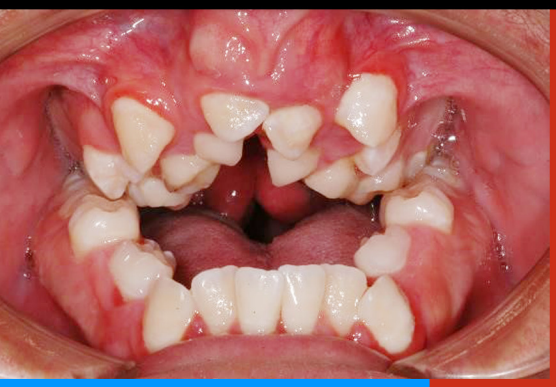
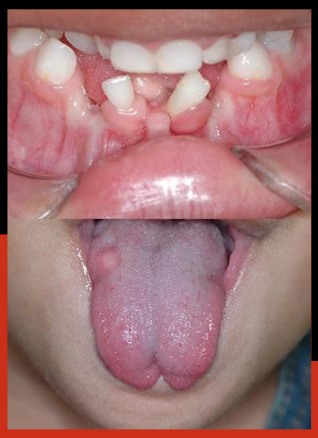
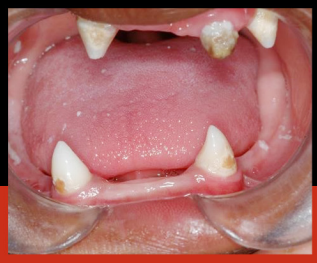
eISBN: 978-1-68108-516-6
ISBN: 978-1-68108-517-3

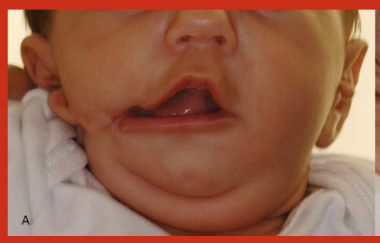
CRANIOFACIAL DISORDERS

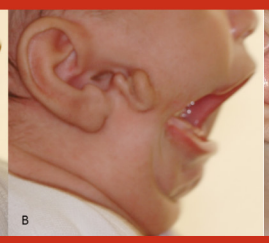
OROFACIAL FEATURES AND PECULIARITIES IN DENTAL TREATMENT

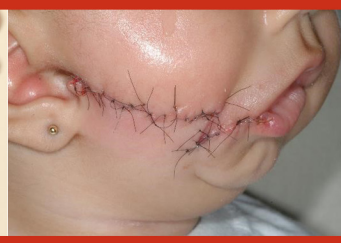


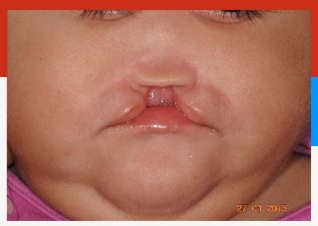












Editors:
Gisele da Silva Dalben
Marcia Ribeiro Gomide

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Craniofacial Disorders – Orofacial Features and Peculiarities in Dental Treatment

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Craniofacial Disorders – Orofacial Features and Peculiarities in Dental Treatment

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eISBN (Online): 978-1-68108-516-6

ISBN (Print): 978-1-68108-517-3

First published in 2017.

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FOREWORD 1

During my life I was assigned several missions: dentist, professor, researcher, manager; all of them were pleasant and full of challenges, with the bonus of knowing and living together with special people. I am proud to be invited to present this book to the world of Dentistry. The experience at the Hospital for Rehabilitation of Craniofacial Anomalies (HRAC-USP) gave me the opportunity to follow the career of several professionals, from undergraduate training up to the highest levels of research and university life. Few feelings are more thorough than following the personal and professional growth of people we respect; and the better reward for a professor is to see the shine of enthusiasm and curiosity in the eyes of young professionals, thirsty for knowledge; for a manager, to follow the vibration with which the team conducts its work. I have learned more than I have taught. At HRAC-USP, the daily routine was always filled with technical and human challenges. The daily care for individuals with different disabilities provides professionals with a rich source of research inspiration, besides demands yet to be explored. It is enough to be willing. The editors Gisele da Silva Dalben, Marcia Ribeiro Gomide and the contributor Beatriz Costa are examples of this thirst for knowledge and clinical sensitivity. They are three great researchers who were shaped at the Pediatric Dentistry clinic of HRAC/USP, where they sharpened and deepened their skills on the needs of patients requiring differentiated attention and treatment, respecting their exceptional birth conditions. Part of the long years of study, investigation and practice of these three brilliant researchers is present in this book, which surely enriches the dental management of patients with craniofacial anomalies. The book gathers experiences, knowledge and tips that the contributors kindly offer to anyone interested in this field. A part of their lives, all of them built inside Pediatric Dentistry. The years have been generous for me, giving me the opportunity to publicly celebrate the scientific maturity of three great pediatric dentists – and friends: Gisele, Marcia and Beatriz. And I say with certainty that another important chapter of Dentistry was written.

Dr. José Alberto de Souza Freitas ("Tio Gastão")
Founder and former superintendent of HRAC/USP,
Full Professor of University of São Paulo,
Brazil

FOREWORD 2

Writing the foreword to this book "Craniofacial disorders – orofacial features and peculiarities in dental treatment" has been a reason of great joy and pride, since this is one more contribution of the Hospital for Rehabilitation of Craniofacial Anomalies of University of São Paulo, gently known as "Centrinho", to the specialized literature.

Both editors are dental professionals graduated by FOB-USP with Master and PhD degrees and are extremely dedicated professionals who, together, add up more than 50 years of contribution to clinical activities, rehabilitating and providing smiles to individuals with craniofacial anomalies, besides actively working in the Teaching and Research scopes of the institution, valuing the scientific production.

The book is composed of nine chapters that bring valuable information for dentists and health professionals caring for individuals with syndromes associated with craniofacial anomalies. The book presents an update approach about Craniofacial Embryology, Concepts of Genetics, Teratogenesis, Dental Management in Rare Facial Clefts, as well as the alterations accompanying the diverse Syndromes with Orofacial Clefts, Craniosynostosis Syndromes, First Pharyngeal Arch Disorders, Syndromes with Characteristic Facies, and an approach about the Surgical Treatment in Craniofacial Malformations: Distraction Osteogenesis.

Further, the HRAC-USP has a strong team working on Genetics associated with craniofacial anomalies, coordinated by the medical geneticist Dr Antonio Richieri Costa, and during 50 years of work the institution concentrates a databank that is a scientific treasure. During her PhD, Dr Gisele da Silva Dalben worked with Dr Richieri Costa, analyzing individuals with Opitz G/BBB syndrome, and has several publications in the subject of craniofacial syndromes.

Since HRAC/USP is a reference center in craniofacial anomalies with participation of an interdisciplinary team, it was possible to prepare this book especially focusing the interest of dental professionals.

I consider this book a precious masterpiece, which shall fill the gap currently existing in the literature, concentrating in a single work the information on dental, skeletal and craniofacial alterations in individuals with different craniofacial disorders.

Dr. Terumi Okada Ozawa
Orthodontist and former Director of Dental Division of HRAC/USP,
Brazil

PREFACE

In 2003, the editors of this book noticed a lack of organized information about dental care for individuals with craniofacial disorders. Then, the editors performed a literature review about different craniofacial disorders and wrote an informal handout, which the editors made available in the local library. As years went by, that handout turned out to be widely borrowed and used as reference in their institution, which encouraged the editors to expand the information and transform that handout in the present ebook.

The editors work as pediatric dentists in a tertiary hospital and are often challenged with a wide array of disorders, frequently facing situations in which individuals and their families must travel even days to attend the institution for accomplishment of dental procedures that could be performed by professionals at their cities of origin, if only they had a little more information about craniofacial disorders. In some international experiences, the editors observed that, worldwide, there is still a lot of misconception and disinformation about when and how to treat the different disorders present in individuals with craniofacial disorders.

The organization of this book into chapters was largely based on the classic book "Syndromes of the head and neck" (Gorlin, 1990), which the editors consider fundamental for professionals who want to dive deeper into the world of craniofacial disorders.

To enhance the understanding on "hows and whys", Chapter 1 presents rich information about craniofacial embryology. This chapter was written by the eminent embryologist Kathleen K. Sulik, who describes craniofacial development in detail with the aid of amazing scanning electron micrographs of embryos, allowing the reader to travel through the stages of normal and abnormal embryonic development.

Chapters 2 and 3 present basic concepts of genetics and teratology, enhancing the knowledge of readers so that they can better understand the information presented in following chapters.

Chapters 4 to 8 describe the different craniofacial disorders in a similar sequence as in "Syndromes of the head and neck", presenting the disorders with their respective etiology, systemic involvement, and peculiarities in dental treatment. All contributors in these chapters have current and/or previous clinical experience in providing dental care to individuals with craniofacial malformations, and much of the information presented in these chapters were observed in investigations conducted at the editors' institution.

Finally, in Chapter 9, the authors describe the surgical steps required for complex dentomaxillofacial reconstruction in different disorders. These surgical procedures aim at both esthetic and functional improvement, and are paramount for the thorough rehabilitation of individuals.

The aim of this ebook is to be a chairside resource for clinical dentists who wish to offer dental care for individuals with craniofacial disorders. The editors' goal, when organizing this ebook, was to enhance the knowledge of dental professionals across the world about craniofacial disorders, their orodental features and peculiarities in dental treatment, so that individuals affected by such syndromes may have increasingly better and easier access to dental care.

We wish the readers all the best when assisting individuals with craniofacial malformations. We hope you will find the present information useful, and we wish you a rewarding

experience in treating these individuals and watching them grow stronger and more self-reassured with your collaboration.

We also wish all the best to individuals with craniofacial malformations and their families, with special consideration to those attending the editors' institution – the Hospital for Rehabilitation of Craniofacial Anomalies, University of São Paulo at Bauru, Brazil, who were the main driving force behind this ebook, and special thanks to individuals and their families who kindly granted permission to publish their images in this ebook. This book was inspired by you, and is dedicated to you.

ACKNOWLEDGEMENT

Chapters 2 to 9 were originally written in Portuguese and translated into English by the author Gisele da Silva Dalben. Signed informed consent was obtained from all individuals whose facial photographs that allow their identification are presented in this ebook.

All photographs presented in Chapter 1 belong to the files of the chapter author. Photographs presented in Chapters 2 through 9 belong to the files from respective chapter authors, from the Hospital for Rehabilitation of Craniofacial Anomalies of University of São Paulo, and from Adriano Porto Peixoto, who kindly granted access to his files.

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DEDICATION

To my dearest parents, Oswaldo and Madalena, who taught me everything that is important for a worthy life;
To my husband Maurício and my precious kids Lucas and Vitor, who make my life even worthier;
To the authors of chapters in this book, all of whom I consider outstanding professionals in their respective fields of work and lifelong companions in this amazing journey of caring for individuals with craniofacial malformations;
Above all, to the individuals with craniofacial malformations, especially those who kindly granted permission to publish their images herein, who teach us so much about the meaning of life and who are the main reason for writing this book.

Gisele da Silva Dalben

To my family, the place chosen by God for me in the world, where I learned, besides unconditional love, honesty with my father Nilton, faith with my mother Linda, fraternity with my brothers Mariângela, Mariza and Nilton, and endless happiness with my husband Wagner and my children Camila, Fernando, Rafael and Andressa.

Marcia Ribeiro Gomide

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Glossary

- Anophthalmia – absence of eye formation
- Anotia – absence of ear formation
- Arachnodactyly – condition in which the fingers are long, thin and curved, resembling the legs of a spider
- Blepharophimosis – combination of small eyelids, reduced palpebral opening, telecanthus, ptosis, arched eyebrows and epicanthal folds
- Brachydactyly – shortening of digits
- Camptodactyly – deformity caused by flexure of the proximal interphalangeal joint, usually of the fifth finger
- Clinodactyly – arched digits
- Coloboma – congenital fissure of any structure of the eye
- Craniosynostosis – premature closure of cranial sutures
- Cryptorchidism – absence of the testicles in the scrotum due to persistence inside the abdomen or inguinal canal
- Dysostosis – defect in ossification
- Dysplasia – abnormal development of organs and tissues causing deformities
- Ectrodactyly – congenital absence of one or more fingers or toes
- Ectropium – eversion of an edge or margin, usually of the eyelid
- Encephalocele – hernia of the brain or cerebellum through a congenital or traumatic opening in the skull
- Etiology – investigation of the causes of a disease
- Exotropia – strabismus in which the eye is directed outwards
- Extrophy – congenital eversion of an organ or part of it
- Glossoptosis – tongue retraction
- Hyperteleorbitism – increased distance between the orbits
- Hypertelorism – increased distance between any two symmetric structures in the body
- Hypoteleorbitism – reduced distance between the orbits
- Hypoacusia – reduced hearing ability
- Hypogonadism – inadequate gonadal function, manifested by deficiency in gametogenesis and/or secretion of gonadal hormones
- Hypohidrosis – reduction of sweat
- Hypospadia – congenital and abnormal opening of the urethra on the inferior part of the penis. It may also affect females, leading the urine to flow through the vagina
- Lagophthalmos – paralysis of an eyelid precluding complete closure of the eye globe when closed
- Meningomyelocele – hernia of part of the spinal cord and its meninges

- Microbrachycephaly – reduction and shortening of head size
- Microcephaly – reduction of head size
- Microphthalmia – reduction of eye size
- Microtia – reduction of ear size
- Nystagmus – fast and involuntary oscillation of the eye globe around its horizontal or vertical axis
- Oligodactyly – reduction in the number of fingers or toes
- Oligohydramnios – significant reduction in amniotic fluid volume
- Pectus excavatum – depression or groove caused by more interior positioning of the sternum
- Polydactyly – increase in the number of fingers or toes
- Polyhydramnios – significant increase in amniotic fluid volume
- Epicanthal fold – skin fold in the internal eye canthus, displacing the upper eyelid toward the internal canthus
- Proptosis – anterior displacement, usually of the eye
- Syndactyly – congenital union between one or more fingers or toes
- Synophrys – conjunction of the eyebrows
- Telecanthus – increased distance between the internal eye canthi, caused by lateral displacement of the medial canthus

CHAPTER 1

Normal and Abnormal Oro-Facial Embryogenesis

Kathleen K. Sulik[1,*]

[1] *Bowles Center for Alcohol Studies, School of Medicine, University of North Carolina, Chapel Hill, USA*

Abstract: The focus of this chapter is on normal oro-facial embryogenesis; on the developmental basis for facial defects that fall within the holoprosencephaly spectrum; and on the genesis of common and unusual oro-facial clefts. A thorough understanding of normal morphogenesis coupled with appreciation of the dysmorphogenic events underlying the defects considered in this chapter should aid the reader in also better appreciating the developmental basis for many of the other abnormalities addressed in this text. The prenatal stages considered in detail are present from the 3rd through the 8th weeks of human gestation, with emphasis being placed on description of the development of the growth centers (prominences/processes) that comprise the human oro-facies. The presence and significance of some of these oro-facial growth centers for both normal and abnormal embryogenesis have been largely overlooked in the past, due in part to the paucity of early human embryos available for careful analyses with modern techniques. To aid in resolving this problem, descriptions provided herein are largely founded on a relatively recent series of scanning electron micrographs of human embryos. Regarding clefting, knowledge of normal oro-facial morphogenesis, coupled with basic research findings, support the premise that the junctions of the various growth centers correspond to the sites of common and unusual oro-facial clefts as described by Tessier in 1976 [45]; that the embryonic period is when the vast majority of oro-facial clefts are induced; and that, in most cases, the proximate cause of clefting is failure of the normal growth and development of single or adjacent oro-facial growth centers. As for holoprosencephaly, both genetic abnormalities and environmental insults can underlie the dysmorphology.

Keywords: Cleft lip, Cleft palate, Embryology, Holoprosencephaly, Malformation, Oro-facial, Unusual facial cleft.

INTRODUCTION

An understanding of normal oro-facial embryogenesis is key to appreciation of the genesis of malformations involving this region. To facilitate learning, in this chapter scanning electron microscopic images of normal early human embryos are utilized as the primary tool to illustrate the complex changes in form that occur

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Gisele da Silva Dalben & Marcia Ribeiro Gomide (Eds.)

during the 1st trimester of gestation. With much of our knowledge regarding embryonic development having been acquired from the study of normal, mutant, and teratogen-treated non-human animals, pertinent animal images and research findings are also included. With a few exceptions as noted herein, the images are from the author's collection; human embryos having been collected by Dr. Michel Vekemans and Tania Attie-Bitacha, Necker Hospital, Paris, France. Cellular events underlying normal oro-facial embryogenesis will be addressed briefly as will developmental events that are pertinent to the generation of facial defects present in the holoprosencephaly (HPE) spectrum and that result in oro-facial clefts. Emphasis is placed on description of the morphogenesis of distinct growth centers of the developing face, on their apparent segmental nature, and on the correspondence of these growth centers and failures of their development, fusion or merging to the majority of the recognized oro-facial clefting sites as defined by Tessier [1]. A thorough understanding of normal morphogenesis coupled with appreciation of the dysmorphogenic events underlying the defects considered in this chapter should aid the reader in also better appreciating the developmental basis for many of the other abnormalities addressed in this text. For more comprehensive instruction, readers are referred to current embryology textbooks and web sites and also to recent review articles [2 - 12].

With the objective of providing the reader a broad perspective on the remarkable developmental changes involved in oro-facial embryogenesis, Fig. (**1.1**) illustrates the developmental progression that occurs from the human 3rd through 8th week post-fertilization [Please note that all age references are to days post-fertilization as opposed to post-last normal menstrual period]. During this 6-week span of time the embryo transitions from having a disk-like shape of only 0.5 mm in diameter to having a fetal form with a crown-rump length of approximately 3 cm. The end of the 8th week after fertilization is considered the end of the embryonic period and the beginning of the fetal period of prenatal life. While the secondary palate closes early in the 9th week and, therefore remains vulnerable to cleft-inducing insult during the early fetal stages, the vast majority of oro-facial clefts, as well as the HPE spectrum and defects including some forms of micrognathia and many ocular and auricular malformations are induced during the embryonic period.

Because the earliest of the developmental stages considered are likely the most unfamiliar/least intuitive to most readers, the majority of the images in Fig. (**1.1**) are of 3 and 4-week-old embryos. For the 3-week-old embryos, both light and scanning electron microscopic images are shown, illustrating the greater surface detail evident in the latter. The 3rd week is marked by neural plate formation and the ventral growth/folding of the embryo that creates a foregut pocket dorsal to the developing heart. In the 4th week, the neural tube closes and the pharyngeal (branchial; visceral) arches become evident. The olfactory placodes, around which

the nose will form, become apparent in the 5th week. And, from the 6th through the 8th weeks the various growth centers/facial prominences surrounding the nose, mouth, and eyes remodel as the face acquires a recognizably human appearance.

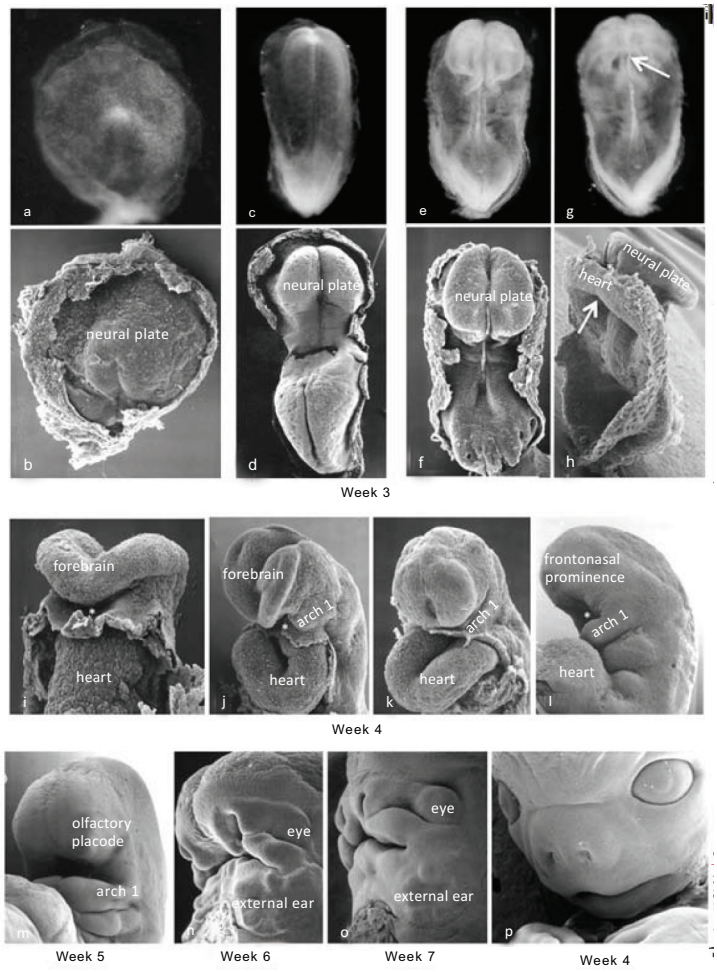

Fig. (1.1). A succession of stages of human embryonic development is shown in light micrographs (a, c, e, g) and scanning electron micrographs (b, d, f, h-p). Approximate ages for each of the embryos shown are as follows: 17 days (a, b), 19 days (c, d), 21 days (e-h), 23 days (i), 24 days (j), 25 days (k), 26 days (l), 32 days (m); 41 days (n); 43 days (o), 52 days (p). Views shown in (a-f) are dorsal; (g) is a ventral view; and (h-p) are ventrolateral views. Arrow in (g, h) = foregut; * = stomodeum (primitive oral cavity). (n) is reprinted from Hinrichsen [13].

NORMAL ORO-FACIAL EMBRYOGENESIS

While the first 2 weeks after fertilization are marked by the initial cell divisions and interactions from which the embryo and its supporting tissues are generated, it is in the 3rd week that all 3 of the embryos' definitive germ layers (the ectoderm,

CHAPTER 2

Concepts of Genetics

Lucimara Teixeira das Neves*, Gisele da Silva Dalben* and **Marcia Ribeiro Gomide***

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Abstract: This chapter aims to explain the basic concepts of genetics for the dental professional. Knowledge on the definitions of types of malformations, as well as the basis and nomenclature of genetic terms, will be fundamental for the readers to allow a thorough understanding on the aspects presented in Chapters 4 to 9.

Keywords: Congenital abnormalities, Embryonic development, Fetal development, Genetic structures, Genetic processes.

The congenital anomalies may involve a single organ, part of an organ or a wider region, and occur in the embryonic and fetal period. These anomalies affect 3 to 5% of the world population. These disorders may be hereditary or not. They are usually characterized as hereditary when they present a probable known genetic component in their etiology, and may present a characteristic inheritance pattern or not, observable by evaluation of the family history. Depending on this pattern, the disorder may or may not be transmitted to the offspring, regardless of its manifestation or extent [1].

The congenital anomalies are classified as:

- Developmental field anomalies: these affect part of the embryo in which the development occurs. They alter the differentiation of totipotent cells into specialized cells, causing anomalies in structures at the same site or stage of embryonic development. When caused by a teratogenic agent, the earlier the

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action of the agent, the greater will be the damage. Example: Opitz G/BBB syndrome.

- Sequences: multiple anomalies in different structures derived from a single primary defect, known or assumed, or even a mechanical factor that triggers a cascade of secondary events determining abnormal characteristics. Example: Robin sequence (micrognathia – glossoptosis – cleft palate) [2, 3].
- Syndromes: patterns of multiple anomalies with pathogenic interrelation that do not represent developmental field anomalies or sequences. Some syndromes present known etiology, such as monogenic syndromes and chromosomopathies. Especially in cases of monogenic syndromes, in many cases there is an identifiable pattern of inheritance in the family; however, they may present variable expressivity and reduced penetrance. One such example is the van der Woude syndrome, which presents high penetrance and variable expressivity, exhibiting characteristic of monogenic disease caused by mutation in the *IRF6* gene [4 - 6].
- Associations: multiple anomalies occurring in higher frequency than expected by casualty, which cannot be classified as developmental field anomaly, sequence or syndrome. They have tendency to appear in combination, yet without family recurrence (only 2% of cases). The signs of associations may vary between children. If an association exhibits an identifiable inheritance pattern, it is then considered a syndrome. Some examples are: coloboma, heart disease, choanal atresia, delayed growth and development, genital alterations, ear anomalies (CHARGE association).
- Isolated defects: these affect only one body system and represent two thirds of all congenital anomalies.

Regarding the magnitude of anomalies, major anomalies are defined as alterations causing important functional impairment, such as cleft lip and palate and heart diseases. Conversely, the minor anomalies cause only esthetic disorders, such as preauricular tags. However, minor anomalies may indicate the presence of more severe disorders or even syndromes. Any child with more than three minor anomalies should be investigated in detail to rule out the possibility of syndromes [7].

There are several pathogenetic mechanisms of congenital anomalies, which include:

- Anomalies of organogenesis: affect an organ, part of an organ or a wider body region. These malformations involve an intrinsically abnormal embryonic primordium (example: cleft lip and palate), thus the term *congenital malformation* is redundant. Disruptions refer to an alteration in normal

development due to an extrinsic factor, especially during the first trimester of pregnancy; and the earlier the action of the disruptive agent, the more severe the anomaly (example: amniotic bands) (Figs. **2.1, 2.2** and **2.3**).

- Anomalies of fetal life development: mechanical forces that affect the configuration of body structures that could potentially present normal development. These affect mainly the bones, cartilages and joints, and are called deformations. Example: isolated craniosynostosis caused by abnormal position in the womb or narrow maternal pelvis.
- Anomalies of histogenesis: structural alterations with clinical evidences, caused by abnormal organization or function of a specific tissue. They may not be visible at birth, worsening and allowing diagnosis over time. Example: skeletal dysplasia.

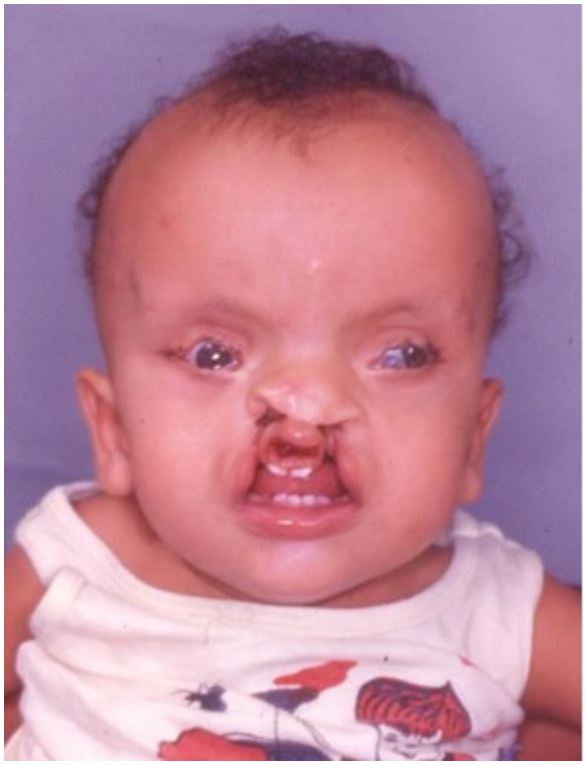

Fig. (2.1). Individual with amniotic band syndrome – facial aspect.

Fetal movement is fundamental for the adequate formation. Its restriction causes deformation (example: lack of amniotic fluid – oligohydramnios). The occurrence of polyhydramnios may also indicate the presence of fetal anomaly (the child may not be swallowing the amniotic fluid).

CHAPTER 3

Teratology and Teratogens

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Abstract: This chapter presents the mechanisms of teratogenesis and depicts the main teratogens involved in disorders of craniofacial development. This knowledge will aid the understanding on aspects presented in Chapters 4 to 9.

Keywords: Teratology, Teratogenesis, Teratogens.

The term teratogenesis (terat=monster) refers to an interference during prenatal development, causing congenital anomalies. Teratology is the investigation of contribution of external factors potentially able to alter the intricate and complex prenatal development. Teratogens are the chemical, physical, biological agents and maternal disorders that may cause these congenital defects. These agents are also investigated as to the means through which they may adversely affect the intrauterine environment of the developing fetus. These factors may act by heterogeneous pathogenic mechanisms, inducing severe alterations with loss of the embryo or fetus, may cause morphological and functional anomalies (including growth) or even neurobehavioral disorders (learning and behavior disorders) [1].

The teratogens may act in isolation or associated with a genetic predisposition, consequently causing an anomaly, and this pattern of occurrence of congenital anomalies is called multifactorial etiology. For many pathologies that present this type of pattern, the weight of contribution of predisposing genetic factors and teratogens, also called environmental factors, are not yet clearly defined. One example of malformation with this characteristic is the non-syndromic (isolated) cleft lip and palate [2].

The mechanisms of action of teratogens usually present some selectivity as to the

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target and effect. Therefore, it is expected that characteristic patterns of anomalies may be associated with specific teratogens. However, the extent to which the individual may be affected by exposure to a certain teratogen is variable. This variability results in differences in clinical phenotypes, due to differences in the dose, period of prenatal development upon exposure, differences in individual susceptibility and interactions between environmental exposures to different agents.

For this reason, it would not be adequate to restrict the consideration only to the most severe end of the spectrum, in which a promptly recognizable pattern – a syndrome – appears frequently. Thus, a terminology that includes several outcomes should be used. The term "fetal effects" describes this variation more adequately and includes the milder end of the spectrum, usually not considered as a classical "syndromic" individual.

Apparently, teratogens do not seem to be effective in causing abnormalities in the first two weeks of development. However, their action at this early and fundamental stage may lead to embryo death. In the following stage, corresponding to the embryonic period (3^{rd} to 8^{th} week), there is greater susceptibility, constituting a critical period for the occurrence of malformations if the embryo is exposed to these agents [3].

It should be highlighted that the action of a teratogen causing abnormalities, as well as the severity of these abnormalities, depends basically on four aspects: timing of exposure, dose, specific pathogenic mechanism and genotype of the embryo and mother, which are related to characteristics of individual resistance to these agents [4].

TERATOGENS

Some of the best known teratogens related with craniofacial malformations and some of their effects are listed below [5]:

- Ethyl alcohol: fetal alcohol syndrome (alterations in the central nervous system, cardiovascular disorders, growth deficiency, short palpebral fissures, short nose, hypoplastic philtrum, hypoplastic maxilla, retrognathia during childhood, microcephaly, microphthalmia, micrognathia, thin upper lip; broad nasal base [6, 7];
- Vitamin A and derivatives: microcephaly, hydrocephaly, facial paralysis, facial asymmetry, hypoplastic middle facial third, metopic synostosis, microphthalmia, oculomotor palsy, cleft lip and palate, microtia, holoprosencephaly, femoral hypoplasia, craniosynostosis, syndactyly, abnormalities in the central nervous system, external ear, thymus, cardiovascular and genitourinary disorders;

- Folic acid antagonists: prenatal growth deficiency, hydrocephaly, intellectual disability, wide cranial sutures with delayed mineralization, cranial lacunae, abnormal cranial shape, craniosynostoses, anencephaly, spina bifida, hypertelorbitism, micrognathia, cleft palate, absence or hypoplasia of digits, syndactyly, alterations in the central nervous system, ear, long bones and ribs;
- Anticoagulant (coumadin): warfarin syndrome, prenatal growth deficiency, delayed neuropsychomotor development (DNPMD), microcephaly, hydrocephaly, agenesis of the brain, occipital meningoencephalocele, agenesis of the corpus callosum, hearing impairment, hypoplastic middle facial third, nasal hypoplasia, mammary hypertelorism, anomalies of the central nervous system, midline, ocular and cardiovascular alterations;
- Hydantoin: prenatal growth deficiency, functional disorders of the central nervous system, craniofacial and limbs dimorphism, hypoplastic middle facial third, short nose, broad and low nasal bridge, epicanthal folds, mild hypertelorbitism, ptosis, strabismus, marked cupid's bow, short neck, cleft lip and palate, cardiac and genitourinary alterations;
- Oxazolidinedione: microcephaly, characteristic facial aspect with flattened middle facial third, short nose, epicanthal folds, strabismus, myopia, meningomyelocele, cleft palate, scoliosis, cardiovascular, ear and genitourinary disorders;
- Valproic acid: trigonocephaly, narrow frontal diameter, hypoplastic middle facial third, short nose with wide nasal bridge, long and wide philtrum, micrognathia, cleft lip and palate, tracheomalacia, lumbosacral meningomyelocele, ear, genital, cardiac and limb disorders;
- Mercury: microcephaly, cerebral palsy, intellectual disability;
- Anti-cancer drugs: DNPMD, cleft palate, ocular, genitourinary and limb alterations;
- Antibiotics (streptomycin, kanamycin, aminoglycosides, chloroquine): hearing impairment;
- Virus (rubella, cytomegalovirus, herpes simplex, varicella zoster): ocular and cardiovascular alterations, hearing impairment, hepatosplenomegaly, DNPMD [8, 9];
- Bacteria (Treponema pallidum): DNPMD, ocular, dental and skeletal alterations;
- Diabetes mellitus: facial clefts, holoprosencephaly, cardiovascular, renal and neural tube alterations;
- Phenylketonuria: DNPMD, microcephaly, cardiac and vertebral defects, fetal death.

CONFLICT OF INTEREST

The author (editor) declares no conflict of interest, financial or otherwise.

CHAPTER 4

Dental Management in Rare Facial Clefts

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Abstract: The rare facial clefts receive this name due to their low prevalence. The most known and used classification was proposed by Tessier and employs a distinct numbering to indicate clefts affecting the soft and hard tissues, taking as reference point the eyelid and the orbit. The oral characteristics of individuals with rare facial clefts are not specific, and in most cases the oral phenotype follows the structures affected by the defect. Due to the complexity of the cleft and the number of affected structures, the surgical and dental rehabilitation is complex and extensive, requiring the participation of a multi- and interdisciplinary team.

Keywords: Dental care, Orofacial cleft, Phenotype, Tooth abnormalities.

INTRODUCTION

The rare craniofacial clefts present low prevalence and wide spectrum of malformation, affecting both the skull and face in a large variety of manifestations [1]. This diversity of manifestations impairs a universal classification. In an attempt to standardize a terminology for these clefts, Paul Tessier, in 1976, published a clear and simple classification, which has been widely used by the scientific community since then [2].

This classification was initially presented at the International Meeting of Cleft Palate Association, Copenhagen, in August 1973 [1, 2], and is still accepted and used for description of craniofacial and laterofacial clefts because it represents an anatomic system ordered along defined axes, assigning numbers to the several cleft sites, depending on their relationship with the midsagittal plane, in 15

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locations numbered from 0 to 14, besides including number 30 for the medial mandibular cleft (Fig. **4.1**) [1 - 4].

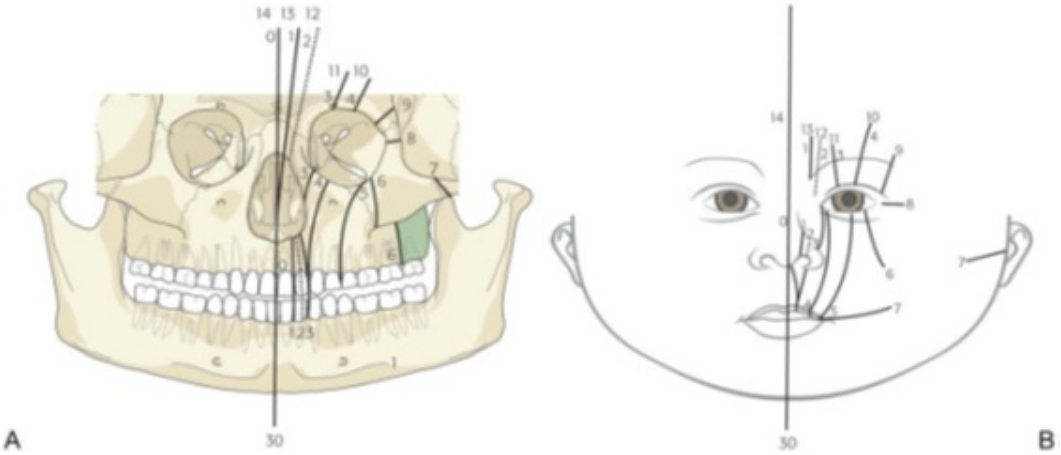

Fig. (4.1). Tessier classification of craniofacial clefts. Source: Ramanathan *et al.,* 2012 [4].

The clefts may affect soft and hard tissues to different extents and in an independent manner. They may occur unilaterally or bilaterally, yet the unilateral clefts are more frequent [1, 2]. The soft tissue anomalies are predominant from the midsagittal plane to the infraorbital foramen, and more severe bone defects are more common from the infraorbital foramen to the temporal bone, except for the ear [3]. It should be highlighted that the vessels and nerves remain unaltered in the soft tissue, even if the bone is absent or hypoplastic due to the clefts [1].

The Tessier classification describes the clefts based on the anatomy of the affected region and considers the eyelids and orbits as reference point, dividing the orbits into two hemispheres for a better understanding. The lower eyelids, together with the cheeks and lip, constitute the southern hemisphere, whose clefts are facial and numbered from 0 to 7. Contralaterally, the upper eyelids constitute the northern hemisphere and clefts at this site are cranial and numbered from 8 to 14. However, the growth centers are not necessarily the same, demanding additional care to define the treatment plan and duration of surgery for cases presenting both cranial and facial clefts. The lines numbering the clefts may have upper (cranial) or lower orientation (facial). The cranial lines have facial correspondents, yet these numbers are different to avoid the erroneous assumption that they necessarily have the same etiopathogenesis [2].

Below, each of these rare craniofacial clefts will be described in detail.

CLEFT #0-14

According to Tessier [2], clefts #0 and 14 represent a median craniofacial dysraphia due to absence of closure of the anterior neuropore. The cleft crosses the frontal bone, giving rise to a "bifid cranium" or a median encephalocele with duplication of the crista galli through the midline, with duplication of the nasal septum, and through the columella, maxilla and lip. The cranial cleft may cause varied degrees of hyperteleorbitism. The occurrence of other milder phenotypic manifestations is possible [5].

CLEFT #1-13

Craniofacial cleft #1 is considered a paramedian cleft; in the soft tissues, the cleft crosses the dome of the alar cartilage (Fig. **4.2**) and occasionally the alveolus and lip, yielding a cleft of the lip and primary palate on the face. It may affect the alar cartilage from a small paramedian notch up to a cleft with structural loss of the nostril. Its cranial correspondent #13 crosses the frontal bone through the olfactory groove of the cribriform plate between the nasal bone and frontal maxillary process, causing hyperteleorbitism and possibly encephalocele [2]. In the soft tissue, the cleft is seen between the eyebrows.

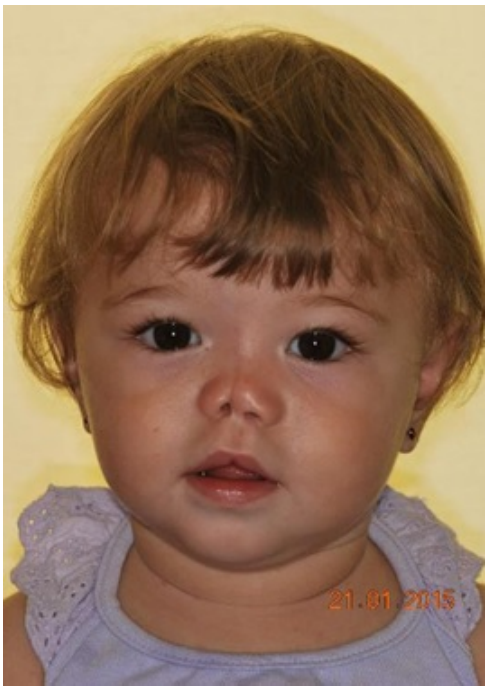

Fig. (4.2). Individual with Tessier cleft #1. To understand the embryogenesis of this cleft, please refer to Figs. (**1.17** and **1.20b**).

CHAPTER 5

Syndromes with Orofacial Clefts

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Abstract: Orofacial clefts are among the commonest malformations affecting mankind; even though most cases of orofacial clefts are non-syndromic, they may also manifest concomitantly with a wide array of syndromes. These syndromes with orofacial clefts often also cause diverse tooth abnormalities; knowledge on these peculiarities is fundamental for professionals to allow proper dental care for affected individuals.

Keywords: Dental care, Ectrodactyly, Ectodermal dysplasia, and cleft-lip-palate syndrome, Holoprosencephaly, Orofacial cleft, Orofaciodigital syndromes, Rapp-Hodgkin syndrome, Pierre Robin syndrome, Richieri Costa Pereira syndrome, Tooth abnormalities, Van der Woude syndrome, 22q11 deletion syndrome.

HOLOPROSENCEPHALY

Holoprosencephaly (HPE) is a structural brain anomaly occurring during the third and fourth weeks of pregnancy, caused by incomplete cleavage of the forebrain into right and left hemispheres [1, 2], thus the name *holoprosencephaly* (Greek: *holos* – whole; *prosencephalon* – forebrain). It is the most common defect of the forebrain and middle face in humans [3], affecting 1 in every 16,000 livebirths and approximately 1 in every 200 spontaneous miscarriages [4]. It may be associated with genetic syndromes, especially the Smith-Lemli-Opitz syndrome. In relatively rare cases, subgroups of individuals may present additional structural brain malformations, such as schizencephaly of extracerebral manifestations as ectrodactyly (refer to the EEC syndrome later in this chapter for a clinical image of this malformation), radial limb defects, agnathia or craniosynostosis [4].

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HPE may be associated with a myriad of craniofacial anomalies, including cyclopia, microcephaly, hypoteleorbitism, depressed nasal bridge, single maxillary incisor, and cleft lip with or without cleft palate (CLP). Some affected individuals also present pituitary dysfunction and feeding disorders [1].

The etiology of both syndromic and non-syndromic HPE is heterogeneous. It is related with genes 21q22.3 and 2q37.1-q37.3 [2]. Chromosomal abnormalities are present in up to 50% of individuals with HPE and may include trisomy 13, trisomy 18, and several other variations in the number of copies [1]. The disorder presents autosomal recessive inheritance, yet autosomal dominant inheritance has been observed in some cases, whose widely variable phenotype is related with a locus on distal 7q.

Among the environmental aspects, gestational diabetes is highlighted, with a prevalence of 1-2% among children of diabetic mothers, which is considered a significant finding [5]. The utilization of folic acid in pregnancy seems to have a protective effect [6]. There are contradictory and inconsistent reports concerning possible associations between HPE and respiratory diseases, anemia, smoking and utilization of salicylates, antiepileptic drugs, sexual hormones, statins and alcohol [7].

The phenotype of HPE is variable between simple cases and between members of a same family with hereditary manifestation of HPE; consequently, subtle facial characteristics may be neglected in members of affected families. If any child is diagnosed with HPE, the first-degree relatives should be questioned and examined to identify individuals with microcephaly, hypoteleorbitism, or single maxillary incisor.

Since some cases of HPE present autosomal dominant inheritance, the identification of other family members that may be affected influences the indication of genetic tests and identification of risk factors [1].

The typical facies of holoprosencephaly (Fig. **5.1**) is observed in approximately 80% of cases. It is characterized by cyclopia or more commonly by hypoteleorbitism, associated with agenesis of nasal bones, median cleft lip with or without cleft palate (Fig. **5.2**) and severe neurological disorders, with short life expectancy. Thus, the treatment of holoprosencephaly should comprise a careful risk-benefit analysis [8].

Some authors have reported correlation between holoprosencephaly and the presence of a single median maxillary central incisor (Figs. **5.3** and **5.4**) [9 - 11], which may affect both the deciduous and permanent dentitions [2], whose inheritance is related with chromosomal region 7q36 [12]. Thus, the presence of a

single median maxillary central incisor in an adult may constitute a risk factor to holoprosencephaly in the offspring, warranting genetic counseling for family planning.

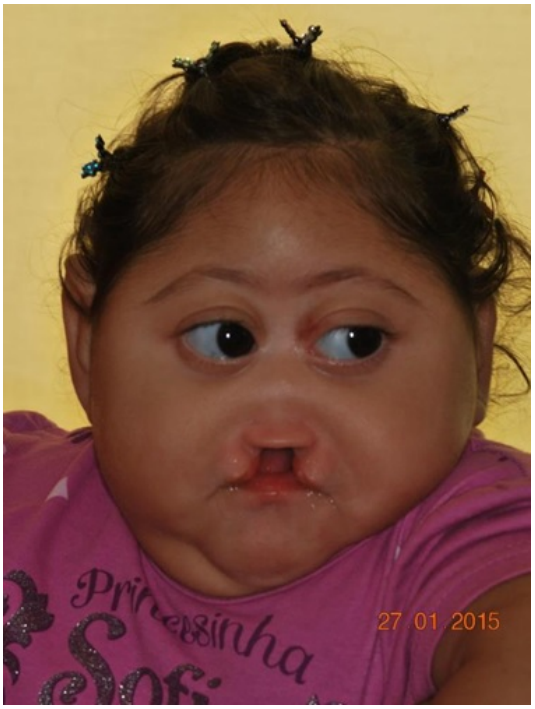

Fig. (5.1). Individual with holoprosencephaly. Notice the hypoteleorbitism and depressed nasal bridge.

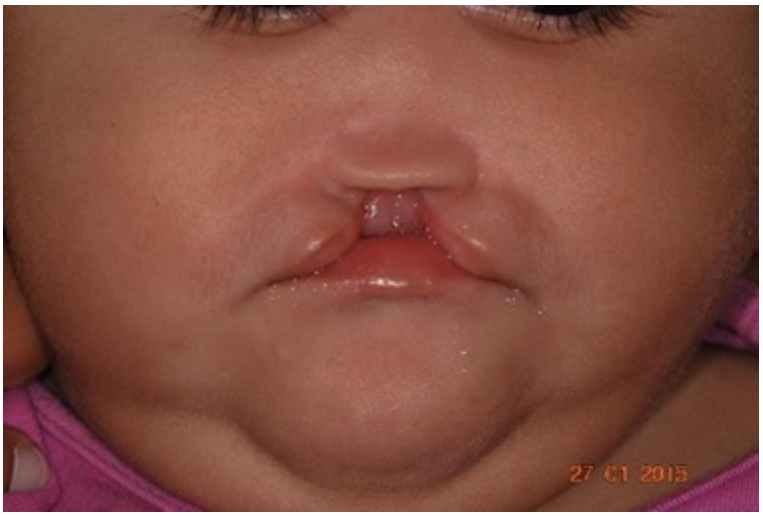

Fig. (5.2). Closer view of individual in Fig. (**5.1**), evidencing the median cleft lip.

CHAPTER 6

Craniosynostosis Syndromes

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Abstract: Craniosynostosis is the premature fusion of cranial sutures. This chapter addresses the craniosynostosis syndromes, which involve this premature fusion of cranial sutures associated with important disorders to the craniofacial complex and teeth, requiring emphasis on prevention, special care during dental treatment, and a multidisciplinary team approach for their full rehabilitation from early infancy through adulthood.

Keywords: Acrocephalosyndactylia, Acrocephalosyndactyly type II, Craniosynostoses, Craniofacial dysostosis, Dental care, Jackson-Weiss syndrome, Kaplan Plauchu Fitch syndrome, Multiple congenital anomalies syndrome with cloverleaf skull, Pfeiffer type acrocephalosyndactyly, Saethre-Chotzen syndrome with eyelid anomalies, Shprintzen Goldberg craniosynostosis, Tooth abnormalities.

Craniosynostosis, or craniostenosis, is a congenital disorder that causes premature closure of cranial sutures [1, 2], caused by mutations in genes CDC45, TWIST1, TCF12, and others, with an important role in cell division. In normal conditions, at birth, the child presents separated cranial bones, yet firmly connected to each other by fibrous structures called sutures. On the margins of these sutures there is intense metabolic activity with bone formation, which is involved with cranial growth. The cranial growth is directly proportional to brain growth and is very marked in the first two years of life. The premature closure of one or several cranial sutures reduces its bone synthesis activity, causing craniofacial deformities.

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In single suture craniosynostosis the cranial deformities are predictable, and the affected suture may be inferred from the cranial shape. Some descriptive denominations of cranial shape are related to the involvement of certain cranial sutures, as follows: scaphocephaly, for sagittal suture craniosynostosis (between the parietal bones), trigonocephaly for the metopic suture (between the fetal frontal bones), anterior plagiocephaly for the coronal suture (between frontal and parietal bones) unilaterally, brachycephaly for the coronal suture bilaterally, and posterior plagiocephaly for the lambdoid suture (between occipital and parietal bones) unilaterally [2, 3].

The craniosynostoses may be classified, according to the number of affected sutures, as simple or multiple; according to the etiology, as primary or of unknown cause, and secondary or of known cause; and according to the association with other malformations, as non-syndromic and syndromic. These classifications are not mutually excluding. The most frequent craniosynostoses are simple, primary and non-syndromic. The syndromes more frequently associated with craniosynostoses are the Apert and Crouzon syndromes, which are usually hereditary. With rare exceptions, the diagnosis of craniosynostoses is established at birth. Besides cranial deformities, the craniosynostoses may cause neurological problems due to the restrictive effect on brain growth if not treated timely, especially in multiple and syndromic craniosynostoses. The diagnosis of craniosynostoses may be suspected by analysis of the cranial shape and confirmed by radiography, computed tomography and magnetic resonance imaging.

The treatment of craniosynostoses is fundamentally surgical. Its correction aims at esthetic improvement and prevention of occasional neurological disorders. Usually, craniosynostoses should be corrected before 6 months of age [4].

APERT SYNDROME

The first description of Apert syndrome, or acrocephalosyndactyly, is assigned to Apert [5], yet it had been previously described by Wheaton in 1894 [6]. It is an autosomal dominant disorder assigned to mutations in the FGFR 2 gene in chromosome 10q26. The estimated prevalence ranges from 1 in 65,000 to 160,000 births to 1 in each 2 millions in the general population due to the high neonatal mortality, especially when craniosynostosis is not treated timely [6 - 8]. It may be diagnosed prenatally by ultrasound examination.

It is characterized by craniosynostosis of the coronal sutures. The face is typical with broad and high forehead, hyperteleorbitism, shallow orbits, proptosis and downslanting palpebral fissures (Fig. **6.1**). The nasal bridge is depressed and there may be choanal stenosis or atresia. The palate is narrow, with possibility of cleft palate and bifid uvula [9, 10]; however, the presence of marked hyperplasia of the

palatal mucosa may lead to a mistaken diagnosis of cleft palate (Fig. **6.2**). Individuals with this syndrome may present cardiovascular alterations; genitourinary disorders with hydronephrosis, cryptorchidism and vaginal atresia; and abdominal disturbances including esophageal atresia and ectopic anus. It is differentiated from other multiple craniosynostosis syndromes by the presence of symmetric severe syndactyly on the hands and feet, involving soft or hard and soft tissues, usually affecting the second, third and fourth digits with a single nail (Figs. **6.3** and **6.4**) [9]. There seems to be alterations in the anterior cranial base cartilage at onset of intrauterine life, with compensatory alterations in cranial development at the onset of postnatal life [6 - 8].

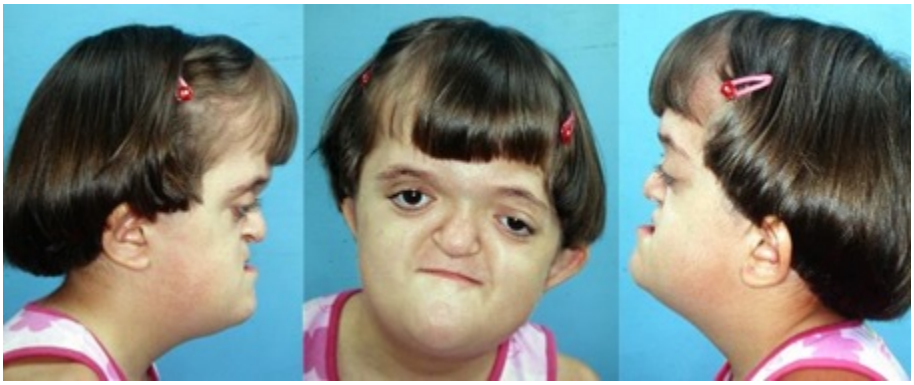

Fig. (6.1). Characteristic facial aspect in Apert syndrome. Notice the high and broad forehead, depressed nasal bridge, proptosis, and Class III facial pattern.

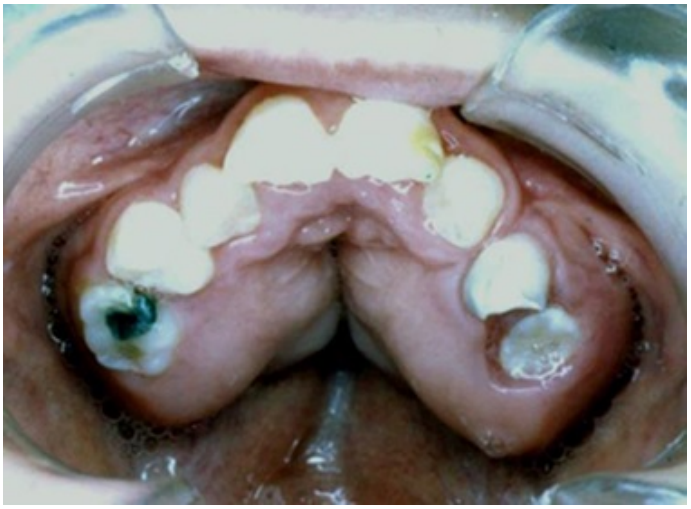

Fig. (6.2). Characteristic marked hyperplasia of the palatal mucosa in the same individual with Apert syndrome shown in Fig. (**6.1**).

CHAPTER 7

Pharyngeal Arch Disorders

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Abstract: The pharyngeal arches develop in the human embryo around five weeks of pregnancy. Disorders in the development of the first and second pharyngeal arches may lead to significant malformations of the face and ears. Syndromes involving the pharyngeal arches often involve tooth abnormalities, requiring regular dental follow-up with specialized management by a multidisciplinary team.

Keywords: Acrofacial dysostosis, Dental care, Goldenhar syndrome, Mandibulofacial dysostosis, Nager type, Tooth abnormalities.

The pharyngeal arches appear in mankind between the 4th to 5th week of intrauterine life, consisting of a series of structures that participate in head and neck development. These structures form laterally to the pharyngeal gut and comprise a center of mesenchymal tissue, which involves muscular, nervous and vascular components, covered by ectoderm and internally by endoderm.[2] When some of these structures are altered, especially the 1st and 2nd pharyngeal arches, which are involved in formation of the face and ears, there may be interference with their constitution resulting in anomalies and malformations in these regions.

TREACHER COLLINS SYNDROME

The Treacher Collins syndrome is one of the disorders affecting the 1st and 2nd pharyngeal arches, also called mandibulofacial dysostosis or Franceschetti syndrome. It is an autosomal dominant disorder of craniofacial development related to chromosomal region 5q32-q33.1 [1 - 4].

The prevalence of the syndrome is 1/50,000 livebirths and it is estimated that 40% of cases present familial history, with the remaining 60% being considered new mutations [4]. It presents clinical and genetic heterogeneity.

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The facial aspect is peculiar (Figs. **7.1** and **7.3**) and may be detected prenatally by ultrasound, which allows observation of the face and also of the ear malformation (Figs. **7.2** and **7.4**) of variable aspect, with possible conductive hearing loss. There may be oblique palpebral clefts, upper eyelid coloboma, partial absence of lower eyelashes, and hypoplasia of the mandible and zygomatic complex. Involvement of the zygomatic region may be understood as a combination of Tessier clefts # 6, 7 and 8 [4 - 6]. The alterations are usually bilateral and symmetrical.

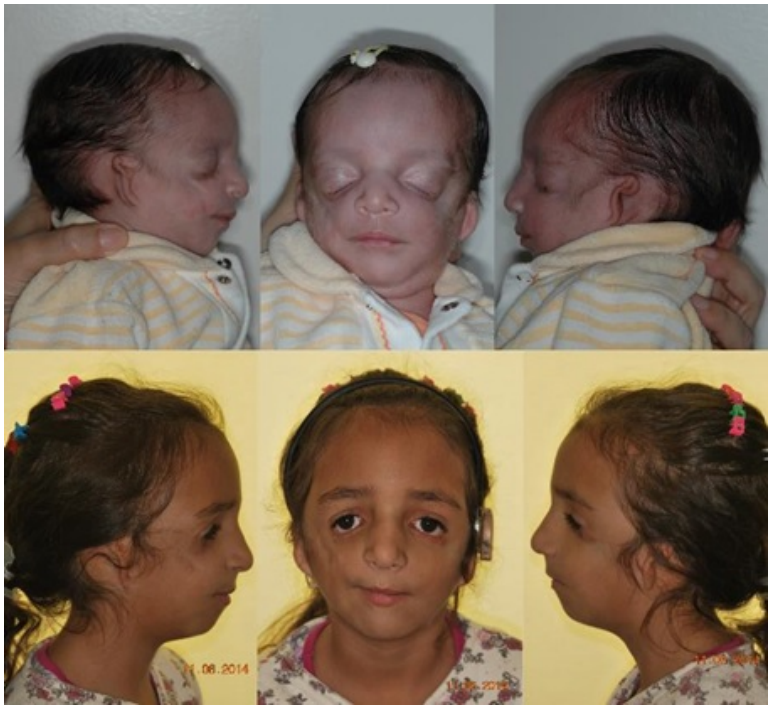

Fig. (7.1). Frontal and lateral facial aspects of individual with Treacher Collins syndrome, at two different ages. Notice maintenance of the syndromic features over time.

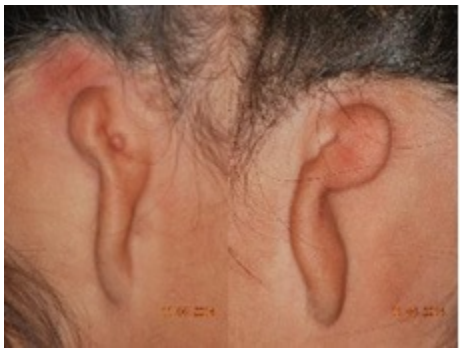

Fig. (7.2). Ear malformation in the same individual presented in Fig. (**7.1**).

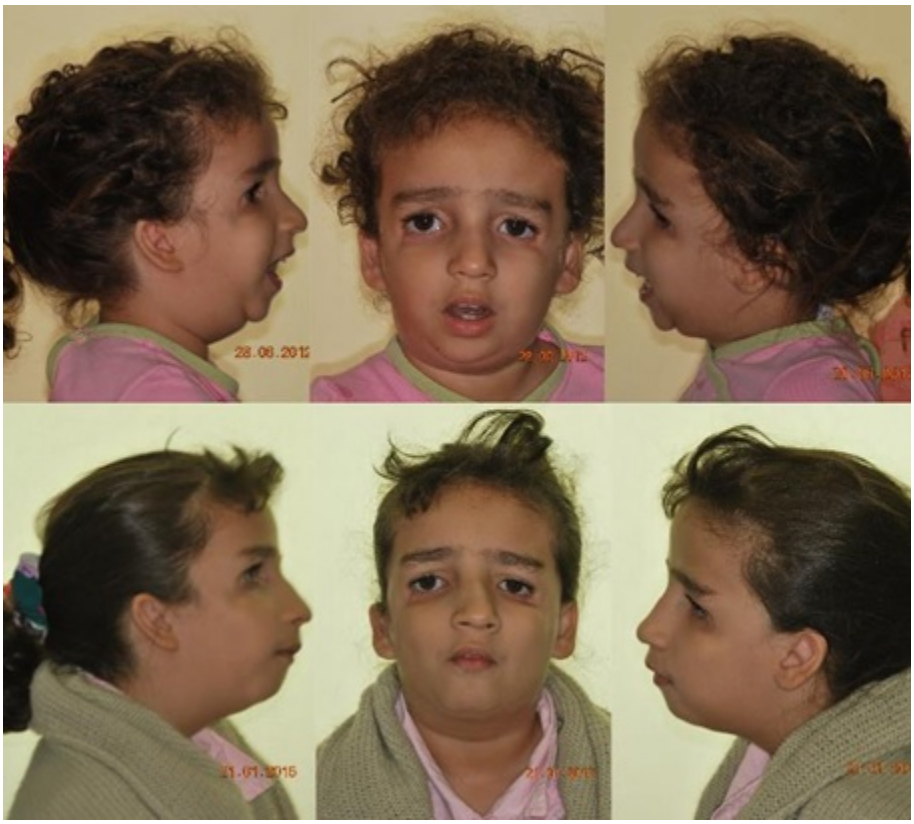

Fig. (7.3). Frontal and lateral facial aspects of individual with Treacher Collins syndrome, at two different ages. Notice maintenance of the syndromic features over time.

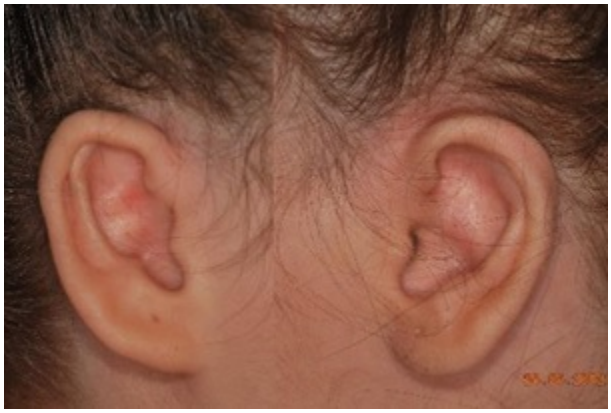

Fig. (7.4). Ear malformation in the same individual presented in Fig. (**7.3**).

With regard to the orodental aspects, there may be hypodontia, macrostomia and cleft palate or cleft lip and palate [4 - 6]. There may be anterior open bite,

CHAPTER 8

Syndromes with Characteristic Facies

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Abstract: A wide array of syndromes reported in the literature have significant impact on the craniofacial complex, with great influence on the facial aspect, which is usually typical of each syndrome. For this reason, this chapter refers to these disorders as "syndromes with unusual facies", as described in the classical book of Gorlin *et al.,*. Affecting the craniofacial complex, these syndromes also often have significant implications for dental treatment and affected individuals may have peculiar dental needs.

Keywords: Autosomal dominant, Autosomal recessive, Craniofrontonasal dysplasia, De Lange syndrome, Dental care, Frontonasal dysplasia, Fronto-faci--nasal dysplasia, Kabuki syndrome, Mobius syndrome, Opitz GBBB syndrome, Robinow syndrome, Tooth abnormalities, X-linked.

FRONTONASAL DYSPLASIA

Frontonasal dysplasia is a craniofacial midline defect, involving combinations of the following characteristics: hyperteleorbitism; broad nasal base; unilateral or bilateral alar cleft; absent nasal tip; and widow's peak [1, 2] (Figs. **8.1** and **8.2**). The associated defects may include median cleft of the nose and/or upper lip (Fig. **8.3**) and rarely of the palate. The individuals may present low-set ears, ear tags, absent tragus and conductive hearing loss. In addition to hyperteleorbitism, there may be lateral displacement of the internal canthi with secondary telecanthus, microphthalmia, epicanthal folds, ptosis, coloboma and cataract. The nose may be bifid to variable extents (Fig. **8.3**).

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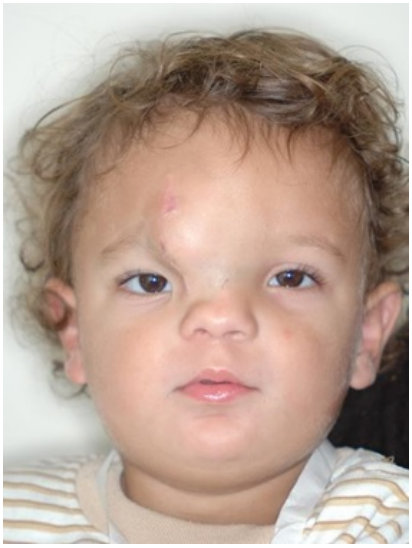

Fig. (8.1). Individual with frontonasal dysplasia exhibiting hyperteleorbitism, broad nasal base and encephalocele.

There may also be tetralogy of Fallot, frontal cutaneous lipoma, hypoplasia or aplasia of the pectoralis muscle, maxillary hypoplasia and hypoplastic frontal sinuses.

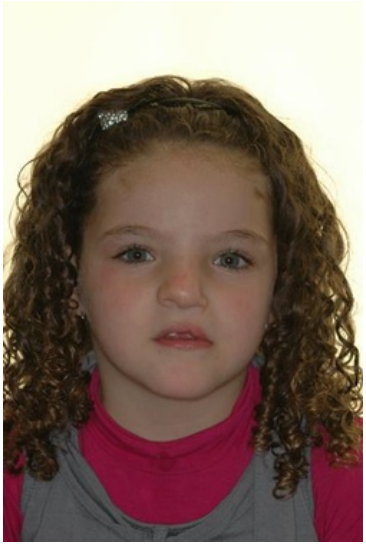

Fig. (8.2). Individual with frontonasal dysplasia exhibiting hyperteleorbitism. Notice the mild phenotype as compared to the individual presented in Fig. (**8.1**).

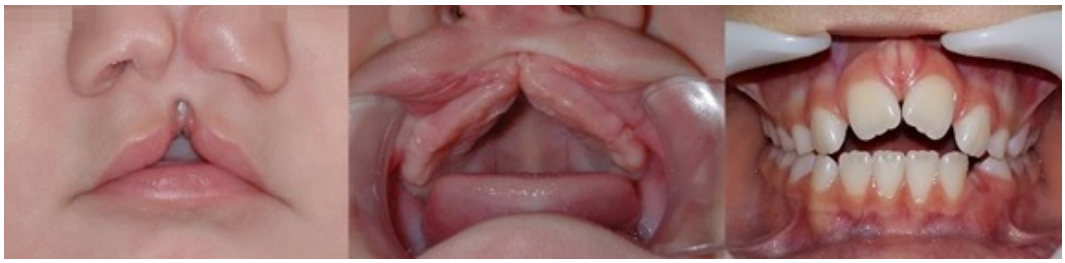

Fig. (8.3). Bifid nose and midline alveolar cleft in individual with frontonasal dysplasia. On the right side, notice the V-shaped anterior open bite at a later age.

There may be occult anterior bifid cranium with possibility of intellectual disability, lipoma or agenesis of the corpus callosum and basal anterior encephalocele (Fig. **8.1**). The intellectual development may vary from normal to severe intellectual disability, yet most individuals present normal intelligence. Intellectual disability seems to be related with extra-encephalic disorders or severe hyperteleorbitism [3].

Even though the etiology of frontonasal dysplasia is unknown, there are reports of association with teratogenic drugs, autosomal dominant inheritance, multifactorial transmission and polygenic inheritance. Studies in animal models suggested that genetic inhibitors were associated with the syndrome, and genes participating in human embryogenesis might be affected in the craniofacial midline syndrome.

It is necessary to analyze the individual with frontonasal dysplasia from a behavioral standpoint; as previously mentioned, the intelligence may be normal or abnormal. Preparation of the individual to achieve compliance with dental treatment is important and necessary. However, most individuals present normal behavior, allowing conventional dental treatment. Little information is available in the literature about the oral characteristics specific of individuals with frontonasal dysplasia. Similar to the wide diversity of craniofacial phenotypes in this syndrome, the same is observed for orodental findings (Fig. **8.4**); apparently, the dental disorders seem to be related with clefts accompanying the syndrome, causing enamel hypoplasia, double teeth, ectopic eruption of permanent first molars, hypodontia of premolars and lateral incisors [1]. Anterior open bite and interincisal diastema are observed in case of anterior clefts.

Orthodontic and orthognathic treatment are performed as necessary based on the treatment planning, according to the clinical and radiographic diagnosis. These procedures may be complex when the alveolar median cleft is wide, evidencing the importance of proper diagnosis and treatment planning.

CHAPTER 9

Surgical Treatment in Craniofacial Malformations: Distraction Osteogenesis

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Abstract: Distraction Osteogenesis (DO), a procedure used for correction of large hypoplasia of facial segments, is a surgical technique that induces new bone formation by gradual separation of two bone surfaces osteotomized by a mechanical device called distractor; the principles of this surgery were initially designed by the Russian orthopedist Gavriil Ilizarov in 1951. Different pathological conditions, mostly syndromic, may present craniofacial deformities that may not be functionally and esthetically corrected by conventional treatment methods. Some examples include the mandibular hypoplasias (Pierre Robin sequence, Oculoauriculovertebral spectrum (OAVS), Treacher Collins syndrome, temporomandibular joint ankylosis, hypoplasia of the midface (common finding in individuals with syndromic craniosynostosis, such as the Apert, Crouzon, Pfeiffer, Muenke and Saethre-Chotzen syndromes). Even though DO is the method of excellence for the treatment of large hypoplasias, it should only be used when a large dentofacial deformity cannot be corrected by conventional orthognathic surgery, which may be used to refine the results achieved by DO in a second auxiliary stage.

Keywords: Congenital anomalies, Distraction osteogenesis, Orthodontics.

Distraction osteogenesis is characterized as a dynamic process, which comprises elongation of the facial skeleton and adjacent soft tissues, obtained by gradual

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traction applied on two osteotomized bone surfaces by a mechanical device called distractor (Fig. **9.1**).

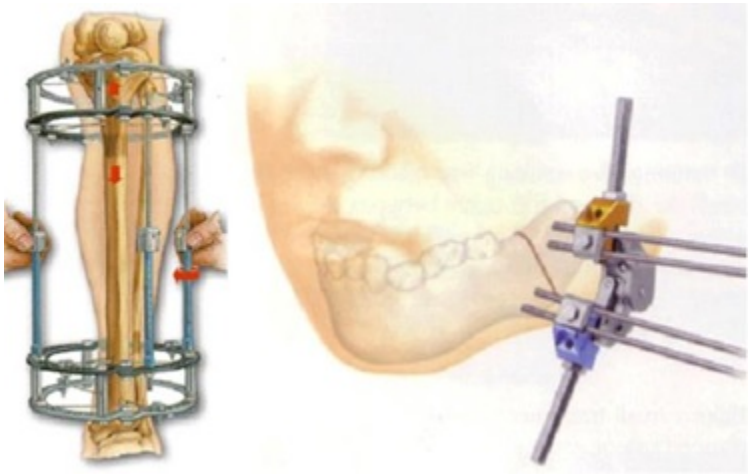

Fig. (9.1). Distractors for mandible and long bone of the leg. Similar principles applied for bone elongation. Source: modified from Hong PA. Clinical narrative review of mandibular distraction osteogenesis in neonates with Pierre Robin sequence. Int J Pediatr Otorhinolaryngol 2011;75(8):985-91.

A sequence of adaptive changes, as observed in the bone tissue, also occurs in the soft tissues. The gradual elongation of these structures minimizes the potential of relapse posed by the resistance of soft tissues in large bone displacements [1 - 4].

DISTRACTION OSTEOGENESIS IN CRANIOFACIAL MALFORMATIONS

1. Principles and Stages

In 1951 the Russian orthopedist Gavriil Ilizarov initiated a series of experimental and clinical studies, establishing the principles of the bone elongation method [1, 3].

Its important contribution was related to the understanding of biological events involved in the process of bone elongation. Distraction osteogenesis, named as such by Ilizarov, is based on the fact that gradual and sustained traction, applied on a living tissue, creates a tension that stimulates tissue regeneration and growth by activating the cellular proliferative and biosynthetic functions.

The success achieved in correcting several types of skeletal deformities by elongation of endochondral bones led to wide acceptance of this method, so as these principles were then also applied on the craniofacial segment.

The first applications of distraction in humans were conducted by McCarthy [5] in 1992, who described the elongation of hypoplastic mandibles, and Cohen *et al.,* [6], who described the first report of utilization of DO to correct deformities of the midface in 1995.

From a didactic standpoint, distraction osteogenesis may be divided in four stages:

- Formation of blood clot;
- Formation of fibrous callus (elongation occurs on the fibrous callus);
- Bone calcification;
- Remodeled newly formed bone.

2. Clinical Indications

Different pathological conditions, mostly syndromic, are accompanied by craniofacial deformities that may not be esthetically and functionally corrected by conventional treatment methods. Therefore, its clinical application is essentially based on correction of large hypoplasias of the facial segments, especially mandibular hypoplasia and hypoplasias of the midface [7].

2.1. Mandibular Hypoplasias

Mandibular growth disorders occur in three main situations:

a. Pierre Robin sequence
b. Oculoauriculovertebral spectrum (OAVS)
c. Treacher Collins syndrome

These disorders may affect the mandible unilaterally or bilaterally. The involvement of other anatomical structures as the maxilla, zygoma, muscles of mastication and adjacent soft tissues further complicates the treatment of these individuals.

The common embryonic origin of the mandible and adjacent structures as the ear, for example, explain the findings of unilateral mandibular hypoplasia associated with ipsilateral microtia (ear malformation), as in the case of oculoauricul-overtebral spectrum (Fig. **9.2**).

The Pruzansky classification is the most used system for classification of mandibular hypoplasia, scoring four different types of involvement (Fig. **9.3**):

- Type I or Pruzansky I: mandible with normal anatomy, yet with reduced size;
- Type II or Pruzansky II: hypoplastic mandible associated with malformation of

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