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Anatomy

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OROFACIAL CLEFTING –AN EXTENSIVE REVIEW

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ABSTRACT

Groove in the palatal vault makes an abnormal communication between oral and nasal cavity is known as oro-facial cleft. It is an uncommon presentation in day-to-day clinical practice. According to World Health Organization, children with the complaint of oro-facial clefts found to be high in India. Children are commonly suffering from functional and aesthetical problems due to Oro-facial clefting. Globally, an estimated 200,000 babies are born with a cleft lip, palate or both each year in the United States. Etiology may be congenital or acquired. Palatal and Alveolar cleft defects are the most common etiological factors. Cleft lip and cleft palate can sometimes develop in combination with a syndrome due to genetic causes. The acquired causes may be infections, trauma, postsurgical complications, neoplasms, periapical pathology, radio and chemo necrosis. Clinical features like defective speech, and upper respiratory tract and ear infections, fetid odor, bad taste, nasal regurgitation of food are the associated consequences of oro-nasal communication. Therefore, this malformation syndrome is an important public health problem. Many cleft palate and cleft lip develops due to the combination of genetic and environmental factors. There are more than 400 genes linked to formation of cleft lip and palate. Some environmental factors associated with cleft includes medications, deficiency of folic acid ,cigarette, drugs or alcohol conception during pregnancy. In this article we review the anatomy ,embryology ,epidemiology clinical manifestations and treatment options of the oro-facial cleft .

Introduction

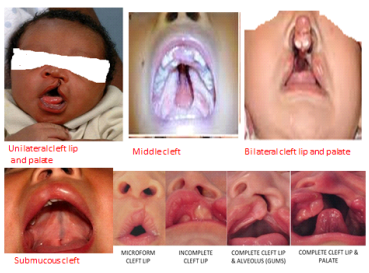
Orofacial cleft are the most common craniofacial malformation of the newborn . Orofacial clefts (cleft lip with or without cleft palate,[CL/P] or cleft palate only [CPO]) occur with a frequency as high as 1 in 700 live births and are the most prevalent birth defects affecting humans [1, 2]

The increased risk of death rate among infants is due to associated complications such as respiratory ,infection diseases, prematurity, and central nervous system abnormalities. In case of affected adults has an increased risk of heart disease, suicide, epilepsy and different tumors .3 It has been suggested that approximately 35,000 newborn cleft patients are added every year to the Indian population.4 Among the cleft lip and palate population, the most common diagnosis is unilateral cleft lip and palate (46%), followed by isolated cleft palate (33%). Cleft palates affect 1:2,000 live births worldwide regardless of race.5 This is in contrast to cleft lips, which show racial variability with the highest incidence in Asian and Native Americans (1:450 live births) and the lowest incidence in African Americans (1:2,000 live births). Isolated cleft palate occurs more in females (57%) than in males (43%). Gender differences may be related to differences in timing of embryologic development6. Etiology may be genetic, nutritional disturbances during development ,physiologic, emotional , traumatic stresses during development, defective vascular supply to the area involved .

Running title : Cleft Lip and Palate An Evidence-Based Review

Various environmental factors like infections eg rubella ,exposure to radiation drug like thalidomide, antiepileptic drugs. hormonal pills quinine, maternal conception of alcohol and smoking The American Cleft Palate Association recommend orofacial cleft management team members should have includes oral maxillofacial surgery ,audiology, anesthesiology, otorhinolaryngology, genetics, neurosurgery, pediatric, dentistry, nursing, ophthalmology, orthodontics, head and neck surgery, prosthodontics, pediatrics, speech-language pathology, physical anthropology, plastic surgery, psychiatry, psychology, and social work. 7 ,8,,9.

Types of Orofacial Cleft [Fig -1]



[Fig-1]

Cleft Classification

A cleft palate may classify on the basis of Morphological as well as Embryological

Morphological and Anatomical Classification

Davis and Ritchie proposed a simple three-group system[Fig.2] that allowed separate description of the lip, alveolus, and palate, using the alveolar process as a dividing line for their categorization: 10,11,12 Group 1: Alveolar process cleft (any cleft involving the alveolar process) a. Unilateral (right/left: complete/incomplete) b. Bilateral (right: complete/incomplete; left: complete/incomplete) c. Median (complete/incomplete) ,Group II: Post-alveolar process cleft (clefts affecting the palate) a. Soft palate b. Hard palate and Group III:Pre-alveolar process cleft (clefts affecting the lip) a. Unilateral (right/left: complete/incomplete) b. Bilateral (right: complete/incomplete; left: complete/incomplete) c. Median (complete/incomplete)

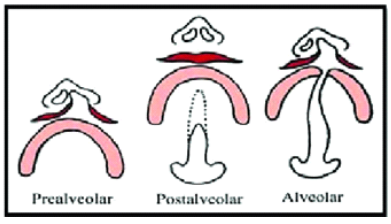


Fig.2 Davis and Ritchie's Classification.

Veau (1931), Victor Veau .The Veau System simply classified orofacial clefting into four morphological forms [Fig.3]by whether the secondary and/or primary palates are affected, Veau Class I: : Hard and soft palate [secondary palate only]up to the incisive foramen (no unilateral/bilateral designation) ,Veau Class II Incomplete cleft, soft palate only (no unilateral/bilateral designation), Veau Class III: Clefts of the soft and hard palate extending unilaterally through alveolar ridge including lip on one side (primary and secondary palates),Veau Class IV: Clefts of the soft and hard palate extending bilaterally through alveolus and lip on both side.[13,14,15]

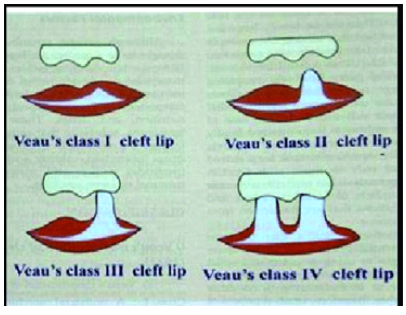


Fig.3. Veau's Cleft Lip/ palate Classification.

Embryological Classification

Fogh-Andersen proposed four groups,1. Harelip (single or double) 2. Harelip with cleft palate 3. Isolated cleft palate 4. Rare atypical clefts, e.g., median cleft lip. 16,17,18 .Classification by (Kernahan, 1991,). Kernahan and Stark proposed three groups [Fig -4] Group-I Cleft of the primary & secondary palate Unilateral - Total, Sub-total (ii) Median - Total, Sub-total (iii) Bilateral -Total, Sub-total Group-II Cleft of the secondary palate only (i) Total (ii) Sub-total (iii) Submucous Group-III Cleft of the primary palate only (i) Unilateral (ii) Bilateral (iii) Total (iv) Sub-total [19,20,21]

Classification by Spina 22,23,24 Group I Pre-incisive foramen clefts (i) Unilateral (ii) Bilateral (iii) Median Group-II Post-incisive foramen clefts (i) Total (ii) Partial Group-III Tran-incisive foramen clefts (i) Unilateral (ii) Bilateral Group-IV Rare facial clefts.

American Cleft Palate–Craniofacial Association (ACPA) classification: 1. Clefts of the prepalate (cleft of lip and embryologic primary palate) a. Cleft lip (cheiloschisis) b. Cleft alveolus (alveoloschisis) c. Cleft lip, alveolus, and primary palate (cheiloalveoloschisis) 2. Clefts of the palate (cleft of the embryologic secondary palate) a. Cleft of the hard palate (uranoschisis) b. Cleft of the soft palate (staphyloschisis or veloschisis) c. Cleft of the hard and soft palate (uranostaphyloschisis) 3. Clefts of the prepalate and palate (alveolocheilopalatoschisis) 4. Facial clefts other than prepalatal and palatal a. Cleft of the mandibular process b. Naso-ocular clefts c. Oro-ocular clefts d. Oroaural clefts.Classification of the lip, alveolus, and palate (based on embryologic principles): 1. Clefts of the anterior (primary) palate 2. Clefts of the anterior (primary) and posterior (secondary) palates 3.Clefts of the posterior (secondary) palate Classification of rare facial clefts (based on topographical findings): A. Median clefts of the upper lip, with/without hypoplasia or aplasia of the premaxilla.

Anatomy

The primary palate present anterior to the incisive fossa , includes the alveolar arch. The secondary palate includes the hard and soft palates. The hard palate is formed by the palatine processes of the maxillae and by the horizontal lamina of the palatine bones. Which is covered by oral and nasal mucosa. The chief blood supply is from the greater palatine artery, which is the branch of internal maxillary artery (internal carotid system) and passes through the greater palatine foramen. Sensory supply is by the anterior palatine and nasopalatine nerves.25 The soft palate (velum) is a fibromuscular shelf made up of five muscles attached as a sling to the posterior portion of the hard palate. It functions to elevate the nasopharynx, effectively closing the communication from the nasopharynx to the oropharynx. It also serves as the anterior wall of the velopharyngeal port, a sphincter mechanism of which the posterior and lateral walls consist of the superior pharyngeal constrictor. This muscular valve aids in breathing, blowing, swallowing, and phonation. The velum consists of the tensor veli palatini muscle innervated by the mandibular nerve, which is the third branch of the trigeminal cranial nerve.26,27 The levator veli palatini muscle is innervated by the pharyngeal plexus ,However some other authors state that this plexus receives contributions from the glossopharyngeal and vagus nerves which elevates the palate.28.29.. The uvulus muscle (CN IX, X), which pulls the uvula cranially and anteriorly and the palatoglossus innervated by the pharyngeal branch of the vagus nerve (CN X)and elevate the posterior portion of the tongue30.31. It also draws the soft palate inferiorly with the palatopharyngeus muscles, The muscle receives motor innervation from the cranial portion of the accessory nerve (CN XI). This occurs via the pharyngeal plexus with branches from the vagus nerve (CN X) and glossopharyngeal nerve (CN IX). which draw the palate inferiorly and constrict the pharynx.32A cleft palate spans many degrees of severity and can include the soft palate, hard palate, and alveolus. Clefting disrupts the palatal sling secondary to abnormal insertions of the soft palate muscles into the posterior margin of the remaining bony palate rather than the midline raphe. As a result, the affected individual loses velopharyngeal competence, which may lead to potential speech distortion, such as nasal air emission and hypernasality.33 Eustachian tube control is often lost as well, manifesting such as recurrent otitis media .[34]

Embryology

Palatogenesis begins at the end of the 5th week and the development of the palate is not completed until the 12th week. 35 The palate develops from two primordial, the primary and the secondary palate. The most important cell types in palate development are the neural crest derived palatal mesenchyme, ectoderm-derived epithelial lining and the most apical layer composed of periderm cells36The soft palate also includes the cranial paraxial mesoderm derived myogenic cells.. The palate begins to form during the fifth week and is not completed until the

twelfth week of gestation. The most critical stage is between weeks 6 and 9. During 6th week, the maxillary prominences merge with the medial nasal prominences beneath the nasal pits, [Fig -5] forming a wedge-shaped mass of mesenchymal tissue. As this mass of tissue grows, it separates the future nostrils from the upper lip and becomes the median palatine process or primary palate . The primary palate is located immediately behind the gum and gives rise to the four central incisors and extends to the foramen incisivum.Approximately the same time as the midline epithelial cells die, the epithelia on the nasal aspect of the palate differentiate into pseudostratified ciliated columnar cells, whilst those on the oral aspect of the palate become stratified squamous, nonkeratinizing cells. The secondary palate develops from the paired lateral palatine processes By twelve weeks, fusion is complete and extends from the maxillary and palatine bones to the palatal shelves, forming the hard palate. Fusion proceeds in a posterior direction from the incisive foramen with the fusion of the maxilla and vomer to form the bony hard palate completed by the ninth week of gestation. This process continues into the 12th week ,till when the soft tissues present posterior to the hard palate meet to form the soft palate. Lack of fusion of the palatal shelves results in clefts of the secondary palate.37,38The posterior parts do not become ossified and extend posteriorly and fuse to form the soft palate,including the uvula.39Although CL and CP often occur together, they have different embryologic origins. Cleft lip results from a failed merging of the maxillary and medial nasal elevations on one or both sides due to the inadequate migration of neural crest cells. Cleft palate results from the failure of the lateral palatine processes to meet and fuse with each other. This can be the result of 1) defective growth of the palatal shelves,

2) failure of the shelves to rise above the tongue, 3) lack of contact between shelves (excessively wide head), 4) failure to fuse or 5) rupture after fusion of the shelves. If the migration fails to occur, or if there is an absence or inadequacy of related cells, clefts and other facial abnormalities may result.40 normally in , children with clefts have a deficiency of tissue, not merely a displacement of normal tissue.41A specific variant of cleft palate, independent of lip formation, results from the failure of tongue dissent due to obstruction from an underdeveloped maxilla. This is known as Pierre Robin sequence, and manifests as a large U-shaped palatal cleft.42,43The female palate is known to close one week later than the male palate, an observation that may explain why isolated clefts are more common in females than males. cleft lip with cleft palate is the most common presentation of orofacial clefting. There is considerable sex difference in the timing of palatal closure. Shelf elevation and fusion begin a few days earlier in males than in females44They have a complex etiology in which both genetic and environmental factors play a role. Risk factors such as vitamin deficiency, especially folic acid deficiency, and maternal smoking, alcohol consumption, drug use, and chemical exposure have been associated with cleft lip and palate development.

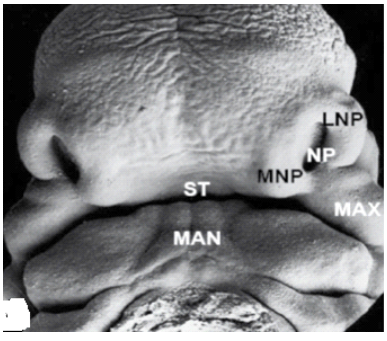


Fig.5 Electron microscopy showing the development of face of a 37-day-old human embryo. The nasal pit (NP) is surrounded by the medial nasal process (MNP) and lateral nasal process (LNP) and maxillary process (MAX]

Incidence

Current knowledge indicates that orofacial clefts occur in approximately 1 in 700 live births, and 3200 new cases per year are expected with the population growth worldwide.45,46The racial prevalence is highest in Whites, followed by Hispanics, Asians, and Africans, respectively 47,48 The national US average rate was 7.75% with the highest value in Maryland (21.46%), and the lowest was found in West Virginia (2.59%). American Indians had the highest ratio [49,50], and African-Americans had the lowest ratio from 0.21 to 0.41 per 1000 live births .51 Whites in Western Europe and the United States had an incidence rate ranging from 0.77 to 1.40 per 1000 live births 52Asian countries demonstrate close ratios. The incidence rates were from 1.14 to 2.13 per 1000 live births in Japanese and 1.81 per 1000 or 1 in 554 live births in South Koreans. 53 Murray and Martelli-Junior 54,55 have reported the incidence rates to be 1.94 and 1.46 per 1000 live births in the Philippines and Brazil, respectively. In Caucasians, the incidence for CL with or without palate was between 0.6 and 1.7 per 1000 live births Literature reviews reported that CLP tends to be unilateral and occurs more frequently on the left side. The International Perinatal Database of Typical Oral Clefts study results showed that 30.2% of the CLP group had bilateral cleft and 69.8% had unilateral cleft. The defect ratios were 41.1% on the right side and 58.9% on the left side 56 CL with or without CP was seen more often in males; however, CP was seen more frequently in females. Van den Akker and Stoll 57,58 found that boys appear to be affected more in bilateral cases, . On the other hand, Meskin and Henriksson 59,60 reported that girls had bilateral CL more than boys, Gender differences in the incidence of CP may be related to differences in the timing of palate development. There is a longer window of vulnerability in a female foetus because palatal fusion occurs one week later than in males

Epidemiology & Inheritance in cleft lip and palate

Exogenous factors that may increase the risk of CL/P break down into four broad categories, they are womb environment, external environment, nutrition, and drugs. Cleft lip increases the likelihood of cleft palate because the tongue gets trapped, preventing it from moving down and therefore increasing the probability of the failure of the shelves to elevate above the tongue.61,62,63,64 Fogh-Anderson was the first to describe genetic factors in clefting. 65Several teratogens are known to increase the risk of CL/P and CP. They include anti-epileptic drugs (phenytoin, valproic acid), thalidomide, dioxins, some pesticides, retinoic acid, maternal cigarette smoking and alcohol use. Teratogens may contribute to CL/P and CP by disrupting a normal developmental patterning process at a critical stage. Continued research has been focused on identifying whether and how these teratogens interact with specific developmental genes. Infants exposed to anticonvulsants have a tenfold increased risk of isolated CL. The exposure to four or more alcoholic drinks daily significantly elevated the risk for clefts, especially in those with Msx1 alteration.66 Alcohol inhibits the migration and differentiation of neural crest cells. The risk for orofacial clefts as a result of embryonic exposure to tobacco smoke during the first trimester has been found to be related to the level of exposure. Twenty or more cigarettes per day result in a twofold increase whereas less than 20 cigarettes per day resulted in a 1.5-fold increase. Intermittent hypoxia induced by nicotine probably affects facial development. A genetically altered form of TGFA, called a2, may result in an eightfold increase of the risk associated with smoke exposure.67 This may be related to maternal nutrition. Maternal nutrition also plays an important role in the prevention of facial clefting. A higher pre-conceptional intake of nutrients predominantly present in fruits and vegetables reduces the risk of offspring affected by orofacial cleft.68The growth of the detailed structures of the head and face is largely determined genetically, and these processes are known to be dependent on an array of signalling molecules, transcription factors, and growth factors interacting with environmental factors.69Some of the investigated gene products are growth factors (e.g., TGFa, TGFb3), some are transcription factors (e.g., Msx1, SATB2), and some influence the metabolism of xenobiotics (e.g., CYP 1A1, GSTM 1, NAT2), nutrient

metabolism (e.g., MTHFR, RARA) or immune responses (5PVRL1, IRF6). The most intensively investigated variants have been of the tumour growth factor alpha (TGFa) and methylenetetrahydrofolate reductase (MTHFR)70IRF6 is the gene to study when a seemingly isolated CL/P patient has minor signs, such as lip pits. Physicians must look for the presence of these lip pits very carefully since they are sometimes not easy to detect. The identification of a mutation in IRF6 is associated with an increase in the risk of having a child with CL/P from 4-6%, the risk of transmission of an isolated cleft, to 50%71 Several teratogens are known to increase the risk of CL/P and CP. They include anti-epileptic drugs (phenytoin, valproic acid), thalidomide, dioxins, some pesticides, retinoic acid, maternal cigarette smoking and alcohol use.[72,73]

Congenital Anomalies

congenital anomalies can be divided into three types a) Malformations: A morphologic defect in an organ from an intrinsically abnormal developmental process, e.g. polydactyly, congenital heart anomalies, cleft lip etc.b) Disruptions: A rare anomaly related to breakdown of the original normal foetal developmental process, e.g. craniofacial cleft resulting from amniotic bands. c) Deformations: These occur secondary to mechanical forces leading to anomalies of a lesser degree when compared to disruption, e.g. club foot, cleft palate, Pierre Robin sequence etc.

COMMON SYNDROMES ASSOCIATED WITH ORO-FACIAL CLEFT

Velocardiofacial syndrome,This is an autosomal dominant condition and is associated with Chromosome 22q abnormality, as a result of a sub-microscopic deletion on the long arm of Chromosome 22 in the"q11"region (deletion22q11). It occurs in approximately one in 2000 live births,and is the most common sub-microscopic deletion syndrome. There are more than 100 physical phenotypic features reported, as VCFS affects every major system in the body. The most common features are cleft palate, cardiac anomaly, characteristic facial appearance (vertical maxillary excess, malar flattening, relative mandibular retrusion, narrow palpebral fissure and small ears), The majority of these patients will need support for their learning problems.[74]

Van der Woude Syndrome,It is one of the commonest syndromes associated with oral cleft. It is transmitted as an autosomal dominant and lower lip pits. These pits are located bilaterally in the lower lip at the junction of dry and wet vermilion and they are either oval or transverse in shape. Pits traverse the underlying orbicularis muscle and end in a blind pouch on the buccal side and communicate with minor salivary glands. The associated features are hypodontia, missing maxillary or mandibular second premolar teeth, absent maxillary lateral incisor and ankyloglosia.[75]

Pierre Robin sequence,syndrome includes with triad of glossoptosis, micrognathia and airway obstruction. Although cleft is not included in the triad, it is frequently associated and may aggravate the obstruction due to tongue fall.. The frequency of occurrence of various deformities are Micrognathia (91.7%), Glossoptosis (70-85%) or Macroglossia and Ankyloglossia (10–15 %) and Cleft Palate (14 %)76. Occasionally a bifid or double uvula with an occult submucous cleft can be present.

Airway obstruction due to tongue fall results in failure to thrive and is a serious problem in these patients.[77,78]

Median facial dysplasia is a unique, distinct, definable group of patients characterized by midline facial deficiencies in the presence of a unilateral or bilateral cleft lip with or without cleft palate.79 From the age of 6 to 9 months onward, the growth pattern of the hard palate varies in the various planes of space. Anatomical distortions such as high-arched, narrow shapes could therefore be interpreted as secondarily acquired in later life. To prevent palatal shape alterations and enhance oral function which also contributes to maxillary development it could be advantageous to begin oral muscular stimulating therapy between 6 and 9 months of age 80Magnetic resonance imaging and [MRI] and prenatal ultrasound are being used for detecting prenatal diagnosis . Other associated syndromes are Ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome , Oro-cranio-digital syndrome, DiGeorge syndrome , Wildervanck syndrome, CHARGE syndrome ,Oro-facio-digital syndrome , Facio-cardio-renal syndrome, Trisomi Cornelia de Lange syndrome ,Cat eye syndrome, Hay–Wells syndrome, Treacher Collins syndrome ,Adams-Oliver syndrome ,Turner syndrome, Larsen syndrome ,Apert syndrome, Fraser syndrome, Gordon syndrome, Klippel Feil syndrome, Goldenhar disease ,Dandy-Walker syndrome, Popliteal web syndrome.

Treatment

The orofacial cleft treatment may have the multidisciplinary team composed of individual in (1)) The medical specialties (genetics, otorhynolaryngology, pediatrics, plastic surgery, and psychiatry), (2) The dental specialties (orthodontics, oral surgery, pediatric dentistry, and prosthodontics), and (3) Allied health care fields (audiology, nursing, psychology, social work, and speech pathology).. The challenge of modern palatoplasty is no longer simply successful closure of the cleft palate. [81] Nonsurgical treatment of the cleft palate is attempted with prosthodontic devices designed to correct velopharyngeal incompetence. For the Orofacial cleft, corrective surgical procedures are known to impair maxillary growth and may lead to midface retrusion.[82] The primary goals of palatoplasty is to restore velopharyngeal function and to ensure normal speech development, The most common surgical techniques for repair of the soft palate are the Furlow double-opposing Z-plasty and the intravelar veloplasty. The bony palate is often repaired using the Von Langenbeck palatoplasty, the Veau-Wardill-Kilner palatoplasty, or a Bardach two-flap palatoplasty. Vomer flaps are used in conjunction with the above hard palate repairs to repair the nasal mucosa.[83,84,85]

Conclusion

The orofacial cleft is the deformity that arises from a genetic or environmental insult during formation of the maxilla and palate in the first trimester of gestation. The etiology of the non-genetic form is multifactorial and likely involves maternal exposures to teratogens such as tobacco. alcohol, maternal diseases, Maternal use of vasoactive drugs, exposure of chemicals in the first trimester of pregnancy.Cleft lip and palate are both birth defects that affect different structure and function such as speech difficulty, aesthetic, eating, nutrition etc. Patients with oro-facial cleft deformity needs to be treated at right time and at right age to achieve functional and aesthetic well-being The main objective remains prevention, not correction. Prevention will be conditional on understanding the causes and devising ways to avoid or neutralize them early primary surgery with radical reconstruction of the anatomy followed by minimal surgical intervention apart from alveolar bone grafting at the age of 8 to 10 years and probable rhinoplasty. The multidisciplinary approach towards this problem led to a steady improvement in its end results. There is a need for more studies to be carried out on cleft genetics since it would help to identify some predisposing factors to the development of clefts.

Conflict Of Interest

The authors have no conflicts of interest to declare.

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