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ORIGINAL ARTICLE

Clinical and epidemiological study of orofacial clefts☆

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Abstract

Objective: Cleft lip with or without cleft palate (CL±P) or cleft palate (CP) are groups of malformations named orofacial clefts (OC), which are the second leading cause of birth defects. This study aimed to analyze clinical and epidemiological features of Brazilian patients with OC, studying cases treated in the reference center of the state of Paraná (PR).

Methods: 2,356 charts were reviewed and 1,838 were evaluated by the same clinical geneticist. Data were collected in the reference center, and compared with those of the Health Department of the state of Paraná. Clinical characteristics, presence of other anomalies, and birth prevalence were evaluated.

Results: 389 (21.2%) patients had CP, 437 (23.8%) had cleft lip (CL), and 1,012 (55%) had cleft lip and palate (CLP). Syndromic OC were identified in 15.3% of patients, 10.4% of patients with CL±P, and 33.9% of patients with CP. Common additional anomalies were: central nervous system, limbs, cardiovascular, and musculoskeletal defects. The number of syndromic cases was lower when clinical evaluation was performed by other medical specialists when compared to that of the clinical geneticist. Birth prevalence was 1/1,010 live births. Lack of notification with the national birth registry was observed in 49.9% of CL±P. The present data suggests a decrease of 18.52% in the prevalence of non-syndromic OC after folic acid fortification in Brazil.

Conclusion: Better understanding of clinical and epidemiological aspects of OC is crucial to improve the understanding of pathogenesis, promote preventive strategies, and guide clinical care, including the presence of clinical geneticists in the multidisciplinary team for OC treatment.

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PALAVRAS-CHAVE
Fissura orofacial;
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Estudo clínico e epidemiológico de fissuras orofaciais

Resumo

Objetivo: Fissura labial com ou sem fissura palatina (FL ± P) ou fissura palatina (FP) são grupos de malformações chamados fissuras orofaciais (FO) e são a segunda causa de defeitos congênitos. O objetivo do estudo foi analisar características clínicas e epidemiológicas de pacientes brasileiros com FO, estudando casos tratados no centro de referência do estado do Paraná (PR).

Métodos: Foram analisados 2.356 gráficos. Destes, 1.838 foram avaliados pelo mesmo geneticista clínico. Os dados foram coletados no centro de referência e analisados na Secretaria de Estado da Saúde do Paraná. Foram avaliadas as características clínicas, a presença de outras anomalias e a prevalência de nascimentos.

Resultados: No total, 389 (21,2%) pacientes apresentaram fissura palatina (FP), 437 (23,8%) apresentaram fissura labial (FL) e 1.012 (55%) apresentaram fissura labiopalatina (FLP). As FO sindrômicas foram identificadas em 15,3% dos pacientes, 10,4% dos pacientes com FL ± P, e 33,9% dos pacientes com FP. Anomalias comuns adicionais foram: sistema nervoso central, membros, sistema cardiovascular e sistema musculoesquelético. O número de casos sindrômicos foi menor nos centros em que a avaliação clínica foi realizada por outros especialistas, em comparação aos locais em que ela foi realizada por um geneticista clínico. A prevalência de nascimentos foi de 1/1.010 nascidos vivos. A ausência de notificação junto ao cartório de registro civil foi observada em 49,9% dos casos de FL ± P. No Brasil, nossos dados sugerem uma redução de 18,52% na prevalência de FO não sindrômicas após a fortificação com ácido fólico.

Conclusão: Um melhor entendimento dos aspectos clínicos e epidemiológicos das FO é fundamental para melhorar a compreensão de sua patogênese, promover estratégias de prevenção e promover orientações com relação a cuidados clínicos, com a presença de geneticistas clínicos na equipe multidisciplinar para tratamento de FO, por exemplo.

Introduction

Cleft lip with or without cleft palate (CL±P) and cleft palate (CP) are a group of malformations called orofacial clefts (OC), the second leading cause of congenital anomalies in live births.[1] It is estimated that 1 to 2/1,000 live births have OC.[2-4] Most patients with OC do not show any other abnormalities (non-syndromic OC), but a significant number (30% to 50%) have other malformations and can be part of a syndrome (syndromic OC).[2,3]

Non-syndromic OC is a group of malformations with multifactorial origin, in which genetic and environmental factors contribute to the etiology. Several studies have been conducted in order to expand knowledge of the etiology of isolated OC.[5] The knowledge of etiologic factors, prevalence, and variable expression of this phenotype and its associated malformations can help in clinical management and patient approach, as well as contribute to a better understanding of its etiology and pathogenesis.

Surveillance of congenital anomalies in Brazil is primarily performed through live birth declarations (LBDs). Since 1990, the Brazilian Ministry of Health established an information system on live births (ISLB) based on LBD.[6] There is an open field on the LBD inquires for any congenital malformation; if positive, thefield is filled out. This field is supposed to be completed by a pediatrician, but in practice that rarely occurs.[7] Also, until 2011, it could only be identified by a unique ICD-10 code. After 2011, the LBD allowed several ICD-10 codes, but this is still under implementation. Information based on LBD or ISLB is not reliable, due to lack of diagnosis, and omissions and misclassifications that occur both at the time of LBD completion and at the moment of entering and coding data.[7]

A second source of information for monitoring birth defects in Brazil is the network of hospitals working in collaboration with the Latin American Collaborative Study of Congenital Malformations (ECLAMC). However, Brazilian maternity hospitals that are part of ECLAMC cover less than 2% of births in the country.[8] According to ECLAMC, between the years 1982 to 2002, the birth prevalence of isolated OC was 1.5 per 1,000 live births.[9] A third source of information is derived from centers for orofacial treatment, but the data collected in hospitals and clinics where patients are treated are strongly influenced by the socioeconomic status of the population attending these centers, as well as by the severity of defects.

This study aimed to describe the main clinical and epidemiological aspects of OC in the population of the state of Paraná, Southern Brazil. The information provided may be helpful to other clinicians involved in the treatment of

children with OC and to improve public health efforts in this area.

Material and methods

This study was approved by the Institutional Review Board of the Pontificia Universidade Católica do Paraná (PUC/PR), protocol No. 1015 from December, 2007).

Patients with typical OC and born in the state of Paraná were included. Patients with atypical OC, submucosal cleft, and velopharyngeal incompetence were not included. Patients were selected in the the Centro de Atendimento Integral ao Fissurado Lábio Palatal (Assistance Center for Cleft Lip and Palate – CAIF), the state reference center for patients with craniofacial deformities. CAIF is an unit of the Health Department of Paraná (SESA), and is a member of the reference network for treatment of craniofacial deformities, created by the Brazilian Federal government in 1998 for accreditation of specialist services for treatment of craniofacial deformities.[10] All care is provided by the Brazilian Unified Health System (Sistema Único de Saúde – SUS), and social and organization contributions.

Medical charts were reviewed and the subjects were divided in two groups: group 1 - all patients attended to by the same clinical geneticist from January, 2006 to January, 2009, regardless of year of birth; and group 2 - all patients born between 2002-2008, and treated in CAIF.

Group 1 was the group used to evaluate the presence or absence of other anomalies associated with OC, since all patients were evaluated by the same clinical geneticist. Data were collected including age, gender, place of birth, type of OC, presence of other anomalies, and family history. Classification of syndromic OC was assigned in patients presenting with at least one other major anomaly, or three or more minor anomalies beyond the OC, in accordance with Saal.[1] The exception to this rule was the presence of a clearly known syndrome even without the major or minor anomalies, such as van der Woude syndrome. The associated anomalies were subdivided by systems: central nervous, urogenital, digestive, respiratory, musculoskeletal, limbs, cardiovascular, ocular, and integumentary. Also, the presence of intellectual disability was evaluated using the definitions of the American Association on Intellectual and Developmental Disabilities (AAIDD).[11]

Group 2 was established to estimate the birth prevalence of OC in Paraná. The charts of all 1,198 patients attended to at CAIF who were born between the years 2002 to 2008, whether or not evaluated by the clinical geneticist, were reviewed. All patients were evaluated by a plastic surgeon and/or a pediatrician. Data were recorded including age, gender, place of birth, type of OC, and the presence of other anomalies. Information also was collected through the ISLB in SESA, and compared with CAIF data. The birth prevalence was estimated by dividing the higher number of live births with non-syndromic OC by the total live births registered during the period. Data from SESA was collected in January of 2010. Data on live births after this date may have changed due to late registration of birth or late treatment at CAIF.

Descriptive analyses were conducted for the type of OC, age, gender, presence of associated anomalies, syndromic OC classification, and system involved in syndromic OC. To evaluate the association among the multiple parameters CL, CLP and CP, the chi-squared test was used. The odds ratio (95% confidence interval) was used to compare the type of OC and gender, and the birth prevalence of OC before and after wheat flour fortification with folic acid in Brazil. Values of $p < 0.05$ were considered statistically significant.

Results

The study included 2,356 patients: 1,838 from Group 1 and 1,198 from Group 2. The latter included 680 patients evaluated and 518 patients not evaluated by the clinical geneticist. Mean age of patients at the time of evaluation for Group 1 was 12.9 years and the median was 9.9 years, ranging from 2 days to 87 years old. Of the 838 patients with OC, 389 (21.2%) had CP, 437 (23.8%) had CL, and 1,012 (55%) had CLP. In patients with CL±P, 24.9% were bilateral: 30.1% of those with CLP and only 12.8% of patients with CL ($p < 0.001$. When unilateral, CL±P was preferentially on the left side in 65.9% ($p < 0.001$). In patients with CP, the proportion of incomplete fissure was higher, affecting 61.7% of cases ($p < 0.001$). Male gender was more prevalent in the total sample (55%, $p < 0.001$), comprising 60.4% of CL±P patients and 35% of CP ($p < 0.001$). When assessing CL±P, the ratio between males and females was 1.52 (95% CI: 1.37 to 1.69), while for CP the ratio was 0.54 (95% CI: 0.44 to 0.66) (Table 1).

282 patients had syndromic OC (15.3% of the sample): 10.4% and 10.3% of patients with CL and CLP, respectively, and 33.9% of patients with CP ($p < 0.001$ when comparing CL±P and CP, and no statistical difference for CL and CLP, Table 1). There was no significant difference between the syndromic diagnosis in cases with unilateral or bilateral OC (Table 2). Regarding gender and syndromic OC, it was observed that females were more associated with other anomalies than males in the total sample ($p = 0.021$). When analyzing OC types (CL±P and CP), 12.2% of females with CL±P had the diagnosis of syndromic OC, compared to only 9.1% of males ($p = 0.038$). This was reversed for CP, where syndromic cases were observed mainly among males (43.4% *versus* 28.9%, $p = 0.005$, Table 2).

Among all cases with syndromic OC, the most affected systems were: central nervous (33.3% of syndromic OC and 5.1% of the total sample), limbs (29.8% and 4.6%), cardiovascular (20.6% and 3.2%), and musculoskeletal (17.7% and 2.7%). Facial changes were observed in 59.6% of cases. Most patients (87.2%) had more than one affected system. Some degree of intellectual disability was observed in 49.32% of syndromic cases (7.99% of the total sample).

When selecting only the cases not evaluated by the clinical geneticist ($n = 518$), it was observed that the proportion of syndromic OC was 10.6% (24.4% for CP and 4% for CL±P, Table 1). Comparing this group with the group evaluated by the clinical geneticist, a difference was observed ($p < 0.001$, Table 1) in diagnosing syndromic OC, demonstrating

Table 1 Classification of orofacial clefts (OC) by severity, laterality, gender, and defect status.

Clinical presentation (patients evaluated by the clinical geneticist, n = 1,838)	CL n = 437 (23.8%)	CLP n = 1,012 (55%)	CP n = 389 (21.2%)
Bilateral	56 (12.8%)[a]	305 (30.1%)[a]	n/a
Unilateral	381 (87.2%)[a]	707 (69.9%)[a]	n/a
Unilateral, right	122 (32%)[b]	249 (35.2%)[b]	n/a
Unilateral, left	259 (68%)[b]	458 (64.8%)[b]	n/a
Complete	n/a	n/a	149 (39.3%)
Incomplete	n/a	n/a	240 (61.7%)
Male	258 (59.04%)[c]	617 (60.97%)[c]	136 (35%)[d]
Female	179 (40.96%)[c]	395 (39.03%)[c]	253 (65%)[d]
Non-syndromic	392 (89.7%)[e]	907 (89.6%)[e]	257 (66.1%)[e]
Syndromic			
Clinical geneticist	45 (10.3%)[e]	105 (10.4%)[e,f]	132 (33.9%)[e,f]
Pediatric/surgeon (n = 518)	5 (4%)[e,f]	9 (4%)[e,f]	41 (24.4%)[e,f]

CL, cleft lip; CL±P, cleft lip with or without cleft palate; CLP, cleft lip and palate; CP, cleft palate; n/a, not available.
[a]Chi-squared analysis comparing the proportion of uni and bilateral defects between CL and CLP ($p < 0.001$).
[b]Chi-squared analysis comparing the proportion of right and left involvement in unilateral CL±P ($p < 0.001$).
[c]Chi-squared analysis comparing the proportion of male and female gender between CL and CLP ($p < 0.001$).
[d]Chi-squared analysis comparing the proportion of male and female gender between CP ($p < 0.001$).
[e]Chi-squared analysis comparing the proportion of syndromic OC between CL±P and CP ($p < 0.001$). There was no difference in proportion of syndromic OC between CL and CLP
[f]Chi-squared analysis comparing the proportion of syndromic OC diagnosis between clinical geneticist and other medical specialists for CL±P and CP and ($p < 0.001$).

Table 2 Classification of syndromic orofacial clefts by laterality and gender.

Clinical presentation	CL±P, n = 150 (10.4%)	CP, n = 132 (33%)	Total, n = 282 (15.3%)
Bilateral	42 (11.6%)	n/a	42 (11.6%)[a]
Unilateral	108 (9.9%)	n/a	108 (9.9%)[a]
Male	80 (9.1%)[b]	59 (43.4%)[b]	139 (13.7%)[b]
Female	70 (12.2%)[b]	73 (58.9%)[b]	143 (17.3%)[b]

CL±P, cleft lip with or without cleft palate; CP, cleft palate; n/a, not available.
[a]Chi-squared analysis comparing the proportion of bilateral or unilateral CL±P not significant.
[b]Chi-squared analysis comparing the proportion of male and female total cases ($p = 0.021$); of male and female CL±P cases ($p = 0.038$); of male and female CP cases ($p = 0.005$)

a higher proportion in the group evaluated by the clinical geneticist.

Birth prevalence

Birth prevalence between the years 2002 and 2008 was 1/1,010 live births (1/1,334 for CL±P and 1/3,953 for CP). Data provided by SESA are included in the table, and when this data is compared with that from CAIF, a lack of notification of 49.94% of CL±P cases is evidenced (Table 3). There was no sub-notification for CP.

When comparing the prevalence of non-syndromic OC to the period of onset of wheat flour fortification with folic acid in Brazil (July, 2004), a decrease of 18.52% of OC cases can be verified (OR = 0.81, CI 0.72 to 0.93, $p = 0.002$). That reduction was mainly for CL and CP in males, whereas there were decreases of 33.59% and 39.66% of cases, respectively (Table 4).

Discussion

Clinical characterization

The proportion of OC type is similar and relatively constant in most of published studies.[2,12-14] The CL±P was unilateral in most cases. The left side was more affected, as reported in the literature.[7,12-14] The reason for this predilection is not understood. Patterns of laterality in defects are known to be seen in various types of anomalies such as microtia, clubfoot, and congenital dysplasia of the hip.[15] Groups of genes expressed asymmetrically during the early stages of embryonic development may contribute to this preference, however no study has demonstrated this yet.

Patients with CLP had bilateral involvement twice as often as those with CL. This has also been reported by other authors,[13,16] a fact that supports the hypothesis discussed in

Table 3 Non-syndromic orofacial clefts birth prevalence in Paraná – 2002 to 2008.

Year	SESA	Cases registered at CAIF	Sub-notification	Live births	Birth prevalence
2002				165,125	
Total	119	181	34.25%		1/912
CP	57	45	12.3%*		1/2,897
CL±P	62	136	54.41%		1/1,214
2003				157,333	
Total	121	166	27.11%		1/947
CP	41	34	17.07% *		1/3,837
CL±P	80	132	41.67%		1/1,191
2004				159,636	
Total	104	166	37.35%		1/962
CP	39	43	9.30%		1/3,712
CL±P	65	123	47.15%		1/1,297
2005				160,324	
Total	97	153	36.60%		1/1,047
CP	41	43	4.65%		1/3,728
CL±P	56	110	49.09%		1/1,457
2006				153,598	
Total	47	141	66.67%		1/1,089
CP	12	36	66.67%		1/4,266
CL±P	35	105	66.67%		1/1,462
2007				147,554	
Total	94	151	37.75%		1/980
CP	37	39	5.13%		1/3797
CL±P	57	112	49.11%		1/1322
2008				151,437	
Total	106	126	15.87%		1/1,201
CP	50	23	54% *		1/3,028
CL±P	56	103	45.63%		1/1,470
Total - 2002 to 2008				1,095,007	
Total	688	1084	36.53%		1/1,010
CP	277	263	5.05% *		1/3,953
CL±P	411	821	49.94%		1/1,334

CAIF, Centro de Atendimento Integral ao Fissurado Lábio Palatal; CL±P, cleft lip with or without cleft palate; CP, cleft palate; SESA, Health Department of the State of Paraná.
*There was no subnotification.

some studies that CL and CLP are pathogenetically distinct and should be analyzed separately.[17]

Most patients with CL±P in this study were male, which is consistent with other reports.[2,12-14] According to Croen et al.,[3] CP is more frequent in females, a finding also observed in the present study. Gender-dependent susceptibility of OC is not well understood. According to Blanco et al.,[18] susceptibility of males to CL±P appears to be, at least partially, a consequence of the variation of the *MSX1* gene, located on chromosome 4. The hypothesis that genes related to the X chromosome should have an important role in the etiology of OC was also raised, but not confirmed.[19] Regarding CP, it is proposed that the timing of embryonic closure of the secondary palate is the reason for gender differences.[20] In males, the merging and closing of the secondary palate occurs earlier than in females. This fact may have some relation to the increased incidence of CP in women.

Syndromic orofacial cleft

Data from other studies show great variability in the classification of syndromic cases, from 4.3% reported by Jensen et al.[21] to 63.4% reported by Shprintzen et al.[22] This discrepancy is mainly due to the differences between the methodologies employed in classification and the lack of consensus on what should be considered a congenital defect associated with OC. Other factors are the training and experience of the professional responsible for the physical examination, and the fact that many authors do not report all individuals born in a particular location, instead only patients referred for treatment in a certain unit.[2,4]

An important finding was the difference observed in the presence of syndromic OC in relation to gender. Females with CL±P have more associated anomalies than males. This finding is the opposite for CP, in which the proportion

Table 4 Non-syndromic orofacial clefts birth prevalence before and after wheat flour fortification with folic acid in Brazil (2002 to 2004 vs. 2006 to 2008).

	2002 to 2004	2006 to 2008	Decrease (%)	Odds ratio	95% CI	
					Inferior	Superior
Total OC	513	418	18.52	0.81	0.72	0.93
CL±P	391	320	18.16	0.82	0.71	0.95
CP	122	98	19.67	0.80	0.62	1.05
CL	191	149	21.99	0.78	0.63	0.97
Male	131	87	33.59	0.66	0.51	0.87
Female	60	62	-3.33	1.03	0.72	1.47
CLP	200	171	14.50	0.86	0.70	1.05
Male	130	114	12.31	0.88	0.68	1.13
Female	70	62	11.43	0.89	0.63	1.25
CP	122	98	19.67	0.80	0.62	1.05
Male	58	35	39.66	0.60	0.40	0.92
Female	64	63	1.56	0.98	0.70	1.39

95% CI, 95% confidence interval; CL, cleft lip; CL±P, cleft lip with or without cleft palate; CLP, cleft lip and palate; CP, cleft palate; OC, orofacial clefts.

of males was more associated with other anomalies. This can be explained by the threshold theory of multifactorial disease, which observes that when a defect is less prevalent in a specific gender, abnormalities in patients of this gender are more severe and complex.

Regarding the involvement of other systems, and considering all cases with syndromic OC, the most affected systems were: central nervous, limbs, cardiovascular, and musculoskeletal. Similar results were observed by Genisca et al.[13] and Stoll et al.[2] Most patients had more than one system affected, as also observed by Shprintzen et al.[22]

Some degree of intellectual disability was observed in half of patients with syndromic OC. Strauss and Broder[23] also observed a high prevalence of intellectual disability among individuals with OC (10.1%), mainly mild and moderate intellectual disability (42.8% and 44.6% of this population, respectively).

Regarding the classification of syndromic cases, a limitation of the study was the lack of karyotype in the majority of cases. This results from the lack of availability of such analysis through the public health system in this institution and in most public healthcare centers in Brazil. This is one factor that made the percentage of patients with chromosomal anomalies in the present study significantly lower than that reported by Tolarova and Cervenka[14] and by Stoll et al.[2] (4% *versus* 22.9% and 21.3%, respectively).

When comparing the percentage of syndromic OC diagnosis made by a clinical geneticist and by another medical specialist, it was observed that the diagnosis increases from 10.6% to 15.3%. The presence of a clinical geneticist is one of the international standards for care of OC patients.[24] According to Lin et al.[25] a clinical geneticist trained in dysmorphology is able to differentiate the importance of facial features, body habitus, and development, which are essential for the diagnosis of cases with multiple congenital anomalies. Despite the importance of the presence of a medical geneticist on the team, Monlleó et al.[10] observed that they were present in only 50% of the reference centers for the treatment of craniofacial deformities in Brazil. Their presence was even less common among other specialties of rehabilitation, surgery, and special care.

Birth prevalence

This study represents the first effort to estimate the birth prevalence of OC in Paraná. According to the CAIF records, the birth prevalence in Paraná was estimated in 1 per 1,010 live births (0.99/1,000 births). Similar data were observed by Genisca et al.[13] The prevalence of CL±P was 0.8/1,000 births and that of CP was 0.4/1,000 births. Tolarova and Cervenka[14] observed a prevalence of 0.77/1,000 for CL±P and 0.31/1,000 for CP. In Brazil, few studies have been conducted with this goal. Rezende and Zollner[26] observed a birth prevalence of 1/672 live births in the city of Taubaté/São Paulo, and Nunes[7] found 1.35/1,000 live births in Campos dos Goytacazes/Rio de Janeiro.

A significant sub-notification to the SESA/ISLB was observed. The fact that one in two live births with OC was not notified is worrisome, and this was surprisingly observed only for CL±P, an external anomaly easily observed at birth and sometimes even prenatally.[27] Furthermore, this value may be underestimated, since some cases may not have been treated in CAIF. This lack of notification was not observed for CP, which is also unexpected, because CP is more difficult to diagnose at birth. Kubon et al.[28] reported a lack of registration in Norway, and observed it was directly linked to the severity of the OC. These notified CP cases could be incorrectly classified, an observation made by Nunes,[7] who found almost 100% of wrongly classified cases.

Some recent publications suggest the importance of folic acid for the prevention of OC, but it is still controversial.[9,29-31] In Latin America, some countries have adopted a policy of

food fortification with folic acid in order to reduce the incidence of neural tube defects. Brazil, through a resolution of Ministry of Health, made mandatory the fortification of wheat flour with 1.5 mg/kg of folic acid from July 1, 2004 (RDC No.344 of 13/12/2002). The incidence of non-syndromic OC patients treated at CAIF was evaluated and compared to the period of onset of wheat flour fortification with folic acid in Brazil; a decrease in cases of non-syndromic OC was observed, mainly for males with CL and CP. Tolarova was the first author to demonstrate the effect of folic acid on the incidence of OC;[31] she showed a reduction of 65.4% in the recurrence of non-syndromic CL±P after multivitamin supplementation associated with high doses of folic acid (10 mg). A meta-analysis by Johnson and Little[32] observed that multivitamins during the periconceptional period decrease the risk of CL±P. However, there was no significant evidence showing that folic acid alone could decrease this risk. Recently, Lopez-Camelo et al.,[9] through data from ECLAMC, evaluated the effect of food fortification with folic acid on the incidence of congenital anomalies in Brazil, Argentina, and Chile. There was no significant change in the number of cases of OC in any country. In the present study, it appears that wheat flour fortification with folic acid decreased the number of OC cases in Paraná. However, other variables that could also influence the incidence and recurrence of OC were not evaluated.

Based on the present study, it can be estimated that approximately 20 new cases of OC are born in the state of Paraná per month, and most of them are not registered at the corresponding national agency. Most of these patients have non-syndromic OC, and evaluation by a clinical geneticist could improve the diagnosis of syndromic cases.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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