AFRICAN JOURNAL OF MEDICINE and medical sciences

VOLUME 34 NUMBER 1 MARCH 2005

ISSN 1116—4077

Afr. J. Med. med. Sci. (2005) 34, 1-7

Review Article

Incidence and aetiology of oral clefts: a review

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Summary
Craniofacial anomalies, most especially cleft lip and palate, are major human birth deformities with a world wide incidence of 1 in 700 and associated substantial clinical and psychosocial impact. Wide ranges of studies in developmental biology have shown that both genetics and environmental factors are involved in the etiology of oral clefts. However, genetics of cleft lip alone or accompanied by cleft palate, are different from those of isolated cleft palate. The prevention of oral clefts is not possible without knowing the precise etiology. Genetic counseling can now identify high risk families; the clefts themselves may be visible at 20 weeks gestation, but beyond early identification, we can only look into the future on the possibility of preventing oral clefts. This article reviews the available literature on the gene-environment contributions to nonsyndromic forms of clefting and their implication for possible preventive measures.

Keywords. *Incidence, aetiology, cleft lip and palate.*

Résumé
Les anomalies Craniofacial, surtour les Gercures de la lèvre et du palais, sont des difformités majeures de la naissance humaine avec une fréquence large mondiale de 1 en 700 et y ont associé l'impact substantiel clinique et psychosocial. De grandes gammes d'études dans le développement biologique ont montré que la génétique et environnementaux sont impliqués dans l'etiologie des gercure orales. Cependant, la génétique de gercure de levre seule ou accompagné par la gercure de palais isolé. La prévention gercurr orales n'est pas possible sans savoir l'etiologie précise. Les conseilles génétiques peuvent identifier de ce fait les familles a haute risque, les gercures elles-memes peuvent être visibles à 20 semaines de gestation, mais au-delà identification assez tôt, nous pouvons seulement voir a l'avenir la possibilité de prévenir des gercures orales. Cet article examine les ouvrages disponible sur les contributions du milieu genetique aux formes non-syndromiques de gercures et leur implication afin de prendre les mesures preventives possibles.

Introduction.

Craniofacial anomalies such as cleft lip and or palate (CL/P) comprise a significant component of morbid human birth defects. This malformation has intrigued a wide range of professionals in trying to expand their understanding of its incidence and aetiology. Over the years, several etiological possibilities have been considered [1-3]. Warkany [4] reported that as early as 1757, Traw recognized that hereditary played an important role in the occurrence of CL/P. Genetic studies of twins with cleft have been particularly informative. Concordance in monozygotic twins ranges between 40% and 60%, and is 5% in dizygotic twins [3]. The lack of 100% concordance in monozygotic twins suggests that genetic event alone is not responsible for clefting phenotype. Possible suggestions include the presence of some degree of non penetrance, perhaps based around random developmental events [3], or the dissimilar environmental effects found in what might not be a homogeneous *in utero* environment [3,5].

There seems to be a general consensus in the literature on the clinical importance of a reliable epidemiological data on orofacial clefts in a given population. Incidence rates can stimulate genetic and epidemiologic investigations of heritable and environmental factors while prevalence rates can be used to document current clinical care needs and project future caseloads of oral clefts [6].

CL/P has continued to receive increased attention in the medical literature, probably due to its gross cosmetic deformity as well as the psychosocial and emotional trauma on parents of such patients [2]. Insight into its etiology as well as identifying individuals at high risk, may perhaps pave the way for preventive programs [2,3]. The purpose of this paper is to provide an overview of the incidence and aetiology of cleft lip and or palate, with special implications for preventive measures.

Embryology

The development of the orofacial region is a complex process involving exact timing and multiple interactions between different primordial structures. By the 4th week of intra uterine life (i.u.l), the primitive face consists of the frontonasal process above, a maxillary process on either side and two mandibular processes below, all of which are derived from the first pair of pharyngeal arches, and forms the boundary of the stomodeum. The frontonasal process shows olfactory pits which divide it into medial and lateral nasal processes. The rounded end of the medial nasal process (globular process) gives rise to the premaxilla, prolabium, columella and the apex of the nose. The lateral nasal processes forms the alae.[7]

At the 7th week of i.u.l, each maxillary process grows forward above the stomodeum and fuses with the lower edge of the lateral nasal process. It then extends across

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the lower margin of the olfactory pit to reach and unite with the medial nasal fold. The fusion of the maxillary processes with the nasal processes eventually forms a continuous ridge above the stomodeum from which the upper lip develops [2].

Two maxillary extensions of mesoderm grow medially beneath the olfactory pits, joining in the midline and forming the primary palate. On each side of the face, the maxillary mesoderm gives a medially directed shelf-like projection called the palatal process, which extends as a free edge [8]. The two palatal process fuse at about the 9th week and fusion occurs in the soft palate area by the 11th week of i. u l. These processes are first directed vertically downward on either side of the tongue, with the tongue projecting posteriorly between them. The palatal processes take a horizontal position as the tongue descends which eventually lead to fusion. The palate behind the incisive foramen, which is formed by the fusion of the two palatal shelves, is referred to as the secondary palate.

Classification

There is no entirely satisfactory system of classification for orofacial clefts and this is reflected in the wide variety of presentations [2]. It is however, generally agreed that cleft lip with or without cleft palate represents varying degree of the same embryologic defect while isolated cleft palate represents a separate entity [3].

Kernahan and Stark [9] proposed a classification using the incisive foramen as the dividing line between the primary and secondary palate;

- clefts of the primary palate: may involve only the lip or the lip and the alveolar process as far back as the incisive foramen.
- clefts of the secondary palate: may involve the soft palate only or the soft palate and hard palate as far forwards as the incisive foramen
- clefts involving both the primary and secondary palate.

Clefts of the lip and the primary palate may be unilateral or bilateral. Clefts of the primary and the secondary palate can also be a complete or an incomplete cleft.

The search for a universally accepted system of classifying cleft lip and palate has yielded many models of varying complexity. Recently, there has been a trend toward symbolic classification systems that allow members of the cleft team to quickly asses the nature of the deformity. Kernahan (1971) [10] introduced the "striped Y" to described clefts (Fig.1). The small circle at the junction of the Y signifies the incisive foramen. This method describes the extent of the cleft by cross-hatching the appropriate squares, and as the advantage of being used in computerized records. A modification of Kernahan 'Y' classification was proposed by Smith *et al* [11] and was able to describe all varieties of clefts as opposed to the 70-80% the Kernahan method could accommodate. The complexity of nomenclature in this new method of classification however has been noted as a major disadvantage [12,13].

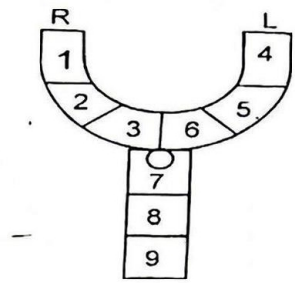

Fig. 1: The symbolic representation of Kernahan (1971). Reproduced courtesy of Williams and Wilkins *Inc.*

Keys:

- *Segments 1-3 on the right arm and 4-6 on the left arm stands for lip, alveolus, and the area from the alveolarprocess to the incisive foramen respectively*
- *The stems is segmented into the hard palate (7-8) and the soft palate (9).*
- *The incisive foramen is shown as a small circle within the intersection of the arms and the stem of the Y.*

Incidence

Reported incidence and prevalence of cleft lip and palate shows a wide variation both within and between geographic areas and for different racial or ethnic groups [6,14]. It is not possible in most cases to draw meaningful conclusions from this difference in rates, which may be spurious or real, as many factors could be responsible. The controversies surrounding the use of epidemiologic terms 'incidence' and 'prevalence' have been reported to be responsible for some of the validity problems often associated with data analysis [14,15].

Incidence denotes the new occurrence of orofacial clefts in a defined population over a specified period of time [15]. Incidence rate for any condition is cohort specific and refers to one or more groups in the population, such as 'all products of conception' or 'all live birth' in a given year. To be counted, newly diagnosed cases of clefts must come to medical attention [6,15,16]. Incidence rates of clefts can stimulate genetic and epidemiologic investigations of heritable and environmental factors [6]. Prevalence refers to the total numbers of cleft cases in a defined population, at given point in time or during a specified, delimited period. Prevalence rates are cross-sectional in nature and therefore cover all existing birth cohorts in the defined population. It provides a picture of the cumulative personal and societal burdens of clefts [6.17].

The lack of uniformity in the sources of data collection by various investigators has also been identified as one of the factors that influence the variation in the reported incidence and prevalence of cleft lip and palate [6]. The use of hospital records, birth and death certificates could lead to underreporting, as these often produce as-

certainment bias and/or selection bias. Another problem identified in the literature was the inclusion of subjects that differ in the risk of developing orofacial clefts during data collection. The risks of clefts in stillborn and aborted fetuses have been reported to be three times higher than in babies born alive [14]. Clefts with associated malformations are also different epidemiologically from clefts without associated malformations [18], Hook [15], Vanderas [18] and Sayetta [6] were of the opinion that the incidence and prevalence of orofacial clefts should be studied separately for each group (live births, stillbirths and abortions) and should be reported separately for clefts without associated malformations.

When racial differences were considered, the incidence of cleft lip and palate has been found to vary from 2.1/1000 in Asians, 1.0/1000 in Caucasians and 0.41/1000 in Blacks [6,15,19,20] Leck [20] reported that the incidence of CL/P is highest in Mongoloids, low in black people and intermediate in Caucasians. Isolated cleft palate however rarely shows any coherent pattern of variation among races. In a similar study, Shaw [21] reported that the incidence of orofacial clefts was lower in black non-Hispanic than in white non-Hispanic people. Sullivan [22] in a study noted that the familial incidence of cleft lips in blacks was significantly lower than in whites. Actual rate differences for clefts are usually attributable to underlying variation in the populations from which the different samples have been drawn. Such variations include variation in genetic susceptibility, basic differences in facial width among races and variation in environmental exposure [3,6,14].

Studies of the incidence and prevalence of cleft lip and palate also shows large variations in pattern among countries. The figures obtained vary from 18.2 per 10,000 live births in China [23] to 700 live birth in the United States of America [24]. In Malaysia, Boo and Arshad [25] reported 1.24 per 1,000 live births. Iregbulum [26] reported an incidence figure of 0.34 per 1,000 for cleft lip with or without cleft palate and 0.05 per 1,000 for isolated cleft palate in a study in Nigeria. Among the British, long term studies have demonstrated a steady increase in the prevalence of cleft lip and palate over the last century with definite geographic distribution, the prevalence being lowest in the south-east of the country and steadily increasing towards the north and the west [27]. In Wales, the incidence was found to be over 2 per 1,000 live births [28]. Rintala and Stegars [29] summarized several factors that might be responsible for the increased incidence over time:

1. Better general and specific treatment for clefts, resulting in better social acceptance and higher fertility and fecundity
2. Intermarriage of cleft patients or carriers
3. Decreased mortality among cleft patients
4. Better diagnosis and registration of cases
5. Increasing exposure to environmental factors (drugs, diseases, pollution, and others).

A review of the literature has shown that the multiple articles on the incidence and prevalence of cleft lip and palate was an attempt to clarify variables associated with the clefting phenomena. However, only a few variables associated with CL/P have remained consistent within all of these reports, and these are:

- A distinct racial gradient in the incidence of cleft lip and palate (Orientals with the highest incidence, blacks the lowest, and whites intermediate). For isolated cleft palate, the gradient is not as dramatic, although the trend remains the same as with cleft lip and palate [6,30,31].
- Difference in the incidence of congenital clefts by sex. More males are born with cleft lip or a combination of cleft lip and palate. In cases of combined clefts of the lip and palate, males are affected more severely, while more females are affected with isolated clefts of the palate [6,26].
- A higher incidence of isolated cleft lip or cleft lip and palate occurs on the left side, but cleft palate is more often associated with unilateral cleft of the lip [6].
- Clefts are often associated with other congenital anomalies and are frequently a part of a distinct syndrome [6].

Aetiology

The interest in the etiology of cleft lip and palate dates back to antiquity when the ancients blamed clefting on encounters between pregnant women and rabbits or gaping fish [32]. Despite decades of intensive investigation into the cause of this defect, the pathogenesis is still not clear [2,6,14,33]. The aetiology is attributed to a deficiency of neural crest cells due to insufficient mesenchyme migration and penetration, cell necrosis or decreased cell proliferation. A combination of genetic and environmental factors has been implicated [3,34].

Leck [35] reported that CL/P and CP are developmentally and genetically different. Hereditary factors play a more important role than environmental factors in the etiology of CL/P, while the reverse is the case for CP [35]. This observation is based on experimental evidence that shows that the developing palate is particularly sensitive to exogenous agents [14,36] and also on epidemiological data that suggest a positive family history more often for CL/P than for CP [35,37]. Hereditary is now regarded as being responsible for about 40-50% and 20-25% of the etiological factors implicated in CL and CL/P respectively [14,38].

Heredity

During the 1930's attempts were made to describe all facial clefting by use of the recently recognized rules of Mendelian inheritance. Fogh-Anderson's monograph in 1941 was the first major attempt to define the role of genetic factors in clefting in a major population study among the Danish population [39]. Further studies however, have shown

that with very few exceptions, observed data from familial aggregations do not fit any simple Mendelian pattern of inheritance in the case of non-syndromic cleft lip and palate [3]. Occasionally a CL/P is seen in syndromes that demonstrate both autosomal dominant or recessive inheritance. Gorlin *et al* [40] have listed more than 100 syndromes that include cleft lip and palate among their definitions. Some of these syndromes are attributed to recognizable chromosome aberrations such as trisomy D syndrome, which include cleft lip and trisomy E syndrome which include cleft palate along with other malformations.

The data of Fogh-Anderson dominated thought until the genetic model of the multifactorial threshold was proposed as a mechanism for clefting [41,41]. This mathematic model is used to describe inheritance of discontinuous physical characteristics (e.g., cleft lip and noncleft). In the case of facial clefts, the multifactorial or polygenic inheritance model proposed that the hereditary component in its etiology is the result of many genes acting together in the presence or absence of environmental factors. Therefore a given case of CL/P usually result from the contribution of many genes ('polygenic'), which, when in combination with environmental factors, exceeds a threshold level so that the phenotype occurs.

Recent advances in both quantitative and molecular analysis have made linkage and association approaches to CL/P etiology practical [43]. Dense genetic maps [44] provide resources for family-based studies. The comparative increase concordance in monozygotic twins strongly point to a major genetic component in the etiology of clefts [3].

Genetic linkage studies of CL/P have been limited by insufficient numbers of families and genotyping resources. However studies [3,45] using from one to forty families suggest loci for clefts on chromosomes 4, 6, 17 and 19. Association studies have also been used extensively to examine candidate genes in cleft lip and palate. Ardinger *et al* [46] reported that transforming growth factor alpha (TGFA) plays an important role in the etiology of clefts. Although some studie [3,33] have failed to replicate this association, a recent meta-analysis supports a role for TGFA as a modifying factor in cleft lip and palate [47]. Chromosomal anomalies have also been used to provide important clues for genes involved in clefting. A comprehensive survey of chromosomal deletions [48,49] and duplications was carried out to identify phenotypes significantly associated with particular aneuploidies, the following regions were identified as significantly associated with clefts; 1q25, 3p21, 4p15, 4q32 and 10p15.

Environmental factors

Several studies have linked environmental factors to the development of oral clefts. The following factors have been considered:

1. *Seasonality*. Many contradictory studies have been reported on the effect of seasonal variation on the incidence of clefts. Rintala [50] reported a significant seasonal difference in CL/P group, the incidence being highest among infants born in April and lowest among those born in September. Results of studies by Fraser *et al* [51] however, proved no such relation, neither with season of birth nor with time of conception.
2. *Parental age*. Shaw *et al* [21] reported that women above 35 years of age had a double risk of having a child with CL/P and those above 39 years of age had a triple risk of having a child with CP, compared with women between 25-29 years of age. Hay [52] also presented evidence of a correlation between the incidence of CL/P and high maternal age. Furthermore, Saxen *et al*. in an epidemiological study in Finland found that when both parents were more than 30 years, the incidence of CP in their children was more than the control [53]. Stoll [54] and Jensen [55] however, claimed that parental age did not significantly affect the incidence of oral clefts in their own studies.
3. *Social Class*. In the Philippines, report of studies [56,57] have indicated an incidence of 2/1000 for CL/P in indigent population while complementary studies showed an incidence of 1.2/1000 in native Filipinos living in areas of higher socioeconomic status (SES) [57]. When SES did not change through a geographic move, no change in frequency of oral clefts was noted by Christensen *et al* [58]. Habib [2] postulated that the state of nutrition of pregnant women is the link between the social class and the incidence of oral clefts.
4. *Birth order*. The birth rank of children with oral clefts is, on the whole, not significantly different from that of normal children [2]. However, many of the mothers of female children with cleft lip were noticed to be primiparas [51].
5. *Teratogenic factors*. With respect to teratogenic factors that could influence the incidence of oral clefts, results of a study from Leeds, England have shown that congenital malformations were three times commonly seen in the children of epileptic mothers taking anticonvulsant drugs such as phenobarbitone and phenytoin than in the general population [59]. Furthermore, results of another study demonstrated that the incidence of oral clefts was higher in the offspring of women treated for seizure disorders than in no treatment group [60]. A collaborative study including 50,897 pregnancies also confirmed that the incidence of oral clefts was almost ten times greater in

women taking diphenylhydatoin in early pregnancies than in nonepileptic women [61] Studies on the effect of benzodiazepines-diazepam, oxazepam and chlordiazepines on pregnancy have found a significant association between the use of these drugs during the first trimester of pregnancy and the occurrence of cleft palate in the offspring of those mothers [62]. Other recognized teratogens that have been associated with clefts include rare exposures such as phenytoin, valproic acid and thalidomide [3].

A positive association between maternal smoking and cleft palate and lip was found in a retrospective study of 18,631 births in Cardiff [63]. Further studies by Ericson *et al* [64] demonstrated a significant increased rate of smoking among women who gave birth to infants with CL/P.

Diagnosis and Prevention

Studies of genes and environmental interactions with orofacial clefting have provided some insights into better diagnosis and prevention [3]. Avoiding common exposures in pregnancy such as smoking and alcohol may likely decrease the risk of having a child with a cleft [63,64]. Drugs for medical treatment, particularly anticonvulsant medications, need to be evaluated carefully, as they pose risks to the fetus. This, however, will have to be balanced against the possible risks of withdrawal for a mother on treatment for seizure disorder. Adequate nutritional supplements especially the use of folate, vitamin B6 or other micronutrients during pregnancy may possibly reduce the risk of clefts [3].

Conclusion.

At present, the prevention of oral clefts is not possible without knowing the precise etiology. Several attempts have been made to clarify the cause of this deformity, but in most cases contradictory results have been found. However, there seems to be a general agreement on its multifactorial heredity nature which is partly due to genetic and partly due to environmental factors. Genetic counseling can identify high risk families. The clefts themselves may be visible at twenty weeks gestation, but beyond early identification, we can only look into the future on the possibility of preventing oral clefts.

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Received: 30/06/04
Accepted: 21/12/04