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Cleft Lip and Palate: Etiology, Epidemiology, Preventive and Intervention Strategies

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Abstract

Cleft lip and palate represent a major public health problem due to the possible associated life-long morbidity, complex etiology, and the extensive multidisciplinary commitment required for intervention. It affects about 1.5 per 1000 live births (250,000 new cases per year) worldwide, with tremendous variations across geographic areas and ethnic groups. It is considered a debilitating condition that is associated with significant feeding, hearing, speech, and psychological impairments. The wide surgical, dental, speech, social, and medical involvement emphasize the importance of understanding the underlying determinants of these defects to allow optimizing the treatment options and predicting the long-term course of the affected individuals development. Optimal and early surgical intervention is necessary and folic acid supplementation proved to be a highly efficient preventive strategy. However, there are still many challenges to be addressed for cleft care especially in the developing parts of the world.

Keywords: Cleft lip and palate; Genetics; Epidemiology; Intervention

Introduction

Cleft lip and palate are considered one of the most common birth defects that possess significant medical, psychological, social, and financial implications on the affected individuals and families. Clefts have a complex etiology with both genetics and environment playing a role. Risk factors such as folic acid deficiency, maternal age, and maternal smoking have been linked to the development of clefts. In addition to the aesthetic disfigurement, a child with cleft lip and/or palate suffers substantial functional morbidity such as restricted maxillofacial growth, speech anomalies, swallowing and feeding difficulties, hearing loss and/or recurrent ear infections. Although not generally life-threatening, living with a cleft elicits a significant health burden [1,2].

Orofacial clefts (OFCs) describe a range of neonatal anomalies that involve structures around the oral cavity and may extend to the surrounding facial structures resulting in extensive craniofacial deformity. The main categories are isolated cleft palate (CP) and cleft lip with or without cleft palate (CL/P). Both types may present either isolated or as part of a syndrome or other associated abnormalities. Affected children suffer a range of medical problems that include feeding difficulties at birth due to problems with oral seal, swallowing and nasal regurgitation, hearing difficulties due to abnormalities in the palatal musculature, and speech difficulties due to nasal escape and articulation problems. These cleft defects have a long term, adverse influence on the health and social integration of affected individuals because even though they can be surgically repaired early in childhood, residual deformity due to scarring and abnormal facial development results in continuing functional and psychosocial problems [3,4].

A multidisciplinary approach to the OFC treatment is widely accepted all over the world. The multidisciplinary team usually includes plastic surgeons, oral surgeon, otolaryngologist, speech therapist, audiologist, orthodontists, psychologist, social worker, and a specialist nurse. The optimum treatment plan includes primary surgery to close the defect, ongoing speech therapy and orthodontic plan, and secondary and tertiary surgeries to refine the initial surgical results. In most cases the primary surgery has to be planned within the first six months after birth. However, in most developing countries the shortage of the qualified surgeons and other specialists as well as financial disparities and the unavailable equipped facilities result in inappropriate case management and sometimes many OFC children even remain untreated [5].

Etiology

CL/P is etiologically heterogeneous with both genetics and environmental contributions. With the advent of the genomics era and advances in both quantitative and molecular analysis techniques, there have been great improvements in the identification of causative genetic mutations and associations underlying syndromic forms of CL/P (Table 1). On the other hand, there is currently little progress in identifying and understanding of the genetic etiology of isolated (non-syndromic) CL/P cases [6-9].

A variety of genetic polymorphisms have been studied in population based association studies and candidate genes studies. Results have suggested a role for genes responsible for growth factors (e.g. TGFα, TGFβ3), transcription factors (e.g. MSX1, IRF6, TBX22), factors which influence xenobiotic metabolism (e.g. CYP1A1, GSTM1, NAT2), nutrient metabolism (e.g. MTHFR, RARA), and immune response (e.g. PVRL1, IRF6). TGFα and MTHFR genes have been amongst the most widely investigated variants over the years. A comprehensive survey of chromosomal deletions and duplications was

done to identify phenotypes significantly associated with particular partial aneuploidies. Regions that were significantly associated with clefts were identified at 1q25, 3p21, 4p15, 4q32 and 10p15. The 4p15 region is of particular importance in that it contains the MSX1 homeobox gene that is also the site of deletions causing the Wolf–Hirschhorn syndrome, which is commonly associated with orofacial clefting as well. Although extensively studied, due to factors such as the genetic heterogeneity, departure from Mendelian inheritance patterns, the limited availability and high cost of genomic tools, and the necessity for very large data sets, the exact genetic association, especially in non-syndromic OFC cases, remains poorly characterized [6-14].

Cleft lip ± cleft palate (CL/P)
Autosomaldominant developmental malformations
Deafness and dystonia — ACTB
Familial gastric cancer and CLP — CDH1
Craniofrontonasal — EFNB1
Roberts — ESCO2
Holoprosencephaly — GLI2
Hydrolethalus — HYLS1
Van der Woude/popliteal pterygium — IRF6
Xlinked mental retardation and CL/P — PHF8
Gorlin — PTCH1
CLP, ectodermal dysplasia — PVRL1
Holoprosencephaly — SHH
Holoprosencephaly — SIX3
Branchiooculofacial — TFAP2A
Holoprosencephaly — TGIF1
Ankyloblepharonectodermal dysplasiaclefting — TP63
Tetraamelia with CLP — WNT3
Cleft palate only (CP)
Oculofaciocardiodental — BCOR
CHARGE — CHD7
Lethal and Escobar multiple pterygium — CHRNG
Stickler type 1 — COL2A1
Stickler type 3 — COL11A2
Desmosterolosis — DHCR24
Smith–Lemli–Opitz — DHCR7
Miller — DHODH
Craniofrontonasal — EFNB1
Crouzon — FGFR2
Apert — FGFR2
Otopalatodigital types 1 and 2 — FLNA
Hereditary lymphedemadistichiasis — FOXC2
'Orofacialdigital' — GLI3
Van der Woude/popliteal pterygium — IRF6
Andersen — KCNJ2
Kabuki — MLL2
Cornelia de Lange — NIPBL
Xlinked mental retardation — PQBP1
Isolated cleft palate — SATB2
Diastrophic dysplasia — SLC26A2
Campomelic dysplasia — SOX9
Pierre Robin — SOX9
DiGeorge — TBX1
Treacher Collins — TCOF1
Midline cleft lip
Opitz G/BBB — MID1
Orofacialdigital type I — OFD1

Table 1: Cleft associated syndromes in which the mutated gene has been identified [6]

Gene-environment interaction in cleft lip and palate
TGFA/Smoking
TGFA/Alcohol
TGFA/Vitamins
MSX1/Smoking
MSX1/Alcohol
TGFB3/Smoking
TGFB3/Alcohol
RARA/Smoking
MTHFR/Vitamins
P450/Smoking
GST/Smoking
EPHX1/Smoking

Table 2: Currently reported gene-environment interaction in cleft lip and palate [14].

Most of the OFC epidemiologic studies support a role for environmental factors in the etiology of clefting. The most common risk factors reported were maternal exposure to tobacco products, alcohols, nutritional deficiencies, some viral infections, medications, and teratogens in the workplace or at home in early pregnancy.

Recognized teratogens included rare exposures such as phenytoin, valproic acid, thalidomide, and herbicides such as dioxin. Suggested gene-environment interactions are listed in Table 2 [14-22].

Some Key Epidemiological Findings

GBD region	Total OFCs/ 1,000	CP/ 1,000	CL/P/ 1,000	CP, % of total
Latin America, Southern	2.39	0.72	1.67	30
Latin America, Tropical	2.39	0.72	1.67	30
Australasia	2.01	1.02	0.98	51
North America, High Income	2.00	0.83	1.17	41
Oceania	1.85	1.13	0.72	61
Europe, Western	1.66	0.59	1.07	35
Asia Pacific, High Income	1.65	0.64	1.00	39
Asia, South	1.60	0.30	1.30	19
Latin America, Central	1.54	0.39	1.15	25
Europe, Central	1.45	0.67	0.77	47
Asia Southeast	1.36	0.28	1.08	20
Latin America, Andean	1.29	0.17	1.12	13
Asia, East	1.28	0.27	1.01	21
Europe, Eastern	1.22	0.59	0.63	49
Asia, Central	1.19	0.62	0.57	52
Middle East	1.02	0.30	0.72	29
Caribbean	0.93	0.31	0.62	34
Sub-Saharan Africa, Central	0.54	0.04	0.51	7
Sub-Saharan Africa, West	0.54	0.08	0.46	15
Sub-Saharan Africa, Southern	0.45	0.15	0.30	33
North Africa	0.44	0.15	0.29	35
Sub-Saharan Africa, East	0.38	0.12	0.27	31
World	1.25	0.31	0.94	25

Table 3: Estimated birth prevalence of OFCs by GBD region [29].

The incidence and the geographic distribution of OFC varies tremendously around the world due to differences in birth prevalence as well as the deficiencies in recording of births and birth defect surveillance systems, particularly in many parts of the developing world. Worldwide, there is a six-fold variation in the prevalence at birth of cleft lip with or without cleft palate (CL/P), and a three-fold variation in the prevalence at birth of cleft palate as reported by the IPDTOC Working Group, 2011. Native Americans show the highest incidences at 3.74 per 1000 live births, whereas a fairly uniform incidence of 1:600 to 1:700 live births is reported among Europeans. The incidence appears high among Asians (0.82-4.04 per 1000 live births), intermediate in Caucasians (0.9-2.69 per 1000 live births) and low in Africans (0.18-1.67 per 1000 live births). Comparisons between the ethnic groups within the US and the UK related to the immigrants from Asia and China indicated that immigrants reports OFC rates closer to their original region. African Americans reported lower prevalence than whites in the US. Although data from African countries are sparse, the available evidence indicates low prevalence rates for OFCs [23-26].

Isolated CL comprises about 25% of all clefts, while combined CL/P accounts for about 45%. CL/P occurs more frequent and more severe in boys than in girls. Unilateral clefts are more common than bilateral clefts with a ratio of 4: 1, and for unilateral clefts, about 70% occur on the left side of the face. CL/P is frequently associated with other developmental abnormalities and majority of cases are presented as part of a syndrome. Syndromic clefts account for about 50% of the total cases in some reports with about 300 syndromes described. Although the percentage of cases directly linked to genetic factors is estimated to be about 40%, all clefts appear to show a familial tendency. Table 3 demonstrates the estimated birth prevalence by Global Burden of Disease (GBD) region and Figure 1 shows the EUROCAT registries data aggregated by country. It was reported that there is more than 2 to 3 fold difference in prevalence of non-syndromic, OFCs in different European parts. This ranged between 2/1,000 in Northern Europe to 1/1,000 in Italy [26-28].

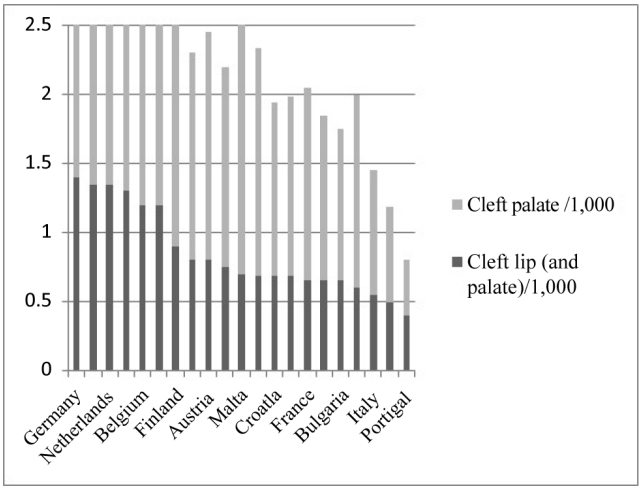

Figure 1: Prevalence of CL/P in Europe [29].

There is always a problem of underreporting of OFC cases. As congenital abnormalities, they should be recorded on the birth certificates, but up till now, there is no national or international standardized protocol for this procedure. Pediatricians and nurses in the delivery room are responsible on examining the newborn and thus are expected to report any anomalies and describe them on the medical record. Misdiagnosed and undiscovered cases greatly contribute to the underreporting. A clear example for those cases are the submucous clefts, in which an intact mucosal surface covers the palatal cleft, often goes unnoticed at birth and is only discovered later when patients develop hypernasal speech. Another dilemma in the reporting of OFCs is that some studies include all births in the rate calculations while others include only live births. Since clefts are more frequent among stillborn and spontaneously aborted infants, their inclusion in the denominator impact the results significantly [29-31].

The IPDTOC Working Group, 2011 have summarized the conclusions of all recent epidemiologic data on OFC as follows [32,33]:

- There is ample evidence of the distinctly different nature of CL/P and CP, and emerging evidence of distinct differences in subgroups within these overall conditions.
- There is significant geographical variation, which is more apparent for CL/P than for CP. There is considerable variation in the proportion of OFC cases with additional congenital anomalies and syndromes.
- There is no consistent evidence of time trends, nor is there consistent variation by SES or seasonality, but these areas have not been adequately studied. There is a need to investigate such parameters within as well as between different populations.
- There is considerable international variation in the frequency of OFCs, but validity and comparability of data are adversely affected by numerous factors, among which are: source population of births considered (hospital vs. population), time period, method of ascertainment, inclusion/exclusion criteria, and sampling fluctuation.
- There is little or no information on the frequency of OFCs for many parts of the globe, including parts of Africa, Asia, and Eastern Europe

Prevention and Intervention Strategies

Prevention should be considered the ultimate objective for OFCs. Extensive research on the exact etiology, successful implementation of prenatal vitamins and folic acid preventive strategies, together with improvements in surgical procedures, dental and orthodontic interventions, speech pathology, social and psychological support, pediatric care, and all other fields involved in the care of the child with OFC provides a hope for a better quality of care for those children.

Several epidemiological and observational reports have indicated a protective effect of prenatal use of multivitamins and folic acid on incidence of clefts. A decrease in CL/P risk with supplements containing folic acid has ranged from 18% to 50% in humans and from 69% to 76% in experimental animals. Low maternal B6 and B12 levels measured after pregnancy was reported to increase the risk of CL/P especially in cases associated with low serum folate. Animal studies have also confirmed the anti-teratogenic effects of prenatal folic acid supplementation and dietary folate [34-36].

Treatment of CL/P is complex in nature. It requires an extreme multidisciplinary collaboration committed to managing the patient from birth to maturity. The available evidence suggests that there is a strong relationship between positive treatment outcome and the availability of centralized care by a high quality dedicated team. Diagnosis of OFC is currently possible from about 17 weeks intrauterine because of the advances in ultrasound scanning techniques; however, most of the cases are only diagnosed after birth. Services and treatment options for infants with CL/P generally vary depending on the severity of the cleft, the child's age and medical condition, and the association with other anomalies or syndromes. In high-income settings, the surgery to repair the defect is usually planned in the first few months of life and is recommended before the age of 12-18 months. Most of the cases also require additional surgical interventions later in life. Surgical repair results in correction of the facial deformity as well as improving the feeding, speech, breathing, and hearing problems. Children later require special dental or orthodontic care, speech therapy, as well as social and psychological services. The optimal management protocol entails a range of services that need to be provided in a coordinated manner from birth into adolescence and sometimes adulthood stages [35-39].

In developing parts of the world, management of OFC patients exemplifies the health disparities and inequality. One obvious factor is the numbers of patients. Out of the estimated 250,000 child born each year with OFC, the majority are born in developing countries. The inequality is further complicated by the fact that most of them are born in rural areas where medical care is usually substandard. Most of the available reports suggest that in absence of any intervention, mortality due to OFC is very high. A study investigating tribal areas in rural India found that 'children born with cleft deformities all died within a few days of birth - they had been put to the breast but since they could not suckle they died of starvation. Spoon-feeding was unheard of and there were no visiting doctors or health workers to tell parents how to feed the infants'. A study has even indicated that in some parts of rural India, it was suspected that the birth of an infant with a highly disfiguring congenital malformation leads to "purposeful neglect". This is also expected to be the case in other similar parts of the world where there is ample poverty and deprivation levels such as in the Sub-Saharan Africa region [28,40,41].

Cleft lip and cleft palate can have a significant impact on the health economics of countries around the world. The substantial numbers of surgical procedures that are performed each year and the complexity of the skills required to complete these procedures safely and effectively clearly presents a major burden especially in low-income countries. When surgical interventions are inaccessible, facial deformities become lifelong disabilities, exerting additional burden not only on the individual and his surroundings but on the society and the country [42].

The Disability-adjusted life years (DALYs) debuted by the World Development Report have become the health metric of choice used to measure the mortality and physical impairment associated with an illness. It compares the cost effectiveness of competing health priorities by combining the years of life lived in a disabled health state with the number of years lost from a disease or injury. It was estimated that about 11% of the global burden of disease is caused by surgical conditions. Of this, 9% are thought to be associated with congenital anomalies. Several cost-effectiveness studies who analyzed OFC surgeries performed by the Smile for Children volunteer surgical mission team for children in developing countries indicated that the average cost of the repair surgery was in the range of $56 to $97 which is considered, based on the currently accepted international criteria, "highly cost-effective". This claim was based on an estimate of the cost per DALY averted for OFC surgery which proved to be even less than the estimates of cost per DALY averted for a number of other standard public health programs and on the fact that the cost per DALY averted through OFC surgery is within the range of cost-effectiveness defined by the World Health Organization (WHO) and the World Bank [43,44].

In conclusion, OFCs impact a considerable proportion of the global society. It affects around 1.5 per 1,000 live births (about 220,000 new cases per year), with wide variation across geographic areas and ethnic groups, with substantial evidence of both health inequality and inequity. The global burden incurred from OFCs in terms of physical morbidity, health care expenses, emotional distress, and social dysfunction are significant for affected individuals, their families, and over all the society. There is also substantial variation both within and between countries. Globally, extensive research on the exact etiological

factors and epidemiological data is still required to explore the most applicable attempts to decrease the burden of the disease and to improve the quality of care provided for the affected individuals.

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