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Cleft Lip and Cleft Palate: A Comprehensive Understanding of Etiology, Pathogenesis and an Oral Physician's Role in Comprehensive Care

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Abstract: Cleft lip with or without cleft palate (CL/CP) is one of the most common structural birth defects, with treatment in multiple surgeries, speech therapy, and orthodontic treatments over first 18 years of life. Of special interest is etiology, incidence, risk factors and prevention. Better understanding of the embryology and genetics of orofacial clefting is crucial for development of a biologically relevant orofacial cleft classification system. The recent identification of specific genes involved in syndromic and non-syndromic orofacial clefting shows a correlation between both conditions with an overlapping genetic basis. However, it has limited application with screening of specific candidates, association studies and genome-wide scans in revealing the molecular basis of human clefting. With a heavy bearing of this condition on the patient and the family alike, providing care for these patients and families can be challenging. Surgically repaired clefts have residual deformity due to scarring and abnormal facial development affecting the social integration of the patient. It is of paramount importance, as the first contact professional, the oral physician must be patient, understanding and empathetic and must record a complete prenatal and natal history; urge the parents to seek immediate care and stress the importance of genetic counselling and prenatal diagnosis in the event of a future pregnancy.

Keywords: Cleft Lip and Palate, Etiology of Cleft, Oral Physician and Cleft, Prenatal Diagnosis of Cleft, Genetic Counselling for Cleft Deformities

1. Introduction

According to Berkowitz (1996) a cleft of the lip and/or palate is "a structural defect that usually affects other functional areas" (e.g. speech, hearing, feeding) and causes repeated middle-ear infections [1]. This definition shows that Cleft lip and palate (CLP) patients have a diversity of problems that cannot be handled by one specialist. In developed countries a multidisciplinary team of specialists is therefore involved in the treatment of cleft patients. The Cleft Palate Team includes a plastic surgeon, an orthodontist, a pediatrician, an Oral and Maxillofacial surgeon, an ENT specialist, a speech therapist, a geneticist, nurses, a psychologist and a social worker. These specialists not only participate in the active treatment of the individual patient but should also, in an ideal situation, perform research on the topic.

As the initial contact, the oral physician plays a significant role by diagnosing this debilitating condition and classifying it appropriately, recording the details of extent and impaired functions, any relevant maternal history, prenatal and natal. Also of significance is choosing and prescribing the right radiographs which can delineate the extent and guide the surgeon in its management.

2. Embryology of Cleft Lip and Palate

Facial development is from the cranio-neural crest cells. The frontonasal process forms the nose and prolabium (central upper lip). The premaxilla (anterior maxilla and four incisors), together with the hard palate anterior to incisor foramen, are termed the primary palate. The secondary palate

consists of the soft palate and the remainder of the hard palate. The primary palate starts developing at about 35 days with the formation of paired medial and lateral nasal and maxillary processes. Fusion of these processes completes the development of the primary palate. Thus, failure of fusion, hypoplasia, breakdown or mechanical obstruction to fusion leads to cleft lip. Following the development of the primary palate, the palatal shelves form as medial outgrowths from the maxillary processes. These initially grow vertically down the side of the tongue, but elevate horizontally above the dorsum of the tongue to fuse with each other. Elevation of the palatal shelf is thought to occur as a result of hydration of hyaluronic acid constituents of the shelves. This occurs over a few hours and it is thought that most cases of cleft palate are due to interference with the elevation step. However, the phenotypic variability of cleft palate is an indication of multiple mechanisms involved in its pathogenesis.

3. Etiology

Race is the only demographic variable that has been consistently associated with the prevalence of cleft lip with or without cleft palate [2]. Compared with Caucasians, the prevalence is higher in Asians (particularly Japanese) and lower in individuals of African descent. These differences appear to persist after migration, suggesting that they are genetically, rather than environmentally, mediated. Hence, based on both family and epidemiologic data, the evidence for a genetic component is the best etiologic clue that exists for cleft lip with or without cleft palate (CL/P) [3, 4]. The subgroup of birth defects with largely unknown etiologies includes many structural malformations, such as orofacial clefts, neural tube defects and cardiac malformations [5]. These malformations are generally referred to as being non-syndromic in order to differentiate them from phenotypically identical conditions which occur as part of recognized malformation syndromes (e. g., trisomy 13, Van der Woude syndrome, Velocardiofacial syndrome). Although they are clearly not inherited in a simple Mendelian fashion, many of the non-syndromic structural malformations tend to aggregate within families [3]. Hence, genetic factors are thought to be involved in their etiology [6, 7].

Several segregation analyses of cleft lip with or without cleft palate family data have been unable to discriminate between alternative genetic models of inheritance [8-10]. Moreover, among the studies that have been able to discriminate between alternative models, there is no consensus regarding the most appropriate model of inheritance for this condition [11-16]. For example, models which included a single major locus and a multifactorial threshold component were found to provide the best fit to family data in an English [11] and a Danish [12] data set, but different modes of inheritance were ascribed to the major locus in the two samples.

Risch unequivocally rejected single major locus inheritance of CL/P, and indicate that this condition is most likely determined by a multiplicative model of inheritance, under which a few genes of moderate effect act against a multifactorial background [17-19]. Hence, it seems likely that the mixed results obtained in segregation analyses reflect the fact that neither the single major locus nor the multifactorial threshold model adequately describe the inheritance of CL/CP.

Association is another technique that has been used to identify potential genes for CL/CP. There are several advantages to using association, instead of linkage.

1. Large number of cases can be used that occur in isolation with no other affected family member, therefore, small numbers of human offspring do not hinder application.
2. The understanding of developmental biology can be applied to identify which genes are expressed at different times in facial development, thereby providing possible candidate genes [20].

Transforming growth factor alpha (TGFA), transforming growth factor beta 3 (TGFB3), and MSX1, AP2 [20], Interferon Regulatory Factor 6 (*IRF6*) [21] are genes that have been identified as having a major role in the development of CL/CP through linkage and association studies. Animal models, often mice, are an additional means of locating and testing candidate genes as the result of spontaneously arising or transgenic mice.

4. Epidemiology

It is estimated that the overall global prevalence of Orofacial cleft (OFC) is one in every 600 new born babies. Despite efforts to record the frequency of birth defects over the years, accurate data on the epidemiology do not exist in many countries [22]. From the available data, it may be concluded that:

- There is evidence for distinct differences between isolated CP and cleft lip with or without cleft palate (CL/P).
- There is a great deal of geographical variation, more apparent for CL/P than CP.
- There is apparent variation in the proportion of OFC cases with additional congenital anomalies and syndromes.
- There is considerable international variation in the frequency of OFC, but validity and comparability of data are adversely affected by numerous factors.
- There is no consistent evidence of time trends; nor is there consistent variation by seasonality or socio-economic status.
- There are many parts of the world where little or no information on the frequency of OFCs is available, in particular in most of Africa, Central Asia, Eastern Europe, Indian sub-continent and the Middle East.

5. Urgent Need for Care

India is one of the many regions of the world where documentation of the rates of birth anomalies is incomplete.

Reliable and complete record of statistics is difficult because of the population and lack of efficient methods. It is known, however, that in many parts of India the parents of a child born with a cleft have no access to counselling for the care and treatment of their children. Cleft lip and palate are perceived to be a life threatening abnormality and there may be little awareness of the fact that clefts can be surgically repaired with considerable success both aesthetically and functionally. The lack of knowledge and resources results in unacceptable delay in seeking and receiving adequate medical care, due to which, many infants with OFC die of malnutrition or infection. This grim situation is further compounded by (a) failure of healthcare authorities to recognize craniofacial anomalies as a notifiable disease, and (b) the World Health Organization (WHO) in their continuing use of the diagnostic rather than functional classification of clefts [22]. Both these perceived problems are, however, currently being addressed.

6. Role of an Oral Physician

The patient first approaches the Oral physician. This first point of visit itself makes our role inevitable and of paramount importance. The country is still under the curse of ancient beliefs and taboos. Many a patient is unwilling to disclose all information. Hence the need for creating a conducive and reassuring environment. Instead of accounting for these patients just as one in a 100 per day for whom we offer treatment, there is urgent need to soothe their worries and earn their trust. Specifically the occurrence of consanguineous marriage poses a high risk for occurrence of genetic abnormalities. This stresses the need for recording a proper case history. The need for recording family history, especially in the cases of the various genetic abnormalities, is not stressed enough.

As early intervention plays a very significant impact on surgical care of orofacial clefts, the patient counselling should also be effective. The oral physician must record proper prenatal and natal history to rule out any high risk behaviour. Some drugs may cause cleft lip and cleft palate. Among them are anti-seizure/anticonvulsant drugs, acne drugs containing accutane, and methotrexate used for treating cancer, arthritis, and psoriasis. Cleft lip and cleft palate may also occur as a result of exposure to viruses or chemicals while the foetus is developing in the womb. Acquiring relevant prenatal details plays a vital role in educating the patient and prevention of such a condition in future pregnancies.

Next step is that as a radiologist in recording the appropriate radiographs and also classifying the cleft for ease for the further consulting specialists. And then for informing the patient the various treatment options, the required modifications for feeding, the possible treatment outcome and the need for multiple consult, credible knowledge in these areas is very essential. This responsibility must be handled appropriately, urging the patient to be prompt and regular in appointments and co-operate for best results. It is the responsibility as their consulting physician to educate the parents of the patient regarding prenatal diagnosis and most importantly, prevention. The patient's family is suggested to attend genetic counselling. Of utmost significance is the fact that the physician's knowledge must be updated regarding the epidemiology of orofacial clefts, various treatment modalities, the feeding interventions, etc without which no guidance is possible.

7. Prenatal Diagnosis and Prevention

The purpose of prenatal diagnosis is to provide information that will allow individuals and/or couples to make decisions about child-bearing.

7.1. Cleft Lip With or Without Cleft Palate

Between 85 and 90% of individuals with this type of cleft have no other physical problems. When seen in isolation, this condition is believed to result from an interaction between genes and the environment [23].

Prenatal diagnosis for cleft lip with or without cleft palate depends on the ability of ultrasound to see the baby's face in the womb. Many factors influence the accuracy of ultrasound studies, including the following:

- Sophistication of the scanning equipment;
- Experience and skill of the sonographer;
- Number of weeks into the pregnancy (optimum time is 18-20 weeks or later);
- Baby's position in the womb;
- Maternal body structure (it is much harder to see fetal anatomy in overweight women);
- Presence or absence of amniotic fluid, which is the liquid surrounding the baby in the womb (reduced amounts of amniotic fluid limit visualization).

A procedure called targeted Level II ultrasound is designed to check the baby's anatomy and is therefore the best method for prenatal diagnosis of cleft lip with or without cleft palate. The cleft palate that is seen on ultrasonography, however, is actually the alveolar ridge, or gum-line. Current technology does not routinely visualize most of the hard palate or the soft palate of a developing baby.

The Centers for Disease Control and Prevention and the American College of Medical Genetics already recommend a daily vitamin supplement of 400mg of folic acid for all pregnant women, which is intended to reduce the baby's risk for spina bifida, other neural tube defects, and possibly cleft lip and palate [23].

7.2. Isolated Cleft Palate

Between 50 and 60% of individuals with cleft palate (without cleft lip), have the cleft as their only structural defect. Unfortunately, prenatal diagnosis is not yet reliable for diagnosing cleft palate alone. Although ultrasound sees the outside surface of the baby's face, the palate is not readily seen with the equipment currently in use.

7.3. Clefts That Occur as Part of a Syndrome

Approximately 10-15% of individuals with CL/P also have a related syndrome, while about 40-50% of individuals with cleft palate alone do [24]. Most of these syndromes include other physical problems that are obvious at or before birth. Recurrence risk counselling for these individuals can be complicated, and genetic counselling is highly recommended. If the cleft is believed to be the result of exposure to a specific teratogen, then avoiding that exposure in subsequent pregnancies is the best approach, if possible.

For individuals or families with a confirmed diagnosis of a chromosomal or molecular genetic condition, invasive prenatal testing may be a consideration. The most common tests of this type are amniocentesis and Chorionic Villus Sampling (CVS). Amniocentesis is currently the best method for obtaining foetal cells. It is performed at 15-20 weeks of pregnancy (ideally at 16-18 weeks) and carries a risk of miscarriage of 0.5% (1 in 200 procedures).

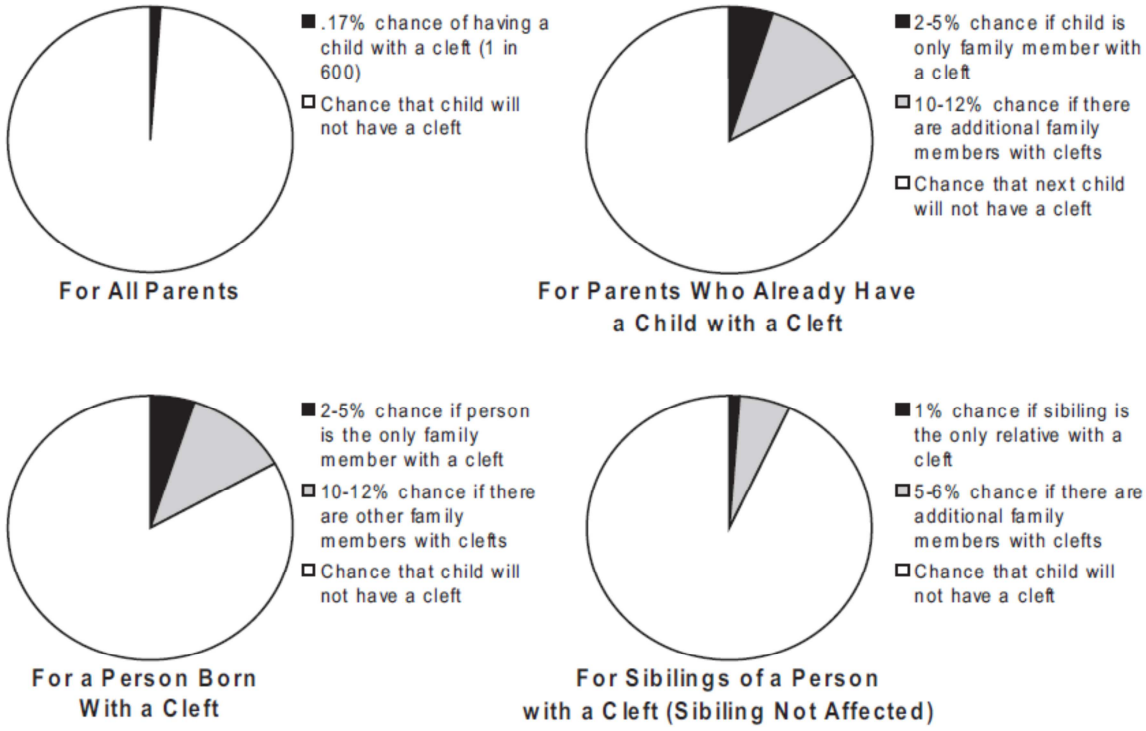
Amniocentesis does not screen for all birth defects or for isolated (non-syndromic) clefts. CVS takes advantage of the fact that the placenta develops from the first cell that is the baby. By taking a piece of placental tissue, various genetic tests may be performed. CVS is performed at 11 weeks into a pregnancy, either through the abdomen or through the vagina and cervix. CVS carries a miscarriage risk of 1% (1 in 100 procedures). CVS does not screen for all birth defects or for isolated clefts. *For this reason, neither CVS nor amniocentesis is recommended for individuals or couples for whom the only question is recurrence of isolated cleft lip and/or palate* [23].

8. Foetal Surgery

Experimental intrauterine correction of CLP has been lately performed using the feto-endoscopic approach. This procedure offers two major advantages: first, scar-less foetal wound healing and bone healing without callus formation, which would also allow a better/normal maxillary growth, and second, significant decrease of foetal and maternal morbidity. Animal models have been extensively used for accumulating experimental data in support for foetal surgery in the repair of cleft lip and palate [25-27]. The major advantages of foetal healing over adult healing are made use of in this modality.

9. Genetic Counselling

The risk for recurrence of a cleft condition is determined by a number of factors that are often unique in a particular family. These include the number of family members with clefts, how closely related these people are, the race and sex of the affected individuals, and the type of cleft each person has. After a syndrome or complex disorder is excluded, recurrence risk counselling for cleft lip and/or palate can be offered to families. There is no genetic test currently available to determine a person's individual chance of having a child with a cleft. However, information is advancing so rapidly with respect to genetic testing that couples are advised to ask whether any new tests have been developed when they are planning future pregnancies.



Courtesy: Genetics and You. Cleft Palate foundation. 2nd edition 2008 reprint. www.cleftline.org.

Figure 1. *Recurrence Rates for Cleft Conditions.*

Components of Genetic Evaluation

1. Verifying that the cleft is isolated, not part of a syndrome.
2. Consideration of whether other relatives have similar conditions, and if so, how many and how closely related they are.
3. The type and severity of the cleft.
4. Laboratory testing. Eg: Chromosome tests (karyotypes), molecular testing and clinical photographs.
5. Information regarding the risk for recurrence is conveyed to the individual, the family, or extended family members. For families interested in options for managing this risk in future pregnancies, strategies for prenatal (before birth) diagnosis may be discussed.

10. Conclusion

Cleft lip and palate, as much as is a challenge for the patient and his/her family, it continues to be a problem at large all over the world. Wide studies regarding the etiology of orofacial clefts as a whole are projected to help understand this complex problem to the clinician. Genetic studies with their multitude of prospects are practiced and are constantly being improved on. As an oral diagnostician, our contribution to this problem may be summarized as:

1. Diagnosis, classification and establishing reassuring and reassuring rapport with patient.
2. Recording complete and relevant prenatal, natal and postnatal history.
3. Choosing the appropriate imaging technique to visualize the cleft in full extent.
4. Imparting information regarding the available treatment options, surgical and non- surgical rehabilitation options with latest information and appropriate referral.
5. Introducing the idea of genetic counselling and early prenatal diagnosis for the family.

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