Annals of Surgical Education

ISSN: 2692-7926

Research Article

Environmental and Genetic Risk Factors of Nonsyndromic and Syndromic Cleft Lip and Palate - A Literature Review

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Abstract

Orofacial clefts encompass a range of congenital abnormalities of the orofacial region which commonly presents as cleft lip with or without Cleft Palate (CLP) or isolated cleft palate. Studies on CLP have implicated a multifactorial etiology involving environmental factors, teratogens and genetics. The aim of this literature review was to determine the currently accepted etiologic factors of CLP. We conducted literature searches for articles on the environmental risk factors, teratogenic effects and genetic factors implicated in both non-syndromic and syndromic CLP. Etiologic factors of CLP were itemized according to environmental factors implicated in the etiology of CLP, teratogenic effects implicated in the etiology of CLP, genetic factors implicated in the etiology of non-syndromic CLP and their genetic basis and some of the more common syndromes associated with CLP and their underlying genetic basis. This review not only brings to the fore, the wide array of etiologic factors implicated in cleft lip and palate but also highlights the vast amount of data on etiology of cleft lip and palate still being collected and studied.

Keywords: Environmental factors; Genetic factors; Cleft lip and palate

Introduction

Orofacial Clefts (OFC) encompass a range of congenital abnormalities of the orofacial region which commonly presents as cleft lip with or without Cleft Palate (CLP) or isolated Cleft Palate (CP). OFC is recognized as the most common craniofacial diagnoses in humans with a worldwide prevalence of 1.2/1,000 live births [1] but can be up to 1/700 live births [2]. Generally, CLP presents as complete (involves the entire vertical height of the lip including the nasal floor) or incomplete (involves only part of the vertical height of the lip) unilateral, median or bilateral discontinuity of the lip with or without alveolus and palate involvement. CLP may present as an isolated congenital anomaly or may be part of a syndrome with affected individuals presenting with other congenital anomalies [2]. Non-syndromic forms are the best studied and occur in 70% of cases [3,4]. The remaining 30% of newborns with CLP have additional congenital anomalies occurring as part of a syndrome [3,4].

The etiology of CLP has been a major area of study among clinicians and geneticists for years in both developed and developing countries [5]. Results from these studies [5-8] suggest that CLP has a multifactorial etiology with environmental factors, teratogens and genetics being implicated. Although the exact etiological factor causing CLP in a particular patient may not be easily identified, it's usually predisposed by a combination of environmental factors, teratogens and genetics [5]. An understanding of these etiologic factors will guide clinicians in counseling of patients and their caregivers as well as encourage more health promoting behaviors in pregnant women and women of child bearing age in general. Therefore, the aim of this literature review was to determine the currently accepted etiologic factors of cleft lip and/or cleft palate.

Methodology

Literature searches were conducted in PubMed (NLM), Cochrane, Ovid Medline, OpenGrey and Google scholar databases to identify publications on etiologic factors of cleft lip and palate published till June 2021. The following search strategy was used for PubMed (NLM): (cleft lip and palate OR orofacial cleft OR cleft lip OR cleft palate) AND (etiological factors OR risk factors OR environmental factors OR genetic factors) AND (cleft syndromes OR syndromic cleft). Similar search strategies were used for other database searches. Due to the large number of CLP related publications, the inclusion criteria used for screening were articles written in English language, which reported on the etiologic risk factors of CLP.

The titles and abstracts of all articles identified through the electronic database searches were screened. Studies that fulfilled the inclusion criteria were selected and their abstracts and/or full texts obtained. Data extraction was done if the paper provided original data regarding etiology of CLP in accordance with the aim of this review and when available, qualitative and quantitative analysis of study data was extracted and reported. The reference section of selected studies was also hand-searched for relevant citations and results of these studies were also included in the review.

Results

CLP has a complex etiology which may include any combination of environmental factors, teratogenic effects of drugs, chemicals, chronic diseases or infections, and genetic factors [5-8]. Environmental risk factors such as maternal smoking, maternal alcohol consumption and vitamin deficiency, particularly folic acid deficiency have been

Citation: Egbunah UP. Environmental and Genetic Risk Factors of Nonsyndromic and Syndromic Cleft Lip and Palate - A Literature Review. Ann Surg Edu. 2022;3(1):1025.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Jan 12th, 2022

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associated with cleft lip and palate development [9]. The teratogenic effects of corticosteroids, vasoactive drugs (dopamine, adrenaline, aspirin, and ibuprofen), anticonvulsants, chemical exposure to pesticides and cosmetics, diabetes mellitus and infections causing fever above 400C have all been implicated in fetal cleft development [10]. Implicated genetic factors of CLP may or may not present with associated syndrome [10].

Environmental factors implicated in the etiology of cleft lip and palate

Smoking: Several studies have consistently yielded a relative risk of fetal cleft development of 1.3-1.5 in pregnant women who smoke [11]. However, the relationship between maternal smoking and CLP though significant, is not strong when smoking is the only etiologic factor [10]. When maternal smoking and a positive genetic background were considered together, the combined effect was more significant [10]. Similarly, a study by van Rooij et al. [12] found that maternal smoking combined with maternal glutathione s-transferase (GSTT1) genotype, significantly increased the risk of CLP with an odds ratio of 4.9. Beaty et al. [13] reported that maternal smoking and infant *MSX1* genotypes had a synergistic effect, increasing the risk of CLP development by 7.16 times.

Alcohol consumption: Heavy maternal drinking, in addition to causing fetal alcohol syndrome may increase the risk of CLP in developing fetus [10]. Studies have shown that CLP is 1.5-4.7 times more likely to develop in a dose-dependent manner when pregnant women consume alcohol [14]. And pregnant women who consume more than five drinks per occasion are 3.4 times more likely to have children with CLP [15]. Low level alcohol consumption, however, does not seem to increase the risk of CLP development [16].

Vitamin deficiency: Vitamin deficiency, particularly folic acid and cobalamin triple the risk of CLP development especially during the first trimester of fetal development [17]. Studies have shown that even low dose folic acid supplementation by folic acid fortified food products e.g. cereal grains cannot effectively protect against fetal CLP development [18]. However, high dose folic acid, taken as antenatal supplements (10 mg/day) significantly reduces the risk of CLP development by 65% [19]. The risk of CLP is further increased when folic acid deficiency is present with a pre-existing fetal TGFA TaqI C2 genotype [20]. Also, reduced metabolism of the maternal vitamin-dependent homocysteine increases risk of CLP in the offspring [10]. This was confirmed by a case-control study which reported higher level of homocysteine and lower level of whole-blood vitamin B6 in mothers of CLP children [21].

Teratogenic effects implicated in the etiology of cleft lip and palate

Corticosteroids: They are commonly used in the management of several conditions in women of child bearing age. However, they have also been implicated in the development of CLP when administered to pregnant women [10]. The clefting role of corticosteroids has been proven extensively in animal studies; glucocorticoids induced CLP in the progeny of pregnant mice, [22] cortisone induced CP, [23] and triamcinolone hexacetonide induced teratologic effects on lip morphogenesis [24]. Several human studies over the years have corroborated this evidence. Studies have shown an association between peri-conceptional (one month before conception to three months after conception) use of corticosteroids and infant anomalies in general particularly CLP [25-28]. The study by Park-Wyllie et al. [29] reported that even at therapeutic doses, prednisolone increases the risk of fetal CLP development by 3.4 folds.

Vasoactive drugs: Several epidemiological studies have reported that maternal use of vasoactive drugs such as NSAIDs (aspirin, ibuprofen); antiepileptic drugs (phenytoin); anti-psoriasis drugs (retinoids), anti-rheumatic drugs (hydroxychloroquine, methotrexate) and chemotherapeutics, particularly during the first trimester significantly increases the risk of fetal cleft development [30,31].

Anticonvulsants: Women with epilepsy have an increased risk of having offspring with CLP [32]. This could either be due to the teratogenic effects of anticonvulsants or may be due to underlying genetic factors associated with epilepsy [32]. A strong and significant correlation has been established between the use of anticonvulsants such as phenytoin/hydantoin, oxazolidinones, and valproic acid during pregnancy and development of fetal congenital anomalies [33]. A study by Saxen et al. [34] reported a significant increase in benzodiazepine use by mothers of children with CP and a non-significant increase for CLP. Another study reported association between diazepam exposure in first trimester and fetal clefting [35].

Chemical exposure: A study reported that about 30% of expectant women come in contact with chemicals from cleaning products, pesticides and cosmetics which may predispose to fetal clefting especially when exposure is during the first trimester of fetal development [36]. Garlantézec et al. [37] reported that exposure to harmful solvents present in these chemicals is associated with CLP formation. Studies have also reported an increased incidence of CLP in children of mothers working as hairdressers, farmers, and manufactures of leather or shoes where they were exposed to lead, aliphatic acids and other organic solvents [38,39].

Diabetes mellitus: Several studies [40-42] have identified metabolic diseases such as obesity, metabolic syndrome and diabetes mellitus as risk factors of fetal birth defects when seen in women during their periconceptional period. Gestational Diabetes Mellitus (GDM) is any degree of glucose intolerance developing for the first time during pregnancy [43]. It's diagnosed as elevated fasting plasma glucose levels on glucose tolerance testing at 24 to 28 weeks of gestation more commonly seen in obese women [44]. Studies have shown that obese and diabetic women are 3-times more likely to have children with craniofacial abnormalities; however, the exact mechanism is unclear [45]. In addition to GDM, preconceptional diabetes has been suggested as a risk factor for fetal orofacial cleft development [46]. Studies have reported an increased risk of craniofacial abnormalities of up to 80% in the offspring of mothers with long-standing poorly controlled diabetes diagnosed before pregnancy [47].

Infections: An increased risk of craniofacial anomalies following hyperthermic exposure during early stage pregnancy has been confirmed in animal studies but human population studies still yield conflicting results [48]. A study by Hashmi et al. [48] conducted on over 2,000 cleft patients reported that fever of over 400C during the first trimester increased the risk of fetal cleft development 1.28 times with risk estimates being higher for women who had fever but did not control it with antipyretics. Adequate control of fever led to a reduced risk of CLP formation.

Genetic factors implicated in the etiology of non-syndromic cleft lip and palate

Transforming growth factor-alpha: Transforming Growth

Factor-Alpha (TGFA) was first associated with non-syndromic CLP in 1989 [49]. Several follow-up studies involving different races and ethnicities have given mixed results. Machida et al. [50] in a genetic analysis study sequenced the TGFA gene in a group of non-syndromic CLP patients and discovered five mutations etiological to non-syndromic CLP. However, the combined effect of TGFA mutations and the presence or absence of synergistic environmental factors may explain mixed results in follow-up studies [50]. The rare TGFA variant (TaqI C2 allele) increases the risk of CP 6-8 times [51] and increases the risk of CLP 2 times [52] when combined with maternal smoking. Also, if the fetus has the TGFA TaqI C2 allele and multivitamins are not consumed during the first trimester, it increases the relative risk of fetal orofacial cleft formation 3 to 8 times [53].

Transforming growth factor-beta-3: Animal studies revealed that mutations of the transforming growth factor-beta-3 (TGFB3) led to defective adhesion of palatal shelves leading to CP development [54]. This result was corroborated by two human studies in different populations [55,56]. A Single Nucleotide Polymorphism (SNP) of TGFB3 (IVS5+104 A>G) has been associated with a16-times increased risk of CLP development [57].

Drosophila msx homeobox homolog-1: Several animal studies have shown that mutation of the autosomal dominant drosophila msx homeobox homolog-1 (*MSX1*) gene leads to development of CP and tooth agenesis [58]. In humans, *MSX1* mutation was first shown to cause tooth agenesis [59]. Follow-up familial studies revealed the presence of etiologic *MSX1* mutations in patients with cleft and tooth agenesis [60]. A large scale genetic sequence analysis reported that *MSX1* can be responsible for both CP and CLP formation and that *MSX1* is responsible for at least 2% of all non-syndromic clefts [61]. The study by Jugessur et al. [55] reported that gene-gene interaction between mutations of TGFA/TGFB3 and *MSX1* will increase the risk of fetal cleft development up to 9.7 times.

5, 10-Methylenetetrahydrofolate reductase: 5, 10-Methylene Tetrahydrofolate Reductase (MTHFR) is the enzyme responsible for conversion of 5, 10-methylene tetrahydrofolate into 5-methyl tetrahydrofolate in the folate metabolism pathway [10]. Mutation of this gene in pregnant mothers may cause inherent maternal folate deficiency increasing the risk of non-syndromic fetal clefting [62].

Other genes and chromosomal loci: Some other genes and chromosomal aberrations have been implicated in the etiology of non-syndromic clefts although supporting evidence is weak. The special *AT-rich sequence-binding protein-2 gene* (*SATB2*) located at chromosome 2q32-33 has been implicated in CP development [63]. The *acyl-coenzyme-A desaturase-4 gene (ACOD4)* located at chromosome 4q21 has been implicated in familial CLP [64]. The *cleft lip and palate-associated transmembrane protein-1' (CLPTM1) gene* located on chromosome 19q13 has also been implicated in non-syndromic CLP [65].

Syndromes associated with cleft lip and palate and their underlying genetic basis

There are about 400 known syndromes associated with CLP. Studies have noted varying amount of cleft associate with syndromes form about 1.5% to over 4% depending on population studied [66-68]. However, these studies all agree that their numbers irrespective of variability do not completely underestimates the true frequency with which CLP is associated with syndromes. Some of the more common syndromes associated with CLP are included below.

Van der woude syndrome and popliteal pterygium syndrome: Van Der Woude Syndrome (VDWS) is the most common form of syndromic CLP and is said to account for 2% of all CLP cases [69]. It is characterized by CLP/CP, pits or mucous cysts on the lower lip, and hypodontia. Popliteal Pterygium Syndrome (PPS) is a less common syndrome characterized by all the features of VDWS plus popliteal pterygium (webs of skin on the back of the knee joint preventing flexion), syngnathia, syndactyl (and other digit abnormalities) and genitourinary malformations [10]. Both syndromes exhibit phenotypic heterogeneity as not all associated features are present in all cases. The genetic loci for both VDWS and PPS have been linked to 1q32-q41 [70]. In addition, monozygotic twin studies of VDWS patients revealed that abnormality was the result of a point mutation in the *Interferon Regulatory Factor-6 gene (IRF6)*, located within the VDWS genetic locus [71]. This result was corroborated when mutations of IRF6 were discovered in 45 unrelated patients with VDWS as well as in 13 patients with PPS [71]. The variable presentations of VDWS and PPS can be explained by the different types of IRF6 mutations [10]. The *interferon regulatory factor 6 (IRF6)* genes is also associated with non-syndromic CLP4 in which specific parental alleles at the VDWS locus were preferentially transmitted to their progeny invariably leading to non-syndromic CLP [72].

Cleft lip/palate ectodermal dysplasia syndrome: Cleft Lip/Palate Ectodermal Dysplasia Syndrome (CLPED) is characterized by CLP, hidrotic ectodermal dysplasia (Clouston syndrome), syndactyly and mental retardation [10]. CLPED inheritance is autosomal recessive and mutations of the *poliovirus receptor-like-1 gene (PVRL1)* have been implicated [73]. Also, heterogenous mutation of the *PVRL1* (*W185X*) has been implicated in the etiology of non-syndromic CLP [74].

X-linked cleft palate syndrome: X-linked Cleft Palate Syndrome (CPX) has a variable presentation but generally presents as isolated cleft palate (high arched palate with bifid uvula) and ankyloglossia [10]. Genetic linkage analysis has identified the mutated gene locus on chromosome Xq21 [75]. Inheritance of this mutation is X-linked semi-dominant hence females may either be asymptomatic carriers or may exhibit full blown features of the disease. Extensive mutation analysis on mutated gene locus revealed mutations of the *T-box transcription factor-22 gene (TBX22)* as genetic etiologic factor [76].

Apert syndrome: Apert syndrome is a rare autosomal dominant disorder characterized by craniosynostosis, craniofacial abnormalities (including CLP, hypertelorism, proptosis, down-slanting palpebral fissures), midface hypoplasia and severe symmetrical syndactyly of the hands and feet [77]. Several studies have implicated S252W or P253R gain-of-function missense mutations of *Fibroblast Growth Factor Receptor-2 (FGFR2) gene* on chromosome 10q in the etiology of Apert syndrome [10,78].

Crouzon syndrome: Crouzon syndrome, also known as craniofacial dysostosis is a rare autosomal dominant disorder characterized by craniosynostosis, craniofacial abnormalities and syndactyly (less common compared to Apert syndrome) [79]. It is the mildest form of all craniosynostosis syndromes considered to be allelic to Apert syndrome as it is caused by mutations in *FGFR2* and *FGFR3* on chromosome 10q [10].

Hemifacial microsomia: Hemifacial microsomia also called craniofacial microsomia or Goldenhar syndrome is an asymmetric craniofacial malformation, variably affecting structures derived from

the first and second pharyngeal arches, characterized by structural abnormalities of the orbit, maxilla, mandible, external and middle ear, cranial nerves, and facial soft tissues [80]. The exact genetic etiology is unknown but the *Spalt Like Transcription Factor 1 (SALL1) gene* seen in Townes-Brocks syndrome has been implicated [81].

Frontonasal dysplasia: Frontonasal Dysplasia (FND) also called frontonasal malformation, median cleft face syndrome, frontorhiny is characterized by ocular hypertelorism, flat broad nose, a vertical groove along the midline of the face with or without a frontal bone defect (anterior cranium occultum). There are three genetically distinct types of FND: FND-1, FND-2 and FND-3. FND-1 is caused by mutations in the ALX3 gene; FND-2 by mutations in the ALX4 gene and FND-3 by mutations in the ALX1 gene. FND-1 and FND-3 are inherited in an autosomal recessive pattern while FND-2 is inherited in an autosomal dominant pattern. The phenotypic presentation of FND varies between the types and may vary greatly from person to person.

Median facial dysplasia: Median facial dysplasia is characterized by midline facial deformities plus unilateral, midline or bilateral cleft lip with or without cleft palate [82]. These midline facial deformities usually present as hypoplasia and may involve the frontal corpus callosum of the brain [83]. The midface is also characteristically hypoplastic, presenting as retrognathic, dished in maxilla in Class II skeletal pattern relationship.

Pierre robin syndrome: Pierre Robin Syndrome (PRS) now more correctly referred to as Pierre Robin sequence, is a rare congenital birth defect characterized by micrognathia, glossoptosis, and airway obstruction [84]. It may also present with other craniofacial abnormalities including CLP. It has been associated with deletion mutation on chromosome 2q32.3-q33.2 [85].

Treacher collins syndrome: Treacher Collins Syndrome (TCS) also known as mandibulofacial dysostosis and Franceschetti-Zwahlen-Klein syndrome is an autosomal dominant condition characterized by reduced growth of craniofacial structures derived from the first pharyngeal arch, groove and pouch, diminished symmetrically and bilaterally [86]. Typical features include hypoplasia of facial bones particularly the mandible and zygomatic complex, CLP, dental malocclusion, down-slanting palpebral fissures, notching of the lower eyelids, and alterations in the size, shape and position of the external ears [86]. The *Treacher Collins-Franceschetti syndrome 1 gene (TCOFI)* has been implicated in its etiology [87].

Velocardiofacial syndrome: Velocardiofacial Syndrome (VCFS) is an autosomal dominant condition associated with sub-microscopic deletion mutation on the long arm of chromosome 22 region q11 (deletion22q11) [83]. It occurs in approximately 0.05% of live births [88] with several phenotypic presentations as can affect every major organ in the body. The most common features include characteristic facial features (narrow palpebral fissures bilaterally, flattened malar eminence, maxillary prognathism, mandibular retrognathism, and microtia), cleft palate associated speech and feeding challenges, congenital cardiac anomalies and minor learning problems [83]. VCFS is significantly associated with DiGeorge syndrome which is also a chromosomal disorder caused by a defect in chromosome 22 [88]. It has similar features with VCFS including plus immune system dysfunction (due to small or absent thymus, tonsils, and adenoids), hypocalcemia and medially displaced carotid artery over the cervical vertebrae.

Stickler syndrome: Stickler syndrome is a hereditary connective tissue disorder characterized by vision impairment (myopia, retinal detachment), hearing impairment, underdeveloped midface and orofacial clefts, mitral valve prolapse and hyperextensible joints with eventual osteoarthritis [89]. It can be inherited in an autosomal dominant or autosomal recessive manner and is caused by genetic mutations in any one of six genes that code for collagen: COL2A1, COL11A1, COL11A2, COL9A1, COL9A2, or COL9A3 [90].

Down syndrome: Down syndrome also known as Trisomy-21 is a genetic disorder caused by deranged cell division which results in an extra genetic material on chromosome-21. The phenotype of Down syndrome comprises of several anomalies of varying presentation including brachycephaly, small head circumference, flat face, epicanthic fold, oblique palpebral fissures, single transverse palmar crease, and clinodactyly [91]. Congenital heart defects are also found in 33% of Down syndrome patients [91]. The study by Kallen et al. [91] also showed that CLP can be found in 0.45% of Down syndrome patient.

Conclusion

Orofacial clefts can either present in combination with other genetic anomalies or as lone standing conditions. Irrespective of its presentation, its etiology has been proven to involve environmental factors, genetic factors or both. Result of this review itemizes currently accepted environmental and genetic factors implicated in the etiology of non-syndromic and syndromic cleft lip and/or cleft palate. This review not only brings to the fore, the wide array of etiologic factors implicated in cleft lip and palate but also highlights the vast amount of data on etiology of cleft lip and palate still being collected and studied.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

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