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A RETROSPECTIVE STUDY ON RECOGNIZABLE SYNDROMES ASSOCIATED WITH CRANIOFACIAL CLEFTS

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ABSTRACT

Objective: There are about 300 to 600 syndromes associated with clefts in the craniofacial region. The cleft lip, cleft palate and cleft lip palate are the most common clefts seen in the craniofacial region. Sometimes these clefts are associated with other anomalies which are known as syndromic clefts. The objective of this study is to identify the syndromes associated with the clefts in the craniofacial region. **Materials & methods:** This retrospective study consists of 270 cases of clefts in the craniofacial region. The detailed case history including the maternal history, antenatal, natal, perinatal history and family history were taken from the patients and their parents. Based on the clinical examination, radiological findings and genetic analysis the different syndromes were identified. **Results:** 18 syndromic clefts were identified which belong to 10 different syndromes. It shows 6.67% of clefts are syndromic and remaining are nonsyndromic clefts. **Conclusion:** Median cleft face syndrome, Van der woude syndrome and Pierre Robin sequence are the common syndromes associated with the clefts in the craniofacial region.

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INTRODUCTION

The craniofacial clefts are the most disfiguring anomaly in the craniofacial region. The clefts in the craniofacial region may vary from the cleft lip and palate to extensive craniofacial clefts. The craniofacial clefts affect the cranium and face and it includes a series of malformations. When the cleft is associated with other malformations it is called syndromic clefts and if not associated with any anomalies, it is known as non syndromic cleft. The majority of the orofacial clefts are non syndromic. The incidence of anomalies associated with cleft is varying from 4.3% (Leth et al. 1988) to 63.4% (Shprintzen et al 1985). The associated anomalies are differentiated into syndromes, sequences and association. The syndromes are due to the structural or numerical variations in the chromosomes. It can be deletions or aneuploidy. When the associated anomalies are due to a structural defect and this defect results a series of events known as sequence. The occurrence of different morphologic defects in a specific manner, but not identified as syndrome or a sequence is an association. It is also called multiple congenital anomalies (Tolorova et al 1998) and its etiology is unknown. Oral clefts are sometimes associated with congenital heart defects (Venkatesh 2009).

The orofacial clefting involves structures around the oral cavity that can be extended on to the facial structures resulting in facial and craniofacial clefts. The cleft lip with or without cleft palate, isolated cleft palate, facial cleft and craniofacial cleft are included in the craniofacial anomalies. The birth prevalence of craniofacial anomalies in India is 1.10 per 1000. Three multicentric study in India showed that the cleft lip palate frequency is 0.93 and isolated cleft palate is 0.17 per 1000. The number of orofacial clefts is 28,600 per year which means 78 cleft cases are born everyday (Mossey P et al 2009). If we are going into the broad spectrum of craniofacial clefts which includes all the clefts in the oral, facial and cranial region the frequency would increase further.

The prevalence of anomalies associated with orofacial clefts can differ among different populations. In black population, the anomalies associated with orofacial clefts are clubfoot and polydactyly compared to other ethnic population (Sullivan et al 1989).

The present study is to identify the percentage of occurrence of syndromic clefts and which are the syndromes associated with the clefts of craniofacial region in Indian population.

MATERIALS AND METHODS

The cleft cases in the plastic surgery department and maxillofacial surgery departments of two tertiary hospitals in Bangalore over a period of 02 years are considered for the study. New cases and follow up cases of clefts are included in the study. Total 270 cases of clefts in the craniofacial region were included in this retrospective study.

The patients were seen with parents and the maternal history, antenatal, natal, perinatal history and family

history were taken. The data included the age, gender, locality of residence, parental age at conception were recorded.

The syndromes associated with clefts in the craniofacial region are identified through the clinical examination, comprehensive medical history, physical examination, documentation of data and by laboratory and radiological evaluations. In the physical examination, all the organs and systems are checked and identified the anomalies involved. The maternal medical history, life style and nutrition had taken into consideration. The maternal life style includes the maternal exposure to tobacco smoke, alcohol, poor nutrition, socioeconomic status, health problems, medication, organic solvents exposure, agricultural chemical exposure, alcohol consumption and teratogenic exposure during pregnancy or even before are checked to identify the risk factors.

The cleft type and associated dysmorphology were examined by clinical examination. The clinical examination is done by a team of geneticist, physician, pediatrician, surgeon and dysmorphologist. Patients who were diagnosed with a known syndrome or had one or more major developmental defects were classified as syndromic clefts.

The study was approved by instituitional ethics committee and informed consent was obtained from the participants or from their parents prior to the study. Patients were asked about any such abnormalities in their family. Photographic documentation and cytogenetic analysis are performed. The radiological findings and the genetic analysis were used to identify the different syndromes.

RESULTS

The syndrome occurred as a sporadic feature in 16 cases and 02 cases were with affected sibling or relatives. Among 270 cases of clefts 18 clefts were found syndromic clefts. The syndromic clefts were 6.67% of the total clefts in this study. The syndromes associated with the clefts were identified by physical examination, documentation of data, radiological examination, cytogenetic analysis and molecular genetic analysis. Total 10 different syndromes were identified among the 18 syndromic clefts (Table 1).

Based on the X-ray, CT(3 dimensional computed tomography), MRI(Magnetic resonance imaging), Karyotyping and FISH(Flouroscent In Situ Hybridisation) analysis the syndromic clefts are identified. The anomalies identified are shown in (Table2).

The study showed Median cleft face syndrome, Van der woude syndrome and Pierre Robin sequence are the most common syndromes associated with the clefts in Indian population. Ellis Van Creveld syndrome, Patau syndrome, Charge association, Lohmann syndrome and Apert syndrome are the least common syndromes associated with the clefts in the craniofacial region.

Table 1 showing the distribution of syndromic clefts

Sl. No	Syndrome	No. of cases
01	Goldenhar syndrome	02
02	Treacher Collins syndrome	02
03	Ellis Van Creveld syndrome	01
04	Median Cleft Face syndrome	03
05	Patau syndrome	01
06	Van Der Woude's syndrome	03
07	CHARGE association	01
08	Lohmann syndrome	01
09	Pierre Robin Sequence	03
10	Apert syndrome	01

Table 2 shows the abnormalities identified in each syndromic cleft cases

Syndromes	Abnormalities identified
Goldenhar syndrome	Coloboma, hypertelorism, epibulbar dermoids, macrostomia, hypoplasia of ramus of mandible, external ear deformity, cleft palate
Treacher Collins syndrome	Antimongoloid slant of palpebral fissure, hypoplasia of maxilla and mandible, coloboma, external ear deformities, fishy mouth, choanal atresia, auro-oral cleft
Ellis Van Creveld syndrome	Disproportionate dwarfism, postaxial polydactyly, small chest, congenital heart defects, V-shaped short cleft in upper lip
Median Cleft Face syndrome	Midline defect in frontal bone, hypertelorism, anterior encephalocele, broad nose, nasal tip divides nostrils and hypoplasia, midline facial cleft, absence of premaxilla, cleft lip
Patau syndrome	Microphthalmia, hypotelorism, malformed nose, severe cleft lip palate
Van Der Woude's syndrome	Lip pits, cleft palate
CHARGE association	Ocular coloboma, microphthalmia, choanal atresia, auricular anomalies, left oblique facial clefting, congenital heart defect, short stature
Lohmann syndrome	Microphthalmia, hypotelorism, maxillary hypoplasia, high arched palate, syndactyly, camptodactyly, aplasia of fingers,
Pierre Robin Sequence	Micrognathia, glossoptosis, cleft palate, mandibular hypoplasia
Apert syndrome	Craniosynostosis, midfacial hypoplasia, hypertelorism, cleft palate, agenesis of corpus callosum, hydrocephalus

DISCUSSION

The present study shows that 93.33% of clefts are nonsyndromic and only 6.67% are syndromic clefts. This is differing from the report in which approximately 70% of CL/P (cleft lip with or without cleft palate) cases are nonsyndromic and remaining 30% are syndromic which are associated with other abnormalities(Jones MC et al 1988,Schutte BC et al. 1999).The reason can be the chance of malformations is more than the reported due to the exclusion of still births and early deaths(Jensen et al.1981)

In a population based study in Sweden showed the malformations associated with oral cleft are found in 1% of cleft patients. The associated malformations were found more in cleft lip palate (28%) than the isolated palate(22%).The anomalies were affected the skeletal system(33%), cardiovascular system(24%),chromosomal anomalies(15%) (Milerad J et al. 1997). In France, the associated anomalies were found in 36.7% cleft cases. The malformations were more frequent in cleft palate (46.7%) than the cleft lip palate (36.8%) and cleft lip (13.6%).The malformations found were associated with central nervous system, skeletal system, urogenital system and cardiovascular system(Stoll C et al.2000)

The present study shows 50% syndromes are associated with the cleft palate. Facial clefts are present in 20% syndromes and cleft lip is present in 10% syndromes and remaining 20% is seen in association with cleft lip palate. The other anomalies found in these syndromes are associated with eye(30%), skeletal system (30%), ear (13%), nose (9%), congenital heart anomalies(9%), tongue (4.5%) and nervous system (4.5%).

The institutional based studies from China showed only 2.89% orofacial clefts had associated anomalies. The frequency of malformation is more in cleft lip palate (3.35%) followed by cleft lip (2.24%) and cleft palate(2.22%) (Zhou et al 2006). A referral centre study in Iran showed 7.73% orofacial clefts had malformations. The malformations were found associated with cleft lip palate in 4.5% and with cleft palate in 3.1%.The malformations were found in skeletal system.(Rajabian et al.2000)

In India, a tertiary care centre study identified 198 anomalies from 2600 clefts. The anomalies were more

frequent with cleft lip palate cases(32%) than the cleft lip alone (11%) and cleft palate alone (22%). The organs or systems involved in the anomalies were eye, ear, cardiovascular system, skeletal system, tongue and skin. The cases of mental retardation and growth retardation were also present. The syndromic cases were 36%. The syndromes mainly involved were Van der woude syndrome, median facial dysplasia and Pierre Robin sequence.(Cohen M et al.2002)

The present study differs from the previous Indian study. The present study shows more cleft palate (50%) followed by facial cleft (20%), cleft lip palate(20%) and cleft lip(10%), but the previous study showed more cleft lip palate followed by cleft palate and the least by cleft lip. This study is in accordance with the previous Indian study as the two studies pointed out that the common syndromes involved in Indian population are Van der woude syndrome, median facial dysplasia and Pierre Robin sequence.

The orofacial clefts are found in association with 600 genetic syndromes, more commonly with isolated cleft palate(Wong FK 2004 et al). The reported proportion of cleft lip with or without cleft palate associated with specific syndromes is 5% to 7%(Tolarova MM 1998 et al). According to Livia et al. more than 300 syndromes are associated with the clefts with or without cleft palate (Livia 2013 et al).

The normal craniofacial development is a complex process of highly regulated sequences(Murray et al 2004). A wide range of studies on murine models, human syndromes, association and expression studies showed the involvement of transcription factors, growth factors and signaling molecules in the complex craniofacial development(Van den et al.2000, Murray et al. 2002, Fitz et al 2003, Loeys et al. 2005,). Any disruption in the structure or expression of any one of the gene in the sequence can result in a cleft. Sometimes, the cleft is occurring in association with other recognized anomalies or in the isolated condition (Jones MC et al 1988, Schutte BC et al. 1999). The syndromic forms of clefts are mainly due to the genetic alterations (Ghasisibe et al.2005). Any factor which can prevent fusion of facial processes by slowing down the migration and multiplication or apoptosis at the line of fusion might cause a persistence of cleft(Taghavi 2012 et al). The chromosomal syndromes, Mendelian disorders and teratogens can cause the syndromic clefts (Murray JC 2012 et al).

In an 8-year hospital based descriptive study in Saudi Arabia on craniofacial anomalies showed Apert syndrome (38.5%), Crouzon syndrome(27.7%) followed by Pierre Robin sequence, Goldenhar syndrome and Van der woude syndrome. The anomalies were found more in association with cleft palate(56.8%), followed by cleft lip palate(32.9%) and cleft lip in 7.6% cases. The congenital anomalies in the cardiovascular system were found in 20.5% (Aziza A 2011 et al).

1. Goldenhar syndrome: It is also known as oculoauicular dysplasia, oculoauriculo-vertebral spectrum or OAV. Goldenhar syndrome occurs with a frequency of one in every 3,000-5,0000 live births. Males are affected more(3:2) frequently than females. Based on animal model, the disorder is due to the interference with vascular supply and focal haemorrhage in the developing first and second branchial arches (Jones et al 2013). It affects the head, face, and spine. Symptoms vary greatly and may be mild or severe. Goldenhar syndrome was first diagnosed by American ophthalmologist and general practitioner, Maurice Goldenhar in 1952. Goldenhar syndrome is a variant of hemifacial microsomia. Goldenhar syndrome usually affects one side of the face(fig.1a,1b,1c), but can affect both sides. Most cases are sporadic(www.craniofacial.net).

2. Treacher Collins syndrome (TCS): It is also known as Franschetti-Klein Syndrome or Mandibulofacial dysostosis. First time, it was described by Thompson in 1846(Dubey et al 2006). But, the syndrome is named after Edward Treacher Collins, a British surgeon and ophthalmologist who described two cases in 1900(Tay et al 1991) and the first elaborate description of the condition was given by Franceschetti and Klein in 1949 in which they coined the term Mandibulofacial Dysostosis (Martelli 2009 et al). The estimated incidence of TCS is 1 in 50,000 live births(Trainor 2009 et al). It is a rare autosomal dominant disorder of craniofacial development. This congenital anomaly affects the first and second branchial arch derivatives(fig.2a,2b,2c) which may affect the size and shape of the ears, eyelids, cheek bones, and jaws(Shete P et al 2011).

Approximately 60% of the autosomal dominant occurrences arise as de novo mutation(Neville 2009 et al).The etiology of the disorder is the mutation of the treacle gene (TCOF1). The Treacle gene is found on chromosome 5q31.3-32 and encodes a serine/alanine rich nucleolar phosphoprotein responsible for the craniofacial development. It helps in neuroepithelial survival and neural crest cell proliferation for the normal craniofacial development. Mutations in TCOF1 gene leads to high degree of neuroepithelial apoptosis and consequent loss of neural crest cells. General cranioskeletal hypoplasia occurs due to insufficient generation of neural crest cells. The mutation may be inherited from the parents (40%). Individuals with TCOF1 mutation have a 50% chance of passing it on to their children. The mildly affected TCS patients might be diagnosed retrospectively after the birth of a more severely affected child(Hertle et al 1993, Martelli et al 2009, Trainor et al 2009, Sakai et al 2009).

The common linical features of TCS include hypoplasia of the facial bones, particularly the mandible and zygomatic bone. The palate is high arched or clefted. The zygomatic arches may be completely absent if the severity of the disorder is more (Trainor et al 2009).

3.Ellis-van Creveld syndrome: It is also known as chondroectodermal dysplasia and mesoectodermal dysplasia(Kamal et al 2013). It is an autosomal recessive genetic disorder found in about 60% of cases. The mutation in EVC and EVC2 genes located on chromosome 4p16 is responsible for this syndrome. The genes are EVC and EVC2, which play a role in the development of cilia**(** Ruiz et al 2003, Das et al 2010).

The EVC syndrome was first reported by McIntosh in 1933, but Richard W.B. Ellis of Edinburgh and Simon van Creveld of Amsterdam in 1940, first described this condition and defined it as EVC syndrome. The estimated birth prevalence of EVC is 7 per 10,00,000 population and more than 300 cases has been reported in the literature. The parental consanguinity was reported in 30% of cases (Atasu et al 2000). The exact prevalence of this rare syndrome is still unknown. This syndrome doesn't have any gender predilection(Shilpy et al 2007).

Diagnosis at birth can be made by observing the typical symptoms (fig.3) of the disease and an X-ray of the skeleton. Chest radiography, ECG, and echocardiography may also help in diagnosis of EVC syndrome. The molecular diagnostic methods can be used for definitive diagnosis for a mutation in the EVC and EVC2 genes(Kamal et al 2013).

4. Frontonasal dysplasia (Median cleft face syndrome): Frontonasal dysplasia (FND) is also known as Burian's syndrome(Fox et al 1976). It is also called frontonasal dysostosis, and craniofrontonasal dysplasia(fig.4 & 5). In 1967, De Meyer first described the midface defects as median cleft face syndrome. This is also a rare developmental defect of craniofacial region cause of which is not known(Sharma et al 2012). The occurrence can be sporadic or familial. The important genes involved in the midline craniofacial development are the SHH, TGIF, GLI2, TBX22, ZIC2, SIX3, TDGF1(Richieri et al 2009). It is a polygenetic dysmorphic syndrome inherited as a dominant and sometimes as a recessive trait. The expected risk for the next child is 25% for the parents of an affected child(Fox et al 1976, Lorenz et al 1990, Bader et al 2005).

The syndrome originates in the embryonic period prior to the 28-mm crown-rump length stage. During the third week of gestation, ectoderm gets thickened in two areas and form the olfactory placodes, appear under the forebrain on either side of the frontonasal prominence in the anterior wall of the stomodeum, Gradually it forms olfactory pits, a medial and two lateral nasal processes. The deficiency of the remodelling of the nasal capsule causes the freezing of the future fronto-naso-ethmoidal complex in the fetal form. Experiments show that a reduction in the number of migrating neural crest cells results in these multiple defects(Goodman et al 1983).

5. Patau syndrome(Trisomy 13): The etiology of the disorder is due to the trisomy of all or larger part of chromosome 13. The older maternal age might be a factor in the occurrence of this aneuploidy. Patau syndrome (fig.6) is the least common syndrome and most severe of the viable autosomal trisomies. Eventhough the syndrome was described by Bartholin in 1657, it is identified as a cytogenetic syndrome by Patau in 1960. The incidence is approximately 1 in 5000 births. The median survival for children with this disorder is 7 days. 90% live birth with this disorder die within first few years(Jones et al. 2013).

6. Van Der Woude's Syndrome: It is an autosomal dominant disorder characterized by a cleft lip / cleft palate, or distinctive pits of the lower lips, or both. Demarquay in 1845 first described mucous secreting fistula of the lower lip. Murray (1860) first reported association of fistulae with cleft lip and palate. Anne Van Der Woude in 1954 presented the syndrome in five generations. The prevalence of Van der Woude syndrome has been reported to be 1:75,000 to 100,000. Lip pits are the characteristic feature of the syndrome . The lip pits are the depressions of the lower lip that contain the orifice of mucous glands or minor salivary glands. Lip pits are usually bilateral, occasionally median or paramedian or unilateral, most often found on the left side (Hercilo et al 2007, Bhavna et al 2014). The lip pits may be the only symptom(fig.7). Cleft lip / cleft palate and absence of the upper lateral incisors are also seen in the syndrome. The gene responsible for the disorder is the interferon inhibiting factor 6(IRF6) which is located at 1q32-41(Jones et al. 2013).

7. CHARGE syndrome: It is an autosomal dominant genetic disorder typically caused by mutations in the chromodomain helicase DNA-binding protein-7 gene(CDH7). The typical clinical diagnosis of CHARGE syndrome requires the presence of at least 4 major features or 3 major and at least 3 minor features. Major features include ocular coloboma or microphthalmia, choanal atresia, cranial nerve abnormalities, and characteristic auditory and/or auricular anomalies**.** Minor features include distinctive facial dysmorphology, facial clefting, tracheoesophageal fistula, congenital heart defects, genitourinary anomalies, developmental delay, and short stature**.** CHD7 mutation analysis is diagnostic feature in 58-71% of individuals referred with presumptive CHARGE syndrome. High-resolution karyotype (chromosome analysis),Fluorescent in situ hybridization (FISH) or array comparative genomic hybridization (aCGH) can be used to detect submicroscopic copy number variations involving CHD7 and at other loci in individuals in whom CHD7 sequencing is uninformative(Jones et al. 2013).

8. Oculo-Dento-Digital Dysplasia (Lohmann syndrome): Also called hereditary Oculo-dento osseous dysplasia or Familial Microphthalmos syndrome. It is first described by Lohmann in 1920. It is an autosomal dominant inheritance. The GJA1 gene encoding the connexin protein are responsible for the disorder.The characteristic syndromic features are microphthalmos with microcornea, hypotelorism, persistent pupillary membranes, hyperplasia of maxilla with other cheek bones, small mandible with wide alveolar ridge, high arched palate with malocclusion, microdontia or anodontia, camptodactyly. Hands and feet are narrow, partial or complete syndactyly(fig.8) of the fourth and fifth fingers, partial fusion of 2nd 3rd & 4th toes, mid phalangeal hypoplasia or aplasia of one or more fingers and toes(Jones et al. 2013).

9. Pierre Robin Syndrome: The initiating defect of this disorder may be the hypoplasia of the mandibular area prior to the third month of intrauterine life, which makes the tongue to locate posteriorly and impairing the closure of posterior palatal shelves.The Robin sequence also be a result of early in utero mechanical constraint ,with the chin depressed in such a manner as to limit its growth before palatine closure. The features are micrognathia, glossoptosis, cleft in soft palate, or early mandibular hypoplasia(Latham et al 1966).

10. Apert Syndrome: The condition was reported by Wheaton in1894. Apert syndrome was named after French pediatrician, Eugene Apert as he documented multiple cases of congenital skull malformations in 1906. The craniosynostosis is one of the commonest anomaly associated with this syndrome. The craniosynostosis or early fusion of the sutures of skull affects the growth of the brain. The birth prevalence is 1 in 80,000 live births. There is 50% chance of having a child, if any of the parent is affected.

The disorder has an autosomal dominant inheritance pattern. The majority of cases are sporadic and have been associated with older paternal age. Mutations in Fibroblast growth factor receptor 2 gene (FGFR2) which maps to chromosome 10q25-10q26 cause the syndrome. In craniosynostosis, the FGFR-2 gene may not produce the FGFR-2 protein properly, so that it is leading to abnormal growth patterns. The FGFR-2 gene produces the protein which regulates the cell growth rate and cell growth limits. This protein direct immature cells to become bone cells and immature cells to stop becoming bone cells. The other anomalies(fig.9a,9b,9c) are mid facial hypoplasia,

syndactyly, broad distal phalanx of thumb and big toe, flat facies, hypertelorism, small nose, downslanting palpebral fissure, cleft palate, agenesis of corpus callosum and progressive hydrocephalus(Jones et al 2013).

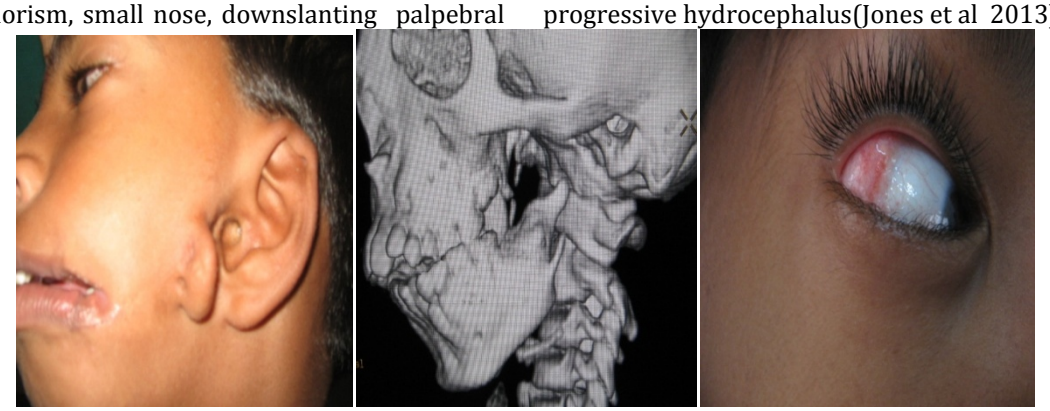

Fig.1a **fig.1b** **fig.1c**

Figure 1a, b, c show features of **Goldenhar Syndrome**. 1a&1b show macrostomia, hypoplasia of ramus of mandible, extra ear tags and absence of external acoustic meatus, and fig.1c shows epibulbar dermoids

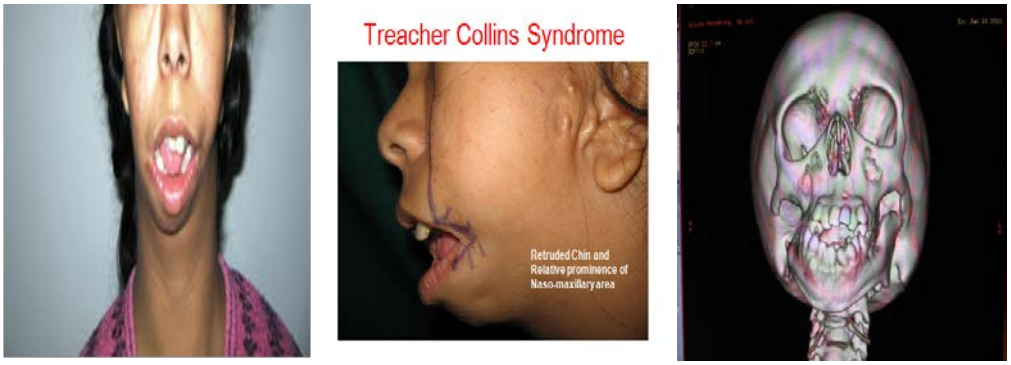

Fig. 2a fig.2b fig.2c

Figure 2a shows large fish like mouth, external ear tags (fig.2b) and hypoplasia of mandible(fig.2c)

Figure 3 **Figure 4** **Figure 5**

Fig.3 shows v-shaped notch in the upper lip **(Ellis Van Creveld syndrome)**

Fig.4 & 5 shows anterior encephalocele, hypertelorism and flattened nasal tip **(Median Cleft Face syndrome)**

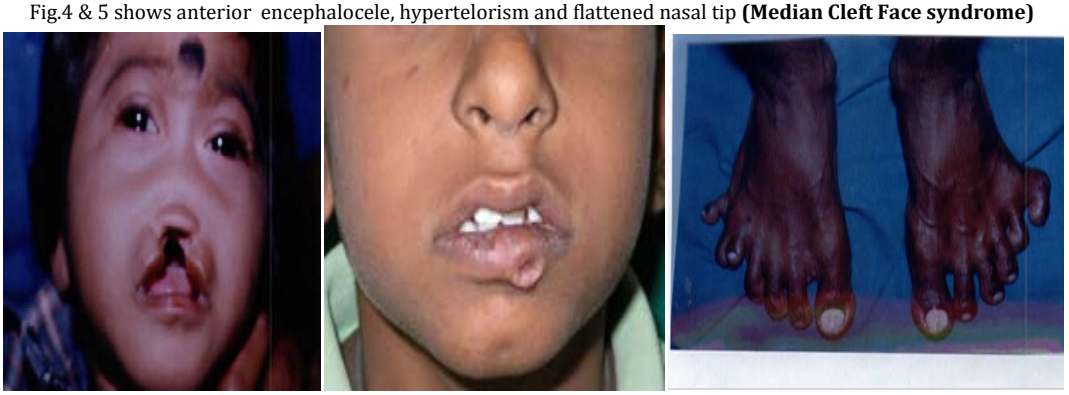

Figure 6 **figure 7** **figure 8**

Fig.6 shows severe midline clefting of lip and palate and absence of nose **(Patau syndrome),** Fig.7 shows pits on lower lip **(Van Der Woude's Syndrome),** Fig.8 shows syndactyly and camptodactyly **(Lohmann syndrome)**


fig.9a

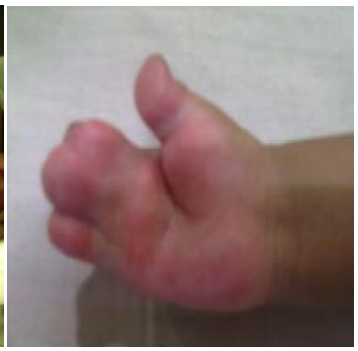
fig.9b

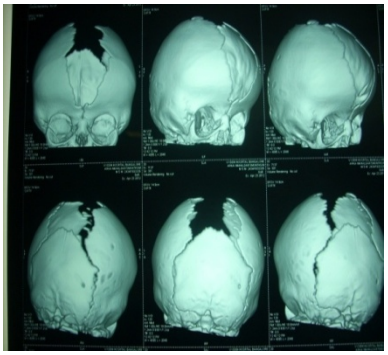
fig.9c

Figure 9a, 9b &9c **(Apert syndrome**) shows facial appearance, syndactyly and radiological examination of skull

CONCLUSION

Identifying the syndromes associated with the cleft is essential to provide the proper guidance and counselling to the parents to avoid the further complications. The earliest the identification and treatment of anomalies, better the survival of the affected.

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