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Congenital Anomalies Associated With Syndromic And Non-Syndromic Cleft Lip And Palate – Review Article

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Abstract:

Cleft lip and palate are congenital abnormalities that affect the upper lip and roof of the mouth in the craniofacial region . It is the most common genetic disorder affecting children with variable phenotype. Some babies have only a cleft lip and many have cleft palate as well. The aim of this review is to make the point in literature knowledge about cleft lip and palate their anomalies and treatment. There are a lot of phenotypes and environmental factors causing this malformation, which differ according to the anatomical structures involved. Cleft Lip and Palate can be classified as syndromic and non-syndromic, respectively. Both forms of Cleft Lip and Palate are characterized by a strong genetic component , which can be treated surgically. Both forms of cleft lip and palate are characterized by a strong genetic component.

Key words: Genes, Syndromic and Non syndromic, Cleft Lip, Palate, Environmental factors

INTRODUCTION:

Cleft lip and cleft palate describe an abnormal gap in either the upper lip or the palate. It occurs when some parts of the mouth fail to join together during early pregnancy. Cleft is believed to be caused by the interaction between genetic and environmental factors .When environmental factors interact with a genetically susceptible genotype during the early stage of embryonic development clefts occur which can classified into Syndromic and Non-syndromic ,respectively . Micronutrient deficiency has also been implicated in the causation of cleft in our country [1]

Embryology:

The nose and mouth of a baby develop between the 5th and 12th weeks of life inside the mother's womb. 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 defective growth of the palatal shelves, failure of the shelves to rise above the tongue, lack of contact between shelves (excessively wide head), failure to fuse or rupture after fusion of the shelves. [2]

Classification:

Several authors have classified (Fig 1) the cleft lip and palate into four main groups:

1. Clefts of soft palate
2. Clefts of hard palate.
3. Unilateral clefts of the lip, alveolus and palate.
4. Bilateral clefts of the lip, alveolus and palate [3]

Figure 1: a. Normal palate b. unilateral cleft lip and palate c bilateral cleft lip and palate

ETIOLOGY:

I. **Environmental factors:**

1. Smoking and alcohol

2. Nutritional factors: Nutritional status plays an essential role in developing cleft lip and palate. Vitamin B6, folic acids and zinc deficiency were the main reasons of increased risk of clefts .The deficiency of these nutrients cause cleft lip and palate. It is observed that mothers with children with clefts had lower concentrations in comparison to mothers with children without clefts.

3. Medications: Clefting of the lip and palate can result from some medications such as corticosteroid steroids in which some pregnancies take due to insomnia and anxieties. In addition, retinoid drugs are considered as one of the main reasons that cause clefts in infants because of exposing pregnant women to these drugs.

4. Organic chemicals and solvents: Exposure to chemicals and solvents can cause clefts of the lip, palate or both.

II .**Genetic Factors:**

Family history is considered as one of the reasons may lead to cause cleft lip and palate. For example, the risk of transfer one parent having cleft lip and palate to their child is 9%., the risk of transfer unaffected parents having a child with a cleft lip and palate to their second child is 4% which was found in a study by Firas Abd Kati[3]

SYNDROMIC CLEFT LIP AND PALATE:

I. **Monogenic syndrome:**

When the anomalies are aetiologically related and due to a single gene , the constellation of associated anomalies constitutes a monogenic syndrome.A review by Gorlin **,** described 72 monogenic syndromes involving Oral clefts. A follow-up report by Cohen[5]says 154 monogenic syndromes . [6]Monogenic syndromes include Van der Woude with most of these cases linked to Chromosome 1q32-q41 and Treacher Collins (an autosomal dominant) syndrome.[4]

II. Chromosomal syndrome:

These syndromes involve a clinically significant structural and/or numerical chromosomal abnormality. The deletion of Chromosome 22q11.2, for example, causes the Velocardiofacial syndrome (Shprintzen syndrome-Cleft palate, cardiac anomalies, typical facies, and learning disabilities). Trisomies 13 and 18, and the 4p- are other chromosomal abnormalities leading to different syndromes often found with oral clefts.[7]

Non Syndromic Cleft Lip And Palate :

Non-syndromic cleft lip and palate is a multifactorial disease derived from the interaction between genes, phenotype and environment. The role played by environmental factors is demonstrated by the variable birth prevalence of the disease in different countries[8] .Non-syndromic cleft lip with or without palate is a frequent malformation of the facial region. Numerous genes have been reported in studies demonstrating associations and/or linkage of the cleft lip and palate phenotypes to alleles of microsatellite markers and single nucleotide polymorphisms within specific genes that regulate transcription factors, growth factors, cell signalling and detoxification metabolisms. [9]

Genes Involved In Susceptibility To Non-Syndromic CL/P [10]

1. Growth factors
   TGFA, TGFb3
2. Transcription factors
   MSX1, IRF6, TBX22
3. Genes involved in the metabolism of xenobiotics
   CYP1A1, GSTM1, NAT2
4. Genes involved in the nutritional metabolism
   MTHFR, RARA
5. Genes involved in immune response
   PVRL1, IRF6

Congenital Anomalies:

Common problems associated with cleft lip and palate causes many problems, [3]

1. Speech problem: Patients with a cleft palate have speech problems which are result from velopharyngeal dysfunction. Inability of the soft palate to move upward to provide a contact with nasal cavity results in a passing of air through the nose instead of oral cavity. This condition is known as hypernasality speech. This case can be treated with a surgery to provide the velopharyngeal closure. Pharyngeal flap and sphincter pharyngoplasty are considered as the reliable surgeries for correcting the velopharyngeal deficiency in patients with a cleft lip and palate.

2. Hearing problem and ear infection: Otitis media is a condition where a fluid is accumulated in the middle ear and results in ear infection. This is due to the abnormal action of Eustachian tube opening by two muscles which are tensor veli palatine and levator veli palatine. This leads to the lack of ventilation to the middle ear cavity and accumulation of fluid inside the middle ear. This condition is presented in the child with cleft palate in the first six months of life.

3. Dental problems: Dental problems involve abnormalities in the size and shape of the teeth, for example, the permanent lateral incisor shows abnormalities in size and shape in the side of cleft, abnormalities in the position of teeth, delay of eruption of permanent teeth and delay of formation of permanent teeth.

4. Feeding and nutritional problems: Feeding problems in babies with cleft lip and palate occur because babies are incapable of sucking either their mother's nipple or from a bottle. Therefore, this affects the weight and growth of the baby because the amount of milk or food is not enough

for growth. There are a variety of methods that enable the baby to feed and gain a normal weight such as the use of disposable syringe, spoon and cup and prosthetic obturator device.

5. Cosmetic problems: Patients with cleft lip have cosmetic problems and also cause problems for production of labial sounds. Babies with cleft lip face difficulty when they try to make a contact between upper and lower lips.

6. Psychological problems : All above problems impair the psychological side of a patient with cleft lip and patient where they suffer from depression, anxiety and lack of esteem and they are incapable of communicating with their peers in the school. Furthermore, some patients feel anxiety due to the other people's reactions and worried about meeting people in social events.
The occurrence of cleft lip and palate is either associated with many syndromes such as [11]

- Pierre Robin syndrome is characterized by a small lower jaw (Fig 2) (micrognathia) and displacement of the tongue toward the back of the oral cavity (glossoptosis). Some infants also have an abnormal opening in the roof of the mouth (cleft palate)

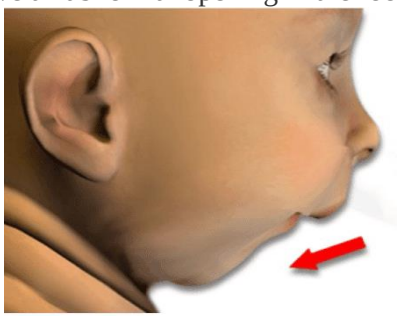


Figure 2: Picture showing micrognathia

- Sticklers syndrome is a rare connective tissue disorder that most often affects the eyes, ears, skeleton, and joints. Signs and symptoms may include: near-sightedness (myopia), a detached retina (separation of the retina of the eye from the layers of the eyeball that support it), hearing loss, a characteristic facial appearance with mid-facial flatness, and joint pain.
- Treacher Collins syndrome is a rare genetic disorder characterized by distinctive abnormalities of the head and face (Fig 3), notably severe micrognathia. Associated manifestations include malformation of the eyes, anomalies of the ear that may lead to hearing loss, and more. Complications may include breathing problems, problems seeing, cleft palate, and hearing loss.

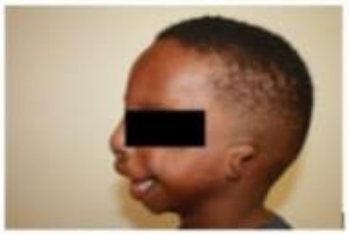


Figure 3: Showing abnormalities of head and face

- Ectodermal dysplasia is a group of disorders in which two or more of the ectodermally derived structures — the skin, sweat glands, hair, nails, teeth and mucous membranes (fig 4) develop abnormally. Each person with an ectodermal dysplasia may have a different combination of defects.

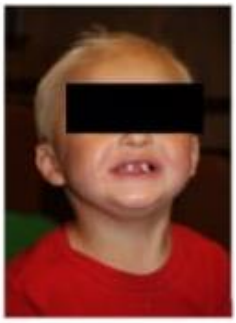


Figure 4 : Picture showing abnormally developed tooth and mucous membrane

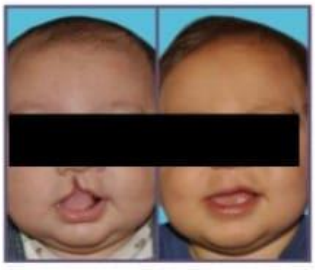
- Velocardiofacial syndrome is alsocalledChromosome 22q11.2 deletion syndrome is a disorder caused by a small piece of chromosome 22 missing. 22q11.2DS is associated with a range of problems including congenital heart disease, palate abnormalities, immune system dysfunction including autoimmune disease,

low calcium and other endocrine abnormalities such as thyroid problems and growth hormone deficiency, gastrointestinal problems, feeding difficulties, kidney abnormalities, hearing loss, seizures, skeletal abnormalities, minor facial differences, and learning and behavioural differences.
So, in these cases, it is called syndromes cleft palate. In addition, other genetic factors which cause cleft lip and palate related to Trisomy 13 ,Trisomy 18 ,Trisomy 21

Diagnosis:
Using ultrasound scanning is also possible to diagnose cleft lip in utero from about 17 week of gestation, even if false positives and missed defects are also seen. This method can fail in case of small cleft lip and palate, that is why orofacial clefts are often not discovered until birth. It is clear how the gynaecologist plays an important role for an early diagnosis .[12]

Treatment:
Early treatment and evaluation Initial assessment of a child with cleft lip is undertaken to know the extent of the cleft. The most important thing is the feeding of the infant. A variety of feeding devices are available and this depends on the type of clefts. For example, for infants with an isolated cleft lip, a bottle or breast can be used. On the other hand, infants with cleft lip and palate face challenges when feeding they are incapable of sucking either their mother's nipple or from a bottle. For that reason, feeding devices such as nipples, cross curt nipples and longer nipple can be successfully assist the infant when feeding. The mother can try feeding her child if she wishes. In case of cleft lip, the mother can place her finger over the lip to provide a seal between her nipple breast and lip defect. In case of unilateral cleft palate, the mother can put her nipple breast on the non-affected side of the palate.In case of cleft palate, the mother can put their nipple breast on the side of the defect with supporting her breast by fingers. The child should be evaluated genetically by an assessment of the following: Prenatal medical history, any family medical history with clefts, examination of child for congenital heart disease , limb and ocular abnormalities, any birth abnormalities that may occur with clefts , evaluation of family members should be undertaken to assess any genetic factors. The child is referred for examination in many departments .Repair of the cleft palate is usually performed after 9 months of age. In the past, surgery was performed around 4-6 years of age, but this was deleterious for the patient's speech development. Surgical revision may be necessary, but they have to be performed after the complete healing has occurred and inflamed tissues have softened (Fig 5) [12]

Figure 5 : Treated cleft lip and palate



The surgery is undertaken for about 3 months of child life and it involves the mobilization of the tissue in the defect side of the lip and dissection of orbicularis oris muscle. This permits the closure of the lip .[3]

CONCLUSION:
The syndromic and Non syndromic Cleft lip and palate are birth defects that are seen to affect the normal functions such as language, breathing, nutrition and esthetics, growth, development of the craniofacial district. Though the real etiology is still unknown, environmental and genetic factors play an important role in this pathology. This is because there is not only one phenotype concerning this pathology, and this is why it is so difficult to find a unique way to treat this abnormality. The surgical treatment is the most common treatment use for this pathology, together with the orthodontic treatment.

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