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Congenital Anomalies Associated With Cleft Lip and Palate

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***Abstract**: Clefts of the lip and palate generally represent a heterogeneous group of disorders affecting the lips and oral cavity. Cleft palate affects almost every function of the face except vision. Effects on speech, hearing, appearance, and psychology can lead to long lasting adverse outcomes for health and social integration. Typically, children with these disorders need multidisciplinary care from birth to adulthood and have higher morbidity and mortality throughout life than do unaffected individuals. Objectives of this study were to describe congenital malformations associated with cleft lip and palate and to describe the ratio of cleft palate in males and females. The study aims at highlighting the presence of congenital malformations associated with cleft lip and palate. And the relationship between the type of cleft and associated malformations.*

***Keywords**: Cleft lip, Cleft palate, Associated congenital malformations.*

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I. Introduction

A short review of the normal embryonic development of the facial primordiais necessary before reviewing the factors that may interfere with thisdevelopment leading to clefts of the lip and the palate.[1]In the developing embryo migration of cell masses, fusion of facial processesand the differentiation of tissues are three important events that lead eventuallyto an adult appearance. [2]The pattern of development as well as cells respond to environmental signals. Since both factors are present and interact, it is difficultto ascertain the exact role of each of them.[3]The facial primordia (a series of small buds of tissue that forms around theprimitive mouth) are made up mainly of neural crest cells that originate from thecranial crest .[1.2]Neural crest cells migrate to the primitive oralcavity where, in association with ectodermal cells, form the maxillary processes.Palatal shelves from these processes arise at embryonic day 45 in humans.[3] Anintrinsic force, mainly produced by the accumulation and hydration ofhyaluronic acid-1, is progressively generated within the palatal shelves andreaches a threshold level which exceeds the force of resistance factors .[4] Synthesis and hydration of hyaluronic acid by palatal mesenchyme is stimulated by epidermal growth factor and transforming growth factor beta. The erectile shelf elevating force is partly directed by bundles of type I collagen which run down the center of the vertical shelf from its base to its tip. [5]Moreover the epithelial covering and associated basement membrane of the palatal shelf exhibit differential traction, which serve to constrain and direct the swelling osmotic force. In addition the palatal mesenchymal cells are themselves contractile andsecrete various neurotransmitters that affect both mesenchymal cell contractility and glycosaminoglycan dehydration and therefore play a role in palatemorphogenesis .[1]At this precise developmental stage the shelves rapidly elevate to a horizontal position above the dorsum of the tongue. Self-elevation probably occurs within minutes orhours. [2]The medial edge epithelia of the approximating palatal shelves fuse with each other developing cell adhesion molecules and desmosomes to form a midlineepithelial seam. The epithelial seam starts to thin by expansion in palatal height and epithelial cell migration onto the oral and nasal aspects of the palate and thendegenerates establishing mesenchyme continuity across the intact horizontal palate. [1,2]Medial edge epithelial cells cease DNA synthesis 24-36 hours prior to shelf contact and this is referred to as programmed cell death (PCD). The basement membrane on each side of the epithelial seamremains intact even when it has completely thinned.[1,2,3]Epithelial-mesenchymal recombination experiments have demonstrated that epithelial differentiation is specified by the mesenchyme and that medial edge epithelial cell death is a "murder" by the underlying mesenchyme rather than an intrinsic epithelial suicide .[4,5] The ways in which mesenchyme could signal epithelialdifferentiation is either through extracellular matrix molecules (i.e. collagen molecules), through soluble factors (i.e. growth factors), direct cell-to cell contact, orcombinations of all of the above. The actual period of fusion of the mesenchymal shelves may be just a matter of minutes, but complications in events leading up to andduring fusion will result in a palatal clefting of varying severity.[6,7]Seam disruption also occurs by migration of a large number of epithelial seam cells (perhaps 50%) into the palatal mesenchyme

(Ferguson, 1988). These fragmentsvery quickly become indistinguishable from other palatal mesenchyme cells. [2,3]The epithelia on the nasal aspect of the palate differentiate into pseudostratified ciliated columnar cells whilst that on the oral aspect of the palate differentiateinto stratified squamous nonkeratinized cells.[8,9,10] Osteogenic blastemata for the palatal processes of the maxillary and palatine bones differentiate in the mesenchyme of the hard palate while several myogenic blastemata develop in the soft palate.[2,3,7]During the period of shelf elevation, there is almost no growth in head width but constant growth in head height. This establishes a conductive orofacial environment that permits the expanding palatal shelves to occupy a position above the dorsum of the tongue.[2,3,4,5]In human embryos palatal shelves elevate simultaneously on day 43 (22-24 mm CRL), and the palate is closed by 55 days (33-37 mm CRL). The mesenchymal fusion is complete by 60 days (45-46 mm CRL)-12.[1,2,3,4,5]

From an anatomic standpoint the cleft surgeon must have an appreciation forthe failure of embryogenesis that results in clefting. There are critical points in the development of the fetus when the fusion of various prominences creates continuity and form to the lip, nose, and palate.[1,37,8,9]Anomalies occur when the normal developmental process is disturbed between these components. Each of these prominences is made up of ectomesenchyme derived from neural crest tissue of the mesencephalon and rhombencephalon. Mesoderm is also present within these prominences as mesenchymal tissue.[3,7,11] The prescribed destiny of each of these cells and tissues is controlled by various genes to alter the migration, development, and apoptosis and form the normal facial tissues of the fetus. At the molecular level there are many interdependent factors such as signal transduction, mechanical stress, and growth factor production that affect the development of these tissues. [12]Currently only portions of this complex interplay of growth, development, and apoptosis are clear. At approximately 6 weeks of human embryologic development the median nasal prominence fuses with the lateral nasal prominences and maxillary prominences to form the base of the nose, nostrils, and upper lip. [,113]The confluence of these anterior components becomes the primary palate. When this mechanism fails, clefts of the lips and/or maxilla occur. At approximately 8 weeks the palatal shelves elevate and fuse with the septum to form the intact secondary palate. [1,7]When one palatal shelf fails to fuse with the other components, then a unilateral cleft of the secondary palate occurs. If both of the palatal shelves fail to fuse with each other and the midline septum, then a bilateral cleft of the palate occurs. [3,7]Fusion occurs when programmed cell death (apoptosis) occurs at the edges of the palatal shelves. The ectodermal component disintegrates and the mesenchyme fuses to form the intact palate. Soon after this the anterior primary palate fuses with the secondary palate and ossification occurs. At any point, if failure of fusion occurs with any of the above components, a cleft will occur of the primary and/or secondary palates. Clefts may be complete or incomplete based on the degree of this failure of fusion.[3,7,11,12,13]

The occurrence of oral clefts in the United States has been estimated as 1 in 700 births.' Clefts exhibit interesting racial predilections, occurring less frequently in blacks but more so in Asians. Boys are affected by orofacial clefts more often than girls, by a ratio of 3:2. Cleft lip and palate (together) occurs about twice as often in boys as in girls, whereas isolated clefts of the palate (without cleft lip) occur slightly more often in girls. Oral clefts commonly affect the lip, alveolar ridge, and hard and soft palates. Three fourths are unilateral deformities; one fourth are bilateral. The left side is involved more frequently than the right when the defect is unilateral. [1,3,7]The cleft may be incomplete, that is, it may not extend the entire distance from lip to soft palate.[14] cleft palate may occur without clefting of the lip. A useful classification divides the anatomy into primary and secondary palates. The primary palate involves those structures anterior to the incisive foramen-the lip and alveolus; the secondary palate consists of those structures posterior to the incisive foramen-the hard and soft palates.[1,3] Thus an individual may have clefting of the primary palate, the secondary palate, or both.Clefts of the lip may range from a minute notch on the edge of the vermilion border to a wide cleft that extends into the nasal cavity and thus divides the nasal floor. Clefts of the soft palate may also show wide variations from a bifid uvula to a wide inoperable cleft. [1,3,7,11]The bifid uvula is the most minor form of cleft palate, in which only the uvula is clefted. Submucosal clefts of the soft palate are occasionally seen. These clefts are also called occult clefts, because they are not readily seen on cursory examination.[1,12,13] The defect in such a cleft is a lack of continuity in the musculature of the soft palate. However, the nasal and oral mucosa is continuous and covers the muscular defect.[1,3,7] To diagnose such a defect, the dentist inspects the soft palate while the patient says "ah".This action lifts the soft palate, and in individuals with submucosal palatal clefts, a furrow in the midline is seen where the muscular discontinuity is present. [8,11,12,13]The dentist can also palpate the posterior aspect of the hard palate to detect the absence of the posterior nasal spine, which is characteristically absent in submucosal clefts.[8] If a patient shows hypernasal speech without an obvious soft palatal cleft, the dentist should suspect a submucosal cleft of the soft palate.[1,14]The study aims at highlighting the presence of congenital malformations associated with cleft lip and palate. And the relationship between the type of cleft and associated malformations.

II. Causes f Cleft Lip, Cleft Palate And Craniofacialbirth Defects:

2.1 General factors[3,7]:

1. Teratogenic agents:
a. Infectious agents – Rubella virus
b. X-Irradiation
c. Drugs – Aminopterin, Trimethadione, Amphetamine, Phenytoin
d. Hormones- Corticosteroids
e. Smoking and Alcohol
2. Maternal nutrition – Folic acid deficiency, excess intake of Vitamin A (more than 10,000 IUs)

Local factors[3,7]:

1. Hypoxia
2. Defective shelf fusion,
3. Failure of medial-edge epithelial cell death,
4. Possible postfusion rupture, and
5. Failure of mesenchymal consolidation and differentiation
6. Persistent high tongue position during development
7. Inadequate shelf force
8. Enzymes

Genetic factors:

Isolated cleft lip and palate unaccompanied by any other malformation i.e. non-syndromic cleft lip with or without cleft palate is found to be autosomal dominant in inheritance, the gene being located on the short arm of chromosome 6.[1] Other pedigrees show an autosomal recessive pattern of inheritance not mapped so far. In some families, clefting of the secondary palate or bifid uvula are inherited following an "X-linked recessive" pattern. In one of these families from Iceland the single gene has been mapped to the long arm of chromosome X.[1,3,7]

Genes TGFA, IRF6 TGFB-2, TGFB-3 and MSX1 have been identified to be contributing for non syndromic CL&P in different ethnic populations.[1,3,7]

2.3 Cleft Lip And Palate Associated With Congenital Anomalies:

There are various classifications of cleft palate, most common are Kernahan and Stark classification and Veau classification. According to Kernahan and Stark the incisive foramen is the dividing line between the primary and secondary palate.[7] In Veau the palatal defects have been assigned different classes i.e., Class I Defects of the soft palate only. Class II: Defects involving the hard and soft palates (not extending anterior to the incisive foramen). Class III: Defects involving the palate through to the alveolus, Class IV: Complete bilateral clefts.[1.3,7]In most cases, the cause of cleft lip and cleft palate is unknown. Most scientists believe clefts are due to a combination of genetic and environmental factors.[1] There appears to be a greater chance of clefting in a newborn if a positive family history exists. Genetic factors contributing to cleft lip and cleft palate formation have also been identified for some syndromic cases.[3] Environmental influences may also cause, or interact with genetics to produce orofacial clefting e.g. maternal hypoxia, alcohol abuse or some forms of hypertension treatment.[7]

Problems associated with Cleft Palate patients include eating problems because with a separation or opening in the palate, food and liquids can pass from the mouth back through the nose. Ear infections/hearing loss since they are more prone to fluid build-up in the middle ear and if untreated, ear infections can cause hearing loss.[15] Speech problems because the voice may take on a nasal sound, and the speech may be difficult to understand.[16] Dental problems like missing, extra, malformed, or displaced teeth and specifically alveolar ridge defect which can displace, tip, or rotate permanent teeth, may prevent permanent teeth from appearing, and can prevent the alveolar ridge formation. These problems can usually be addressed through surgery.[17]Although the preventive and restorative dental care of children with clefts are the same as for other children however, these children require close monitoring due to some special dental problems. [8]This monitoring includes early dental care like proper cleaning with a small, soft-bristled toothbrush, fluoride treatment and good nutrition. The first dental visit to be scheduled at about one year of age or even earlier and routine dental care can begin around 3 years of age. Orthodontic care includes a first orthodontic appointment before any dentition to assess facial growth especially jaw development, assessment of a child's short and long-term dental needs after eruption of deciduous dentition and orthodontic treatment can be applied to align the teeth at permanent dentition. Prosthodontic care like to make a dental bridge for missing teeth, to make special

appliances called "speech bulbs" or "palatal lifts" to help close the nose from the mouth so that speech sounds more normal. [8,18]Treatment usually begins in infancy and often continues through early adulthood. Most common treatment protocol currently used in most cleft centers is: Newborn - Diagnostic examination, general counseling of parents, feeding instructions, palatal obturator (if necessary). Age 3 months - Repair of cleft lip (and placement of ventilation tubes). Age 6 months - Presurgical orthodontics, if necessary; first speech evaluation. Age 9 months - Speech therapy begins. Age 9-12 months - Repair of cleft palate (placement of ventilation tubes if not done at the time of cleft lip repair) Age 1-7 years - Orthodontic treatment. Age 7-8 years - Alveolar bone graft Older than 8 years - Orthodontic treatment continues. [8,17,18,19]

A multidisciplinary approach is usually involved in the management of these children due to a number of oral and medical problems associated with cleft palate.Members of a cleft lip and palate team typically include: Plasticsurgeon, Otolaryngologist, Oral and Maxillofacial surgeon, Orthodontist, General dentist, Prosthodontist, Speech pathologist and Speech therapist, Audiologist, Nurse coordinator, Social worker/ psychologist and Geneticist. [2,5,6,8,20]Although treatment for a cleft lip and/or cleft palate may extend over several years and require several surgeries depending upon the involvement, most children affected by this condition can achieve normal esthetic and functions subsequently.[8]

III. Discussion

The pupose of this study was to describe the congenital malformations associated with cleft lip and palate and to find out the percentage of cleft palate in male and female pediatric patients. The available data and studies on associated malformations in children with cleft, are quite few and inadequate, which led us to undertake this study. Some of these malformations and anomalies if undetected can prove potentially life threatening, particularly while administering medical and surgical care to the patient with cleft deformity..

1. A cleft lip or palate can be a single anomaly or a part of multiple congenital anomalies [21]. 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,
2. Pierre Robin sequence etc.
3. c. Malformations: A morphologic defect in an organ from an intrinsically abnormal developmental process, e.g. polydactyly, congenital heart anomalies, cleft lip [22].
4. However, with the present advancement in embryology and genetics, and its correlations, the associated anomalies need to be differentiated from syndromes, in patients with multiple congenital anomalies [22].

Cleft lip and palate occurring with other anomalies has been widely reported in literature. A cleft patient may have other subtle or sub-clinical abnormalities that may go undetected, if not fully investigated. It is important to determine if relationship exists between abnormalities or defects, so as to deliver comprehensive care to the cleft patient. Health providers need to know what these possible anomalies are, if necessary investigations are necessary, or if consultations should be obtained from
other disciplines before carrying out the proposed treatment.

Frank E. Abyholm the author pegs the real incidence of cleft lippalate in Norway at 2.08/1000 live births, with the following incidence forthe main groups of clefts -Cleft lip – 0.66/1000Cleft lip and palate – 0.77/1000Cleft palate – 0.65/1000Of the total of 1073 cases, 59% were males and 41% were females.The incidence of cleft lip palate among stillbirths was 4/1000. Mortalitywithin the first month and within the first year of life among cleft lip palateinfants was 4.9% and 6.54% respectively. Of the cleft lip palate infantswho died during the first year of life, 80% had congenital malformationsother than cleft lip palate. In the majority of the cases (51.6%), multiplemalformations were the main cause of death. Almost half of the deceasedchildren i.e. 46.7% died within 24 hrs of delivery and 82% within threemonths of delivery. 60 cleft lip palate patients with associated congenitalmalformations died within the first year of life, with heart and centralvessels malformations accounting for the largest group, followed bymalformations of the central nervous system, gastrointestinal system,urogenital system, respiratory system, extremities and D-13 trisomy. The conclusion is that, these circumstances are considered to be of someimportance when timing of cleft surgery is debated.[23]

M. Michael Cohen Jr. in this article the author presents a seriesof tables which help as diagnostic aids for the clinician when he confrontsa patient who has a cleft lip and /or palate together with associatedcongenital anomalies. 154 syndromes were recognized. Syndrome breakdownby etiology are as follows -**Etiology Number**Monogenic 79Autosomal dominant (35)Autosomal recessive (39)X-linked (5)

Environmentally induced 6Chromosomal 29Unknown genesis 40**Syndromes with cleft lip palateCategory Number**Syndrome with cleft lip-palate 28Syndrome with cleft plate 77Syndrome with the Robin complex 18 Chromosomal syndromes with clefts 29Median cleft lip 7Associated with clefting 17The author finishes by saying that since so much etiologic heterogeneity is known to occur in human syndromes with orofacial clefting we should expect some pathogenetic heterogeneity in the productsof clefts as well. A great deal about the pathogenesis of orofacial cleftingremains to be learnt and undoubtedly many new syndromes with orofacial clefting will be delineated in the future.[24]

Robert J. Shprintzen, Vicky L. et al in their study from January 1 1976 to December 31st 1982, evaluated 1000 patients with cleft of the lip,palate or both, including submucous cleft palate and occult submucouscleft palate. Excluded from the study were patients with craniofacialmalformations who did not have clefts or who had atypical clefts (such ascommissural or orbital clefts).Anomalies found were differentiated into minor and majoraccording to definition of Marden et al (1964). Major craniofacialanomalies included severe maxillary or mandibular hyperplasia, severeorbital hypertelorism, orbital clefts, commissural clefts, other facialdefects, nasal defects, facial asymmetry, craniosynostosis, mentalretardation, seizures and so on. Minor anomalies include up-slanting ordown-slanting palpebral fissures, dystopia canthorum, low set of posteriorangulated ears, large or small nose, learning disabilities, perceptual disorders and other "soft signs". 56 patients had cleft lip, 364 patients hadcleft lip with cleft palate and 580 patients had cleft palate (overt cleft palate- 330, submucous cleft palate - 250). 63.4% of the sample had associatedanomalies.The lowest frequency of associated anomaly was seen with cleft lip- 45%, and the highest, with cleft palate - 72% (68% of the patients with overt cleft palate and 77% of those with submucous cleft, had associatedanomalies). Of those with associated anomalies mosthad multipleanomalies, thus reflecting a large number of individuals with multiplecongenital anomaly syndromes, either recognized from genesis or physical examination types. A relatively small percentage - 15.7% - had onlyassociated minor anomalies Small stature, microcephaly and mental retardation were frequentfindings; all occurring most frequently in isolated cleft palate group andleast frequently in isolated cleft lip group. Approximately half the patients with multiple anomalies had recognized syndromes, sequences orassociations, while the other half had physical examination syndromes. Theauthors conclude by saying that high frequencies of associated anomalies have obvious implications for genetic counseling to all patients with cleftsand their parents. The frequency of associated anomalies also raisedquestions regarding validity of past genetic research involving populations of subjects with clefts.[25]

Richard K.H. Wyse, Michael Mars et al in this study, hospitaland departmental records over the past two decades were retrospectivelyexamined and 78 patients were identified in whom congenital heart diseasecoexisted with clefting. Of the 78 patients, 43 were male and 35 werefemale. The prevalence of bilateral cleft lip and palate in patients with heartlesions was much higher than in cleft patients with normal hearts. Cardiac defects were predominantly conotruncal. Tetralogy of Fallotwas present in 24% of the patients; the prevalence of transposition,atrioventricular septal defect and truncus arteriosus was alsodisproportionately high. Patients with conotruncal defects had a greaterprevalence of either unilateral or bilateral cleft lip and palate.Most patients with congenital heart disease had additionalabnormalities. Anomalies of other systems were present in 68 (87%) of the78 patients with congenital heart disease and clefting. The most commonadditional abnormalities were of the external ear - abnormal shape and lowset. Skeletal defects were the next most common abnormality. 34 patientswere dysmorphic, of whom 7 were diagnosed at the time as having Robinsequence.The author concludes by emphasizing the association betweenclefting and congenital heart disease and a variety of other associatedanomalies, since a high prevalence of multiple anomalies is seen in thesechildren.[26]

C. Stoll, Y. Alembik et al studied the epidemiology of oral cleftsduring the period 1st January 1979 to 31st December 1987. 207 new caseswere studied during this period and more than 50 factors were compared inprobands and controls. The incidence of oral clefts was 1.75 / 1000, withcleft lip and palate being 0.98/1000 and cleft palate only 0.77 / 1000. A total of 8.2% of the cleft cases were stillbirths and 5.3% were inducedabortions. The more common types of associated malformations in 76affected cases (36.7%) with at least 1 anomaly other than the oral cleftwere neural tube defects and skeletal malformations. At birth, infants withoral clefts and other malformations were smaller, weighed less and theirhead circumference was lower than in control. There was a significantassociation between clefting and consanguinity. Heritability of the cleft lip palate was 81% and the first degree relatives of probands had more thanthree times the prevalence of non-clefting malformations as controls. Theseresults are of relevance to genetic counseling. Authors infer that ultrasoundexamination for the detection of non-cleft malformations should be offeredin subsequent pregnancies.[27]

Bruce B. Horswell the relationship, incidence and distribution ofcervical spine anomalies were assessed in this retrospective study of 468patients with cleft lip and /or palate. The patients were placed in 4 groups;lip and / or alveolus; complete unilateral or bilateral; isolated palatal andsoft palate or submucous clefts.

Cervical anomalies occurred primarily in the occipital cervical i.e.C1-C2 region - nearly twice the number of anomalies as the lower cervical spine C3-C7.Cervical anomalies were observed in 22% of the cleft patients and in7% in the non-cleft group. Patients with soft palate and submucous cleftshad the highest incidence of vertebral anomalies (45%), whereas patientswith cleft lip and/or alveolus had incidence similar to non-cleft group.Patients with complete unilateral and bilateral clefts also had a higherincidence (15.6% to 19.0%) of anomalies than the non-cleft group.[28] were found out, of whom 345(171 males and 174 females, 21.8%) had an associated anomaly. Moremale patients had cleft lips with or without cleft palate and more femalepatients had cleft palate. The anomalies were divided according toanatomical sites and the biggest category was that of the extremities(29.7%) followed by the cardiovascular system (14.8%) and then, otherfacial anomalies (13%). The smallest category was chromosomalanomalies (2.7%) followed by miscellaneous anomalies (4.1%). A total of560 malformations were found.Most anomalies per proband with clefts were found in bilateral cleftlip and palate subgroup, with the lowest in the subgroup of cleft lip with orwithout cleft alveolus**.** In the cleft palate group a similar trend was found inthe subgroup of submucous cleft palate. A total of 133 probands with 39 different syndromes were delineated; 25 in the cleft lip palate group and 108 in the cleft palate group (8.4% of the total 1586 patients with clefts). Anomalies were more thanthree times as frequent among probands with clefts as among the general
population.[29]

A. Derijcke, A. Eerens, C. Carels the authors reviewedepidemiological studies on the incidence of oral clefts in several regions ofthe world but mainly in Europe and have purported its incidence rangefrom 1.0/1000 to 2.21/1000. It was found that the highest incidence of oralclefting was in Czechoslovakia 1.81/1000, followed by France - 1.75/1000,then Finland - 1.74/1000, Denmark - 1.69/1000, Belgium and Netherlands - 1.47/1000, Italy - 1.33/1000, California - 1.12/1000 and South America -1.0/1000. In Denmark cleft palate was most common in girls (60%)whereas, cleft lip and/or palate was twice as frequent in boys and theincidence of clefting associated with anomalies was 4.3% which wasconsidered far too low. In France of the facial cleft malformations, 36%were associated with at least one other major anomaly, especially skeletalmalformations and neural tube defects. In Italy, 33% of the children withclefts had associated anomalies, of which 44% were with cleft palate and23% cleft lip palate.In Czechoslovakia a significantly larger number of bilateral caseswere found in black people. Of the clefts, 18.6% were a part of a syndromeor associated with other malformations. In Southern America there was ahigh frequency of twinning and neonatal deaths among cleft lip palateprobands. From this study the authors found that there was a higherincidence of cleft lip and/or palate compared with cleft palate. There waspredominance of girls in the cleft palate group, while cleft lip palate group comprised mainly of boys. The left side was affected twice as often as theright side. Black children had a low incidence of clefting compared towhite children.[30]

Catherina Hagberg, Ola Larson, et al children with cleft lip andpalate born between 1991 & 1995 were studied with reference to incidenceand rate ratios of different types of clefts, gender, birth weight, mother age,and length of pregnancy, in this study. Children who had cleft andadditional malformations were compared with children who had clefts butno additional malformations.The incidence of clefts was 2.0 / 1000 live births and it was higheramong males than females. The RR - an index of relative risks - was 1.58.The main groups i.e. children with isolated cleft lip, cleft lip and palate andisolated palate showed similar incidence values (0.6-0.7 / 1000 live births).Children with bilateral clefts had an incidence of 0.3 for 1000 live births.Additional malformations were found in approximately every 6thnew born child when children with Robin sequence were excluded. Therewas a tendency for newborns with bilateral clefts to have additionalmalformations (RR=136). Children with cleft and additional malformationshad lower birth rates and were born earlier than children with clefts only.The conclusion derived is that preterm cleft children with low birthweight should be screened for presence of other birth defects.[31]

Josef Milerad, Ola Larson, Catherina Hagberg and MargaretaIdeberg in their study of 616 cleft infants (367 boys, 249 girls)born between 1992-1995, found that 21% of these infants had associatedmalformations. 28% of infants with cleft lip and palate had associatedmalformations, 22% of infants with isolated cleft palate had malformationsand 8% of infants with isolated cleft lip had malformations.Malformations of the upper or lower limbs or the vertebral columnwere the most common anomalies and accounted for 33% of all associateddefects. 24% of associated malformations were in the cardiovascularsystem and congenital heart disease was the most common isolatedassociated malformation.
15% of all associated malformations were multiple and they werefrequently associated with mental retardation and chromosomal anomalies.The authors conclude that a more extensive cleft seems to beassociated with the high risk associated malformations and high prevalenceof congenital heart disease (16 times that of general population), whichmay justify a routine echocardiographic screening.[32]

Kaare Christensen in this retrospective case note study of 7000cleft lip palate cases, the author summarizes epidemiological and geneticpidemiologicalstudies conducted in a 20th century Danish facial

cleftpopulation. He provides results from analysis of epidemiological data on cleft lip palate cases from 1936 to 1987 including yearly point prevalence,sex differences, seasonality, segregation analysis, recurrence studies amongtwins, sibs, half sibs and more distant relatives, as well as studies ofspecific environmental and genetic risk factors and their interaction. A totalof 4989 cleft lip palate cases were born between 1936 to 1987 out of which323 (6.4%) cases had associated congenital anomalies and syndromes.2301 cleft lip patients were born between the same period out of which 349(15.1%) had associated syndromes.The author ends on a note that the combination of such data and thedevelopment within the genetics induce some hope that, early in the 21stcentury significant progress will be made in the understanding of theetiology of cleft lip palate[33].

Yi N.N., Yeow V.K., Lee S.T. the authors studied 1105 new cleftcases in Singapore general hospital during the period between January1985 to December 1994, which included newborn as well as unoperatedchildren and adult cases. Out of the 1105 new cleft cases seen, 984 wereSingaporeans. The incidence of this hospital-based study of cleftpopulation in Singapore was 2.07 per 1000 livebirths. Chinese had thehighest incidence of 1.64 per 1000 as compared to Malay, Indian and otherraces. The most common type of cleft deformity was complete cleft lip andpalate. The left side was found to be more affected than the right side in alltypes of cleft deformity. There was no significant difference in sex distribution; the male to female ratio was 1.1:1. However, females had ahigher incidence of cleft palate than males. Associated congenitaldeformities occurred in 1.5% of the total cleft population.[34]

C. Stoll, Y. Alembik et al - In their study between 1979-1996,studied 460 cleft infants born during this period, out of which, 36.7% hadassociated malformations. They were more frequent in infants who hadcleft palates (46.7%) than in infants with cleft lip and palate (36.8%) or in infants with isolated cleft lip (13.6%). Malformations in the central nervoussystem and the skeletal system were the most common other anomaliesfollowed by malformations in the urogenital and cardiovascular systems.There were 169 (36.7%) infants with malformations other than the oralclefts. The latter were divided into recognized syndromes (hromosoma -36 cases and non-chromosoml - 15 cases) and non-recognized syndromes(multiple malformations - 118 cases). These 118 cases had 237malformations, as some patients had malformations in more than one site.A single additional malformation was found in 62 children, twomalformations were found in 22 cases and 3 or more associatedmalformations in 34 cases.The overall prevalence of malformations, which was 1 in more than3 infants emphasizes the need for thorough investigation of infants withclets. The authors observed and concluded that a routine screening ofother malformations especially skeletal, central nervous system and cardiacdefects may need to be considered in infants with clefts, and also geneticcounseling seems warranted in most of these complicated cases.[35]

Mund Kiefer Gesichtschir in his retrospective case note study of 1737 individuals with orofacial clefts treated between 1974 and 1998, assesses the frequency of malformations and syndromes. Associated malformations were found to be present in 33% of all cases investigated. In nearly one half of these individuals 48% defects could be attributed to recognizable syndromes. Patients with isolated palatal clefts (45.6%) and those with bilateral clefts of the lip and the palate (35.3%) were particularly well represented. The common anomalies observed frequently included (16%) cerebral anomalies, (14%) facial anomalies, (15%) heart malformations, (9%) extremity anomalies, (8%) and urogenital tract abnormalities. In contrast, endocrine aberrations were identified sporadically (0.5%). A partial situs inversus was found in one case. The gist of the study is that clefts of the lip and palate are frequently associated with additional malformations; hence the importance of thorough interdisciplinary and neonatal screening cannot be over emphasized.[36]

Dilek A. Ugar, Gunvor Semb in this study, the authors examine the prevalence of cervical vertebral anomalies in individuals with isolated cleft palate and bilateral and unilateral complete cleft lip and palate and make comparison with a group without cleft. It is a retrospective comparison in which 611 subjects (334 boys, 277 girls), with three different clefts subtypes, of age 6 years or older and 264 children (121 boys, 143 girls) without clefts were included. Their lateral cephalometric radiographs were studied for cervical vertebral anomalies and categorized into posterior arch deficiencies or fusions. In their total cleft sample, 111 subjects (18.2%) had cervical vertebral anomalies; of whom, 10 had more than 1 anomaly. Posterior arch deficiency was found in 7.7% and fusions in 12.1%. In the sample without clefts, 9.1% had cervical vertebral anomalies, 5% had posterior arch deficiencies and 4.1% had fusions. The prevalence of cervical vertebral anomalies was 25.6% in the cleft palate only group, 16.3% in the bilateral cleft lip palate group, and 11.1% in the unilateral cleft lip palate group. The inference of the study is that cervical vertebral anomalies occur most frequently in individuals with clefts as compared to subjects without clefts. This was statistically significant for isolated cleft palate group, thus confirming an association between clefting and other cervical vertebral anomalies.[37]

T. Shafi., M.R. Khan and M. Atiq 123 children with cleft lip and palate in Pakistan from 1st October 1999 to 31st March 2002 made up the study group. Thirty-five (29%) of these children were found to have associated malformations. The most common of these were congenital heart diseases, which accounted for 51% of all associated malformations, with atrial septal defect being the commonest defect. 30% of cleft palate

children had associated anomalies, while 27% of children with cleft lip with or without cleft palate had associated anomalies. There was significant association between children born of consanguinous marriages and the risk of associated malformations. Consanguinity was present in 74% of the patients with malformations. Dysmorphic features were present in 46% of children with associated anomalies. The authors report conclusively that the likelihood of a cardiac defect is high in a child with dysmorphic features and that consanguinity should be ruled out with a through clinical examination, supplemented with an echocardiogram in a child with clefts.[38]

III. Conclusion

The present study attempts to do the same and provide a platform for advancedresearches on chromosomal, genetic, familial or any other study related tothe cleft patients, which will guide and help many clinicians to providecomprehensive care for the benefit of these unfortunate patients and theirfamilies.

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