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Caracterização clínica de famílias de pacientes com fissuras labiopalatais não-sindrômicas

Clinical characterization of families of patients with non-syndromic cleft lip and palate

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ABSTRACT

Introduction: Cleft lip and/or palate is the most common congenital craniofacial anomaly, with multifactorial causes. The analysis of cases in multiplex families - with more than 1 affected family member, other than 1st degree - can lead to a better delimitation of genetic causes, especially those caused by rare variants.

Objective: Identify the most prevalent types of cleft lip and palate in patients treated at a specialized service, verifying familial recurrence and the presence of other comorbidities in families.

Method: Retrospective, cross-sectional study of medical records analysis. The medical records of 50 patients with cleft lip and palate were selected by type of cleft, family history and concomitant conditions with other comorbidities.

Result: 60% had cleft lip and palate; 30% had only cleft lip and 8% had only cleft palate. Of the cleft lip and palate, 47.8% were unilateral on the left, 15.2% unilateral to the right and 34.8% bilateral. Regarding the location in the incisive foramen, 32% were pre, 8% post and 58% trans. Regarding biological gender, 44% were men and 56% women. In family members, it was observed that 32 families had cleft lip and palate in second and third degree members, characterizing them as multiplex families.

Conclusion: The profile of the patient with cleft lip and palate is that of a woman with unilateral cleft lip and palate on the left and incisive transforamen. In families, it was observed that 64% of those analyzed have multiplex families.

KEYWORDS: Cleft palate. Cleft lip. Genetic variation. Heredity

RESUMO

Introdução: Fissura de lábio e/ou palato é a anomalia craniofacial congênita mais comum, com causa multifatorial. A análise de casos em famílias multiplex - com mais de 1 familiar afetado, sem ser de 1º grau - pode levar à melhor delimitação de causas genéticas, especialmente as causadas por variantes raras.

Objetivo: Identificar os tipos de fissuras labiopalatais mais prevalentes em pacientes atendidos em um serviço especializado, verificando a recorrência familiar e a presença de outras comorbidades nas famílias.

Método: Estudo retrospectivo, transversal, de análise de prontuários. Foram selecionados prontuários de 50 pacientes com fissuras labiopalatais por tipo de fissura, histórico familiar e concomitância com outras comorbidades.

Resultado: 60% eram portadores de fissura labiopalatal; 30% possuía apenas fissura labial e 8% de fissura apenas de palato. Das fissuras labiopalatais, 47,8% eram unilaterais à esquerda, 15,2% unilaterais à direita e 34,8% bilaterais. Em relação à localização no forame incisivo, 32% eram pré, 8% pós e 58% trans. Quando o gênero biológico, 44% eram homens e 56% mulheres. Nos familiares, observou-se que 32 famílias apresentavam fissura labiopalatal em membros de segundo e terceiro graus, caracterizando serem famílias multiplex.

Conclusão: O perfil do paciente portador de fissura labiopalatal é de mulher com fissura labiopalatina unilateral à esquerda e transforame incisivo. Nas famílias, observou-se que 64% dos analisados possuem famílias multiplex.

PALAVRAS-CHAVE:Fenda palatina. Fenda labial. Variação genética. Hereditariedade

Central Message

The epidemiological and clinical analysis of cases with multiplex families - with more than 1 affected member that is not a 1st-degree kinship - can lead to a better delimitation of possible genetic causes of cleft lip and palate, as well as answer questions related to the diagnosis and prognosis of patients and clarify the presence of rare pathogenic variants and risk of recurrence. This study shows the data from a representative sample of carriers.

Perspective

The existing discrepancies highlight the variability in the distribution of fissures between genders and families, raising the need for better understanding through further research. There is still little evidence to understand the underlying influences and genetic factors (genetic variants) that may be involved in causing these fissures.

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INTRODUCTION

Cleft lip (CLF) with or without extending to the palate (CL/P), which characterizes the orofacial cleft group, is a common congenital craniofacial anomaly. The incidence of cleft palates is approximately 1:100 live births and cleft palate (PF) may be present in 1:2500 births. The presence of these malformations is more prevalent in people with oriental ethnicity, followed by Afro-descendants. Comparing genders, they are more frequent in men, while in women PFs are the predominant ones, in a ratio of 2:1, since in the latter the process of palate fusion occurs later.[1]

The anatomical division of the clefts is based on the distinct developmental origin of the lip and the primary and secondary palates.[2] In addition to the anatomical classification, one of the most commonly used to describe the type of orofacial cleft is the classification proposed by Spina (1973)[3], which uses the incisor foramen as a reference point. It is divided into 4 cleft groups: Group I - pre-incisive foramen, labials with or without alveolar cleft, unilateral (total or partial), bilateral (total or partial) or median (total or partial); Group II - incisive, labial, alveolar and palatine transforamen, unilateral (right or left) or bilateral; Group III - total or partial palatine incisor postforamen; Group IV - rare facial, oblique (oro-orbital), transverse (oro-auricular) and lower lip cleft.

FL/P includes both forms in which it is only syndromic part, inherited as a monogenic Mendelian disorder or caused by chromosomal disorders, and non-syndromic or idiopathic ones.[1] The latter have a multifactorial origin, with genetic and environmental factors contributing to their cause.[4]

Thus, the epidemiological and clinical analysis of cases with multiplex families - families with more than 1 affected member that is not a 1st degree kinship - can lead to a better delimitation of possible genetic causes of CL/P, as well as answer questions related to the diagnosis and prognosis of patients and clarify the presence of rare pathogenic variants and risk of recurrence.

The objective of this study was to identify the most prevalent types of CL/P clefts in patients treated at a specialized service, verifying the recurrence and presence of other comorbidities in families.

METHOD

This study was approved by the National Research Ethics Committee (CONEP) under opinion No. 5.293.904 (CAAE 4619221.6.0000.5225). This is a retrospective and cross-sectional analysis of medical records carried out at a reference center for the treatment of cleft lip and palate in the city of Curitiba, PR, Brazil.

The sample consisted of 50 patients with CL/P who had their medical records analyzed, regardless of age group, with non-syndromic CL/P, who were still under follow-up. Medical records with syndromic clefts and those with discharged patients were excluded. The variables analyzed in the medical records were gender, type of cleft, family history, and clinical alterations present in the patients and their families.

RESULT

Of the 50 patients, 44% were men and 56% were women. Regarding the types of clefts, 60% had CL/P, 30% FL and 8% FP. There was 1 patient whose medical record did not have the type of cleft reported. Regarding laterality, approximately 47.8% were unilateral on the left, 15.2% unilateral on the right, and 34.8% bilateral. A patient did not have the laterality reported. Of the 15 cases of CL, 66.7% presented unilaterally on the left, 20% unilaterally on the right, and 13.3% bilaterally. Of the 30 cases of CL/P, 16.7% were unilateral on the right, 40% on the left, and 43.7% were bilateral (Table 1). Regarding location, 32% were pre-incisor foramen, 8% post-incisive, and 58% trans. Of the 4 postforamen cases, 3 were complete and 1 incomplete. In 1 patient, there was no information.

TABLE 1 — Classification of cleft lip and palate according to laterality and gender

Clinical presentation (n=50*)	FL (n=15)	FL/P (n=30)	FP (n=4)
Bilateral	2	13	-
Unilateral	13	17	-
Unilateral to the left	10	12	-
One-sided right	3	5	-
Complete	-	-	3
Incomplete	-	-	1
Female	8	18	2
Male	7	12	2

*=1 patient with no information; FL= cleft lip; FL/P=labia palatine; FP=cleft palate

In the analysis of family members, 59 members with CL/P were identified, 11 of whom were second-degree relatives, 31 third-degree relatives and 1 fourth-degree relative, characterizing multiplex families in 72% of the cases; 4 were sisters, 3 were brothers of the Probands, 6 were mothers, 1 was father, and 2 was sons of the Proband. In addition, 2 cases of CL were identified, 1 in the mother of the proband and 1 in the father. In addition, there were 6 cases of PF, with 5 in a third-degree relative, 1 case in the mother and 1 in the father.

When the presence of comorbidities in family members was analyzed, it was found that Keith's scar was the most reported (10%), followed by heart disease with 3 (6%, Table 2). Among the 50 families, only 1 was found to have consanguinity.

TABLE 2 — Main comorbidities found in families

Sickness	% of comorbidities
Cleft lip and palate	78%
Abortion	16%
Cleft palate	12%
Keith's scar	10%
Keith's scar	10%
Dizygotic twins	8%
Cardiopathy	6%
Cleft lip	4%
Less severe gum fissure	2%
Mental retardation	2%
Limb deformity	2%
Phenylketonuria	2%
Stillbirth	2%
Glaucoma	2%
Bacterial meningitis	2%
Hemangioma	2%
Microcephaly	2%
Kidney disease	2%
Hemolytic disease of the newborn	2%
Bronchiectasis	2%
Cranial malformation	2%
Throat cancer	2%
Body hemihypertrophy	2%
Atrophy of the esophagus	2%

DISCUSSION

Of the clefts, the most frequent were CL/P.[5-7] Regarding laterality, there was a predominance of unilateral laterality on the left, followed by bilateral and right side in a lower percentage.[8] However, the reason for the higher frequency of this handedness is still unknown; but, according to Souza and Raskin[7], groups of genes expressed asymmetrically during the earliest stages of embryonic development may contribute to this preference, although no clinical study has yet demonstrated this fact.[7]

In this study, it was observed that CL/P is more prevalent in women, although authors have shown the opposite: 69.6% in men.[9] In addition, while this analysis showed a higher occurrence of CL in women, Méndez et al.[10] in 2023 identified that, although cleft palate was more frequent in women, CL and CL/P predominated in men.[10] Regarding PF, an equal proportion was found between the sexes, which suggests a more balanced distribution compared to previous studies.[9] These discrepancies highlight the variability in the distribution of fissures between the sexes and underline the need for further research to understand the influences underlying these differences and the genetic factors (genetic variants) involved in their cause. It was observed that transforamen clefts accounted for more than 50% of the cases when compared to pre- and post-cleft fissures, reinforcing preexisting data.[8]

Regarding the presence of comorbidities in the family members of the affected individuals, only 1 family among the 50 analyzed had a history of cancer, which was throat cancer. This finding differs from other authors[11,12] who report coexistence of the disease - colon, brain, leukemia, breast, prostate, skin, lungs and liver - more frequent in relatives of those with non-syndromic CL/P, when compared to the normal population.

Multiplex families are important for defining the genetic cause of clefts, since they are the object of study to determine the presence of rare genetic variants, through exome sequencing of carriers and their families. Bureau et al.[11] identified rare variants in a list of candidate genes for FL/Ps including CDH1, FGF8, FGFR4, TRPS1 and FTCD through whole-exome sequencing analysis of affected individuals from multiplex families. Thus, the importance of these families for screening rare causal variants using whole exome sequencing is shown.[12]

CONCLUSION

The profile of the CL/P patient is a woman with a complete unilateral left incisor transforamen. The analysis of family members revealed that 59 cases of CL/P were identified, distributed in different degrees of kinship, in addition to specific cases of CL and PF, mostly in 1st degree relatives, such as the parents. Regarding comorbidities, Keith's scar and heart diseases were the most frequent. Familial recurrence of CL/Ps occurred in 59 family members, 72% of whom came from multiplex families.

Author contributions

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