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ORIGINAL

Genetic factors associated with cleft lip and palate in children at the "William Soler" hospital, 2021 to 2022

Factores genéticos asociados a la fisura labiopalatina en niños del hospital "William Soler", 2021 a 2022

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ABSTRACT

Introduction: cleft lip and palate are common congenital anomalies and the etiopathogenesis is not well understood, being fundamentally associated with polygenic or multifactorial inheritance. In nonsyndromic oral clefts, the genetic condition represents around 25 % of cases.
Objective: to identify the genetic factors associated with cleft lip and palate.
Method: descriptive, cross-sectional and retrospective study of 104 patients treated for congenital cleft lip and palate in the Maxillofacial Surgery department of the William Soler Ledea Pediatric Hospital from January 2021 to December 2022. The variables studied were: sex, form of presentation of the cleft, isolated congenital defects, previous siblings, intergenetic period, history of family members with congenital malformations, consanguinity of the parents and abortions.
Results: the patients presented with an equal distribution by sex (p=0,890), isolated clefts (90,4 %) occurred regardless of sex. The presence of previous siblings (59,6 %) was significantly associated (p=0,0084), as were a history of family congenital malformations (36,5 %) of second degree consanguinity (50 %), and previous abortions (50 %).
Conclusions: The children studied with cleft lip and palate follow a homogeneous distribution by sex and only a small number presented multiple congenital defects. Slightly more than a third were associated with multiparous mothers, with a high frequency of previous abortions, and evidence of a history of familial congenital malformations, mainly of second degree consanguinity through the maternal line.

Keywords: Labiopalatine Cleft; Congenital defect; Inheritance.

RESUMEN

Introducción: las fisuras labiopalatinas son anomalías congénitas comunes y la etiopatogenia no está bien esclarecida, se asocia fundamentalmente con la herencia poligénica o multifactorial. En las fisuras orales no sindrómicas, la condición genética representa cerca del 25 % de los casos.
Objetivo: identificar los factores genéticos asociados a la fisura labiopalatina.
Método: estudio descriptivo, transversal y retrospectivo en 104 pacientes atendidos con fisura labiopalatina

congénita en la consulta de Cirugía Máxilofacial del Hospital Pediátrico William Soler Ledea en el periodo de enero 2021 hasta diciembre 2022. Las variables estudiadas fueron: sexo, forma de presentación de la fisura, defectos congénitos aislados, hermanos anteriores, periodo intergenésico, antecedentes de familiares con malformaciones congénitas, consanguinidad de los padres y abortos.
Resultados: los pacientes se presentaron con igual distribución por sexo (p=0,890), las fisuras aisladas (90,4 %) ocurrieron independientemente del sexo. La presencia de hermanos anteriores (59,6 %) significativamente (p=0,0084), y antecedentes de malformaciones congénitas familiares (36,5 %) de segundo grado de consanguinidad (50 %), y abortos anteriores (50 %).
Concusiones: los niños estudiados con fisura labiopalatinas siguen una distribución homogénea por sexo y solo una pequeña cantidad presento defectos congénitos múltiples. Algo más de un tercio se asociaron a madres multíparas, *con* alta frecuencia de abortos anteriores, y evidencias de antecedentes de malformaciones congénitas familiares, principalmente de segundo grado de consanguinidad por vía materna.

Palabras clave: Fisura Labiopalatina; Defecto Congénito; Herencia.

INTRODUCTION

Cleft lip and palate (CLP) is the most common craniofacial congenital disability. It has a worldwide incidence of approximately 1 in 700 live births.

The etiopathogenesis of cleft lip and palate is primarily associated with polygenic or multifactorial inheritance, as it is related to the result of complex interactions between a variable number of "minor" genes that act additively (polygenic), generally with difficult-to-identify action and number, broadly referred to as genetic predisposition with usually unknown environmental factors. This particular mode of inheritance has been called multifactorial and does not follow the basic patterns of Mendelian laws.[1,2]

The genetic condition accounts for about 25 % of cases of non-syndromic oral clefts.[3,4] Genomic association studies have detected up to 46 associated genes or loci, with the IRF6 gene having the strongest association in different populations.[5]

Previous studies have been conducted in Cuba showing the epidemiology and clinical characterization of FLP; however, research linking the role of genetics in the onset of this congenital disability is scarce and outdated, which motivated this study intending to identify the genetic factors associated with cleft lip and palate in children at the William Soler Hospital in the period 2021-2022.

METHOD

A descriptive, cross-sectional, retrospective study was conducted. The population consisted of 104 patients treated for congenital cleft lip and palate at the Maxillofacial Surgery Clinic of the William Soler Ledea Pediatric Hospital between January 2021 and December 2022, of both sexes and with prior parental consent to participate in the research.

The variables reviewed were: sex, form of presentation of the cleft (isolated and multiple congenital disabilities), isolated congenital disabilities, previous siblings, intergenetic period, family history of congenital malformations: first degree (parents and siblings), second degree (uncles, grandparents), and third degree (great-grandparents, cousins), consanguinity of the parents, and abortions. A database was created in Excel, and the data were summarized using absolute frequencies and percentages. The chi-square test of independence was used to identify the relationship between variables, which was considered valid if $p < 0,05$. The PubMed/Medline, Lilacs, and Cumed databases were used to search for information, as well as the Google Scholar search engine. The research project was approved by the institution's Ethics Committee for Health Research and the Scientific Council. This research strictly followed ethical precepts relating to the researcher and those relating to research design, reasonable practice procedures, and data care (anonymity, confidentiality, and security).

RESULTS

Table 1. Cleft lip and palate according to sex and form of presentation of the cleft.

Presentation of the fissure	Female Sex		Masculine Sex		Total		Dependency relationship*
	n	%	n	%	n	%	
Isolated	48	46,2	46	44,2	94	90,4	x2=0,072
Multiple congenital defects	5	4,8	5	4,8	10	9,6	p=0,788

Note: n=104. *x2: Corrected chi-square independence (Yates correction).

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Isolated cleft lip and palate were present in 90,4 % of patients, compared with 9,6 % with multiple congenital disabilities; there was no evidence of a relationship between the forms of presentation of CLP and sex (p=0,788). The ratio of females to males with isolated and multiple clefts was 1:1.

Table 2. Cleft lip and palate according to isolated congenital defects

Isolated congenital defects	n	%
Cardiovascular malformations	18	40,0
Malformations of the osteomyoarticular system	9	20,0
Ophthalmic malformations	5	11,1
Ear malformations	4	8,9
Other malformations	9	20,0
Total	45	43,3

Table 2 shows that 43,3 % of patients had congenital defects isolated to cleft lip and palate, with cardiovascular defects being the most common at 40 % and the rest ≤20 %.

Table 3. Patients with cleft lip and palate according to previous siblings and intergenital space

Previous siblings	n	%	Intergeneric space (years)			
			Average	ED	Minimum	Maximum
No	41	39,4*	-	-	-	-
Yes	63	60,6*	5,3	7,2	0	27
One	40	63,5	7,1	5,4	0	19
Two	16	25,4	6,5	4,8	1	19
Three	4	6,3	8,4	5,8	2	17
Four	2	3,2	14,5	0,7	14	15
Five	1	1,6	8,0	-	-	-

Note: n=104. * Comparison of proportions (Z): p=0,0084. DE: standard deviation

Table 3 shows that 60,6 % of patients had previous siblings. It is significant that of the total number of mothers with prior pregnancies, 36,5 % were multiparous, which differs significantly from the proportion of patients without previous siblings (39,4 %), given p=0,0084; with an intergenetic mean of 5,3 years (variable at 7,2 years), a minimum of less than one year and a maximum of 19 years.

Table 4. Patients with cleft lip and palate according to family members with congenital malformations and degree of consanguinity

Family members with congenital malformations	n	%
No previous incidents	66	63,4
With a history (degree of consanguinity)	38	36,5
First grade	11	28,9
Second grade	19	50,0
Third grade	8	21,1

Table 4 shows that 36,5 % of patients with FLP had relatives with congenital malformations, mainly related to second-degree consanguineous relatives (50 %).

Congenital malformations were more common among maternal grandparents than paternal grandparents, while the opposite was true for uncles and aunts. In general, the maternal and paternal contributions across different degrees of consanguinity were similar.

It is worth noting that there were two previous siblings with congenital malformations, one of whom was a twin.

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Table 5. Patients with cleft lip and palate according to parental consanguinity and previous abortions

Parents	Statistics	
No parental consanguinity	104	100,0 %
Previous abortions	52	50,0 %
One	26	50,0 %
Two	10	19,2 %
Three and more	16	30,8 %

Table 5 shows that no parents with consanguinity were found and that 50 % of mothers had had previous abortions. Half of them had two or more abortions before the birth of the child with CLP.

In the specific analysis of children with cleft lip and palate with multiple congenital disabilities (n=10), half of the mothers had previous abortions, and 1/4 had previous siblings. Half had first- and second-degree relatives with congenital malformations on the maternal side. Three-quarters of these children had other congenital anomalies.

DISCUSSION

In this study, the gender distribution of children with CLP was homogeneous, with a male-to-female ratio of 1:1. However, the literature states that the ratio of males to females with cleft lip and palate is up to 7:3. [6] In a study conducted at the Hermanos Cordové University Pediatric Hospital in Manzanillo, Granma, on 142 children with cleft palates between 1986 and 2013, a significant predominance of males (n= 103, 72,5 %) over females was reported.[7]

As documented in the literature, males are more affected by cleft lip and palate than females.[7,8] Godoy et al.[9] make the caveat regarding incidence according to the cleft's type and form of presentation. The incidence of cleft lip is higher in males and cleft palate in females; isolated cleft lip accounts for 21 %, isolated cleft palate for 33 %, and both clefts simultaneously for 46 %. Isolated cleft palate is more common in females.[10]

Although isolated CLF predominated over cleft associated with multiple congenital disabilities, the genetic details of the latter were studied in greater depth. These children were characterized by mothers with previous abortions (between two and four), relatives with congenital malformations (first and second degrees), children with other congenital malformations (cardiovascular, osteoarticular, ophthalmic, auricular, and others), and previous siblings (one of them a twin).

In the small group of children with multiple congenital disabilities, the following syndromes were detected: DiGeorge, Larsen, EEC, pigmentary incontinence, Hay-Wells, and Pierre Robin sequence.

It is reported that in 29 % of cases of cleft palate, there are associated anomalies or syndromes. Up to 400 syndromes include cleft as a component of the congenital disability. The most common are chromosomal abnormalities (Down syndrome, Edwards syndrome, Patau syndrome, among others), non-Mendelian genetics (Pierre Robin sequence, Golderhar syndrome), and Mendelian alterations.[11]

Approximately 1 in 4000 children are born with 22q11.2 deletions (the most common human microdeletion syndrome), most of whom are identified as DiGeorge or velocardiofacial syndrome, which was identified in the study's case series. Cleft palate, abnormal thymus development, parathyroid glands, and conotruncal defects clinically recognize this syndrome. About 75 % of patients with this condition have heart abnormalities, the most common defect being interrupted aortic arch.[12]

According to a Hospital Clínico San Borja Arriarán study in 2015, 10 % of cases correspond to cleft lip and palate associated with multiple congenital disabilities.[7] In a study of patients with EEC syndrome, a prevalence of cleft lip and palate was found in 14 %.[13]

When analyzing isolated congenital disabilities, congenital heart defects, such as atrial septal, ventricular septal, tricuspid, and mitral insufficiency, patent ductus arteriosus, and some in combination, were detected most frequently.

According to reports, CLP is associated with other congenital malformations.[14] The association is evident in a retrospective study of the medical records of 1381 individuals, with a significantly higher prevalence of congenital heart disease in cleft palate and lip.[13]

A similar study reports that most patients did not have isolated congenital disabilities (70,5 %), and when present, the most common were cardiovascular defects (patent ductus arteriosus).[15]

In addition to the congenital cardiovascular malformations found, osteoarticular, ophthalmic, and auricular systems anomalies and the genitourinary, central nervous system, dental, preauricular appendage, hair, and nail abnormalities were identified.

In the etiology of CLP, hereditary factors play a more critical role in cleft lip and palate, as do environmental

factors in cleft palate. Heredity is considered the most crucial factor in cleft lip and cleft palate, probably in 40,5 % of cases and cleft palate in 20,2 %.[16]

Genetic makeup is a determinant of human health. It provides a hereditary predisposition to a wide range of individual responses that affect health status and seems to predispose specific individuals to particular diseases or health problems such as congenital malformations, which are the expression of structural defects in embryonic development that affect approximately 3 % to 5 % of live births and can be detected prenatally, at birth, or later.[3,4]

In the present study, the existence of previous siblings (a twin with a congenital disability) was identified in many cases, ranging from one to five siblings, with an intergenetic interval of less than one year to 19 years. None of the parents were related by blood, but the number of previous abortions was striking, ranging from one to a maximum of eleven abortions.

The prevalence of cleft lip and palate is reported to be related to the number of pregnancies of the mother, being more prevalent when the mother is multiparous. Regarding the short intergenetic period (less than one year), Varandas et al., who studied Latin American children, mention that the short intergenetic period is a predisposing factor for the development of the defect.[17]

In addition, the study found that 35,6 % of patients had relatives with congenital malformations, mainly second-degree relatives (especially paternal grandparents and maternal uncles).

A positive family history of congenital malformations is associated with an increased risk of CLP in children, being twice as high when there is a family history of malformations than when there is none.[15]

The high degree of familial aggregation has led to the hypothesis that there is a major gene related to susceptibility to cleft lip and palate, where the risk of familial recurrence increases according to the degree of kinship, the severity of the defect, or the number of affected individuals in the family. It is 10,3 times more likely to have a cleft if a first-degree relative is concerned, 3,2 times more likely if a second-degree relative is concerned, and 2,6 times more likely if a third-degree relative is concerned, which explains the familial aggregation of clefts.[18]

A survey of 1,521 family members concluded that rare mutations are not associated with oral clefts and that causal variations are only present in 0,24 % to 0,44 % of apparently non-syndromic families.[13]

Parental consanguinity is related to a 10-year longitudinal study (1999 to 2009) conducted in Saudi Arabia on patients with cleft lip and palate and isolated cleft palate with parental consanguinity of 56,8 %.[18]

Araya Vallespir et al.[19] conclude that alterations and modifications in different genes may cause non-syndromic oral clefts.

Hereditary factors play a significant role in the appearance of cleft lip with and without associated cleft palate, while environmental factors play a role in isolated cleft palate. This evidence supports the hypothesis that the developing palate is particularly sensitive to exogenous agents; however, epidemiological data suggest a positive family history of cleft lip and palate. The cause of this condition remains a mystery.[9,16,20,21,22,23]

CONCLUSIONS

The children studied with cleft lip and palate were evenly distributed by sex, and only a small number had multiple congenital disabilities.

Just over a third were associated with multiparous mothers, with a high frequency of previous abortions and evidence of a family history of congenital malformations, mainly second-degree consanguinity on the maternal side.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

LIMITATIONS OF THE STUDY

As this is a retrospective study, there was a possibility of recall bias or memory bias regarding exposure to circumstances that occurred prior to the investigation.

AUTHORSHIP CONTRIBUTION

Conceptualization: Julio Valcarcel Llerandi, Amparo Pérez Borrego, Estela Morales Peralta.
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