Republic of Iraq
Ministry of Higher Education
and Scientific Research
University of Baghdad
College of Dentistry

GROWTH AND CRANIOFACIAL ANOMALIES

A Project Submitted to
The College of Dentistry, University of Baghdad, Department of Orthodontics in Partial Fulfillment for the Bachelor of Dental Surgery

By
Zahraa Ali Hussien

Supervised by
Dr. Shahbaa Abdul Ghafour Mohammed

April 2023

Certification of the Supervisor

I certified hat this project entitled" Growth and Craniofacial Anomalies " was prepared by the fifth-year student (Zahraa Ali Hussein) under my supervision at the College of Dentistry/University of Baghdad in partial fulfillment of the graduation requirements for the bachelor degree in Dentistry.

Dr. Shahbaa Abdul Ghafour Mohammed

2023

DEDICATION

To my parents, who have always been my biggest cheerleaders and provided me with endless love and encouragement. Your unwavering support has been instrumental in helping me achieve my goals.
To a special person who always supported me.

Acknowledgment

I would like to express my gratitude to prof. **Dr. Raghad AL-Hashmi**, dean of college of Dentistry, for providing me this opportunity to study.

My deepest gratitude to prof .**Dr. Dheaa H. Al-Groosh**, Head of the Department of Orthodontic Dentistry.

My deepest gratitude and appreciation go to prof. **Dr. Shahbaa Abdul Ghafour Mohammed** for her scientific support and for help in facilitating the performance of this work.

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List of abbreviations

TCS	Treacher-Collins Syndrome
RAS	Retinoic acid syndrome
NTDs	Neural tube defects
Ach	Achondroplasia
MSX	Muscle segment homeobox hox genes
RAR **β**	Retinoic acid receptor β
ICP	Intracranial pressure
TCOF1	Treacle ribosome biogenesis factor
POLR1D	RNA polymerase I and III subunit D
POLR1C	RNA polymerase I and III subunit C
TGF**α**	Tumor necrosis factor alpha
NADH	Nicotinamide adenine dinucleotide (NAD) + hydrogen (H)
PRS	Pierre Robin sequence

Introduction

Craniofacial anomalies are among the most common of all birth defects. Like many congenital defects, most craniofacial anomalies occur due to a combination of genetic and environmental factors, the latter including maternal exposure to toxins (including tobacco and alcohol) and certain medications (**Bianchi *et al*., 2000, Lin *et al*., 2016**).

Craniofacial anomalies can occur in isolation (the anomaly occurs with no other defects and with no established genetic basis), as part of an established syndrome with a known constellation of defects due to single gene mutation or chromosomal abnormality, or in association with additional development defects, but without a known genetic basis **(Durham *et al*., 2019).**

The pathogenesis of developmental craniofacial abnormalities commonly involves defects in the migration, proliferation, and fate of cranial neural crest cells and their derivatives. These neural crest developmental abnormalities lead to a variety of developmental defect syndromes, overall referred to as neurocristopathies, including those that are found in cleft palate, Treacher-Collins syndrome , Pierre Robin sequence, and craniosynostosis **(Durham *et al*., 2019).**

The coronal cranial suture is prematurely fused in many individuals with syndromic craniosynostosis, and particularly in those with mutations in FGFR2 or Twist **(Azoury *et al*., 2017; Lee, 2018).**

Unlike other cranial sutures, the coronal suture develops between mesoderm-derived parietal and neural crest-derived frontal bone rudiments, and it maintains the boundary between these bone tissues of different embryonic origin during growth **(Twigg *et al*., 2015).**

Therefore, the role of neural crest cell defects in the pathogenesis of coronal craniosynostosis is of particular interest.

Aims of the study

This review was conducted to highlight the genetic, environmental, and developmental factors and the clinical features that contribute to craniofacial anomalies such as cleft lip and palate, craniosynostosis, and facial asymmetry

Chapter one

Review of the literature

1. DEVELOPMENT OF THE CRANIOFACIAL COMPLEX

1.1. Definitions

There are five specific stages for embryonic craniofacial development:

- **Germ layer formation** and initial organization of craniofacial structures.
- **Neural tube formation** and interactions of cell population during initial formation of oropharynx.
- **Origin, migration** and interactions of cell populations, especially neural crest cells.
- **Formation of organ systems**, especially the pharyngeal arches and the primary and secondary palate.
- **Final differentiation of tissues** (skeletal, muscular, and nervous elements).

Any disturbance in each stage will result in a specific type of abnormality **(Premkumar, 2011).**

Fundamental to the development of the craniofacial complex is the central nervous system. The central nervous system arises from the neural plate, rolls up along its anterior, posterior axis to form the neural tube, and the enlarged anterior end divides into three vesicles **(Premkumar, 2011).**

Premkumar (2011) stated these vesicles include:

- Primordial of the forebrain, (prosencephalon)
- Midbrain (mesencephalon)
- Hindbrain (rhombencephalon)

Table 1-1: Stages of development and related abnormalities (Premkumar, 2011).

Stage	*Time (humans) postfertilization*	*Related syndromes*
Germ layer formation and initial organization of structures	Day 17	Fetal alcohol syndrome
Neural tube formation	Days 18-23	Anencephaly
Origin migration and interaction of cell populations, formation of organ systems	Day 19-28	Hemifacial microsomia Mandibulofacial dysostosis Limb abnormalities
Primary palate	Days 28-38	Cleft lip or palate, other facial clefts
Secondary palate	Days 42-55	Cleft palate
Final differentiation of tissues	Day 50-birth	Achondroplasia, synostosis syndromes

1.2. The neural crest cells

Is a highly pluripotent cell population that plays a critical role in development of vertebrate head. Development of the neural structures starts with the infolding of the neural plate ectoderm along the midline forming the neural folds that fuse to form the neural tube which submerges beneath the superficial covering, the cutaneous ectoderm. This process is called **neurulation (Premkumar, 2011).**

In this process, the cells at the margins of the neural folds undergo an epithelial to mesenchymal transition following an inductive interaction between neural plate and presumptive ectoderm. This results in the formation of neural crest cells.Arising from the margins of the crests of the neural folds, the neural crest cells first appear in 7–14 somite stage embryos. This is fundamental in craniofacial growth. The differentiation, development, and migration of neural crest cells are crucial to craniofacial morphogenesis. The neural crest cells exhibit properties of both ectoderm and mesenchyme **(Premkumar, 2011).**

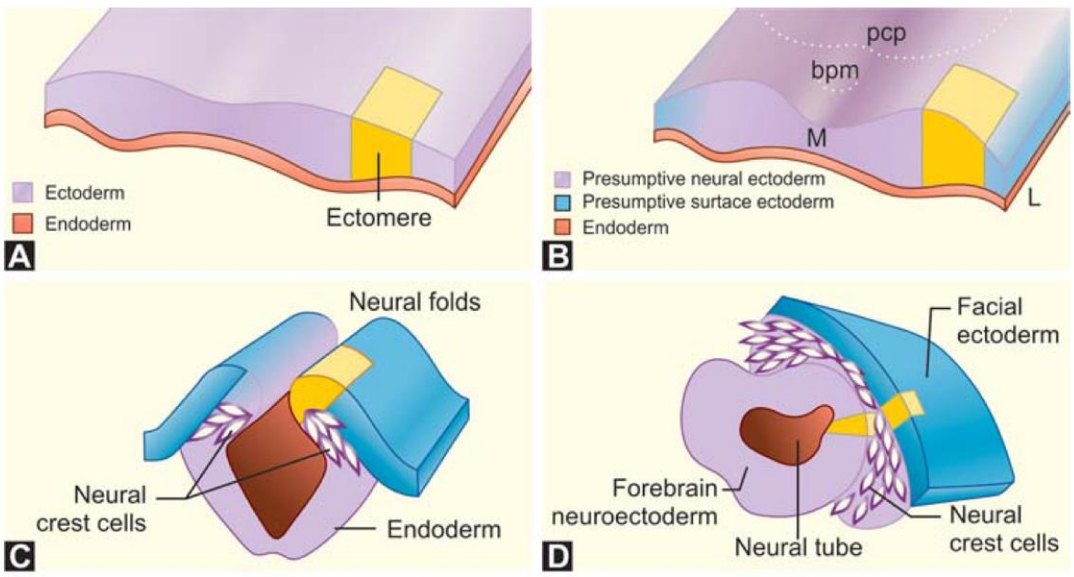

Figure 1-1: Neurulation in the developing vertebrate embryo (Premkumar, 2011).

1.2.1. Characteristics of Neural Crest Cells

Unlike most parts of the body, the facial mesenchyme is derived principally from the neural crest and not the mesoderm of the embryonic germ layer. These neural crest cells migrate to the area of the branchial arches and give rise to the mesenchyme of the pharyngeal arches. The mesenchyme gives rise to the cartilage, bone, and the muscles. The neural crest cells migrate extensively throughout the embryo in four overlapping domains. They are bipolar in configuration. Their elongated form is oriented in the direction of migration. Shape changes are noted and they also round up for cell division during migration. There is also a change in the cell surface receptors, from cell adhesion molecules to fibronectin, which permits make and break connections.The origin, migration and differentiation of the neural crest cells are mainly controlled by the homeobox hox genes **(Premkumar, 2011)**.

Five growth factors control facial growth by regulation of cell proliferation, survival, and apoptosis.

These include:

- ✓ endothelins,
- ✓ fibroblast growth factors (FGFs),
- ✓ sonic hedgehog (Shh),
- ✓ wingless (wnts)
- ✓ bone morpho- genetic proteins (BMPs).

These factors are responsible for the ectomesenchymal interaction which is very important for origin, migration, and differentiation of neural crest cells **(Premkumar, 2011).**

1.3. Ganglionic placodal cells

Another interesting feature in craniofacial development is development of sensory neurons. In the trunk, all sensory neurons develop from the neural crest while in the head, the earliest differentiating neurons in the ganglia are derived from ganglionic placodes **(Premkumar, 2011).**

1.4. DEVELOPMENTAL ANOMALIES

1.4.1. Holoprosencephaly and Fetal Alcohol Syndrome:

1.4.1.1. Aetiology

Exposure to high levels of ethanol at early stages of fetal development produces fetal alcohol syndrome (FAS) which now is recognized as one of the holoprosencephalies. The impact of alcohol use may create mild or severe symptoms. Fetal alcohol spectrum disorder is this group of signs and symptoms on a scale from least to most effects. Fetal alcohol syndrome is the most severe condition on this scale **(Premkumar, 2011).**

Ethanol has direct effects on neural plate or the mesoderm. This results in considerable cell death in anterior neural plate. Normal programmed cell death is necessary for eliminating selected adult cell types. This takes place by apoptosis, which is required for normal sculpting of the embryo. If apoptosis becomes excessive, the embryo's ability to process the debris becomes overwhelmed and leads to abnormal development. The homeobox gene MSX1 and MSX2 are essential for the normal regulation of apoptosis **(Premkumar, 2011).**

1.4.1.2. Characteristics of fetal alcohol syndrome

It is characterized by decreased forebrain and increased tendency for the three ventricles to form a single cavity. The main defect is reduced midline components. Facial defects include defects of medial nasal prominence. Derivatives of the medial nasal process including philtrum and portions of maxilla (premaxilla) are deficient. Contact of olfactory placodes in the midline results in failure of the medial nasal prominences to develop and leads to arhinencephaly. Increasing deficiency leads to progressively smaller eyes which may unite to form one median eye or remain as two small eyes close to the midline **(Premkumar, 2011).**

1.4.2. Retinoic Acid Syndrome:

1.4.2.1. Aetiology

This syndrome appeared after the introduction of the acne drug Acutane in 1982. Retinoic acid contains 13- cis-retinoic acid. The severity of the anomaly depends on the degree of metabolism of the drug. The levels of the metabolite 4-oxo-retinoic acid are 3 to 5 times higher than the original parent drug concentration and act as teratogen. The main target of retinoic acid is the neural crest cells. The neural crest cells are killed before leaving the neural plate which occurs at a later period. It was found that retinoic acid increases the expression of the MSX2 and causes upregulation of retinoic acid receptor β (RARβ), which in turn causes increased affinity for retinoic acid and further increased MSX2 expression causes excessive apoptosis which causes loss in neural crest cells **(Premkumar, 2011).**

The timing of exposure for the most severe facial malformations in the studies coincided with the onset and period of migration of first and second arch crest cells (about day 21 in human embryos) **(Webster *et al*., 1986; Goulding and Pratt 1986).**

1.4.2.2. The clinical features of retinoic acid syndrome

- Microtia.
- Facial bone and calvarial abnormalities.
- Micrognathia.
- Cleft palate.
- Congenital heart disease.
- Aortic arch abnormalities.
- Cerebellar hypoplasia and vermis agenesis.
- Microcephaly.
- Limb abnormalities **(Premkumar, 2011).**

1.4.3. Thalidomide Related Craniofacial Abnormalities

Thalidomide was a drug sold in Germany extensively as an over-the-counter tranquilizer.Many of the early exposures produced craniofacial and cardiovascular malformations similar to retinoic acid. Depending on the time of exposure, it produced malformations similar to retinoic acid syndrome (exposure on 19-23 days) and related syndromes, as well as Treacher-Collin syndrome (exposure on days 25-26 days).Other manifestations include limb defects, both pre- and post-axial hypoplasia. Thalidomide poisoning also causes cleft of the palate **(Premkumar, 2011).**

1.4.4. Neural Tube Defects (NTDs):

It is one of the five most common human malformations. The problems are related to neural tube closure, principally neural fold elevation and contact. Neural tube defects are those involving the brain (anencephaly) and the spinal cord. Anencephalies are usually lethal **(Premkumar, 2011).**

1.4.4.1. Aetiology

Scientists don't yet know the exact cause of neural tube defects (NTDs), but they believe it's a complex combination of genetic, nutritional and environmental factors. In particular, low levels of folic acid in a person's body before and during early pregnancy appear to play a part in this type of congenital condition (**Avagliano *et al.*, 2019).**

Neural Tube Defects arise secondary to abnormal embryonic development of the future central nervous system. The two most common types of NTDs are spina bifida and anencephaly, affecting different levels of the brain and spine, normally reflecting alterations of the embryonic processes that form these structure During neurulation that occurs between days (17 and 28 post-fertilisation) **(Avagliano *et al.*, 2019).**

In the previous developmental phase (gastrulation), the ectoderm is formed, which will thicken in response to specific molecular signals released by the underlying notochord, giving rise to the neural plate. This plate of ectodermal cells will form the neural tube by elevating, juxtaposing and fusing along the midline (primary neurulation) of the body axis **(Avagliano *et al*., 2019).**

In the caudal region, neurulation (secondary) involves cellular condensation and mesenchymal-to-epithelial transition to close the neural tube (**Saitsu *et al*., 2004).** In mammals, primary neurulation is a multi-site process and recent evidence suggest that in humans two closure sites are recognisable (one at the prospective cervical region and one over the mesencephalon-rombencephalic boundary) **(Nakatsu *et al*., 2000; Copp *et al*., 2013).**

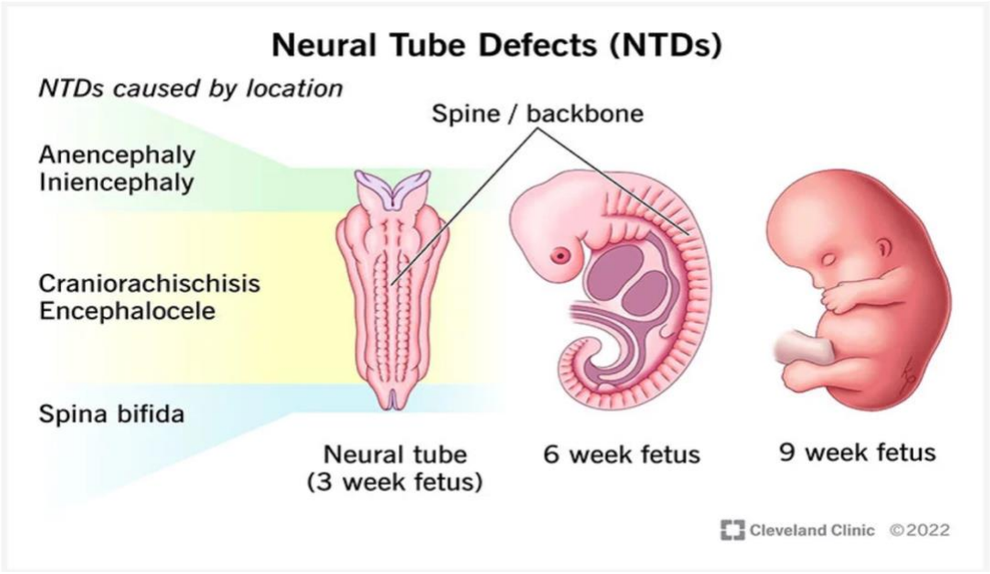

Figure 1-2: An NTD happens when the neural tube doesn't close completely somewhere along its length (Avagliano et al., 2019).

Different types of NTDs reflect the site of the interrupted neurulation. For example, craniorachischisis, which affects the brain and spinal cord, results from a failure of the initial closure site resulting in an open brain and spine, while anencephaly arises from abnormalities in the cranial neurulation process, and spina bifida results from incomplete caudal neurulation **(Avagliano *et al.*, 2019).**

1.4.4.2. Physical characteristics of neural tube defects

NTDs have been classically divided into open defects such as craniorachischisis, exencephaly-anencephaly and myelomeningoceles, and closed defects, including encephalocele, meningocele and spina bifida occulta (**Copp and Greene, 2013; McComb, 2015).**

In general, open defects are characterized by the external protrusion and/or exposure of neural tissue. Closed defects have an epithelial covering (either full or partial skin thickness) without exposure of neural tissue (**McComb, 2015**).

❖ **Anencephaly**

Anencephaly happens when the fetus's neural tube doesn’t close at the top during fetal development. This causes the skull, scalp and brain not to develop properly, and portions of the brain and skull are missing. The brain tissue that does form is usually exposed because there isn’t enough skin and bone to cover it. Infants with anencephaly are either stillborn or die soon after birth **(Wilkins-Haug and Freedman, 1991; Golden and Harding, 2004).**

❖ **Encephaloceles**

Encephalomeningoceles or encephaloceles are protrusions of brain and meninges through an abnormal opening in the skull most commonly in either the occipital or the frontal region **(Bhandari and Thada, 2022).**

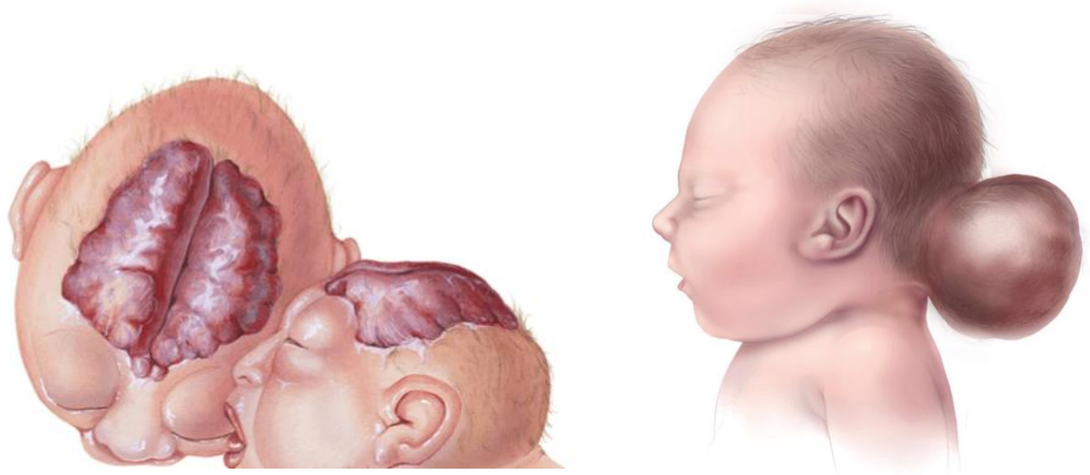

Figure 1-3: Neural tube defects A. Anencephal. B. Encephaloceles (Bhandari and Thada, 2022)

1.4.5. DiGeorge Syndrome:

This syndrome is related to maternal alcoholism. The manifestations are similar to retinoic acid syndrome except for the short upper lip which is not seen in retinoic acid syndrome. A unique feature of this syndrome is the occurrence of pharyngeal gland problems (thyroid and parathyroid deficiencies)**(Premkumar, 2011).**

1.4.5.1. Aetiology

The main etiological agent is ethanol which is lethal for migrating neural crest cells This syndrome is frequently associated with chromosomal deletion 22 **(Premkumar, 2011).**

Each person has two copies of chromosome 22, inherited from each parent. If a person has DiGeorge syndrome , one copy of chromosome 22 is missing a segment that includes an estimated 30 to 40 genes. Many of these genes haven't been clearly identified and aren't well-understood. The deletion of genes from chromosome 22 usually occurs as a random event in the father's sperm or in the mother's egg, or it may occur early during fetal development. Rarely, the deletion is an inherited condition passed to a child from a parent who also has deletions in chromosome 22 but may or may not have symptoms **(McDonald-McGinn *et al.*,2015).**

1.4.5.2. The clinical features of DiGeorge Syndrome

- delays in learning to walk or talk and other developmental and learning delays
- hearing and vision problems
- mouth and feeding problems
- short stature
- frequent infections
- bone, spine, or muscle problems
- unusual facial features, including an underdeveloped chin, low-set ears, and wide-set eyes
- Variable maxillary and mandibular defects deficiencies

a cleft palate or other palate disorder **(McDonald-McGinn *et al.*,2015).**

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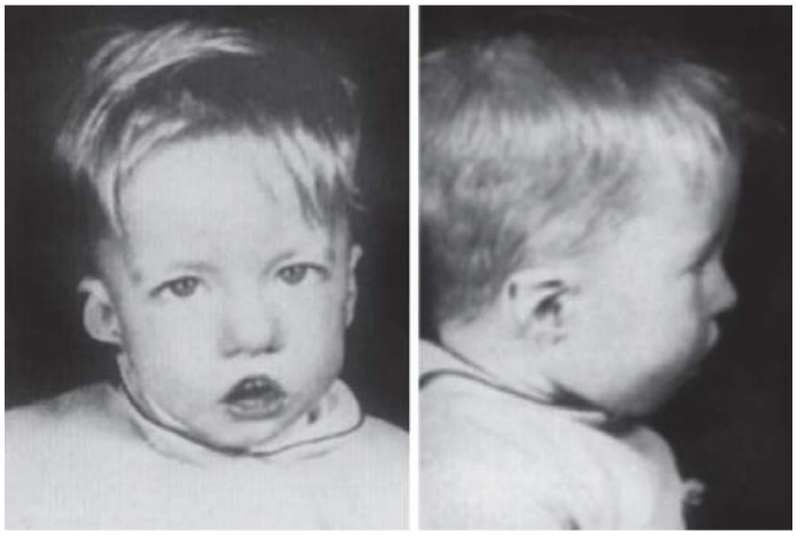


Figure 1-4: Child with the DiGeorge syndrome. In addition to the external ear malformation, the mandible is somewhat underdeveloped. In contrast to the retinoic acid syndrome, the upper lip is short, particularly in its central portion. From Kretchmer et al (1968)

1.4.6. Down's Syndrome:

It is a chromosomal disorder that occurs mainly due to trisomy 21. It can also occur due to translocation in which extrachromosomal material is translocated to chromosome G or D group and rarely due to chromosomal mosaicism **(Premkumar, 2011).**

Clinical features of Down's syndrome:

- flat face
- larger anterior fontanelle with open sutures
- small slanting eyes with epicanthal folds
- open mouth
- frequent prognathism
- sexual underdevelopment
- cardiac abnormalities
- and hypermobility of the joints.
- The clinical features, like the short upper lip in the midline, and a lop-ear are similar to those seen in DiGeorge syndrome **(Premkumar, 2011).**

1.4.7. Hemifacial Microsomia:

It is a common orofacial malformation. It is frequently associated with conotruncal and vertebral abnormalities. There are no clear environmental associations. In most or all cases neural involvement is seen. It is characterized by a lack of tissue on the affected side of the face, usually in the area of the mandibular ramus and external ear **(Premkumar, 2011).**

1.4.7.1. Aetiology

Poswillo (1970) suggested that hemorrhage from stapedial artery and tissue necrosis might be involved in the development of hemifacial microsomia. Stapedial artery forms the temporary blood supply to the area of developing ear and mandibular ramus between (33rd and 40th)day of gestation, which is later taken over by maxillary artery. The outer part of the stapedial artery atrophies and seals off. Poswillo (1970) suggested that hemorrhage from the stapedial artery causes facial defects associated with hemifacial microsomia **(Premkumar, 2011)**The main etiology is the death of neural crest cells with the longest migration path. Those taking circuitous route to the lateral and lower areas of the face are most affected, whereas those going to the central face tend to complete their migratory movement. This explains why midline facial defects including clefts are rarely part of the syndrome **(Premkumar, 2011).**It has a number of key similarities to RAS as well as important differences. Both have major ear involvement of a similar nature, although it is usually bilateral in RAS and unilateral in hemifacial microsomia **(Mark and Micheal, 2002).**

Classification

According to Pruzansky's original classification

- type I mandible is defined as retaining normal morphologic characteristics of the ramus and condyle but diminished in size.
- type II mandible demonstrates significant architectural and size distortion of the ramus, condyle, and sigmoid notch.
- a type III mandible shows gross distortion or complete agenesis of the ramus **(Vento *et al*., 1991).**

Kaban and colleagues later subdivided the type II mandible into two categories reflecting the architecture and function of the temporomandibular joint. According to their modification, a type IIA mandible demonstrates acceptable glenoid fossa anatomy and position with respect to unaffected side and a type IIB mandible demonstrates temporomandibular joint malpositioning (**Kaban *et al*., 1988).**

1.4.8. Treacher-Collins Syndrome:

Treacher-Collins syndrome , also referred to as Franceschetti syndrome or mandibulofacial dysostosis, is a rare developmental disorder This was frequently called as first arch syndrome involving structures derived from first arch **(Premkumar, 2011).**

1.4.8.1. Aetiology

Mutations in the TCOF1, POLR1D, and POLR1C genes are complicit in the development of TCS, resulting in deficient ribosome biogenesis and subsequent neural crest cell insufficiency **(Rovin *et al*., 1964; Gorlin *et al*., 2002).**

The main problem is due to the massive cell death in the trigeminal ganglionic placode, which alters the further development of the placodal cells, ultimately resulting in secondary defects in neural crest cell derivatives **(Rovin *et al*., 1964; Gorlin *et al*., 2002).**

1.4.8.2. Clinical characteristics

Symptoms of TCS are clinically very variable and include following mean malformations/features:

- External and middle ear abnormalities including microtia with conductive hearing loss attributed most commonly to malformation of the ossicles.
- Coloboma or notching of the lateral part of lower eyelids with medial absence or sparse of the eyelashes and tear ducts defect, aberrant facial hair over the malar area.
- Bilateral deficiencies in the lateral orbital rim and zygomatic area in addition to absent or rudimentary mandibular condyles, short mandibular ramus, severe antegonial notching and retrognathia. The shape of the mandible with a markedly down-turned symphysis is a characteristic feature.
- Hypoplasia of the zygomatic bones and mandible can cause significant feeding and respiratory difficulties.
- Other common manifestations include cleft palate, unilateral or bilateral choanal stenosis or atresia and pharyngeal hypoplasia **(Premkumar, 2011).**

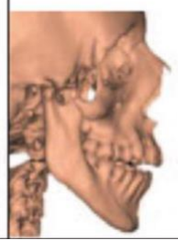
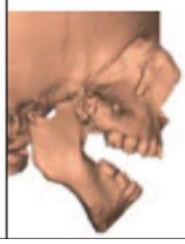
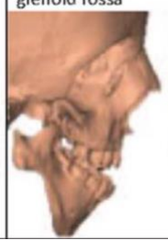
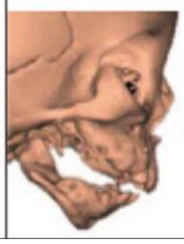
	I	II	III	IV
SNB angle	Greater than 67°	62-67°	56-61°	Less than 55°
Co-Go-Me angle	Less than 135°	135-145°	146-155°	Greater than 155°
Condylar morphology	Normal	Morphologically normal, but hypoplastic/small	Condylar remnant that may not translate with glenoid fossa	Absent
				

Figure 1-5: Proposed classification of mandibular hypoplasia based on 3 categories: condylar morphology, retrognathia/sella–nasion–B point angle (SNB angle) and mandibular plane angle/Co-Go-Me angle. (From Ligh et al. A morphological classification scheme for the mandibular hypoplasia in Treacher Collins syndrome, 2017)

1.4.8.3. DENTITION AND PALATE

Cleft palate occurs with an estimated incidence of one-third of TCS patients. There are no published data to suggest that timing of cleft repair should be any different than non-TCS patients.Malocclusion is another common finding in TCS. An incidence of up to 94% of patients demonstrating some form of malocclusion has been reported **(Peterson *et al*., 1976).**

Typically, an anterior open bite with malpositioned teeth, often associated with a steep occlusal plane, is present **(Plomp *et al*., 2016).**

Some authors advocate the monitoring of dentition and oral hygiene as early as infancy, with sub- sequent orthodontic treatment once eruption of permanent teeth is complete.Orthognathic intervention can take place during late adolescence **(Trainor et al., 2008).**

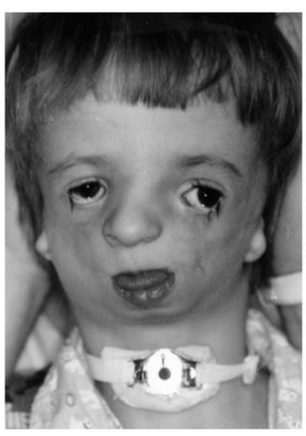


Figure 1-6: patient displaying a severe characteristic phenotype of Treacher Collins syndrome. From Kobus and Wojcicki Surgical treatment of Treacher Collins syndrome. Ann Plast Surg 2006).

1.4.9. Facial Clefting

1.4.9.1. Definitions

The most prevalent congenital defect of dentofacial development is clefting of the lip and or palate, Clefts occur due to any disturbance in the fusion of the facial process namely the medial nasal process, lateral nasal process, maxillary process, and the palatine shelves from the maxillary process **(Premkumar, 2011). Cleft lip:** The failure of fusion of the frontonasal and maxillary processes, resulting in a cleft of varying extent through the lip, alveolus, and nasal floor (an incomplete cleft does not extend through the nasal floor, while a complete cleft implies lack of connection between the alar base and the medial labial element) **(Semer, 2001). Cleft palate:** The failure of fusion of the palatal shelves of the maxillary processes, resulting in a cleft of the hard and/or soft palates (**Semer, 2001).** Thus, the typical distribution of cleft types are

1. Cleft lip alone – 15%
2. Cleft lip and palate – 45%
3. Isolated cleft palate – 40%**(Gaurishankar, 2011).**

1.4.9.2. The aetiology of cleft lip and palate:

Is complex and thought to involve genetic influences with variable interactions from environmental factors. The way in which cleft lip and palate develop has been clarified considerably in recent years as the morphogenetic movements of the involved tissues have been better understood **(Premkumar, 2011).**Three recent findings worth a brief comment are:

- Primary palate is formed by the fusion of the lateral nasal process with the medial nasal process. Forward movement of the lateral nasal process during formation of primary palate keeps it in contact with medial nasal process. Interference with this movement can lead to clefting of the palate. Maternal smoking has been shown to be a major factor in the etiology of cleft lip and palate. The mechanism is thought to be hypoxia induced failure of the movement of the lateral nasal process. It interferes with oxidative phosphorylation of the cells, thereby reducing the synthesis of ATP which supplies energy for the morphogenetic movements **(Premkumar, 2011).**

- A genetic predisposition has also been found. Alterations in the genetic code for TGFα, NADH dehydrogenase were found to be associated with cleft lip and palate **(Premkumar, 2011).**

- Closure of the secondary palate depends on removal of the tongue from between the palatal shelves. A relatively large tongue in the affected twin of a monozygotic pair discordant for cleft palate seems to be a frequent finding. It is now clear that almost all cases of isolated cleft palate are related to problems in tongue removal, shelf elevation and contact of the shelves at the proper time **(Premkumar, 2011).**

1.4.9.3. Facial Clefting Classification:

Syndromic: Here cleft is associated with other malformation. Usually it is due to a single gene such as holo- prosencephalies, hemifacial microsomia and Treacher-Collin's syndrome **(Premkumar, 2011).**

Non-syndromic: Here the cleft is mostly an isolated feature and occurs in the vast majority of individuals having a cleft lip or palate (up to 70% cases). In this form, a cleft is neither a recognized pattern of malformation nor a known cause for the disorder can be identified **(Lakhanpal *et al*., 2014).**

1.4.9.4. Clinical findings:

The various clinical findings in patient with cleft lip and palate can be categorized under two headings:

- **Dental problems in cleft lip and palate**

Various abnormal dental conditions includes:

1. Natal and neonatal teeth: Presence of neonatal teeth does not appear to influence primary or secondary dentition in clefts. Most natal teeth among clefts are located in the lateral margin of the premaxillary and maxillary segments unlike in non-cleft neonates **(Al Jamal *et al*., 2010; Kadam *et al*., 2013).**

2. Microdontia: frequently are found with CL/P. This is usually more common in cases where lateral incisors are not missing Generally peg shaped upper lateral incisors are seen **(Kadam *et al*., 2013)**
3. Taurodontis:Taurodontism has been reported to be associated with certain syndromes and dental developmental disorders **(Cichon and Pack, 1985).**
4. Ectopic eruption: Clefts also contribute to the ectopic eruption of primary lateral incisors which may erupt palatally adjacent to or within the cleft side while permanent canine on side of alveolar clefts may erupt palatally. Delayed eruption of permanent incisors may be seen**(Al Jamal *et al*., 2010; Qureshi *et al*., 2012).**
5. Enamel hypoplasia: Enamel hypoplasia was found to occur more frequently in CL/P subjects compared with non-cleft populations, especially involving the maxillary central incisors **(Al Jamal *et al*., 2010).**
6. Delayed tooth maturation: Several growth factors are of major importance during craniofacial development, and these factors may be overexpressed or underexpressed when a cleft defect occurs. This aberrant expression can modify odontogenesis and cause abnormalities of the dental lamina **(Tan *et al*.,2001).**

❖ **Other associated conditions**: Speech difficulties, Ear infection, Feeding problems.

1.4.10. Achondroplasia:

1.4.10.1. Definition

Achondroplasia is the most common form of skeletal dysplasia. it occurs in all races and ethnicities. The word achondroplasia literally means "without cartilage'' **(Beery *et al*., 2012; Ireland *et al*., 2012).**

Although the literal translation means "without cartilage," people with Ach do form normal cartilage in appropriate places in the body; however, during embryologic development, a mutation results in malformation and undergrowth of cartilage and inhibits proper ossification. These abnormalities and malformations ultimately result in disproportionate development of long bones **(Beery *et al*., 2012).**

1.4.10.2. Aetiology

This is caused by the failure of primary growth cartilages of the limbs and cranial base to grow properly. It is transmitted as an autosomal dominant trait. Forward growth of the mid face is produced by the normal lengthening of the anterior cranial base, which in turn is dependent on the growth at sphenoccipital, inter- sphenoidal and spheno-ethmoidal synchondroses. In achondroplasia, growth is diminished at these synchondroses **(Premkumar, 2011).**

1.4.10.3. Clinical features

Include the following:

- Proximal shortening of the arms and legs
- The anterior cranial base is of normal length and the posterior cranial base length is shorter.
- Short fingers
- Specific facial features: frontal bossing (prominent forehead) and midface hypoplasia (most accentuated at the bridge of the nose)
- Genu varum (bow legs)
- Trident appearance of hands **(Premkumar, 2011).**

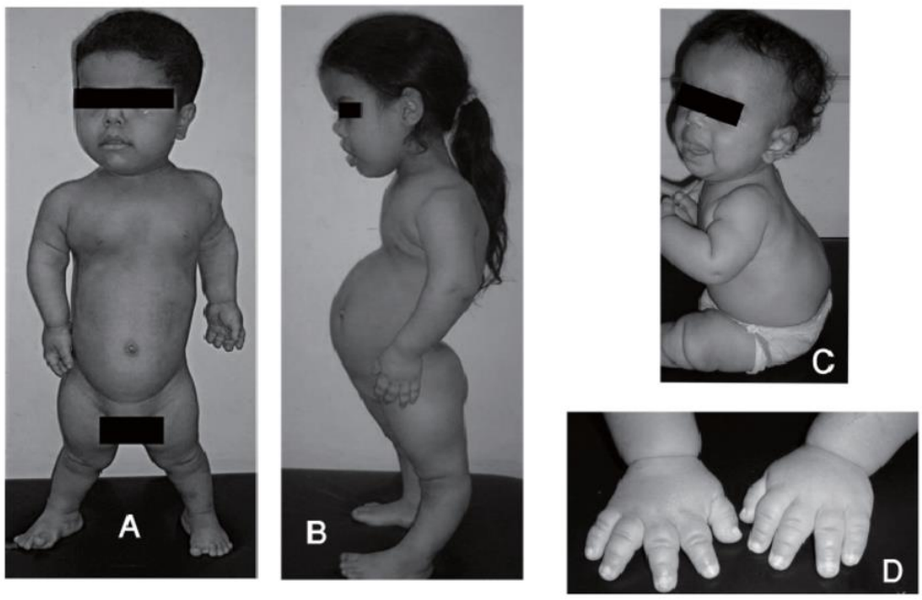


Figure 1-7: The characteristic clinical features of achondroplasia (A), exaggerated lumbar lordosis and short limbs (B), kyphosis (C), brachydactyly and trident hand configuration (D) Aglan and Mona, 2009)

1.4.11. Premature Closure of Cranial and Facial Sutures

1.4.11.1. Aetiology of craniosynostosis

A craniosynostosis is a developmental anomaly which occurs as a consequence of abnormal and non-physiological sutural fusion. When one or more sutures are prematurely closed, the compensatory growth starts perpendicular to the patent sutures since the brain still grows and expands in the direction of lower resistance. The result is an abnormally shaped skull and also, in more severe cases, increased intracranial pressure (ICP), as well as sensory, respiratory and neurological dysfunctions **(Kjaer, 1998; Slater *et al*., 2008; Adrichem *et al*., 2008; Johnson, 2010; Sharma, 2013).**

- **Predisposing factors**

Both environmental factors (e.g., intrauterine fetal head constraint, abnormal position, oligohydramnios, prenatal exposures to teratogens, maternal smoking, and antiepileptic drugs such as valproic acid and phenytoin) and genes (single gene mutations, chromosome abnormalities, and polygenic background) may all be predisposing factors for the disease **(Kjaer, 1998; Slater et al., 2008; Adrichem et al., 2008; Johnson, 2010; Sharma, 2013).**

Craniosynostoses are classified according to the sutures and the frequencies of these different types of craniosynostoses are as follows **(Kjaer, 1998)**:

Sagittal (≈60%), coronal (≈25%), metopic (≈15%), and lambdoid (≈2%).

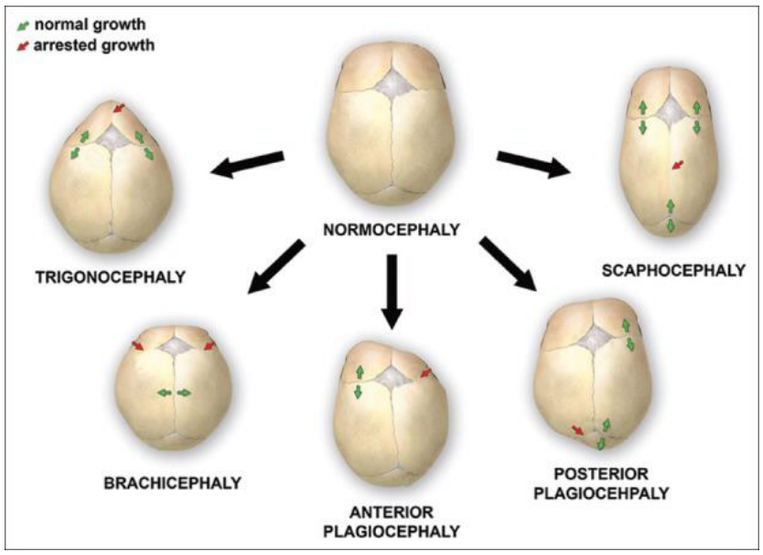


Figure 1-8: Various deformations of the skull, associated with single-suture synostoses (Nina et al., 2018).

❖ **Classification**

Different classifications of craniosynostosis are used .

For instance, if a craniosynostosis develops due to a primary defect of the ossification process it is called primary craniosynostosis. On the other hand, secondary craniosynostosis is the result of known systemic diseases with hematologic or metabolic dysfunction, such as rickets and hypothyroidism. Simple craniosynostosis is a term used when only one suture fuses prematurely, while complex craniosynostosis is used to describe a premature fusion of multiple sutures (**Slater *et al*., 2008).**

1.4.11.2. Crouzon's syndrome

Results from the premature fusion of the posterior and superior sutures of the maxilla along the walls of the orbit with cranial base involvement. It is characterized by symmetric maxillary deficiency that affects the infraorbital area. It is also characterized by shallow orbits resulting in protruding eye balls. The fusion extends to the cranium. Three fourths of the patients have fusion of the coronal, sagittal and or lambdoidal sutures **(Premkumar, 2011).**

1.4.11.3. Apert's syndrome

Characterized by fusion of multiple facial and cranial sutures and early fusion of the synchondroses of the cranial base. These patients have an appearance similar to Crouzon's syndrome and have syndactyly as an additional clinical feature. Another important feature is that the metopic suture and anterior fontanelle are characteristically open at birth and during infancy in these patients, leading to pronounced frontal bossing and a high steep forehead **(Premkumar, 2011).**

1.4.11.4. Pierre Robin Sequence

In 1923, Pierre Robin, a stomatologist from France, coined the term “glossoptosis” to describe the “obstruction of the oral pharynx by the tongue” in the setting of a small mandible. Although others have previously described patients with small mandibles, airway obstruction, and cleft palate, Dr. Robin has been credited with defining the criteria for the Pierre Robin sequence (PRS) (**Cladis *et al*., 2014).**

The clinical triad of micrognathia (small mandible), glossoptosis (backward, downward displacement of the base of the tongue), and airway obstruction defines PRS. Some authors have described PRS as micrognathia, glossoptosis, and cleft palate.Although clefting of the palate is common, it does not occur in all infants with PRS. However, all patients with PRS have airway obstruction, and this is a requirement for the clinical diagnosis (**Cladis *et al*., 2014).**

It is suspected that micrognathia keeps the tongue superiorly positioned between the naturally clefted palatal shelves and prevents normal palatal closure during the first trimester of pregnancy. Although micrognathia appears to be an isolated event for most patients with PRS, there is an association with certain syndromes. Infants with PRS present with respiratory and feeding difficulties. As many as half of these infants will also have associated malformations. Airway obstruction and respiratory distress are the primary respiratory signs (**Cladis *et al*., 2014).**

Chapter Two

Discussion/ comments

Craniofacial anomalies are a group of conditions that affect the skull and facial bones, as well as the soft tissues of the head and neck. Orthodontic treatment can help correct craniofacial anomalies, such as cleft lip and palate, jaw malformations, and dental abnormalities.

One common craniofacial anomaly that orthodontists often treat is malocclusion, or a misalignment of the teeth and jaws. This can lead to problems with biting and chewing, speech difficulties, and self-esteem issues. Orthodontic treatment for malocclusion may include braces, aligners, or other appliances to gradually move the teeth and jaws into proper alignment.

Cleft lip and palate is another craniofacial anomaly that can be treated with orthodontics. Orthodontic treatment may be necessary to correct the alignment of the teeth and jaws, as well as to prepare the mouth for surgical repair of the cleft.

Other craniofacial anomalies that may require orthodontic treatment include syndromes such as Down syndrome or Apert syndrome, which can cause dental and jaw abnormalities. Orthodontic treatment may be used to correct these issues and improve the person's overall oral health and function.

In summary, craniofacial anomalies can have a significant impact on a person's health and appearance, but orthodontic treatment can often help to correct these issues. Orthodontists work closely with other healthcare professionals to develop a comprehensive treatment plan for individuals with craniofacial anomalies, in order to improve their quality of life and overall oral health.

Chapter three

Conclusions and Suggestions

Craniofacial anomalies are a diverse group of conditions that can have significant physical, social, and emotional impacts on individuals and their families. Investigating the causes of these anomalies is an important area of research that can help improve our understanding of these conditions and inform the development of new diagnostic and treatment approaches.

By gaining a better understanding of the underlying causes and mechanisms of craniofacial anomalies, researchers can develop new strategies for prevention, diagnosis, and treatment. This can include the development of new diagnostic tools, such as genetic testing or advanced imaging techniques, as well as the exploration of novel treatment approaches, such as gene therapy or tissue engineering.

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