1,696).

Variable	n (%)	Variable	n (%)
Sex		Family income (minimum wage)	
Male	913 (53.8)	< 2	446 (25.1)
Female	783 (46.2)	2 to 3	336 (18.9)
Age group (years)		> 3	220 (12.4)
Newborn	20 (1.2)	Not defined	694 (39.1)
0–6	466 (27.5)	Family cases of CL/P	
7–9	274 (16.2)	Yes	580 (32.2)
10–14	288 (17.0)	No	1,116 (61.9)
15–19	207 (12.2)	Pregnancy complications	
20–24	179 (10.5)	Yes	361 (21.3)
25–64	255 (15.0)	No	1,335 (78.7)
65 or more	6 (0.4)	Associated defects	
Absent data	2 (0.1)	Absent	1,551 (93.1)
Place of birth		Major	70 (4.1)
Goiás non-capital municipality	495 (29.2)	Minor	31 (1.8)
Brasília	51 (3.0)	Major and minor	16 (0.9)
Goiânia	467 (27.5)	Syndrome	
Aparecida de Goiânia	55 (3.2)	Present	70 (4.1)
Anápolis	106 (6.3)	Absent	1,626 (95.9)
Other Brazilian state capitals	20 (1.2)	Primary surgeries in CERFIS	
Other non-capitals (outside Goiás state)	158 (9.3)	Cheiloplasty	357 (21.0)
Absent data	344 (20.3)	Cheiloplasty and Palatoplasty	512 (30.2)
Residence		Cheiloplasty and Bone graft	20 (1.2)
Goiás non-capital municipality	604 (35.6)	Cheiloplasty and Rhinoplasty	2 (0.1)
Brasília	17 (1.0)	Palatoplasty	281 (16.6)
Goiânia	539 (31.8)	Not performed in CERFIS	524 (30.9)
Aparecida de Goiânia	146 (8.6)	Secondary surgeries in CERFIS	
Anápolis	102 (6.0)	Cheiloplasty	106 (6.25)
Other Brazilian state capitals	10 (0.6)	Palatoplasty	15 (0.9)
Other non-capitals (outside Goiás state)	58 (3.4)	Not performed in CERFIS	1,575 (92.85)
Absent data	220 (13.0)	Multidisciplinary treatment*	
Occupation		Dental	1,189 (70.1)
No professional training	793 (46.8)	Plastic surgery	1,622 (95.6)
Vocational degree	302 (17.8)	Speech therapy	1,562 (92.1)
First degree	57 (3.4)	Psychological	1,597 (94.2)
Soldier	14 (0.8)	Otorhinolaryngological	134 (7.9)
Civil servant	29 (1.7)	Nutritional	12 (0.7)
Student	38 (2.2)		
Absent data	463 (27.3)		

*Multidisciplinary team treatment was considered independently.

Table 2. Frequency of syndromes and other malformations (n= 70).

Syndrome/Malformation	n (%)
Pierre Robin sequence	38 (54.3)
Apert syndrome	7 (10.0)
Down syndrome - Trisomy 21	4 (5.7)
First arch syndrome	4 (5.7)
Van der Woude syndrome	3 (4.3)
Ectrodactyly	2 (2.8)
Edwards syndrome - Trisomy 18	2 (2.8)
Holoprosencephaly	2 (2.8)
Treacher Collins syndrome	2 (2.8)
Arthrogryposis	1 (1.4)
Asperger syndrome	1 (1.4)
Beckwith-Wiedemann syndrome	1 (1.4)
Cornelia de Lange syndrome	1 (1.4)
Inconclusive diagnosis	2 (2.8)

Table 3. Overall and group prevalence of the different types of oral cleft (n= 1,696).

Cleft type	n (%)
Cleft lip	409 (24.1)
Unilateral incomplete (right)	78 (4.6)
Unilateral incomplete (left)	153 (9.0)
Unilateral complete (right)	48 (2.9)
Unilateral complete (left)	66 (3.9)
Bilateral incomplete	39 (2.3)
Bilateral complete	18 (1.0)
Median incomplete	3 (0.2)
Median complete	4 (0.2)
Cleft lip and palate	788 (46.4)
Unilateral (right)	190 (11.2)
Unilateral (left)	349 (20.5)
Bilateral	249 (14.7)
Median	0 (0.0)
Cleft palate	467 (27.5)
Complete	377 (22.2)
Incomplete	74 (4.3)
Submucous	16 (1.0)
Rare cleft	32 (2.0)

higher frequency of syndromic cases associated with CP patients[6,12,19]. Unlike the present study, Monlleó et al.[29] found that the syndromic cleft group outweighed the nonsyndromic cleft group. However, the authors evaluated only 141 patients, and suggested that the results could be related to the broad definition criteria used for syndromes. In addition, they reported that syndromic cases were statistically associated with CP, as also indicated in our results.

Of the syndromes with known genetic causes associated with CL/P, the Pierre Robin sequence is commonly seen in the CP type, and is associated with an altered expression of the *SOX9* gene.[19,24,32] Among the syndromes or malformations identified in the present study, the Pierre Robin sequence represented 54.3% of all the cases of cleft patients and the Apert syndrome, 10%, as also reported in other studies.[19,24] Interestingly, Monlleó et al.[29] did not identify the Pierre Robin sequence in any of the 59.5% of syndromic patients in their sample. Tolarová and Cervenka[6] evaluated 4,433 cases and found that the Pierre Robin sequence represented 3.0% of the total sample. In the present study, the Pierre Robin sequence represented 2.24% of the total sample, but the previous study differed from ours in that it considered this sequence to be "nonsyndromic".[6]

In relation to sex, there was an association between CLP and males, and between CP and females; this corroborates recent studies on the epidemiological profile of clefts in South Africa and China.[33,34] These results were also similar to those for the Brazilian surveys conducted in the states of Alagoas, Ceará, Mato Grosso, Minas Gerais, Paraná, Recife, São Paulo and Sergipe.[12,19,20,22,23,27,29]

One likely explanation for the association of CP with females is that the secondary palate of the male human embryo is more advanced in the fusion process than that of the female during the critical periods of palate formation.[35] Since palatal fusion is delayed in the female embryo, pregnant women are subject to a longer period of susceptibility to teratogenic factors. On the other hand, a study in the Chilean population presented evidence of an association between nonsyndromic CLP and males, owing to a variation in the *MSX1* gene located in chromosome 4.[36]

Table 4. Univariate and multivariate Poisson regression for association between cleft type and associated factors (n= 1,696)

Variable	Cleft Type		X^2	Nonadjusted PR		Adjusted PR	
	Present	Absent	p-value	95%CI	p-value	95%CI	p-value
	n (%)	n (%)					
Cleft lip	n = 409	n = 1,287					
Sex							
Male	173 (42.3)	610 (47.4)	0.072	1.00	0.073		
Female	236 (57.7)	677 (52.6)		1.17 (0.98-1.38)			
Associated defects							
Absent	390 (95.4)	1189 (92.4)	0.095	1.00			
Major	9 (2.2)	61 (4.7)		0.52 (0.28-0.96)	0.038*		
Minor	8 (2.0)	23 (1.8)		1.04 (0.57-1.91)	0.887		
Major and minor	2 (0.5)	14 (1.1)		0.50 (0.13-1.85)	0.304		
Syndrome							
Absent	402 (98.3)	1224 (95.1)	0.005*	1.00	0.012*	1.00	0.012*
Present	7 (1.7)	63 (4.9)		0.40 (0.19-0.82)		0.40 (0.19-0.82)	
Pregnancy complications							
No	321 (78.5)	1014 (78.8)	0.896				
Yes	88 (21.5)	273 (21.2)					
Family cases of CL/P							
No	269 (65.8)	847 (65.8)	0.988				
Yes	140 (34.2)	440 (34.2)					
Cleft lip and palate	n = 788	n = 908					
Sex							
Male	316 (40.1)	467 (51.4)	< 0.0001*	1.00	< 0.0001*	1.00	< 0.0001*
Female	472 (59.9)	441 (48.6)		1.28 (1.15-1.42)		1.26 (1.14-1.40)	
Associated defects							
Absent	739 (93.8)	840 (92.5)	0.241				
Major	34 (4.3)	36 (4.0)					
Minor	10 (1.3)	21 (2.3)					
Major and minor	5 (0.6)	11 (1.2)					
Syndrome							
Absent	772 (98.0)	854 (94.1)	< 0.0001*	1.00	0.001*	1.00	0.001*
Present	16 (2.0)	54 (5.9)		0.48 (0.31-0.74)		0.49 (0.32-0.76)	
Pregnancy complications							
No	630 (79.9)	705 (77.6)	0.247				
Yes	158 (20.1)	203 (22.4)					
Family cases of CL/P							
No	514 (65.2)	602 (66.3)	0.643				
Yes	274 (34.8)	306 (33.7)					
Cleft Palate	n = 467	n = 1,229					

Continue

Continuation							
Sex							
Male	275 (58.9)	508 (41.3)	< 0.0001*	1.00	< 0.0001*	1.00	< 0.0001*
Female	192 (41.1)	721 (58.7)		0.59 (0.51-0.70)		0.61 (0.52-0.71)	
Associated defects							
Absent	421 (90.1)	1158 (94.2)	0.001*	1.00			
Major	25 (5.4)	45 (3.7)		1.33 (0.96-1.85)	0.078		
Minor	12 (2.6)	19 (1.5)		1.45 (0.92-2.27)	0.105		
Major and minor	9 (1.9)	7 (0.6)		2.11 (1.35-3.27)	0.001*		
Syndrome							
Absent	422 (90.4)	1204 (98.0)	< 0.0001*	1.00	<0.0001*	1.00	< 0.0001*
Present	45 (9.6)	25 (2.0)		2.47 (2.04-3.00)		2.33 (1.92-2.82)	
Pregnancy complications							
No	356 (76.2)	979 (79.7)	0.124	1.00	0.118		
Yes	111 (23.8)	250 (20.3)		1.15 (0.96-1.37)			
Family cases of CL/P							
No	312 (66.8)	804 (65.4)	0.590				
Yes	155 (33.2)	425 (34.6)					

*Significant difference; X^2: Chi-square test; PR: prevalence ratio; p: probability value; CI: confidence interval

As regards patient age, the most frequent age group for CP was 0 to 6 years. One possible reason is that children with CLP usually start primary CL surgery (cheiloplasty) during the first twelve months of life, and CP surgery (palatoplasty) up to eighteen months. Thus, early childhood is a phase of multidisciplinary treatment, involving plastic surgeons, oral and maxillofacial surgeons, otorhinolaryngologists, orthodontists, speech therapists, psychologists and other professionals.[17,18]

More than 90% of the CERFIS patients were followed up by plastic surgeons, speech therapists and psychologists, 70.1%, by dentists, and 0.7%, by nutritionists. This is because most patients underwent primary surgery and continued with complementary rehabilitation treatment. Despite the partially absent data (13%), patients came from different cities in Goiás (n = 852), its state capital (n = 539), and out of state (n = 85). In relation to family occupation, the prevalence of "no professional training" and a family income of fewer than 2 monthly minimum wages were reported. These results reinforce the importance of both CERFIS and the National Health Service to low-income patients and the local population, who live in cities with no referral service of cleft treatment.

In contrast to our results regarding the influence of pregnancy-related complications on cleft, other authors found incidences of alcohol consumption, smoking, hypertension, viral infections, low vitamin and mineral supplementation, use of analgesics, antibiotics and antihypertensive drugs in Brazilian women during pregnancy.[7] The high frequency of cases of CL/P in the family and parental consanguinity is also documented in the scientific literature.[7] These findings emphasize the importance of genetic counseling and prenatal care, especially before pregnancy and during its first quarter.

All the data collected and the possible scientific implications of the present study highlight some key points that can contribute to congenital surveillance in health systems, namely: diagnosis, classification and severity of craniofacial congenital anomaly, teratogenic factors, familial and pregnancy history, type of treatment, follow-up data, geographic

distribution, data storage, and others. In addition, the characterization of the patient profile treated at the National Health Service can indicate what type of funds, should be made available—like transport assistance—to patients who live in cities outside the state capital, for example.

There are some limitations to this study. Inmuch as the data was not electronic, there were readability issues. Some of the information reported may have also been incomplete or underreported. In addition, since the study was a secondary database, it was restricted to the information on the patient's medical record; hence, no data other than those already reported by the patient could be investigated. The methodological cross-sectional type design of the study is also not the most suitable for evaluating the etiopathogenesis of CL/P. Therefore, longitudinally designed epidemiological studies are recommended to reinforce the aims of this study, and contribute to the management and planning of health services.

Conclusions

In summary, this study highlights the contribution of a National Health Service public referral center to the rehabilitation of patients with CL/P in Brazil's Midwest. It also points out the importance of collecting and analyzing epidemiological data, managing health service planning, and allocating funds to assist cleft patients.

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