Orofacial Clefts: A Worldwide Review of the Problem

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1. Introduction

Orofacial clefts (OFCs) are common congenital malformations of the lip, palate, or both caused by complex genetic and environmental factors [1]. OFC may involve the lip, the roof of the mouth (hard palate), or the soft tissue in the back of the mouth (soft palate). OFC also involves structures around the oral cavity which can extend onto the facial structures resulting in oral, facial, and craniofacial deformity [2]. A cleft lip/palate may impact negatively on an individual’s self-esteem, social skills, and behaviour especially among girls [3, 4]. Generally, boys are affected more than girls with a ratio of about 3 : 2 [5]. Males are more likely than females to have a cleft lip with or without cleft palate, while females are at a slightly greater risk for cleft palate alone [6, 7]. Since facial mesenchyme is derived from neural crest, it is postulated that periconceptional folic acid supplementation may reduce the occurrence of offspring with orofacial clefts [8]. Zinc also is important in fetal development, and deficiency of this nutrient causes isolated cleft palate and other malformations in animals; other nutrients such as riboflavin and vitamin A are also essential [9]. Preventive efforts might entail manipulation of maternal lifestyle, improved diet and use of multivitamin and mineral supplements, avoidance of certain drugs and medicines, and general awareness of social, occupational, and residential risk factors [2].

Genetic Basis of Orofacial Clefts. Genetic inheritance means that a child’s features are “inherited” or passed from parent to child [10]. There are two types of inheritance: the single-gene inheritance where a feature appears as a result of a single gene carried by one parent and the multifactorial inheritance where a feature appears as a result of a number of genetic and nongenetic factors, such as alcohol, drugs, and environmental factors [10]. Orofacial development is a complex process that involves many genes and signaling pathways [11]. Alterations in one or more of these genes could cause one of the commonest malformations in humans: cleft lip with or without cleft palate or cleft palate alone (CL ± P, CP) [12].

2. The Problem

2.1. Epidemiology. The prevalence of OFCs varies from 1/500 to 1/2500 births depending on the geographic origin, racial and ethnic backgrounds, and socioeconomic status [13, 14]. Also Das stated that Asians have the highest risk (14 : 10,000
births) followed by whites (10:10,000 births) and African Americans (4:10,000 births) [15]. Cleft lip, with or without cleft palate, affects one in 700 babies annually and is the fourth most common birth defect in the United States. Clefts occur more often in children of Asian, Latino, or Native American descent [16]. Reports of birth prevalence of OFCs from different African populations vary widely, from as low as 0.3/1,000 reported in Nigeria [17] to 1.65/1,000 reported in Kenya [18]. In Malawi, there is a reported low prevalence rate for cleft lip and/or palate, 0.7 per 1,000 live births [19]. Suleiman et al. (2005) found that the prevalence rate of clefting among a group of Sudanese hospital newborns in the city of Khartoum is 0.9 per 1,000 live births [20]. In Ghana, a survey conducted in the Wadooba communities revealed a CL/CP prevalence of 5.0 per 1,000 people [21].

2.2. Risk of Occurrence. The risk of recurrence of a cleft condition is determined by a number of factors that are often unique in a particular family, and 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 [22]. Once parents have a child with a cleft, the risk that the next child (each succeeding child) will be affected is 2–5% (2 to 5 chances in 100). If there is more than one person in the immediate family with a cleft, the risk rises to 10–12% (roughly 1 chance in 10). An individual who is the only one in his or her family with a cleft has 2–5% chances that his or her child will have a cleft (2 to 5 chances in 100). If the individual with the cleft also has a close relative with a cleft, the risk increases to 10–12% (roughly 1 in 10) that a child will have a cleft. Finally, the unaffected siblings of an individual with a cleft have a roughly 1% (1 in 100) risk of having a baby with a cleft. This may rise to 5-6% (5 to 6 chances in 100) if more than one close family member has a cleft. If a syndrome is involved, the risk for recurrence within the family could be as high as 50% (1 chance in 2) [22].

2.3. Causes. The aetiology of OFCs is complex, including multiple genetic and environmental factors [23]. Oral clefts frequently occur in combination with a wide range of chromosomal abnormalities and syndromes (trisomy 13, amniotic band anomaly, Fryns syndrome, Meckel syndrome, Stickler syndrome, Treacher Collins syndrome, van der Woude syndrome, Velocardiofacial syndrome, etc.) [24] and environmental factors such as medication during pregnancy, maternal alcohol consumption and smoking, dietary and vitamin deficiencies, diabetes, environmental toxins, altitude, birth order, socioeconomic status, and parental age [25–29]. Other genetic factors that may affect the presence of OFCs include maternal ability to maintain red blood cell zinc concentrations and myoinositol concentrations (a hexahydroxy cyclohexane sugar alcohol) [30]. Maternal ability to maintain adequate levels of vitamins B6 and B12 and fetal ability to utilize these nutrients are also seen as a factor in the development of oral clefts when these nutrients are not metabolized properly since errors in DNA synthesis and transcription may occur [31].

Drugs play a limited role in the aetiology of cleft lip or palate (CL/P), amoxicillin, phenytoin, oxprenolol, and theiethylperazine may have some association with (CL/P), while carbamazepine and oxytetracycline may have some association with posterior cleft palate (PCP) during the early stages of pregnancy [32]. In addition, mothers with the MTHFR 677TT OR MTHFR 1298CC genotype and low periconceptional folate intake were found to have an increased risk for cleft lip with or without palate among their offspring [31, 33]. Drugs which interfere with folate metabolism, such as phenytoin, are known to have teratogenic effects which include oral cleft, growth retardation, limb defects, and other craniofacial deformities. Maternal intake of vasoactive drugs which include pseudoephedrine, aspirin, ibuprofen, and amphetamine as well as cigarette smoking has been associated with higher risk of oral clefts [34–36]. Anticonvulsant medications such as phenobarbital, trimethadione, valproate, and Dilantin have also been documented to increase incidence of cleft lip/cleft palate [37, 38]. Other drugs such as acne medications containing Accutane and methotrexate, a drug commonly used for treating cancer, arthritis, and psoriasis, may also cause cleft lip and cleft palate [16].

2.4. Diagnosis. Sometimes OFCs are diagnosed by prenatal ultrasound, but there is no systematic screening for orofacial clefts [39]. Most often, orofacial clefts are diagnosed after the baby is born. However, sometimes minor clefts (e.g., submucous cleft palate and bifid uvula) might not be diagnosed until later in life. Cleft lip can be easily diagnosed by performing ultrasonography in the second trimester of pregnancy when the position of the fetal face is located correctly [40]. Prenatal diagnosis gives parents the advantage of having time to prepare emotionally for the birth and become knowledgeable about the birth defect.

2.4.1. Ultrasound Diagnosis. New techniques for prenatal diagnosis have been reported by some authors. Campbell et al. reported a novel technique involving a reverse face view using 3D sonography to diagnose cleft lip and palate in the antenatal period [41, 42]. While prenatal diagnosis of cleft is readily attainable using conventional 2D sonography, cleft palate is more difficult to identify especially if it is an associated anomaly [43]. Platt et al. believed that the accurate diagnosis of craniofacial malformations can be enhanced with 3D sonography [44]. Rotten and Levaillant (2004) have also reported that inclusion of 3D and 4D ultrasound imaging allows easier and more precise evaluation of the different cleft constituents [45].

2.5. Effects. Affected children have a range of functional as well as aesthetic problems and these 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 articulation problems and dental problems [4, 39, 46]. Many parents express a feeling of loss of control that despite their plans for a “healthy” pregnancy, they have been unable to control the outcome. Mothers often report feelings of resentment, hurt, and disappointment after discovering that their child has an OFC [47].
Studies have found decreased quality of life of adolescents with congenital and acquired facial malformations compared with unaffected adolescents as well as frequent reporting of stigmatization experiences [48, 49]. Quality of life also decreased with the individuals’ perceptions of increasing severity of facial malformations [50].

2.6. Syndromic and Nonsyndromic Clefts

2.6.1. Syndromic Clefts. Cleft lip or palate can be seen as an associated feature in ≥300 syndromes [3, 10]. Syndromic CL/P cases also indicate a genetic aetiology, because more than 400 known syndromes include orofacial clefting, and many of these follow classic Mendelian inheritance patterns [51]. Cleft palate with ankyloglossia (CPX; MIM 303400) is inherited as a semidominant X-linked disorder previously described in several large families of different ethnic origins and has been the subject of several studies that localized the causative gene to Xq21. Positional cloning identified the CPX locus as the gene encoding T-BOX 22 (TBX22) [52]. TBX22 is a member of the T-box containing transcription factor gene family that is conserved throughout metazoan evolution. Van der Woude syndrome (VWS) (OMIM 119300) is the most common autosomal dominant disorder which is always associated with cleft lip or palate (CL/P) [53]. Interferon regulatory factor 6 (IRF6) which is located in chromosome 1 is the major gene that is associated with VWS [54, 55], and later its variants were found to be significantly associated with nonsyndromic clefts [51, 56]. The Wolf-Hirschhorn syndrome (WHS) (OMIM 194190), which is caused by the partial deletion of the short arm of chromosome 4 (4p), is also characterized by oral clefts [57].

2.6.2. Non-Syndromic Clefts. Gene identification for non-syndromic cleft lip and palate is difficult because of the varying levels of its penetrance, sex differences, and other environmental factors [58]. The complex natures of the non-syndromic clefts that are attributed to the multiple interacting genes conferring moderate effects have been proposed to provide susceptibility to orofacial clefts [59–61]. Studies on these syndromes have given sufficient clues to identify the genes that cause the non-syndromic clefts [62]. Fluorescence in situ hybridization (FISH) analysis of eight Finnish WHS patients revealed five patients not having one copy of Msx1 with oligodontia while the other three had two hybridization signals of which one patient presented with the only case of cleft palate [63]. Analysis of a Dutch family with CL/P, CP, and selective tooth genesis revealed a heterozygous nonsense mutation in Msx1 gene. Furthermore, complete sequencing of the Msx1 gene in 1000 unrelated CL/P individuals showed that mutations in Msx1 alone could account for 2% of isolated CL/P [64].

3. Related Animal Models

Scientists from diverse fields have gravitated to the mouse because of its close genetic and physiological similarities to humans, as well as the ease with which its genome can be manipulated and analyzed [65]. Furthermore, the development of the embryonic face is similar in mice and humans [66]. The development of the upper lip has been well reviewed and presented for use of the CL/P mutants recently [67]. Mouse mutants with disruption in genes such as Gli2, Gli3, Tgfβ2, and Hoxa2 result in CL/P through disturbance to cranial neural crest (CNC) migration and differentiation [68–70]. Several genes have been implicated in palatal mesenchymal proliferation such as Msx1 and Hox8, where CP is seen in the respective null mice due to the palatal shelves failing to meet in the horizontal plane [71, 72]. Mice lacking Msx1 function manifest a cleft of secondary palate, a deficiency of alveolar mandible and maxilla, and a failure of tooth development [69, 73]. Mice lacking EDN1 have shown several craniofacial abnormalities, including cleft palate [70].

4. Economic Impact

Treatment of cleft lip and palate anomalies requires years of specialized care and is costly. The average lifetime medical cost for treatment of one individual affected with a cleft lip and palate is $100,000 [74]. Although successful treatment of the cosmetic and functional aspects of orofacial cleft anomalies is now possible, it is still challenging, lengthy, costly, and dependent on the skills and experience of a medical team. This especially applies to surgical, dental, and speech therapies [40]. The mean and median costs for children ≤10 years of age with an orofacial cleft were eight times higher than those for children of the same age without an orofacial cleft. Mean costs for infants with a cleft and another major unrelated defect were 25 times higher than those for an infant without a cleft and five times higher than those for infants with an isolated cleft with patients continuously enrolled in a fee-for-service [75].

5. Management

Services and treatment for children with OFCs vary depending on the severity of the cleft; the presence of associated syndromes, other birth defects, or both; and the child’s age and needs [76].

5.1. Surgical Management. Orofacial clefts generally require surgical repair. Often multiple surgeries are needed to reconstruct the lip and palate [39]. A palatoplasty is the procedure utilized to close the palate, restore the velopharyngeal sphincter, and help speech function and other processes [77]. The optimum approach to the treatment of children born with cleft defects is a multidisciplinary approach which involves combined efforts of a pediatrician, orthodontist, specialist nurse, cleft surgeon, speech therapist, and ear, nose, and throat specialist to provide the best combined expertise to ensure that the correct interventions are carried out at the appropriate time and to ensure the best functional and aesthetic result [78]. Many children will need additional surgeries as they get older. Surgical repair can improve the look and appearance of a child’s face; it also may improve breathing, and shearing, speech and language [79].
5.2. Medical Management. The supplementation of folic acid currently recommended to protect against neural tube defects is 0.4 mg per day, twice the current average daily intake for women of 0.2 mg [80]. It has been suggested that maternal folic acid supplementation plays a role in the prevention of non-syndromic orofacial clefts, that is, cleft lip with or without cleft palate (CL ± P) [81]. Several studies have reported decreased rates of cleft lip and palate with folic acid use [82–85]. Some ambiguity of the studies may be explained by a recent study that found that oral cleft risk can be reduced only by high doses of folic acid consumed at the time of lip and palate formation [86]. Maternal multivitamin use has also been found to result in a significant reduction in cleft palate risk and a nonsignificant reduction in cleft lip risk [87].

5.3. Psychological Management. The psychological care of the patient with a cleft begins at the time of diagnosis, even if this is before birth. An accurate diagnosis is critical to the process of counseling families. It is the responsibility of the referral centre to define the nature of the structural defect with as much precision as possible. This helps the family to visualize the child and to discuss feeding, especially breastfeeding. It also helps when informing about timing and type of surgery. To plan for the future, parents need to discuss the management and likely the treatment pathway at their own pace and at their own time, so that they are able to absorb the information [88]. Delayed repair of cleft can lead to impaired family and societal relationships with potential long-term psychological effects on the child. As the child matures and faces the task of individuation from the family, there may be a need for psychological work, and since adulthood provides its own set of challenges to the individual, there is potential for further psychological interventions throughout this period of life. Parents need reassurance, support, and time to assimilate the information to be able to provide the child with the support and care needed.

5.4. Social Management. Strong parent support networks may help to prevent the development of negative self-concept in children with cleft palate [89], so it is important that parents discuss with their children ways to handle negative social situations related to their cleft lip and/or cleft palate [3].

5.5. Other Forms of Treatment. For other treatments such as hearing assessment, speech and language therapy, and dentofacial development and treatment, psychologist or other mental specialists are required to ensure effective functioning of the body organs and systems [46, 89]. The role of craniofacial team in the management of cleft lip ± palate cannot be understated. A craniofacial team is a multidisciplinary team which provides multidisciplinary consultations, diagnosis, treatment planning, and procedures for a range of craniofacial anomalies and syndromes [3]. Teamwork is highly recommended in the management of persons with OFC. This team is much dedicated to ensuring that persons with the condition are offered the necessary help, care, and support to help them have a better life.

6. Prevention

It is necessary to understand genetic and environmental causes of syndromic and non-syndromic OFCs in order to prevent them. Having an understanding of multifactorial aetiology helps direct attention toward prevention. It helps to understand much better our own health problems and modify our lifestyle and diet in order to prevent “environmental factors” from triggering the mutated genes inherited from our parents [90]. Genetic counseling, taking of prenatal vitamins and tobacco or alcohol intake should be taken into consideration before and during pregnancy [90]. Research has also recommended folic acid intake as a means of controlling clefts and it is therefore advisable for women to take folic acid as a daily dietary supplement before and in the early weeks of pregnancy [91].

7. Conclusion

Education and awareness on orofacial clefts in general should be promoted so that preventive measures can be put in place and persons suffering from the condition can be well attended to and catered for. Orofacial clefts impact on a person’s quality of life hence the need for better management of this abnormality. 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. Also genetic counseling units should be set up to counsel persons with the abnormality and also expectant mothers.

References


[76] American Cleft Palate-Craniofacial Association, Parameters for Evaluation and Treatment of Patients with Cleft Lip/Palate or other Craniofacial Anomalies, American Cleft Palate-Craniofacial Association, Chapel Hill, NC, USA, 2009.


