
Chromosomal Abnormalities Associated With Cleft Lip and Cleft Palate

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Abstract: Aim and Objective: To enumerate the various chromosomal abnormalities which may lead to cleft lip and cleft palate and to know about their prevention which can prove better than cure and to know the cure as well in cases where the stage of prevention has surpassed. Materials: Various reference articles regarding the chromosomal abnormalities are referred to know about the various categories of chromosomal abnormalities, their etiologies, early diagnosis, prevention and treatment plans for the same. Results: the article enumerates the theoretical part of the topic in detail but has not been conducted practically because of which it doesn't give the idea of prevalence amongst any particular type of regional population. Theoretical part of the article explains all the anomalies, risk factors, preventive measures which can further be used as a base to conduct a practical study. Conclusion: The article is an attempt to understand the abnormalities associated with cleft lip and cleft palate at genetic level. This gives a scenario of what are the conditions causing cleft lip and cleft palate and how important it is to diagnose this at an early age to provide further problems.

Keywords: Chromosomal Abnormalities, Monogenic Syndrome, Chromosomal Syndrome, Velocardiofacial Syndrome, Median Facial Dysplasia

1. Introduction

Orofacial cleft is one of the commonest congenital abnormalities which impacts negatively on the life of the individual and to a large extent affects the family. Caused by the interaction of environmental and genetic factors, this abnormality brings about decreased quality of life. Management of this abnormality entails a team involving a cleft surgeon, speech therapist, dentist, orthodontists, and so forth. This study involves the review of the various literatures on orofacial clefts, discussing the problems on the genetic basis, associated syndromes, and their management. Counseling of prospective mothers should be promoted to ensure that the abnormality is prevented at the early stages. Education on orofacial clefts should be promoted to create awareness on its preventive measures. Much attention must be geared towards cleft genetics studies to identify potential risk factors which might be predisposing individuals to the anomaly [1].

Orofacial clefts (OFCs) are common congenital

malformations of the lip, palate, or both caused by complex genetic and environmental factors [2]. 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 [3]. A cleft lip/palate may impact negatively on an individual's self-esteem, social skills, and behavior especially among girls [4,5]. Generally, boys are affected more than girls with a ratio of about 3:2 [6]. 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 [7, 8]. 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 [9]. 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 [10]. 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 [3].

Genetic Basis of Orofacial Clefts: Genetic inheritance means that a child's features are "inherited" or passed from parent to child [11]. 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 [11]. Orofacial development is a complex process that involves many genes and signaling pathways [12]. 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 \pm P, CP) [13].

2. Etiology

Every congenital structural defect in the body represents an inborn error in morphogenesis and may affect one or more systems. In general, most congenital anomalies can be divided into three types:

- Disruptions:** A rare anomaly related to breakdown of the original normal foetal developmental process, e.g. craniofacial cleft resulting from amniotic bands.
- Deformations:** These occur secondary to mechanical forces leading to anomalies of a lesser degree when compared to disruption, e.g. club foot, cleft palate, Pierre Robin sequence etc.
- Malformations:** A morphologic defect in an organ from an intrinsically abnormal developmental process, e.g. polydactyly, congenital heart anomalies, cleft lip etc [14].

They are generally described in four categories:

1) Monogenic Syndrome

When the anomalies are etiologically related and due to a single gene, the constellation of associated anomalies constitutes a monogenic syndrome. Monogenic syndromes include Van der Woude with most of these cases linked to Chromosome 1q32-q41 and Treacher Collins (an autosomal dominant) syndrome.

It is one of the commonest syndromes associated with oral cleft. It is transmitted as an autosomal dominant and lower lip pits are the hallmark. These pits are located bilaterally in the lower lip at the junction of dry and wet vermilion and they are either oval or transverse in shape. Pits traverse the underlying orbicularis muscle and end in a blind pouch on the buccal side and communicate with minor salivary glands. The associated features are hypodontia, missing maxillary or mandibular second premolar teeth, absent maxillary lateral incisor and ankyloglossia [14].

2) 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 4 p - are other chromosomal abnormalities leading to different syndromes often found with oral clefts.

2.1. Sequence

When the associated anomalies are due to a single known or presumed structural defect, they are termed sequence. The most common sequence observed with oral clefts is the Pierre Robin sequence, which is characterized by mandibular deficiency, cleft palate, and upper airway obstruction.

2.2. Pierre Robin Sequence

The initial event is mandibular hypoplasia between the seventh and eleventh weeks of gestation, which keeps the tongue high in the oral cavity preventing closure of palatal shelves resulting in formation of classic inverted U-shaped cleft palate. Oligohydramnios also plays a role because lack of amniotic fluid leads to deformation of the chin and subsequent impaction of the tongue between palatal shelves. The frequencies of occurrence of various deformities are Micrognathia (91.7%), Glossoptosis (70-85%) or Macroglossia and Ankyloglossia (10-15%) and Cleft Palate (14%). Occasionally a bifid or double uvula with an occult submucous cleft can be present. Airway obstruction due to tongue fall results in failure to thrive and is a serious problem in these patients. A great degree of suspicion is required to diagnose this condition, and management includes proper feeding advice, positioning the baby and early surgical intervention [14].

3) Velocardiofacial Syndrome

Velocardiofacial syndrome (VCFS) is a genetic condition characterized by abnormal pharyngeal arch development that results in defective development of the parathyroid glands, thymus, and conotruncal region of the heart. Shprintzen and colleagues first described the syndrome in 1978.

It is an autosomal dominant condition and is associated with Chromosome 22q abnormality, as a result of a sub-microscopic deletion on the long arm of Chromosome 22 in the "q11" region (deletion22q11).

An estimated 75% of patients with velocardiofacial syndrome have cardiac anomalies. The cardiac defects are usually of the conotruncal type, which occur secondary to abnormal development of the outflow portion of the developing heart. The most common cardiac defects include interrupted aortic arch type B (50%), truncus arteriosus (34.5%) and tetralogy of Fallot (16%). Other cardiac defects include pulmonary atresia with ventricular septal defect, absent pulmonary valve syndrome, ventricular septal defect (especially when accompanied by aortic arch anomalies), aortic stenosis, anomalies of the aortic arch or its major branches, and pulmonary artery anomalies. The presence of an aortic arch anomaly increases the odds of having a 22q11.2 deletion, regardless of the intracardiac anatomy.

Palatal abnormalities predispose to speech and feeding difficulties.

Ophthalmologic abnormalities are seen in 70% of patients with velocardiofacial syndrome, such as posterior embryotoxon, bilateral cataracts, tortuous retinal vessels, and small optic disks. Other rare anomalies include congenital absence of the nasolacrimal duct.

About 10% of patients with velocardiofacial syndrome have DiGeorge syndrome, which consists of at least 2 of the following features:

- Conotruncal cardiac anomaly
- Hypoparathyroidism, hypocalcemia
- Thymic aplasia, immune deficiency

As many as 15-20% of patients have Pierre Robin syndrome, which includes small jaw, U-shaped cleft palate, and glossoptosis. Reports indicate that some patients with velocardiofacial syndrome may be mistakenly categorized as having CHARGE syndrome (i.e., coloboma, heart defect, atresia choanae, retarded growth and development, and/or CNS anomalies, genital hypoplasia, and ear anomalies and/or deafness). Velocardiofacial syndrome is a specific syndrome that includes as part of its phenotypic spectrum the DiGeorge sequence, the Pierre Robin sequence, and disorders associated with CHARGE syndrome [15].

4) Median Facial Dysplasia

Median facial dysplasia is a unique, distinct, definable group of patients characterized by midline facial deficiencies in the presence of a unilateral or bilateral cleft lip with or without cleft palate. The midline hypoplasia may extend into the midline structure of the brain like corpus callosum. If head circumference is <90% of normal, these patients may have associated anomalies of the brain, especially frontal corpus callosum. It is obvious that they will have compromised development of midface resulting in very early dish face, Class III occlusion and severe maxillary hypoplasia. Early recognition of these subgroups of patients helps to plan the course of treatment.

3. Prevention

Identification of modifiable risk factors is the first step towards primary prevention:

Pre-pregnancy planning seems to reduce risk.

- Preventative efforts might involve manipulation of maternal lifestyle, improved diet, use of multivitamin and mineral supplements, avoidance of certain drugs and medicines and general awareness of social, occupational, and residential risk factors.
- Genetic counselling can identify high-risk families. Research continues into likely environmental triggers including influenza, high gravidity, varicella infection, drugs and diet.

4. Diagnosis

The general guidelines for the evaluation of individuals with Cleft lip and palate and Cleft palate (CL/P and CP) in order to identify syndromes are:

- Thorough clinical examination, preferably by geneticist

or dysmorphologist.

- Comprehensive medical history: Description of the cleft, antenatal history, birth history, developmental history, and family history.
- Physical examination: measurement of weight, length or height, and occipitofrontal circumference, identification of anomalies of eyes, ears, heart, extremities and also to look for associated preauricular tags, lip pits, epicanthal folds.
- Documentation by photographs of all affected individuals and first-degree relatives.
- Necessary laboratory and radiological evaluations

Mainly the diagnostic decision involves looking for syndromal cases (around one third) versus isolated cases, and determining the extent of any associated palatal defect.

Associated syndromes include:

- Apert's syndrome.
- Goldenhar's syndrome.
- DiGeorge's syndrome: this is underdevelopment of the third and fourth pharyngeal pouches. The syndrome is often associated with congenital heart defects, abnormalities of the large blood vessels around the heart, failure of the esophageal tube to develop, abnormalities of facial structures, and hypoparathyroidism. In most cases, there is a defect on chromosome 22.
- Coloboma, Heart defect, Atresia choanae, Restricted growth and development, Genital hypoplasia, Ear anomalies/deafness (CHARGE) syndrome.
- 3q29 microdeletion syndrome.
- Pierre Robin sequence.
- Trisomy 18 (Edwards' syndrome), trisomy 13 (Patau's syndrome) and trisomy 15.
- Van der Woude syndrome.

5. Investigations

- Thorough physical examination of the neonate by a pediatrician is needed to exclude presence of any associated syndrome.
- Chromosome analysis may be required.

Associated Diseases

- Females may have increased risk of breast cancer and primary brain malignancy.
- Males have increased risk of primary lung cancer.
- Psychosocial problems may also be associated with clefting, particularly if uncorrected. These include behavioral problems, anxiety and depression. This is particularly true by adolescence, when older studies (1989) observed that young people with uncorrected defects showed high levels of social anxiety and alienation.

6. Treatment

6.1. General Measures

Ideally, patients should be managed by a multidisciplinary

team which includes: plastic surgeons, maxillofacial surgeons, ENT, speech and language therapists, dentists, orthodontists, psychologists and specialist nurses. They will provide support and treatment until growing is complete at around the age of 18 years.

6.2. Surgical

This comprises the bulk of the treatment. A number of operations will be required as the child grows. The absence of a sound evidence base for selection of treatment protocols is shown by a striking diversity of practices across Europe for surgical care.

The approach is a team one, involving cosmetic and craniofacial surgeons, speech therapists, dentists, ENT specialists and pediatricians. Psychologists, social workers and counsellors are usually involved, for parents as well as children.

- Primary lip closure is performed at three months after birth, as long as weight and hemoglobin levels are adequate.
- Palate closure is performed at 6-12 months.
- Further operations are performed to improve appearance.
- If there is a gap in the gums, a bone graft may be required.

Recent advances in fetal (intrauterine) surgery using a fetal endoscopic technique, offer the prospect of scar less wound healing, and bone healing without callus formation. This allows for better or even normal maxillary growth. As the technique improves, the outcome for mother and fetus is improving [16].

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 [17].

Surgical Management

Orofacial clefts generally require surgical repair. Often multiple surgeries are needed to reconstruct the lip and palate [18]. A palatoplasty is the procedure utilized to close the palate, restore the velopharyngeal sphincter, and help speech function and other processes [19]. 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 [20]. 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 [21].

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 [22]. 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 \pm P) [23]. Several studies have reported decreased rates of cleft lip and palate with folic acid use [24-27]. 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 [28]. 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 [29].

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 [30]. 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.

Social Management

Strong parent support networks may help to prevent the development of negative self-concept in children with cleft palate [31], 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 [4].

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 [32, 33]. The role of craniofacial team in the management of cleft lip \pm 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 [4]. 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.

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 a etiology 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 [33]. Genetic counseling, taking of prenatal vitamins and tobacco or alcohol intake should be taken into consideration before and during pregnancy [33]. 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 [34].

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.

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