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ASSOCİATED SYNDROMES IN CLEFT LİP PALATE AND ISOLATED CLEFT PALATE BABİES: A RETROSPECTİVE STUDY IN CYPRUS

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ABSTRACT

Introduction: Whilst clefts of the lip with or without cleft palate (CLP) are most common birth defects among facial clefts, clefts of the palate(CP) are the rarest form of oral clefts. Nevertheless, both facial cleft types are increasing numerically among different populations all over the world. 50% of isolated clefts may be as part of a syndrome while 50% may only be isolated, non-syndromic cleft. The etiologies of both cleft lip palate and isolated cleft palate are still unknown, but both are multifactorial involving genetic and environmental risk factors. Accurate estimates of population frequency are difficult to obtain because of variations in reliability of reporting and the tendency to combine or mislabel cases of CLP and CP. Inclusion of stillbirths may complicate the situation even further.

Materials and Method: At this study, among a total of 27 cleft lip palate and isolated cleft palate babies born between years 2007-2017 in Northern Cyprus (a small Mediterranean Island), syndromic cases were detected. Later, types of syndromes were identified.

Results: Evaluation among 27 oral clefting babies, unilateral or bilateral cleft lip palate distribution was 18, while isolated cleft palate was 9. A total of 6 syndromic cleft cases were detected among which 5 of them were boys and only 1 girl was syndromic which contributes to a ratio of 20:1 males to females. Syndromes detected could be listed as; Pierre Robin Sequence, Treacher Collins Syndrome, Velo-cardio-facial Syndrome, Microlissencephaly and Charge Syndrome.

Conclusion: The etiology of cleft lip palate and isolated cleft palate are not fully known and several infants with oral clefts are born at different rates in different populations.

KEYWORDS : Cleft Lip Palate, Etiology, Multifactorial, Non-syndromic, Syndromic.

Introduction:

Facial clefts are the result of a complex interaction between genetic and environmental factors and are distressing for the patients' families. Clefts of lip with or without palate (CLP) are most common birth defects among facial clefts. Isolated clefts of the palate are the rarest form of oral clefts. Nevertheless, both facial cleft types are increasing numerically among different populations all over the world. 50 % of the isolated clefts may be as part of a syndrome while 50 % may only be non-syndromic .

The etiology of cleft lip palate and isolated cleft palate is still unknown, but both are multifactorial involving genetic and environmental risk factors. Accurate estimates of population frequency are difficult to obtain because of variations in reliability of reporting and the tendency to combine or mislabel cases of CLP and CP. It has been reported that about 20% of liveborn infants with facial clefts have associated malformations, Inclusion of stillbirths may complicate the situation even further.

Materials and Method:

At this study, among a total of 27 cleft lip palate and isolated cleft palate babies born between years 2007-2017 in Northern Cyprus with a population of approximately 300.000. Syndromic cases were detected. Each patient's parent's were separately enquired in detail about the pregnancy period as well as genetic past of their families. The reason of separate inquiry was to have some idea about the etiology of clefting. The enviromental factors such as domestic violence may not be confessed by the if questioned together. The Syndromic babies were detected; gender and types of syndromes were identified (table 1). Informed consent was signed by every relative.

Table 1. Distribution of syndromes among gender and cleft types.

Case Number	Gender	Type of cleft	Syndromes And Symptoms
1	Male	Isolated hard and soft palate,Bifid Uvula	Pierre Robin Sequence; Glossoptosis, retrusive mandible, bird face appearance.
2	Male	Deep And Narrow Palate, Bifid Uvula	Velo-Cardio-Facial Syndrome; facial characteristics, body contractions, serious retardation at development, low weight.
3	Male	Bilateral Lip And Palate	Charge Syndrome; single kidney, ear deformity, serious lack of development, mental retardation, behavioral disorders.
4	Male	Isolated Hard And Soft Palate	Treacher Collins Syndrome; anomalies of eye structures, small clefts at columella, tip of the lip, and the tip of the tongue.
5	Male	Isolated Hard And Soft Palate	Pierre Robin Sequence; Glossoptosis, retrusive mandible, bird face appearance.
6	Female	Isolated Hard And Soft Palate	Lissencephaly with severe multiple syndomes. Developmental anomalies, mental retardation, serious facial deformity.

IDENTIFIED SYNDROMES

PIERRE ROBIN SEQUENCE (PRS)

Pierre Robin Sequence is a triad of glossoptosis, micrognathia and airway obstruction(1). Several theories have been proposed to explain the pathogenesis of PRS, but the most prevailing involves the notion of primary mandibular hypoplasia. This theory states that during embryonic development, an intrinsic or extrinsic factor leads to micrognathia, which in turn causes failure of the tongue to drop from between the palatal shelves resulting in cleft palate. Robin Sequence can be malformational when based on intrinsic mandibular hypoplasia or deformational when based on constraint(2). A patient having a “syndrome” is the one who has multiple anomalies where all of those anomalies have a single pathogenesis. The word “sequence” is different from the word syndrome. In a sequence, the patient has multiple anomalies and all or some of the anomalies are caused secondarily by one of the anomalies present in that patient. In case of Robin Sequence, micrognathia is the primary anomaly.The mechanical theory is the most accepted reason of the sequence. Mandibular hypoplasia between the seventh and eleventh weeks of intrauterin development, keeps the tongue at high level and prevents the closure of palatal shelves resulting in formation of inverted, U shaped cleft palate (3).

The male patient had hard and soft palate cleft, glossoptosis and retrusive mandible. Physical and mental development were compatible with his age

VELOCARDIOFACIAL SYNDROME(VCFS)

This syndrome was first introduced by Dr. Robert J. Shprintzen and is autosomal dominat associated with Chromosome 22q abnormality(4). The most common features are cleft palate, cardiac anomaly, characteristic facial appearance(vertical maxillary excess,malar flattening,relative mandibulsr retrusion, narrow palbebral fissure and small ears), minor learning problems, speech and feeding problems(5).

LISSENCEPHALY

Lissencephaly is aheterogeneous disorder with several locci involved in neuronal migration. The most frequent cause of classical Lissencephaly is deletion of teh LISI gene located at chromosome 17p13.3.(Two types of Lissencephaly is defined; Type I lissencephaly results from a neuro-migrational arrest between 12-16 week gestation and histologically the cortex has four layers instead of six. Type II or cobblestone lissencephaly is characterised by severely disorganised, unlayered cortex(6). All cases are mentally retarded with speech and feeding problebs,they cannot walk. Facial and eye abnormalities, seizures are noteworthy.

The female patient shows the most severe form of Lissencephaly with most of the common features

TREACHER COLLINS SYNDROME(TCS)

TCS is an autosomal dominat craniofacial developmental malformation disorder which arises during early embryonic development from the first and second branchial arches and results from a mutation in the TCOF1 gene(7). The typical clinical featuers are symetrical lateral downword sloping of palbebral fissures, hypoplasia of the mandible and zygomatic complex, cleft palate. Analysis of the craniofacial skeleton reveals abnormalities of maxilla, malar bones, orbits,ears and cranial base. Even the facial soft tissues show anomailes including elelash, eyelid, facial hair and auricular problems. One of the most severe problem is the throat length; so diminished thal it blends into the neck. Severe complications of upper airway is also detected(8).

The male patientcarries the typical features of TCS. Isolated cleft palate, serious upper airway complication and Tracheostomy was made. Facial hair and typical eye sturcture is noteworthy (Figure 3).

CHARGE SYNDROME

Charge syndrome is a complex neurocristopathy and its timing is blastogenesis in the intrauterine period between 3rd and the 9th week of pregnancy(9). CHARGE syndrome (Coloboma of the eye, Heart defects, Atresia of the choanae, Retardation of growth and/or development, Genital and/or urinary abnormalities, and Ear abnormalities (including deafness) is a genetic disorder characterized by a specific and a recognizable pattern of anomalies. De novo mutations in the gene encoding chromodomain helicase DNA binding protein 7 (*CHD7*) are the major cause of CHARGE syndrome.The major clinical features of CHARGE syndrome are ocular **C**oloboma, **H**eart malformations, **A**tresia of the choanae, **R**etardation of growth, **G**enital hypoplasia, and **E**ar abnormalities. Numerous other less consistent features, including hyposmia, cleft lip/palate, and tracheoesophageal fistula, are also reported(10).

The male patient has one kidney, ear deformities, genital hypoplashia, total bilateral cleft lip and palate, behavioral anomalies, serious retardation of growth, mental retardation(Figure 4).

DISCUSSION

As the etiology of cleft lip palate and isolated cleft palate are not fully known in the 21st century, several infants with oral clefts are born at different rates in different populations. The etiologies of lip and palate clefts are multifactorial, including genetic and environmental risk factors. Oral clefts are most common in white, while in Africa are very low. From environmental factors, the use of maternal tobacco has proven to be a very powerful factor in the formation of the lip palate. Genetic and environmental risk factors and gene-environment interactions need to be investigated with more comprehensive epidemiological studies(12).

There is an increase every year in the worldwide number of infants with syndromic cleft lip and/or palate and isolated palate. In a comprehensive study conducted in 1971, 72 syndromes with oral clefts were identified, whereas 154 syndromes with cleft lip palate and isolated cleft palate were identified(11). At this study, evaluation among 27 oral clefting babies, unilateral or bilateral cleft lip palate distribution was 18, while isolated cleft palate was only 9. A total of 6 syndromic cleft cases were detected among which 5 of them were boys and only 1 girl was syndromic which contributes to a ratio of 20:1 males to females. Syndromes detected could be listed as; Pierre Robin Sequence, Microlissencephaly, Treacher Collins Syndrome, Velocardiofacial Syndrome and Charge Syndrome.

CONCLUSION

The etiology of cleft lip palate and isolated cleft palate are not fully known and several infants with oral clefts are born at different rates in different populations. When orofacial clefts accompanied by a syndrome patients and their parents are exposed to a very difficult and tiring life both economically and spiritually. Individuals with improper appearance of facial aesthetics are affected psychologically and there can be ruthless behavior in society towards these clefting people. Proper approaches towards these children will help to provide best treatment and will improve quality of their lives. The aim of this article is to emphasize about syndromic cleft lip and /or palate babies and the incidence at a small population.

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