Syndrome Associated with Cleft Palate and Cleft Lip

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ABSTRACT:

Genetic syndromes often reveal themselves in children who are born with congenital anomalies. Genetic syndromes can occur if a gene mutates or a malformation is inherited. There are over 400 syndromes that involve clefting. Children with genetic syndromes, and more specifically children with clefts, frequently have feeding problems, swallowing/deglutition dysfunction, and breathing difficulties. This review focuses on such common syndromes encountered in cleft lip and palate.

Key words: Syndromes, Cleft lip & Palate

INTRODUCTION:

A syndrome is a pattern of multiple anomalies that are pathogenically related and therefore have a common known or suspected.

Cleft palate (CP) has a prevalence of 6.39 per 10,000 live births . In contrast to cleft lip/ palate, CP is much more likely to be associated with an underlying syndrome or other congenital anomalies.[1,2,3]

Since it can be difficult to distinguish between the malformation of cleft palate and cleft palate as a disruption of normal development, all cases of cleft palate, including those caused by Pierre Robin sequence, will be discussed in this review.

Syndromes associated with cleft lip & palate:

I. Pierre Robin Sequence:

Pierre Robin sequence is a common cause of cleft palate. This sequence can occur in isolation, but is

associated with an underlying syndrome in over 50% of cases. This condition is not a diagnosis unto itself, but rather encompasses the pathogenesis of the cleft palate.

Infants born with Pierre Robin sequence are born with their tongue positioned posteriorly, often causing blockage of the pharynx and airway, a process called gloosoptosis. This affects both breathing and feeding.[1,2]

II. Stickler Syndrome:

Stickler syndrome is by far the most common identifiable cause of cleft palate. It was first studied and characterized by Gunnar B. Stickler in 1965. Stickler syndrome is a subtype of collagenopathy, types II and XI. This is an autosomal dominant disorder with variable expressivity; in other words, there is a great deal of variablitiy in the clinical presentation of patients with this disorder. Individual with this condition may have just a few or all of the clinical features associated with this disorder. Stickler syndrome is characterized by distinctive facial abnormalities, ocular problems, hearing loss, and joint problems

Mutations in the COL11A1, COL11A2 and COL2A1 genes cause Stickler syndrome. These genes are involved in the production of type II and type XI collagen. Mutations in any of these genes disrupt the production, processing, or assembly of type II or type XI collagen. Defective collagen molecules or reduced amounts of collagen affect the development of bones and other connective tissues, leading to the characteristic features of Stickler syndrome.

The classic presentation of Stickler syndrome is Pierre Robin sequence, including cleft palate; early onset osteoarthritis, often in early adulthood but sometimes in later; and myopia .In addition, sensorineural hearing loss is very common in Stickler syndrome. Many individual with stickler syndrome also have characteristic facial features including micrognathia in infancy, a flat facial profile, epicanthal folds and midface hypoplasia. The nasal bridge is often flat, even in adulthood.

Development is usually normal in Stickler syndrome. These individuals do not appear to be increased risk for any particular learning disabilities. Speech and language problems are usually related to the cleft palate and hearing loss.[3-11]

III. Velocardiofacial Syndrome (Deletion 22q11.2 syndrome)

Velocardiofacial syndrome is a relatively common condition with an incidence of approximately 1 in 4000 live births. This disorder is caused by intersitial deletion of chromosome 22q11.2. this is highly variable condition with many names, including Digeorge syndrome and Conotruncal face syndrome. The most common anomalies are palate anomalies (cleft palate and / or velopharyngeal insufficiency), congenital heart defects, hypocalcemia, immunodefeciency and dysmorphic facial features.

The facial characteristics associated with velocardiofacial syndrome include microcephaly, narrow palpebral fissures, a wide nasal root, a bulbous nose, vertical maxillary excess, a thin upper lip, a long face, micrognathia, and minor auricular anomalies.

Individuals with deletion 22q11.2 syndrome can have myriad medical problems, and these can include kidney or urinary tract anomalies. There is a close association between VCFS and DiGeorge syndrome which includes small or absent thymus, tonsils, adenoids and hypocalcaemia. These children may have medial displacement of the carotid artery over the cervical vertebrae and this should be borne in mind while planning any pharyngeal surgery like pharyngeal flap for Velo pharyngeal incompetence (VPI) correction. The majority of these patients will need support for their learning problems.[12-15]

IV. OSMED Syndrome:

Otospondylomegaepiphyseal dysplasia (OSMED) is a skeletal disorder characterized by skeletal abnormalities, distinctive facial features, and severe hearing loss. The condition involves the

ears (oto-), affects the bones of the spine (spondylo-), and enlarges the ends (epiphyses) of long bones in the arms and legs. The features of OSMED are similar to those of another skeletal disorder, Weissenbacher-Zweymüller syndrome.

People with OSMED are often shorter than average because the bones in their legs are unusually short. Other skeletal features include enlarged joints; short arms, hands, and fingers; and flattened bones of the spine (platyspondyly). People with the disorder often experience back and joint pain, limited joint movement, and arthritis that begins early in life. Severe high-tone hearing loss is common in people with OSMED. Typical facial features include protruding eyes; a flattened bridge of the nose; an upturned nose with a large, rounded tip; and a small lower jaw. Virtually all affected infants are born with cleft palate. The skeletal features of OSMED tend to diminish during childhood, but other signs and symptoms, such as hearing loss and joint pain, persist into adulthood.

Mutations in the *COL11A2* gene cause OSMED. Mutations in the *COL11A2* gene that cause OSMED disrupt the production or assembly of type XI collagen molecules. The loss of type XI collagen prevents bones and other connective tissues from developing properly.[16-18]

V. Van der Woude Syndrome:

Van der Woude syndrome is a condition that affects the development of the face. Many people with this disorder are born with a cleft lip, a cleft palate (an opening in the roof of the mouth), or both. Affected individuals usually have depressions (pits) near the centre of the lower lip, which may appear moist due to the presence of salivary and mucous glands in the pits. Small mounds of tissue on the lower lip may also occur. In some cases, people with van der Woude syndrome have missing teeth.

People with van der Woude syndrome who have cleft lip and/or palate, like other individuals with these facial conditions, have an increased risk of delayed language development, learning disabilities, or other mild cognitive problems. The average IQ of individuals with van der Woude syndrome is not significantly different from that of the general population. Mutations in the IRF6 gene cause van der Woude syndrome.

Van der Woude syndrome is believed to occur in 1 in 35,000 to 1 in 100,000 people, based on data from Europe and Asia. Van der Woude syndrome is the most common cause of cleft lip and palate resulting from variations in a single gene, and this condition accounts for approximately 1 in 50 such cases.[19-23]

VI. Treacher Collins Syndrome:

Treacher Collins syndrome also known as Mandibulofacial dysostosis or Franceschetti-Zwahlen-Klein Syndrome. Treacher Collins syndrome is a condition that affects the development of bones and other tissues in the face. The signs and symptoms of this disorder vary greatly, ranging from almost unnoticeable to severe. Most affected individuals have underdeveloped facial bones, particularly the cheek bones, and a very small jaw and chin (micrognathia) and cleft palate. In severe cases, underdevelopment of the facial bones may restrict an affected infant's airway, causing potentially life-threatening respiratory problems.

People with Treacher Collins syndrome often have eyes that slant downward, sparse eyelashes, and a notch in the lower eyelids called a coloboma. Some affected individuals have additional eye abnormalities that can lead to vision loss. This condition is also characterized by absent, small, or unusually formed ears. Defects in the middle ear (which contains three small bones that transmit sound) cause hearing loss in about half of cases. People with Treacher Collins syndrome usually have normal intelligence.

Mutations in the *TCOF1* gene cause Treacher Collins syndrome. Mutations in the*TCOF1* gene reduce the amount of treacle that is produced in cells. Researchers believe that a loss of this protein signals cells that are important for the development of facial bones to self-destruct (undergo apoptosis). This abnormal cell death may lead to the specific

problems with facial development found in Treacher Collins syndrome.[24-28]

VII. Shprintzen-Goldberg Syndrome:

Also called as Marfanoid-Craniosynostosis Syndrome, Shprintzen-Goldberg Craniosynostosis Syndrome, Shprintzen-Goldberg Marfanoid Syndrome. Shprintzen-Goldberg syndrome (SGS) is characterized by craniosynostosis (involving the coronal, sagittal, or lambdoid sutures), distinctive craniofacial features, skeletal changes (dolichostenomelia, arachnodactyly, camptodactyly, pes planus, pectus excavatum or carinatum, scoliosis, joint hypermobility, or contractures), neurologic abnormalities, mild-to-moderate intellectual disability, and brain anomalies. Cardiovascular anomalies (mitral valve prolapse, mitral regurgitation, and aortic regurgitation) may occur. Minimal subcutaneous fat, abdominal wall defects, cryptorchidism in males, and myopia are also characteristic findings.

Craniofacial findings includes dolichocephaly, high prominent forehead, ocular proptosis, hypertelorism, telecanthus, downslanting palpebral fissures, maxillary hypoplasia, cleft palate with prominent palatine ridges, micrognathia, and apparently low-set and posteriorly rotated ears.

FBN1. Mutations in *FBN1* have been reported in three individuals with a clinical diagnosis of Shprintzen-Goldberg syndrome (SGS). Treatment include surgical repair of abdominal hernias, physiotherapy for joint contractures, and placement in special education programs.[29-31]

VIII. Simpson Dysmorphia Syndrome:

Also called as Bulldog Syndrome, DGSX Golabi-Rosen Syndrome, Dysplasia Gigantism Syndrome, X-Linked SDYS, SGB Syndrome, Simpson-Golabi-Behmel Syndrome Simpson dysmorphia syndrome types 1 and 2 are two forms of a rare, X-linked recessive, inherited disorder characterized by unusually large fetuses (prenatal overgrowth) and unusually large babies (postnatal overgrowth). In addition, affected individuals have characteristic facial features, more than two nipples (supernumerary nipples), and multisystemic malformations that may vary from child to child. Chief among these are cardiac malformations, mild to moderate mental retardation, cleft palate, and more than the five fingers and/or toes (polydactyly).

Symptoms associated with the more common form, Simpson dysmorphia syndrome type 1 (SDYS1), are less severe than those presented in SDYS2.

Individuals usually reach an above-average height. The general distinguishing features typically become less apparent in adulthood.[31]

IX. Holoprosencephaly, type 3:

Holoprosencephaly (HPE) is a structural anomaly of the brain in which there is failed or incomplete separation of the forebrain early in gestation. Classic HPE encompasses a continuum of brain malformations including (in order of decreasing severity): alobar, semilobar, lobar, and middle interhemispheric variant (MIHV) type HPE. Other CNS abnormalities not specific to HPE may also occur. HPE is accompanied by a spectrum of characteristic craniofacial anomalies in approximately 80% of individuals with HPE. Developmental delay is present in virtually all individuals with the HPE spectrum of CNS anomalies.

A spectrum of craniofacial anomalies accompanies HPE in approximately 80% of affected individuals. The spectrum of facial anomalies begins with cyclopia, the most severe presentation, and extends in an unbroken continuum to the normal face as seen in individuals who have, but are not expressing, a mutation for HPE inherited in an autosomal dominant manner. Common clinical features in individuals without obvious findings such as cyclopia, synophthalmia, or a proboscis, include microcephaly (although hydrocephalus can result in macrocephaly), ocular hypotelorism (which can be severe), flat nasal bridge, single maxillary central incisor, and cleft lip and/or palate.[32,33]

X. Nevoid basal cell carcinoma syndrome/ Gorlin syndrome :

Nevoid basal cell carcinoma syndrome (NBCCS), also known as basal cell nevus syndrome, multiple basal cell carcinoma syndrome, Gorlin syndrome, and Gorlin-Goltz syndrome, is an inherited medical condition involving defects within multiple body systems such as the skin, nervous system, eyes, endocrine system, and bones.People with this syndrome are particularly prone to developing a common and usually non-life-threatening form of non-melanoma skin cancers.

First described in 1960, NBCCS is an autosomal dominant condition that can cause unusual facial appearances and a predisposition for basal cell carcinoma, a malignant type of skin cancer. The prevalence is reported to be 1 case per 56,000-164,000 population. Recent work in molecular genetics has shown NBCCS to be caused by mutations in the *PTCH* gene found on chromosome arm 9q. If a child inherits the defective gene from either parent, he or she will have the disorder.[34]

Facial abnormalities incude macrocephaly, broad facies, frontal and biparietal bossing, mild mandibular prognathism, odontogenic keratocysts of jaws, misshapen and/or carious teeth, cleft lip and palate, ectopic calcification of falx cerebri.

Conclusion :

Recognition of the associated syndromes and anomalies with the oral cleft is essential to assess the problem and risk faced by the child and for counselling the parents. Proper knowledge and details of anomalies associated with OFC will help to provide necessary treatment and improve survival of these children. Proper epidemiology, dysmorphology assessment and genetic study may lead researchers to the identification of the causative agent.

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