LUPINE PUBLISHERS

Interventions in Pediatric Dentistry Open Access Journal

DOI: 10.32474/IPDOAJ.2023.08.000283

ISSN: 2637-6636

Review Article

Cleft Lip and Palate and their Genetic Relationship

Solano Nicolas1, Macias, Gabriela[2]*, Sierraalta Maria[3], Ramos Salomon[4], Patricia Lopez[1] and Roger Hidalgo[5]

[1]*DDS, Department of Oral and Maxillofacial Surgery Unit, Autonomous Hospital Service University of Maracaibo, Venezuela Postgraduate Residency Training Program in Oral Surgery, La Universidad del Zulia, Venezuela*

[2]*DDS, Postgraduate Residency Training Program in Oral Surgery, The University of Zulia, Venezuela*

[3]*DDS, Pediatric Dentist, Postgraduate Residency Training Program in Oral Surgery. Madre Rafols Hospital, Venezuela*

[4]*DDS, Oral Surgeon, Postgraduate Residency Training Program in Oral Surgery. Madre Rafols Hospital, Venezuela*

[5]*DDS, Oral and Maxillofacial Postgraduate Residency Training Program. Hospital Dr Adolfo Prince Lara, Venezuela*

***Corresponding author:** Macias Gabriela, Department of Oral and Maxillofacial Surgery. Dentistry Service. University Hospital of Maracaibo, Venezuela*

Received: December 19, 2022 **Published:** January 20, 2023

Abstract

Cleft lip and palate are congenital malformations, caused by a failure in the fusion of facial processes during crucial periods in embryonic development. In Venezuela, every day, two children are born with a cleft lip and palate and one with a cleft palate. It is estimated that by 2030, the number of people with this risk will be 24,035.

Aim: To describe the etiology of this malformation, as well as its genetic and environmental commitment.

Method: This research is a descriptive review of the literature with a retrospective bibliographic design. For the collection of information, a review of the PubMed, Scielo and EBSCO databases was carried out. The search yielded 67 related articles; it was carried out in the month of June 2022 electronically.

Results: There is sufficient scientific evidence to show that different genetic factors along with environmental factors may play an important role in the etiology of cleft lip and palate (CLP).

Conclusions: It is important for the mother and the health team to adequately carry out prenatal control, to prevent any condition that determines maternal and perinatal morbidity.

Keywords: Cleft lip and palate; congenital anomalies; malformation; genetics; environmental

Introduction

Cleft lip and palate, also known as cleft lip and palate, is the most frequent congenital craniofacial malformation, produced by a failure in the fusion of facial processes during crucial periods in embryonic development [1]. The etiology of cleft lip and palate (CLP) is complex and involves both genetic and environmental factors [2]. In addition to the occurrence of clefts, numerous studies have reported the presence of dental anomalies in association with various forms of cleft lip, palate, or both [3], which cause dental malocclusion, problems with masticatory function, and abnormalities in eruption, increasing the risk of impacted teeth [4]. CLP is one of the most frequent congenital anomalies in men and stands out for its long life expectancy and its complex etiology. Asian and South American populations record the highest prevalence rates of this entity (1/500-1/700) [5]. Various epidemiological studies have shown that an average of 3% of newborns have some type of congenital malformation at the time of delivery. Within

these congenital malformations, cleft lip and palate is one of the most predominant. The Latin American Collaborative Study of Congenital Malformations (ECLAMC) showed a global rate of around 10.49 × 10,000. For this malformation, the countries with the highest incidence and prevalence are Bolivia, Ecuador and Paraguay [6]. CLP can be divided into syndromic (SCLP) or non-syndromic (NSCLP), depending on the presence or absence of other physical or developmental defects in the individual. Syndromic cases can in turn be divided into chromosomal syndromes (more than 350 Mendelian disorders), teratogenic (alcohol, drugs) and uncategorized6, but it has been reported that 70% of cases of cleft lip with/without cleft palate are of non-syndromic origin and 30% of cases of isolated cleft palate are of syndromic origin [7]. The repercussions of this malformation are negatively reflected in feeding, nasal breathing, alterations in facial growth, phonation, hearing, as well as affectations in dental development, in addition to the fact that people are more prone to caries and periodontal disease [8]. The treatment of cleft lip and palate implies a multidisciplinary management, directed mainly by the reconstructive maxillofacial surgery area that generates high social and economic costs.

Methodology

This research is a descriptive review of the literature with a retrospective bibliographical design. For the collection of information, a review of the PubMed, Scielo and EBSCO databases was carried out. The search yielded 67 related articles; it was carried out in the month of June 2022 electronically. The criteria for selection included review articles, clinical studies, epidemiological investigations, without a publication time period. The descriptors for the search were cleft lip, cleft palate, genetic factors. Articles were selected based on content regardless of year of publication. Only 13 articles were included as a sample for the presentation of results.

Results

Worley et al.9, in 2018, reported that the cleft lip and palate is a congenital craniofacial malformation that is caused by the lack of partial or complete fusion of the embryonic facial processes during the first weeks of embryonic development, the jaws and soft tissues are also affected. Cleft palate occurs when the fusion of the anterior and posterior palates does not occur properly, leaving a connection between the oral cavity and the nasal cavity. It can extend from the anterior part of the hard palate to the soft palate. Rai [10], in a publication indicates that this congenital malformation occurs specifically at two points of embryonic development. Between week five and seven of gestation due to the absence of fusion of the frontal processes and between week seven and [12] due to the absence of fusion of the palatine processes; or due to inadequate formation of structural tissue (either bone or soft tissue, structures such as the lip, palate, alveolar ridge). Berryhill et al. [11], in 2016, cites that these alterations occur for two reasons, on the one hand, we have the genetic component and on the other, the environmental part.

a) Genetics: In this component we find subdivisions according to the type of inheritance that converge in the cleft lip and palate [12].

b) Monogenic inheritance: Autosomal dominant, autosomal recessive, X-linked recessive, X-linked dominant, and Y-linked dominant.

c) Polygenic inheritance: This is the most common cause of cleft lip and palate.

This inheritance is understood as those traits controlled by a large number of genes, but at the same time they can be affected and influenced by the environment. This theory is reaffirmed, since several studies have shown that the majority of mothers of children with cleft lip and palate had a history of taking drugs such as NSAIDs or anticonvulsants (phenytoin), a history of recurrent abortions, maternal age at risk, psychiatric pathologies (such as depression) and even gestational diabetes, showing the association between the genetic component and the external environmental component in organogenesis and embryo development.

Chromosomal aberrations

Environmental: They are subdivided according to the type of aggression to which a pregnant patient may be exposed, which alters the organogenesis and structuring process in the product of conception, having the behavior of teratogenic agents. These can be physical, chemical and biological aggressions. Van den Bosch et al. [12], Some studies have begun to demonstrate the association between maternal malnutrition and the presence of newborns with cleft lip and palate. The study by Gutiérrez and Otero [13] Genetic etiology of cleft lip and palate and hypodontia. Entities that share the same gene? published in 2006 in its results, it indicates that the cleft lip occurs when there is an incomplete closure of the lip that involves the vermilion or the cutaneous portion of the lip. This fissure may compromise only the free edge of the vermilion (incomplete fissure) and may extend to the floor of the nostrils (complete fissure). Most incomplete clefts and all complete clefts involve the insertion of the orbicularis oris and may present unilaterally or bilaterally.

Both the cleft lip that includes the palate (CLP) and the cleft lip that does not include it (CL) have been considered a genetic and embryologically different entity from the isolated cleft palate (CP), although none of the two entities has yet been identified completely, the model of inheritance and the sociodemographic variables that act as teratogenic factors in the development of these two pathologies. These researchers Gutiérrez and Otero13, in their study cite results provided by researchers such as: Kaartinen [14], Wyszynski [15] and Blanco [16]; where they refer that genes definitely play a determining role in the normal and pathological development of craniofacial structures, for this reason the knowledge of their pathophysiology leads to a better understanding of the mechanisms involved in their neoformation. To date, more than 20 genes related to the CLP etiology of non-syndromic origin (NSCLP) have been described and the list continues to grow, reflecting the complexity

of the mechanisms involved in the etiology of this entity. Among the genes that can be highlighted are TGFA (transforming growth factor alpha), TGFB3 (transforming growth factor beta 3), Ap-2 (retinoic acid-dependent transcription factor) and MSX1. When the structure or function of any of these genes is altered, an orofacial cleft can occur. Genetics and embryology suggest that clefts of the hard palate involve different mechanisms than clefts that affect the soft palate [15].

Alterations in the MSX1 gene appear to play an important role in the development of NSCLP. This gene is involved in the craniofacial and dental development of the human embryo19-20. In a recent study, Blanco et.al. [16], demonstrated that the genetic variation of the MSX1 locus predisposes to NSCLP with different manifestations depending on the evidence or not of other affected relatives, additionally they observed a component of sexual dimorphism with respect to four allelic variants of the gene MSX1 in patients with cleft lip and palate. Viera et al. [17], indicates that the mutations reported in the MSX-1 gene contributed to the development of cleft lip and palate in the Brazilian population and proposed an interaction between the MSX-1 gene and the TGFB3 gene, as risk factor for developing NSCLP. Jugessur et al. [18], (2003) also reported a slight association between one of the allelic variants (N4) of the MSX-1 gene and NSCLP, in a case-control study carried out with trios of patients affected with cleft lip/palate in the Norwegian population. However, this association appears to be evident only when an allelic variant of the TGFA gene (N2) is present. Lidral et al. [19], also suggest a positive association between mutations and allelic variants found in the MSX-1 gene with the susceptibility of presenting NSCLP in the Filipino population. Marazita et al. [20], They do not report a positive association between the MSX-1 gene and NSCLP in the Chinese population.

Scapoli et al. [21], They do not find a positive association between MSX-1 and the Italian population. Beaty et al. [22], In a study carried out with trios of parents and children with NSCLP, they observed the possible association between the MSX-1 gene, the TGFB3 gene and the presence of cleft. Their results not only demonstrated an association between MSX-1 and NSCLP, but also a possible interaction between this gene and cigarette consumption, in the cases of patients born to mothers who smoke. On the other hand, in their findings, the interaction between MSX-1 and TGFB3 in patients with NSCLP was not evidenced. Romitti et al. [23], demonstrated a positive interaction between the MSX-1 gene and alcohol and cigarette consumption in the mother, as risk variables to trigger NSCLP. Mitchell et al. [24], did not find a positive interaction between MSX-1, TGFB, and alcohol and cigarette consumption as risk factors for developing this pathology. Although they were able to determine a positive association between the MSX-1 gene and the possibility of developing NSCL. Summarizing, Gutiérrez and Otero [13] state that the differences found in the studies carried out in various populations probably have their answer in the ethnic and sociodemographic differences that exist between the different peoples and regions. Murray [25] and Vieira [17] refer that the differences between the studies carried out could possibly be due to the different mutations and polymorphisms found in the MSX-1 gene, and to the possible multigenetic origin of NSCLP.

Finally, Pérez-González et al. [26] state that there is sufficient scientific evidence to show that different genetic factors, along with environmental factors, may play an important role in the etiology of cleft lip and palate (CLP).

Discussion

There is evidence showing that genetic factors play a primary role in the etiology of cleft lip and palate (CLP), along with other conditioning factors. The literature expresses that the etiology of cleft lip and palate is multifactorial and may be affected by both genetic and environmental causes. Smoking, alcoholism and nutritional deficiencies of the mother, age of both mother and father are also considered as factors. It is important for the mother and the health team to properly carry out prenatal care to prevent any condition that determines maternal and perinatal morbidity.

References

1. Palmero PJ y col (2019) Labio y paladar hendido. Acta Médica Grupo Ángeles 17(4): 372-379.
2. Ranta R (1982) Comparison of tooth formation in noncleft and cleft-affected children with and without hypodontia. ASDC J Dent Child 49: 197-199.
3. Shapira Y, Lubit E, Kuftinec MM (2000) Hypodontia in children with various types of cleft. Angle Orthod 70: 16-21.
4. Becker A, Ziberman Y, Tsur B (1984) Root length of lateral incisors adjacent to palatally displaced cuspids. Angle Orthod 54: 218-225.
5. Carinci F, Pezzetti F, Scapoli L, Martinelli M, Carinci P, et al. (2002) Genetics of nonsyndromic cleft lip and palate: a review of international studies and data regarding the Italian population. The Cleft Palate-Craniofacial Journal 37(1): 33-40.
6. Palmero PJ y Rodríguez MF (2019) Labio y paladar hendido. Conceptos actuales. Acta Médica Grupo Ángeles 17(4): 372-379.
7. Young Greg MD (1998) Cleft lip and palate.
8. Gailey D (2016) Feeding infants with cleft and the postoperative cleft management. Oral Maxillofac Surg Clin North Am 28(2): 153-159.
9. Worley M, Patel K, Kilpatrick L (2018) Cleft lip and palate. Clin Perinatol 45(4): 661-678.
10. Rai V (2018) Strong association of C677T polymorphism of methylenetetrahydrofolate reductase gene with nosyndromic cleft lip/palate (nsCL/P). Indian J Clin Biochem 33(1): 5-15.
11. Berryhill W (2016) Otologic concerns for cleft lip and palate patient. Oral Maxillofac Surg Clin North Am 28(2): 177-179.
12. Van den Bosch S, Koudstaal M, Versnel S, Maal T, Xi T, et al. (2016) Patients and professionals have different views on online patient information about cleft lip and palate (CL/P). Int J Oral Maxillofac Surg 45(6): 692-699.
13. Gutiérrez y Otero (2006) Etiología Genética Del Labio Y Paladar Fisurado E Hipodoncia, ¿Entidades Que Comparten Un Mismo Gen? Univ Odontol 25(57): 34-40.
14. Kaartinen V, Voncker JW, Shuler C (1995) Abnormal lung development and cleft palate in mice lacking TGF-B3 indicates defects of

ephitelialmesenchymal interaction. Nature Netet 11: 415-421.

15. Wyszynski DF, Maestri N (1996) Genetics of nonsyndromic oral clefts revisited. J Cleft palate Craniofacial 33: 406-417.

16. Blanco R, Chakraborty R, Barton SA (2001) Evidence of a sex dependent association between the MSX1 locus and nonsyndromic cleft lip with or without cleft palate in the Chilean population. H Biol 73(1): 81-89.

17. Vieira AR, Orioli IM, Castilla EE, Cooper ME, Marazita ML, et al. (2003) MSX1 and TGFB3 contribute to clefting in South America. J Dent Res 82(4): 289-292.

18. Jugessur A, Lie RT, Wilcox AJ, Murray JC, Taylor JA, et al. (2003) Variants of developmental genes (TGFA, TGFB3, and MSX1) and their associations with orofacial clefts: a case-parent triad analysis. Genet Epidemiol 24(3): 230-239.

19. Lidral AC, Murray JC, Buetow KH, Basart AM, Schearer H, et al. (2002) Nonsyndromic cleft lip with or without cleft palate in China: assessment of candidate regions. Cleft Palate Craniofac J 39(2): 149-156.

20. Scapoli L, Martinelli M, Pezzetti F, Carinci F, Bodo M, et al. (2002) Linkage disequilibrium between GABRB3 gene and nonsyndromic familial cleft lip with or without cleft palate. Hum Genet 110(1): 15-20.

21. Beaty TH, Hetmanski JB, Zeiger JS, Fan YT, Liang KY et al. (2002) Testing candidate genes for nonsyndromic oral clefts using a case-parent trio design. Genet Epidemiol 22(1): 1-11.

22. Romitti PA, Lidral AC, Munger RG, Daack-Hirsch S, Burns TL, et al. (1999) Candidate genes for nonsyndromic cleft lip and palate and maternal cigarette smoking and alcohol consumption: evaluation of genotype-environment interactions from a population-based case-control study of orofacial clefts. Teratology 59(1): 39-50.

23. Mitchell LE, Murray JC, O'Brien S, Christensen K (2001) Evaluation of two putative susceptibility loci for oral clefts in the Danish population. Am J Epidemiol 153(10): 1007-1011.

24. Murray JC (1995) Face facts: genes, environment, and clefts. Am J Hum Genet 57: 227-232.

25. Vieira AR, Castillo Taucher S, Aravena T, Astete C, Sanz P, Tastets ME, et al. (2004) Mutational analysis of the muscle segment homeobox gene 1 (MSX1) in Chilean patients with cleft lip/palate. Rev Med Chil 132(7): 816-822.

26. Pérez-González Araceli, Lavielle-Sotomayor Pilar, Clark Patricia, Tusie-Luna María Teresa, Palafox Damián (2021) Factores de riesgo en pacientes con fisura de labio y paladar en México. Estudio en 209 pacientes. Cir plást Iberolatinoam 47(4): 389-394.

DOI: 10.32474/IPDOAJ.2023.08.000283