

Clinical and Descriptive Study of Orofacial Clefts in Colombia: 2069 Patients From Operation Smile Foundation

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Alejandro Silva Espinosa, MSc¹, Julio Cesar Martinez, MSc, Esp¹ ,
Yubahhaline Molina, MD¹, María Alejandra Bermúdez Gordillo¹,
Daniel Ramos Hernández, MD¹, Daniela Zárate Rivera, MD¹,
Blanka Pacheco Olmos, MD¹ , Nathaly Ramírez¹, Liliana Arias, MD¹,
Andres Zarate¹, Diana Marcela Diaz Q., MD, MSc, Esp¹ ,
Andrew Collins, PhD², Álvaro Mauricio Herrera Cepeda³,
and Ignacio Briceño Balcazar, MD, PhD¹

Abstract

Objective: To describe the population of patients with cleft lip and/or palate (CL/P) in terms of cleft phenotypes, gender, age, ethnic group, family history, clinical presentation (syndromic vs nonsyndromic), some environmental and behavioral factors, and some clinical features.

Design: Descriptive retrospective study.

Setting: Patients attending the genetics counseling practice in Operation Smile Foundation, Bogotá, Colombia, for over 8 years.

Participants: No screening was conducted. All patients requiring clinical genetics assessment in Operation Smile Foundation were included in the study.

Results: Left cleft lip and palate (CLP) and nonsyndromic forms were the most frequent types of malformations in this population. Psychomotor retardation and heart disease were the most frequent comorbidities in these patients. A low proportion of mothers exposed to passive smoking during pregnancy was observed and low birth weight accounted for an important number of cases. Aarskog, velocardiofacial, and orofacioidigital syndromes were the most frequent syndromic forms of CLP in this population.

Conclusions: In this study, the most frequent type of CL/P was the nonsyndromic complete left CLP. Aarskog, velocardiofacial, and orofacioidigital syndromes were the most frequent syndromic forms of CL/P in this population.

Keywords

epidemiology, maternal factors, nonsyndromic clefting

Introduction

Cleft lip and/or palate (CL/P) are a group of common and heterogeneous craniofacial malformations in humans, including several subtypes. Molecular and genetic causes are still not fully understood, but these malformations originate due to alterations in early embryonic development, specifically the incomplete fusion or lack thereof of maxillary prominences and/or nasal processes, which form the upper lip and palate (Farronato et al., 2014).

The causes of orofacial clefts are believed to be multifactorial and polygenic (Howe et al., 2018), which means there are

¹ Human Genetics Group, Universidad de La Sabana, Chía, Cundinamarca, Colombia

² Genetic Epidemiology & Genomic Informatics, Southampton University, Southampton, UK

³ Operation Smile Foundation, Bogota, D.C., Colombia

Corresponding Author:

Ignacio Briceño Balcazar, Campus del Puente del Común, Km 7, Autopista Norte de Bogotá, Chía, Cundinamarca, Colombia.

Email: ignacio.briceno@unisabana.edu.co

not only several genes implicated (each with small effects) but also numerous environmental factors influencing the incidence of this heterogeneous group of malformations. Many cases of CL/P report prenatal exposure to teratogenic drugs (eg, diazepam, phenytoin), previous abortions, complications during pregnancy (eg, first-trimester metrorrhagia, diabetes), emotional disorders, and maternal age older than 40 years (Watkins et al., 2014; Mai et al., 2017).

The CL/P malformations are the most frequent craniofacial birth defect, with an estimated global prevalence of 1.4 in 1000 live births (Mossey et al., 2009), but regional differences have been observed (Orioli et al., 2020). In general, the highest prevalence has been described in Amerindian populations (2.62/1000 live births) and the lowest prevalence in populations of African descent (0.58/1000 live births; Panamonta et al., 2015). Since CL/P malformations can be considered a common outcome of a complex interaction between diverse genetic and nongenetic factors, prevalence and incidence variations of CL/P malformations can be explained by local differences in allele frequencies and cultural/environmental conditions (Poletta et al., 2007).

The Latin American collaborative study of congenital malformations reported a CL/P prevalence for the region as high as 1.5 per 1000 live births (Castilla & Orioli, 2004), representing the sixth most frequent malformation diagnosed at birth. A recent study in Colombia (Rengifo & Guarnizo, 2020) showed that, between 2010 and 2015, CL/P had an overall prevalence of 0.6 per 1000 live births, but in Orinoquia and Amazonia (where Amerindian populations are dominant) and in Bogota, prevalence increased to 0.8 per 1000 live births.

Regarding socioeconomic impacts on the affected family, CL/P is the second most expensive malformation in Latin America, following Down syndrome (Guerrero-Abello et al., 2016). Agbenorku (2013) reports that a complete treatment for a patient with CL/P throughout his/her life is approximately US\$100,000 and that the average health care costs for children affected by CL/P younger than 10 years are 8 times higher than the costs for children without CL/P of the same age.

In Colombia, according to data from the Pan American Health Organization, in 2008, birth defects had a mortality rate of 303.8 males and 252.3 females per 100 000 live births, representing the second most frequent cause of death among males and the first among females (Guerrero-Abello et al., 2016).

The most extensive studies related to this condition have been performed in populations of European descent in the developed world (Moreno Uribe et al., 2017). In Latin America, a few investigations have been performed to study the genetic factors of CL/P and their implications on this phenomenon (Vieira et al., 2008). Given the fact that such polygenic and multifactorial diseases are related to population-specific variants and local environmental factors (such as diet or smoking and alcohol consumption habits; Dixon et al., 2011), it is clear that population-specific studies should be carried out in Colombia and Latin America to determine not just CL/P subtype frequencies and significant environmental contributing

factors but also population-specific single-nucleotide polymorphisms (SNPs) and loci implicated in this condition.

Additionally, in order to truly harness the potential of revolutionary technologies such as whole-genome sequencing and RNAseq, it is critical to clearly differentiate between CL/P phenotypes since the power to detect individual effects of SNPs or loci is diminished when different phenotypic entities are considered a homogeneous group (Dixon et al., 2011). Within this framework, an epidemiological characterization of the Colombian population with CL/P would be important to make inferences about the importance of a specific SNP or loci suspected to produce a specific phenotype.

Also, the description of frequencies of known risk factors and comorbidities, as well as frequencies of specific syndromes associated with CL/P cases, is important for proper monitoring and to design public policies aiming to address this issue in Colombia. With this in mind, the present study aimed to describe a Colombian population of patients with CL/P in terms of cleft phenotypes, gender, age, ethnic group, family history, clinical presentation (syndromic vs nonsyndromic), some environmental and behavioral factors, and some clinical features.

Methods

A descriptive cross-sectional study was performed for 2069 patients who attended the clinical genetics counseling practice in Operation Smile Foundation from 2008 to 2016. A team lead by a trained clinical geneticist interviewed each patient (or their relatives when the patient was a minor) recording a standard clinical genetics medical history, which included, gender, family background, prenatal information, and comorbidities. The geneticist also performed a thorough physical examination on every patient, and findings were documented in their medical record (specifically, the type and laterality of the CL/P, other congenital malformations, and any other clinical findings). Also, patients brought with them laboratory results, imaging tests, and other medical records requested by other specialists of the Operation Smile Foundation team (eg, pediatricians, cardiologists, plastic surgeons, speech therapists). Most patients with suspected cardiac malformations had echocardiograms performed to confirm such malformations. All of this information was recorded electronically in a medical history software and was annotated with the physical examination observations performed during the visit.

The study aimed to describe the frequencies of the different types of CL/P in the studied population and we looked into several factors potentially influencing the incidence of CL/P, such as previous maternal abortion, previous use of drugs and other substances, exposure to chemical substances during pregnancy, and history of parental consanguinity. Also, the most frequent comorbidities and syndromes (diagnosed clinically by the medical geneticist) in patients with CL/P were documented. When a patient had characteristics of a syndromic CL/P, each clinical feature was documented. For instance, Aarskog syndrome was diagnosed mainly on the basis of a combination of

Table 1. Percent Distribution of Age Groups.

Age group	Percent distribution
>0-≤2 years	21
>2-≤12 years	34
>12-≤18 years	22
>18 years	15
Missing data	7
Total	100

Table 2. Population Composition by Ethnic Group (Self-Reported).

Ethnic origin	Women, n (%)	Men, n (%)
Mestizos	919 (44.4)	1135 (54.8)
Amerindian	3 (0.14)	3 (0.14)
African Colombians	3 (0.14)	6 (0.28)
Total	925 (44.68)	1144 (55.22)

shawl scrotum, brachydactyly, hypertelorism, and CL/P (one case of Aarskog syndrome was confirmed by exome sequencing). Other syndromes were confirmed by cytogenetic testing (eg, 22q11, Xq27 fragility, trisomy 13, Turner, Down, Klinefelter).

Data from all the patients were introduced into an MS Excel spreadsheet, and the information was tabulated in order to analyze via pivot tables, with which frequencies and percentages were calculated.

We followed all required ethical principles laid down by the Helsinki Declaration of the World Medical Association; every patient (or a legally acceptable representative) signed an IEC-approved consent form.

Results

Clinical data were obtained from medical records and physical examinations for a total of 2069 patients of Operation Smile Foundation in Bogotá, Colombia, who attended the genetic counseling practice since 2008.

Different clinical, biological, and exposure-related features were examined during the investigation. Patients age ranged from 30 days to 57 years. Table 1 presents the percent distribution of age groups for the studied population.

All of the examined patients were included; there was no recruiting nor screening of patients. A total of 1149 (55.29%) patients were male and 925 (44.71%) were female, representing 22 departments of Colombia (Bogotá, Cundinamarca, Meta, Boyaca, Valle, Tolima, Cordoba, Caqueta, Putumayo, Huila, Atlantico, Cesar, Magdalena, Santander, Norte de Santander, Nariño, Cauca, Sucre, Bolivar, Vichada, Caldas, Guainia, and Casanare). Regarding ethnicity, 2054 (99.28%) patients declared themselves as “Mestizos” (mixed race), 9 (0.43%) patients as African Colombians, and 6 (0.29%) patients as Amerindians (Table 2). The self-declared ethnicity is problematic since there are no genetically well-defined ethnic groups nor is the self-report accurate since most patients are

Table 3. Frequencies of Patients by Type of CL/P.

Type of cleft	N	Percent
Complete left cleft lip and palate	587	28.37
Complete right cleft lip and palate	394	19.04
Complete bilateral cleft lip and palate	358	17.30
Complete cleft palate	282	13.63
Right cleft lip	124	5.99
Left cleft lip	112	5.41
Incomplete cleft palate	51	2.46
Cleft lip with left alveolar cleft	48	2.32
Bilateral cleft lip	43	2.08
Incomplete right cleft lip and palate	20	0.97
Incomplete left cleft lip and palate	18	0.87
Cleft lip with right alveolar cleft	13	0.63
Incomplete bilateral cleft lip and palate	10	0.48
Cleft lip with bilateral alveolar cleft	9	0.43
Total	2069	100

Abbreviation: CL/P, cleft lip and/or palate.

not totally aware of their origin or that of their ancestors. Nonetheless, most Amerindians and African Colombians have a clearly defined phenotype and “mestizos” is clearly a combined ethnic group per definition. These are, in general terms, the 3 main phenotypic ethnicities in Colombia, and their report here seeks to help in future comparisons with other studies in which ethnicity is a variable or a stratification variable.

The most frequent CL/P subtype was complete left cleft lip and palate (CLP) with 587 (28.37%) patients, followed by 394 (19.04%) patients with right CLP and 358 (17.30%) patients with complete bilateral CLP. The other subtypes had frequencies below 10%: right cleft lip (CL; 124 patients; 5.99%), left CL (112 patients; 5.41%), incomplete cleft palate (CP; 51 patients; 2.46%), CL with left alveolar cleft (48 patients; 2.32%), bilateral CL (43 patients; 2.08%), incomplete right CLP (20 patients; 0.97%), and incomplete left CLP (18 patients; 0.87%). The least frequent subtypes were CL with right alveolar cleft (13 patients; 0.63%), incomplete bilateral CLP (10 patients; 0.48%), and CL with bilateral alveolar cleft (9 patients; 0.43%; Table 3).

Regarding clinical presentation, 20.83% (431) of patients were syndromic cases, whereas 66.54% (1364 patients) had nonsyndromic forms of the condition and 274 (13.24%) patients had missing information. Within the group of syndromic patients, the most frequent pathologies were Aarskog syndrome with 53 (2.56%) patients, velocardiofacial syndrome or 22q11 with 26 (1.26%) patients, orofaciocigital syndrome with 12 (0.58%) patients, and Waardenburg syndrome with 9 (0.43%) patients. It is noteworthy that at least 1 case of other uncommon syndromes were also observed: Turner, Down, Goldenhar, Apert, Pierre-Robin, Ehlers-Danlos, Sotos, Cornelia de Lange, cardiofaciocutaneous, Xq27 fragility, Opitz Frias, Larsen, ectrodactyly, ectodermal dysplasia, and CLP syndrome 1 (EEC1), popliteal pterygium, Klinefelter, trisomy 13, Noonan, and Treacher Collins syndromes (Table 4).

Table 4. Less Frequent Syndromes Associated With CL/P.

Syndrome	N	Percent ^a
Turner	7	0.33
Down	7	0.33
Goldenhar	6	0.28
Apert	5	0.24
Pierre-Robin	3	0.14
Ehlers-Danlos	3	0.14
Sotos	3	0.14
Cornelia de Lange	3	0.14
Cardiofaciocutaneous	2	0.09
EECI	2	0.09
Popliteal pterygium	2	0.09
Trisomy 13	2	0.09
Xq27 fragility	1	0.04
Opitz-Frias	1	0.04
Kabuki ^b	1	0.04
Larsen	1	0.04
Noonan	1	0.04
Klinefelter	1	0.04
Treacher Collins	1	0.04
Total (other syndromes)	52	2.38

^aOf the total 2069 patients in the study.

^bConfirmed by exome sequencing.

Table 5. Medical History.

Variable	N	Percent ^a
Family history of CL/P	444	21.46
Low birth weight	135	6.52
Active smoking	65	3.14
Passive smoking	42	2.03
NSAID use	11	0.53
Use of combined oral contraceptives (OC)	11	0.53
Alcohol consumption	6	0.29
Insecticide exposure	5	0.24
Smoking and alcohol consumption	3	0.14
Abortifacient use	2	0.10
Total	724	34.99

Abbreviations: CL/P, cleft lip and/or palate; NSAID, nonsteroidal anti-inflammatory drug.

^aOf the total 2069 patients in the study.

A total of 724 (34.99%) of 2069 patients were reported with several background factors influencing pregnancy outcome (Table 5): Family history of any type of CL/P was reported in 444 (21.46%) patients, low birth weight (which can be associated with maternal malnutrition; Jia et al., 2011) was reported in 135 (6.52%) patients, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) during pregnancy (11 patients; 0.53%), insecticide exposure (5 patients; 0.24%), and the use of combined oral contraceptives (OCs; 11 patients; 0.56%), including 2 (0.10%) reports from mothers of patients using abortifacient drugs during their first trimester.

At least during their first trimester of pregnancy, the mother of 110 (5.32%) patients smoked (no mother specified a number of cigarettes per day), with 42 (2.03%) mothers being exposed

to passive smoking throughout pregnancy, 3 (0.14%) mothers smoked and consumed alcohol until intoxication throughout their pregnancy, and 6 (0.29%) mothers consumed alcohol (without mentioning an amount) during at least their first trimester of pregnancy.

Regarding maternal history of abortions, the mother of 100 (4.83%) patients reported previous abortions, one of which was a voluntary provoked abortion. Also, a total of 21 (1.01%) patients had a history of parents with positive consanguinity (ie, parents being siblings or first-, second-, or third-degree cousins).

The following common clinical features associated with CL/P were also reported: psychomotor retardation in 153 (7.39%) patients, mental retardation in 54 (2.61%) patients, hypoacusis in 39 (1.88%) patients, cardiovascular disease in 115 (5.56%) patients, clubfoot in 13 (0.63%) patients, and positive amniotic bands in 13 (0.3%) patients.

Discussion

A sample of 2069 patients with syndromic and nonsyndromic CL/P who visited the genetics counseling practice in Operation Smile Foundation in Bogotá, Colombia, was analyzed. This study contributes to the descriptive epidemiology of this group of malformations and determines the most frequently associated clinical features. In relation to gender ratio, clinical presentation (syndromic vs nonsyndromic) and laterality, findings in this study are roughly in line with previous reports across many different countries (Elahi et al., 2004; Sepúlveda et al., 2008; Beltrán, 2009; Nazer et al., 2010; Sekhon et al., 2011; Souza & Raskin, 2013; Arias et al., 2015; Burg et al., 2016; Sarmiento et al., 2018; Silva et al., 2018).

Regarding clinical presentation, in the study population, a lower frequency of syndromic CL/P versus nonsyndromic forms was observed, which has been previously reported as more common in this type of craniofacial malformations. Additionally, as has been widely reported, we observed a higher proportion of males with CL/P forms (47.7%) than females (36.0%) and a higher proportion of females (9.2%) with CP than males (7.1%; Sepúlveda et al., 2008; Nazer H et al., 2010; Souza & Raskin, 2013; Silva et al., 2018).

In terms of laterality, our study population found that complete left CLP is the most frequent anomaly (43.8% of the total complete CLP cases = 358), followed by the complete right CLP (29.4%) and complete bilateral CLP (26.7%), which is similar to findings from a recent study of dental anomalies in Colombia (Yeziro-Rubinsky et al., 2020). They report a 47.6% frequency for complete left CLP, 30.0% for complete right CLP, and 22.3% for complete bilateral CLP. This similarity suggests that both studies were drawing their samples from the same or very similar populations.

As the data in this study have been collected as the consecutive cases arriving in a non-for-profit organization dedicated exclusively to patients with any form of CL/P, there is no background population nor controls to which this population of patients can be contrasted. Unfortunately, this makes it

impossible to calculate prevalence and incidence rates in order to compare our data to other local, national, and regional reports (Sarmiento et al., 2018; Orioli et al., 2020; Rengifo & Guarnizo, 2020).

Nevertheless, in a sample of 448 930 birth records from Bogotá and Cali (Colombia), Sarmiento et al. (2018) also found a higher proportion of CLP cases (73%) versus CP ones (27%). In our study population, CLP cases accounted for 83.9% and CP cases accounted for 16.1%.

The most frequent syndromes observed in this population, in decreasing order, were Aarskog syndrome, velocardiofacial syndrome, orofaciocardial syndrome. These findings differ from previous reports in which Van der Woude is the most frequent syndrome, with a ~2% global incidence, followed by velocardiofacial syndrome (22q11), with associated features of Pierre Robin sequence (Setó-Salvia & Stanier, 2014). This latter form was the most frequent syndrome in Hong Kong and Pakistan (Elahi et al., 2004; Chan et al., 2013; Arias et al., 2015; Burg et al., 2016). In a Colombian population, Sarmiento et al. (2018) found that Edwards was the most frequent syndrome (28%), followed by the brain-lung-thyroid syndrome (17%), Down, Dandy-Walker, Patau, and Pierre Robin syndromes (11% each), which is in stark contrast with the types and frequencies of syndromic forms found in our population. We hypothesize that the difference in these results may be attributed to the methodology through which the syndromes are diagnosed, and the base populations are also different.

Since clinical diagnosis of these CL/P-associated syndromes has a wide and heterogeneous phenotypic range, no precise data are available. Clinicians must have prior training, and molecular examinations are required to confirm the diagnosis and to establish the specific prevalence of each disease in Colombia (Lidral et al., 2008; Shprintzen, 2008; Boldrini et al., 2014; Fakhouri et al., 2014; Arias et al., 2015; Bruel et al., 2017; Edel et al., 2017).

The low birth weight variable was observed in 6.52% of cases in the study population. Embryofetal development is regulated by maternal, embryonic, and placental factors, whose normal behavior allows the embryo a normal growth in size and weight (Sepúlveda et al., 2014).

A Cuban study assessed some birth weight-related factors in an infant population with CL/P. This study estimated a population-specific risk of low birth weight and proposed a significant association between the most severe forms of CL/P and low birth weight. Since Operation Smile Foundation provides a free-of-charge service for low-income families, we hypothesize that the low birth weight observed in these patients is related with suboptimal nutrition of the mothers, which has been observed in other studies (Zamora & Soriano, 2013).

In contrast, Jagomagi et al. (2010) confirmed by their study results that birth weight in children with CL/P was similar to that of children without CL/P, which was consistent with the findings of Barakati and Alkofide (2002). The present study in Colombia is in line with this finding since a low proportion of patients had low birth weights.

The NSAIDs are commonly prescribed and used all over the world. In the study population, a small fraction of pregnant women used NSAID during pregnancy, but type of drug and trimester data are missing. Although NSAIDs are useful in diverse medical fields, their teratogenic effects are wide but inconsistent (Siu et al., 2002). Theoretically, NSAIDs can cause fetal adverse effects due to their ability to disrupt prostaglandin homeostasis, which, according to Klein et al. (1984), may cause fetal malformation. However, there is still little information available about such effects during embryofetal development (van Gelder et al., 2011).

Maternal exposure to organic solvents, pesticides, and certain metals may be involved in human birth defects causality (Thulstrup & Bonde, 2006). Pesticide exposure has been associated with anencephaly (Yang et al., 2014), a 2 times higher risk for CL/P (Thulstrup & Bonde, 2006), and exposure to organic solvents (eg, glycol ethers) has been positively related to neural tube defects and an increased risk for orofacial clefts, CL/P, and CP (Spinder et al., 2019). Nonetheless, maternal exposure to pesticides is associated with a modest but marginally significant risk of CL/P (Romitti et al., 2007; Yang et al., 2014; Spinder et al., 2019), which could explain the low proportion of cases observed in our study.

Occurrence of genetic malformations due to OCs depends on multiple factors such as specific agents, dosing, length of fetal exposure during pregnancy, and maternal and fetal genetic susceptibility (Hiremath et al., 2019). Progestogen doses in OCs have been associated with increased risk of birth defects if maternal exposure occurs during the first trimester in contrast with estrogen doses, which may have lower risk or may not be associated at all with congenital malformations. Regarding combined OCs, there are no studied adverse effects associated with CL/P (Bracken et al., 1978; Lammer & Cordero, 1985; Charlton et al., 2016).

This study included a small proportion of patients with OC use in the first trimester of pregnancy. This could be associated with CL/P as an etiologic component within the multifactorial disease model in Colombia. Lammer and Cordero (1985) studied OC exposure in the first trimester of pregnancy and found 11 different types of malformations, especially CL/P and digestive tract malformations, among others.

These observations are consistent with those found by Bracken et al. (1978), who also reported occurrence of fetal malformations such as CL/P, tracheoesophageal fistulae, and pyloric stenosis, among others. The patients also showed other malformations (eg, polysyndactyly and musculoskeletal anomalies), but without significant associations among individual types of malformations (Bracken et al., 1978). It was not possible to observe in the study population OC use as a defining factor for CL/P occurrence, due to information scarcity in data collection.

Active exposure to cigarette smoke, at least on the first trimester of pregnancy, and passive exposure throughout pregnancy have been considered an external risk for nonsyndromic CL/P occurrence in comparison with children of nonsmoking mothers (Reis et al., 2015; Sabbagh et al., 2015; Panamonta

et al., 2017). Nonetheless, the small proportion of patients exposed to cigarette smoke in our study does not allow to draw any important conclusions in this regard.

Likewise, a previous study in nonsyndromic patients with CL/P determined that active and passive maternal exposure to cigarettes, as well as alcohol consumption, have a positive relation with fetal nonsyndromic CL/P occurrence due to gene–environment interactions, although results from different studies are not always consistent (Torres et al., 2012; Aschard, 2016).

We observed a low number of mothers reporting prenatal alcohol consumption (and none of them reported amounts). We consider this to be a nonsyndromic CL/P risk underestimation in this population due to the fact that there is a considerable social stigmatization and shame for the mother to answer questions about alcohol consumption, as well as due to the lack of measurements of amounts alcohol consumption by the exposed mothers (DeRoo et al., 2008). Identification of these modifiable risk factors for nonsyndromic CL/P is the first step to implement primary prevention schemes (Reis et al., 2015).

The observed rate of mothers with previous abortions was lower in this study in comparison with a significant difference observed in a case–control study in China (20.1% vs 28.8% of mothers with and without previous abortions; Xu et al., 2017). Xu et al. (2017) reported that a history of previous abortions in a Chinese population may increase 2.5-fold nonsyndromic CL/P risk. No reports were found regarding associations between nonsyndromic CL/P and previous abortions of the mother in Western populations, which makes the finding in this study a primer for new research in this field.

Patients whose parents have any degree of consanguinity have an increased risk of birth defects due to a higher probability of inheriting 2 disease-related alleles. With a first degree of consanguinity, the risk is 50%; with the second, the risk is 5% to 10%, and for the third degree, the risk is 3% to 5% (Jose et al., 2015). We observed in Operation Smile's patient population a low frequency of parental consanguinity consistent with other reported populations in the United States, France, and the United Kingdom (Jose et al., 2015).

Ravichandran et al. (2012) analyzed the relation between parental consanguinity and the risk of CL/P and CP occurrence, as well as recurrence of clefts among siblings. Results showed a higher rate of parental consanguinity (56.8%) in comparison to our results of the Operation Smile population (1.01%). Ravichandran et al. state that there is no increase in recurrence risk among siblings related to parental consanguinity, but there is indeed a higher risk for children when parents have a history of oral clefts versus unaffected families.

Regarding common clinical features associated with CL/P, the most frequent in this study was psychomotor retardation in 153 (7.39%) patients, which is in line with literature reports where neurodevelopment disorders are more frequent in individuals with CL/P: Their neuropsychomotor development is slower during the first year of life in comparison with normal children (Cavalheiro et al., 2019), and this could not be explained by familial factors (Tillman et al., 2018).

Additionally, it has also been considered that facial malformations could be associated with anomalous brain development, which is correlated with a higher incidence of central nervous system abnormalities in patients with CL/P (Tillman et al., 2018; Gallagher & Collett, 2019). Mental retardation is one of numerous birth defects associated with CL/P (Chetpak-deechit et al., 2010), and it was observed in 2.61% of study patients. Patients with CL/P have been shown to have higher incidences of mental disability compared to the general population (Schreiber, 2018) and more severe forms are associated with certain types of CL/P: There is a higher risk for CP, followed by CLP; it seems that CL has no increased risk (Berg et al., 2016; Pedersen et al., 2016). Identifying the association between CL/P and mental retardation would be crucial, since 46.5% of mental retardation cases are related to a syndrome or a structural anomaly (Strauss & Broder, 1993).

Hypoacusis is a frequent comorbidity in patients with CL/P, especially in those with palatal involvement. Muscular alterations of the soft palate, which produce Eustachian tube dysfunctions, can derive in hearing loss (Rivelli et al., 2018). Hypoacusis in our study population was the third most frequent clinical feature associated with CL/P, with 1.88% of patients. However, this prevalence is strikingly lower compared to previous reports of 19% to 25% (Alfwaress et al., 2017), and this finding could be a consequence of a less-than-optimal diagnostic rate of this disease, which would encourage the implementation of better assessment protocols to examine patients with CL/P.

Likewise, congenital cardiopathies have been described as the most frequent diseases associated with CL/P. These include cyanotic or noncyanotic forms, such as tetralogy of Fallot, transposition of the great vessels, tricuspid atresia, Ebstein anomaly, hypoplastic left heart syndrome, septal ventricular defect, aortic coarctation, and lung and aortic stenosis (Kasatwar et al., 2018).

Cardiopathies are also frequent comorbidities in our study population, which were observed in 115 (5.56%) patients with CL/P. Similarly, in a Sudanese cohort study with 381 patients with CLP, 11% of patients had heart defects, with septal ventricular defect being the most frequently reported anomaly (AlHammad et al., 2020).

Amniotic band syndrome is another rare congenital anomaly associated with CL/P, which, according to literature reports (Doi et al., 2011), has a prevalence of 1 per 12 000 to 15 000 live births. Results of this study show 13 (0.63%) patients with CL/P with associated amniotic band syndrome, a remarkable figure given the reported scarcity of this syndrome.

Finally, it is noteworthy that the incidence of these types of congenital structural alterations ranges from 4.3% to 63.4% (Venkatesh, 2009), considering the abovementioned ones. Within this group of anomalies, clubfoot is included as a rare musculoskeletal condition, with an incidence of 1 per 1000 live births of diverse ethnicities (Masquijo et al., 2011).

When patients with CL/P have concurrent clubfoot, it is important to have a differential diagnosis regarding syndromes

and/or inherited conditions due to the scarcity of isolated cases of this condition (Venkatesh, 2009). Similar to other anomalies discussed previously, only 13 (0.63%) patients with CL/P in our study population had concurrent clubfoot. Although clubfoot occurrence is idiopathic, this is a medical condition with a relatively good prognosis if a timely and multidisciplinary management is applied.

Conclusion

This study presents a description of the population of patients with CL/P malformations, represented by 2069 patients attending the genetics counseling practice in Operation Smile Foundation in Bogotá, Colombia, from 2008 until 2016. The study describes the population in terms of the cleft phenotypes (CL, CLP, CP), gender, age, ethnic group, family history, clinical presentation (syndromic vs nonsyndromic), some environmental and behavioral factors, and some clinical features.

The most frequent type of CL/P was the nonsyndromic complete left CLP. Aarskog, velocardiofacial, and orofaciogigital syndromes were the most frequent syndromic forms of CL/P. An important number of cases with low birth weight was observed, which could be related to suboptimal nutrition of the mothers in this low-income population. Among the CL/P-associated comorbidities, psychomotor retardation and cardiopathies were the most frequent.

This study has the limitation that molecular confirmation could not be performed for all patients.

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Declaration of Conflicting Interests

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ORCID iD

Julio Cesar Martinez, MSc, Esp  <https://orcid.org/0000-0003-0704-472X>

Blanka Pacheco Olmos, MD  <https://orcid.org/0000-0001-8314-5958>

Diana Marcela Diaz Q., MD, MSc, Esp  <https://orcid.org/0000-0002-6488-9334>

References

- Agbenorku P. Orofacial clefts: a worldwide review of the problem. *ISRN Plastic Surg.* 2013;2013(Article ID 348465):1-7. doi:10.5402/2013/348465
- Alfwaress FSD, Khwailah FA, Rawashdeh MA, Alomari MA, Nazzal MS. Cleft lip and palate: demographic patterns and the associated

- communication disorders. *J Craniofac Surg.* 2017;28(8):2117-2121. doi:10.1097/SCS.00000000000003984
- AlHammad Z, Suliman I, Alotaibi S, Alnofaie H, Alsaadi W, Alhusseini S, Aldakheel G, Alsubaie N. The prevalence of non-syndromic orofacial clefts and associated congenital heart diseases of a tertiary hospital in Riyadh, Saudi Arabia. *Saudi Dental J.* 2020. doi:10.1016/j.sdentj.2019.12.002
- Arias L, Briceño I, Lozano JM, Collins A, Uricoechea D. Aspectos clínicos asociados a fisuras orofaciales en una población Colombiana. *Colombia Med.* 2015;46(4):162-167.
- Aschard H. A perspective on interaction effects in genetic association studies. *Genet Epidemiol.* 2016;40(8):678-688. doi:10.1002/gepi.21989
- Barakati SF, Alkofide EA. Growth status of Saudi patients with cleft lip and palate. *Saudi Med J.* 2002;23(7):823-827.
- Beltrán MD. Características epidemiológicas en pacientes con fisura labiopalatina. *Arch Investig Materno Infantil.* 2009;1(3):105-109. www.medigraphic.org.mx
- Berg E, Haaland ØA, Feragen KB, Filip C, Vindenes HA, Moster D, Lie RT, Sivertsen A. Health status among adults born with an oral cleft in Norway. *JAMA Pediatr.* 2016;170(11):1063-1070. doi:10.1001/jamapediatrics.2016.1925
- Boldrini MP, Giovo ME, Bogado C. Síndrome orofaciogigital tipo I. Expresión fenotípica variable. *Arch Argentinos Pediatr.* 2014;112(6):e242-e246. doi:10.5546/aap.2014.e242
- Bracken MB, Holford TR, White C, Kelsey JL. Role of oral contraception in congenital malformations of offspring. *Int J Epidemiol.* 1978;7(4):309-316.
- Bruel A-L, Franco B, Duffourd Y, Thevenon J, Jago L, Lopez E, Deleuze J, Doummar D. 15 years of research on oral-facial-digital syndromes: from 1 to 16 causal genes. *J Med Genet.* 2017;54(6):371-380. doi:10.1016/j.physbeh.2017.03.040
- Burg ML, Chai Y, Yao CA, Magee W, Figueiredo JC. Epidemiology, etiology, and treatment of isolated cleft palate. *Front Physiol.* 2016;7(67):1-16. doi:10.3389/fphys.2016.00067
- Castilla EE, Orioli IM. ECLAMC: the Latin-American collaborative study of congenital malformations. *Commun Genet.* 2004;7(2-3):76-94.
- Cavalheiro MG, Cusin DA, Rocha S, Maximino LP. Child development skills and language in toddlers with cleft lip and palate. *Int J Pediatr Otorhinolaryngol.* 2019;116:18-21. doi:10.1016/j.ijporl.2018.10.011
- Chan KW, Lee KH, Pang KKY, Mou JW, Tam YH. Clinical characteristics of children with orofacial cleft in a tertiary centre in Hong Kong. *Hong Kong J Paediatr.* 2013;18(3):147-151.
- Charlton BM, Mølgaard-Nielsen D, Svanström H, Wohlfahrt J, Pasternak B, Melbye M. Maternal use of oral contraceptives and risk of birth defects in Denmark: prospective, nationwide cohort study. *BMJ (Online).* 2016;352(h6712):1-8. doi:10.1136/bmj.h6712
- Chetpakdeecheit W, Mohlin B, Persson C, Hagberg C. Cleft extension and risks of other birth defects in children with isolated cleft palate. *Acta Odontol Scand.* 2010;68(2):86-90. doi:10.3109/00016350903258003
- DeRoo LA, Wilcox AJ, Drevon CA, Lie RT. First-trimester maternal alcohol consumption and the risk of infant oral clefts in Norway: a

- population-based case-control study. *Am J Epidemiol.* 2008; 168(6):638-646. doi:10.1093/aje/kwn186
- Dixon MJ, Marazita ML, Beaty TH, Murray JC. Cleft lip and palate: synthesizing genetic and environmental influences. *Nat Rev Genet.* 2011;12(3):167-178. doi:10.1038/nrg2933.Cleft
- Doi Y, Kawamata H, Asano K, Imai Y. A case of amniotic band syndrome with cleft lip and palate. *J Maxillofac Oral Surg.* 2011;10(4):354-356. doi:10.1007/s12663-011-0174-4
- Edel T, Zárte-Sanabria AG, Briceño-Balcázar I, Martínez-Lozano JC. Paciente con síndrome oral-facio-digital tipo II. Reporte del caso. *Iatreia.* 2017;30(1):86-91. doi:10.17533/udea.iatreia.v30n1a09
- Elahi MM, Jackson IT, Elahi O, Khan AH, Mubarak F, Tariq GB, Mitra A. Epidemiology of cleft lip and cleft palate in Pakistan. *Plastic Reconstr Surg.* 2004;113(6):1548-1555. doi:10.1097/01.PRS.0000117184.77459.2B
- Fakhouri WD, Rahimov F, Attanasio C, Kouwenhoven EN, Ferreira de Lima RL, Felix TM, Nitschke L, Huver D, Barrons J, Kousa YA, et al. An etiologic regulatory mutation in IRF6 with loss- and gain-of-function effects. *Human Mol Genet.* 2014;23(10):2711-2720. doi:10.1093/hmg/ddt664
- Farronato G, Cannalire P, Martinelli G, Tubertini I, Giannini L, Galbiati G, Maspero C. Cleft lip and/or palate. *Minerva Stomatol.* 2014;63:111-126.
- Gallagher ER, Collett BR. Neurodevelopmental and academic outcomes in children with orofacial clefts: a systematic review. *Pediatrics.* 2019;144(1):e20184027. doi:10.1542/peds.2018-4027
- Guerrero-Abello P, Ariza-Araujo Y, Caycedo-García DJ, Pachajoa H. Necesidad de guías clínicas para el manejo integral de pacientes con labio paladar hendido. *Rev Salud Pública.* 2016;18(1):82-94. doi:10.15446/rsap.v18n1.41884
- Hiremath P, Patange RP, Salunkhe JA, Mohite VR, Naregal P. Is hormonal contraceptive risk for congenital malformation? *Int J Commun Med Public Health.* 2019;6(4):1784-1787. doi:10.18203/2394-6040.ijcmph20191422
- Howe LJ, Lee MK, Sharp GC, Davey Smith G, St Pourcain B, Shaffer JR, Ludwig KU, Mangold E, Marazita ML, Feingold E, et al. Investigating the shared genetics of non-syndromic cleft lip/palate and facial morphology. *PLoS Genet.* 2018;14(8):1-18. doi:10.1371/journal.pgen.1007501
- Jagomagi T, Soots M, Saag M. Epidemiologic factors causing cleft lip and palate and their regularities of occurrence in Estonia. *Stomatol Baltic Dental Maxillofac J.* 2010;12(4):105-108.
- Jia ZL, Shi B, Chen CH, Shi JY, Wu J, Xu X. Maternal malnutrition, environmental exposure during pregnancy and the risk of non-syndromic orofacial clefts. *Oral Dis.* 2011;17(6):584-589. doi:10.1111/j.1601-0825.2011.01810.x
- Jose B, Subramani S, Mokhasi V, Jayan M. Consanguinity and clefts in the craniofacial region: a retrospective case-control study. *J Cleft Lip Palate Craniofac Anomal.* 2015;2(2):113-117. doi:10.4103/2348-2125.162965
- Kasatwar A, Borle R, Bhola N, Rajanikanth K, Prasad GSV, Jadhav A. Prevalence of congenital cardiac anomalies in patients with cleft lip and palate – its implications in surgical management. *J Oral Biol Craniofac Res.* 2018;8(3):241-244. doi:10.1016/j.jobcr.2017.09.009
- Klein K, Clark K, Scott W. Prostaglandin synthesis in rat embryo tissue: the effect of non-steroidal anti-inflammatory drugs in vivo and ex vivo. *Prostaglandins.* 1984;27(5):659-672. doi:10.5858/arpa.2018-0375-RA
- Lammer EJ, Cordero JF. Exogenous sex hormone exposure and the risk for major malformations. *JAMA.* 1985;255(22):3128-3132. doi:10.1097/00006254-198701000-00014
- Lidral AC, Moreno LM, Bullard SA. Genetic factors and orofacial clefting. *Semin Orthod.* 2008;14(2):103-114. doi:10.1053/j.sodo.2008.02.002
- Mai CT, Isenburg JL, Canfield MA, Meyer RE, Correa A, Alverson CJ, Lupo PJ, Riehle-Colarusso T, Cho SJ, Aggarwal D, et al. National population-based estimates for major birth defects, 2010–2014. *Birth Defect Res.* 2017;1-16. doi:10.1002/bdr2.1589
- Masquijo JJ, Marchegiani S, Allende V. Diagnóstico prenatal del pie bot. *Rev Argent Radiol.* 2011;75(4):335-339.
- Moreno Uribe LM, Fomina T, Munger RG, Romitti PA, Jenkins MM, Gjessing HK, Gjerdevik M, Christensen K, Wilcox AJ, Murray JC, et al. A population-based study of effects of genetic loci on orofacial clefts. *J Dental Res.* 2017;96(11):1322-1329. doi:10.1177/0022034517716914
- Mossey PA, Little J, Munger RG, Dixon MJ, Shaw WC. Cleft lip and palate – ProQuest. *Lancet.* 2009;374(9703):1773-1785. doi:10.1016/S0140-6736(09)60695-4
- Nazer HJ, Ramírez RMC, Cifuentes OL. 38 Años de vigilancia epidemiológica de labio leporino y paladar hendido en la maternidad del Hospital Clínico de la Universidad de Chile. *Rev Méd Chile.* 2010;138(5):567-572. doi:10.4067/s0034-98872010000500006
- Orioli IM, Dolk H, Lopez-camelo J, Benavides-lara A, Gimenez LG, Ascurra M, Correa DM, Hurtado-villa P, Zarante I, Piola M, et al. The Latin American network for congenital malformation surveillance: ReLAMC. *Am J Med Genet.* 2020;184C(October):1078-1091. doi:10.1002/ajmg.c.31872
- Panamonta O, Wiromrat P, Wongswadiwat Y, Chaikitpinyo A, Panamonta M, Wichajarn K. Maternal tobacco smoke exposure during pregnancy and the occurrence of orofacial clefts: a systematic review of reported meta-analyses. *J Med Assoc Thai.* 2017; 100(suppl 6):S270-S277.
- Panamonta V, Pradubwong S, Panamonta M, Chowchuen B. Global birth prevalence of orofacial clefts: a systematic review. *J Med Assoc Thai Chotmaihet Thangphaet.* 2015;98(suppl 7):S11-S21.
- Pedersen DA, Wehby GL, Murray JC, Christensen K. Psychiatric diagnoses in individuals with non-syndromic oral clefts: a Danish population-based cohort study. *PLoS One.* 2016;11(5):e0156261. doi:10.1371/journal.pone.0156261
- Poletta F, Castilla EE, Orioli IM, Lopez-Camelo J. Regional analysis on the occurrence of oral clefts in south America. *Am J Med Genet.* 2007;143A:3216-3227. doi:10.1002/ajmg.a
- Ravichandran K, Shoukri M, Aljohar A, Shazia NS, Al-Twaijri Y, al Jarba I. Consanguinity and occurrence of cleft lip/palate: a hospital-based registry study in Riyadh. *Am J Med Genet Part A.* 2012;158A(3):541-546. doi:10.1002/ajmg.a.34432
- Reis D, Coletta RD, Oliveira EA, Oliveira M, Rodrigues LAM, Oliveira MC, Martelli H. Association between maternal smoking, gender, and cleft lip and palate. *Braz J Otorhinolaryngol.* 2015; 81(5):514-519. doi:10.1016/j.bjorl.2015.07.011

- Rengifo HA, Guarnizo S. Analysis of the prevalence and incidence of cleft lip and palate in Colombia. *Cleft Palate-Craniofac J*. 2020; 57(5):552-559. doi:10.1177/1055665619886455
- Rivelli RA, Casadio V, Bennun RD. Audiological alterations in patients with cleft palate. *J Craniofac Surg*. 2018;29(6): 1486-1489. doi:10.1097/SCS.00000000000004808
- Romitti PA, Herring AM, Dennis LK, Wong-Gibbons DL. Meta-analysis: pesticides and orofacial clefts. *Cleft Palate-Craniofac J*. 2007;44(4):358-365. doi:10.1597/06-100.1
- Sabbagh HJ, Hassan MHA, Innes NPT, Elkodary HM, Little J, Mossey PA. Passive smoking in the etiology of non-syndromic orofacial clefts: a systematic review and meta-analysis. *PLoS One*. 2015;10(3):1-21. doi:10.1371/journal.pone.0116963
- Sarmiento K, Valencia S, Gracia G, Hurtado-Villa P, Zarante I. Clinical and epidemiologic description of orofacial clefts in Bogota and Cali, Colombia, 2001–2015. *Cleft Palate-Craniofac J*. 2018;55(4): 517-520. doi:10.1177/1055665617741062
- Schreiber J. Orofacial clefts may be a window into identifying common psychopathology development. *J Am Acad Child Adolesc Psychiatry*. 2018;57(11):826-827. doi:10.1016/j.jaac.2018.08.009
- Sekhon PS, Ethunandan M, Markus AF, Krishnan G, Rao CB. Congenital anomalies associated with cleft lip and palate – an analysis of 1623 consecutive patients. *Cleft Palate-Craniofac J*. 2011; 48(4):371-378. doi:10.1597/09-264
- Sepúlveda CP, Gratacos. Restricción de crecimiento intrauterino. *Rev Méd Clín Las Condes*. 2014;25(6):958-963. doi:10.1016/s0716-8640(14)70644-3
- Sepúlveda G, Palomino H, Cortés J. Prevalencia de fisura labiopalatina e indicadores de riesgo: Estudio de la población atendida en el Hospital Clínico Félix Bulnes de Santiago de Chile. *Rev Espan Cirugía Oral Maxilofac*. 2008;30(1):17-25. doi:10.4321/s1130-05582008000100003
- Setó-Salvia N, Stanier P. Genetics of cleft lip and/or cleft palate: association with other common anomalies. *Eur J Med Genet*. 2014;57(8):381-393. doi:10.1016/j.ejmg.2014.04.003
- Shprintzen R. Velo-cardio-facial syndrome: 30 years of study. *Dev Disabil Res Rev*. 2008;14(1):3-10. doi:10.1002/ddr.2.Velo-Cardio-Facial
- Silva HPV, da Arruda TTS, Souza KSC, de Bezerra JF, Leite GCP, Brito MEF, de Lima VMGDM, Luchessi AD, Bortolin RH, Ururahy MAG, et al. Risk factors and comorbidities in Brazilian patients with orofacial clefts. *Braz Oral Res*. 2018;32(e24):1-12. doi:10.1590/1807-3107bor-2018.vol32.0024
- Siu SSN, Yeung J, Lau T. An in-vivo study on placental transfer of naproxen in early human pregnancy. *Hum Reprod*. 2002;17(4): 1056-1059. doi:10.1093/humrep/17.4.1056
- Souza J, Raskin S. Clinical and epidemiological study of orofacial clefts. *J Pediatr*. 2013;89(2):137-144. doi:10.1016/j.jpmed.2013.03.010
- Spinder N, Prins JR, Bergman JEH, Smidt N, Kromhout H, Boezen HM, de Walle HEK. Congenital anomalies in the offspring of occupationally exposed mothers: a systematic review and meta-analysis of studies using expert assessment for occupational exposures. *Hum Reprod (Oxf Engl)*. 2019;34(5):903-919. doi:10.1093/humrep/dez033
- Strauss RP, Broder H. Children with cleft lip/palate and mental retardation: a subpopulation of cleft-craniofacial team patients. *Cleft Palate-Craniofac J*. 1993;30(6):548-556.
- Thulstrup AM, Bonde JP. Maternal occupational exposure and risk of specific birth defects. *Occupat Med*. 2006;56(8):532-543. doi:10.1093/occmed/kql115
- Tillman KK, Hakelius M, Höijer J, Ramklint M, Ekselius L, Nowinski D, Papadopoulos FC. Increased risk for neurodevelopmental disorders in children with orofacial clefts. *J Am Acad Child Adolesc Psychiatry*. 2018;57(11):876-883. doi:10.1016/j.jaac.2018.06.024
- Torres EA, Gómez G, Pinzón Z. Asociación entre el consumo de cigarrillo y alcohol en la gestante como factor de riesgo para labio y/o paladar hendido no sindrómico. *UstaSalud*. 2012;11(2):88-94. doi:10.15332/us.v11i2.1121
- van Gelder MMHJ, Roeleveld N, Nordeng H. Exposure to non-steroidal anti-inflammatory drugs during pregnancy and the risk of selected birth defects: a prospective cohort study. *PLoS One*. 2011;6(7):1-8. doi:10.1371/journal.pone.0022174
- Venkatesh R. Syndromes and anomalies associated with cleft. *Indian J Plast Surg*. 2009;42(suppl):S51-S55.
- Vieira AR, Cooper ME, Marazita ML, Castilla EE, Orioli IM. Reduced folate carrier 1 (RFC 1) is associated with cleft of the lip only. *Braz J Med Biol Res*. 2008;41(8):689-693. doi:10.1590/S0100-879X2008000800009
- Watkins SE, Meyer RE, Strauss RP, Aylsworth AS. Classification, epidemiology, and genetics of orofacial clefts. *Clin Plast Surg*. 2014;41:149-163.
- Xu DP, Qu WD, Sun C, Cao RY, Liu DW, Du PG. A study on environmental factors for nonsyndromic cleft lip and/or palate. *J Craniofac Surg*. 2017;29(2):364-367. doi:10.1097/SCS.00000000000004214
- Yang W, Carmichael SL, Roberts EM, Kegley SE, Padula AM, English PB, Shaw GM. Residential agricultural pesticide exposures and risk of neural tube defects and orofacial clefts among offspring in the San Joaquin Valley of California. *Am J Epidemiol*. 2014; 179(6):740-748. doi:10.1093/aje/kwt324
- Yeziro-Rubinsky S, Eslava-Schmalbach JH, Otero L, Rodríguez-Aguirre SA, Duque ÁM, Campos FM, Gómez JP, Gómez-Arango S, Posso-Moreno SL, Rojas NE, et al. Dental anomalies in permanent teeth associated with nonsyndromic cleft lip and palate in a group of Colombian children. *Cleft Palate-Craniofac J*. 2020; 57(1):73-79. doi:10.1177/1055665619861498
- Zamora CE, Soriano JN. Evaluación del peso al nacer en 92 niños con fisuras del labio y del paladar. *Rev Cubana Pediatr*. 2013;85(2): 173-179.