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REVIEW ARTICLE

Craniofacial malformations and their association with brain development: the importance of a multidisciplinary approach for treatment

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Abstract
The craniofacial complex develops mainly in the first trimester of pregnancy, but its final shaping and the development of the teeth extend into the second and third trimesters. It is intimately connected with the development of the brain because of the crucial role the cranial neural crest cells play and the fact that many signals which control craniofacial development originate in the brain and vice versa. As a result, malformations of one organ may affect the development of the other. Similarly, there are developmental connections between the craniofacial complex and the teeth. Craniofacial anomalies are either isolated, resulting from abnormal development of the first two embryonic pharyngeal arches, or part of multiple malformation syndromes affecting many other organs. They may stem from gene mutations, chromosomal aberrations or from environmental causes induced by teratogens. The craniofacial morphologic changes are generally cosmetic, but they often interfere with important functions such as chewing, swallowing and respiration. In addition, they may cause hearing or visual impairment. In this review we discussed only a small number of craniofacial malformations and barely touched upon related anomalies of dentition. Following a brief description of the craniofacial development, we discussed oral clefts, craniofacial microsomia, teratogens that may interfere with craniofacial development resulting in different malformations, the genetically determined craniosynostoses syndromes and few other relatively common syndromes that, in addition to the craniofacial complex, also affect other organs. The understanding of these malformations is important in dentistry as dentists play an integral role in their diagnosis and multidisciplinary treatment.

Keywords Craniofacial development and malformations · Microsomia · Oral clefts · Craniosynostosis · Multidisciplinary diagnosis and treatment

Introduction

The development of the craniofacial complex is a typical example of the intimate interaction that generally occurs between the nervous system and the developing organ in the embryo and fetus. The cranial neural crest cells, derived from the rostral part of the brain, are the most important contributors of tissue to the craniofacial complex and its sense organs (i.e., eyes, ears, nose, tongue). This close interaction between different parts of the brain and the face is a result of complex cellular and tissue interactions (i.e., epithelium–mesenchyme interactions) as well as the effects of regulatory genes that originate from both organs—the brain and the face. Since the craniofacial complex serves many functions, such as chewing and swallowing (nutrition), respiration and protection for the brain and sense organs, its active development is most complex and of relatively short duration.

There are many malformations of the craniofacial complex and it is impossible to cover them all in this review. Hence, we chose to discuss briefly only the more common malformations with only partial description of the pertinent literature. In addition, the development of the teeth and dental anomalies are discussed only briefly, although they are sometimes part of the craniofacial anomalies presented here.

Many craniofacial anomalies have very complex etiology and the exact diagnosis is often difficult. Hence, imaging

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techniques are often inadequate for the proper diagnosis of these anomalies, and genetic tools, including the most advanced methods in molecular biology, should be used. Different medical disciplines must be available for consultation such as clinical genetics, pediatric neurology and neurosurgery, plastic and/or orofacial surgery, pathology and proper imaging facilities. It is therefore advisable that the diagnosis and treatment of craniofacial malformations are performed in hospitals where all these facilities are available.

Development of the craniofacial complex

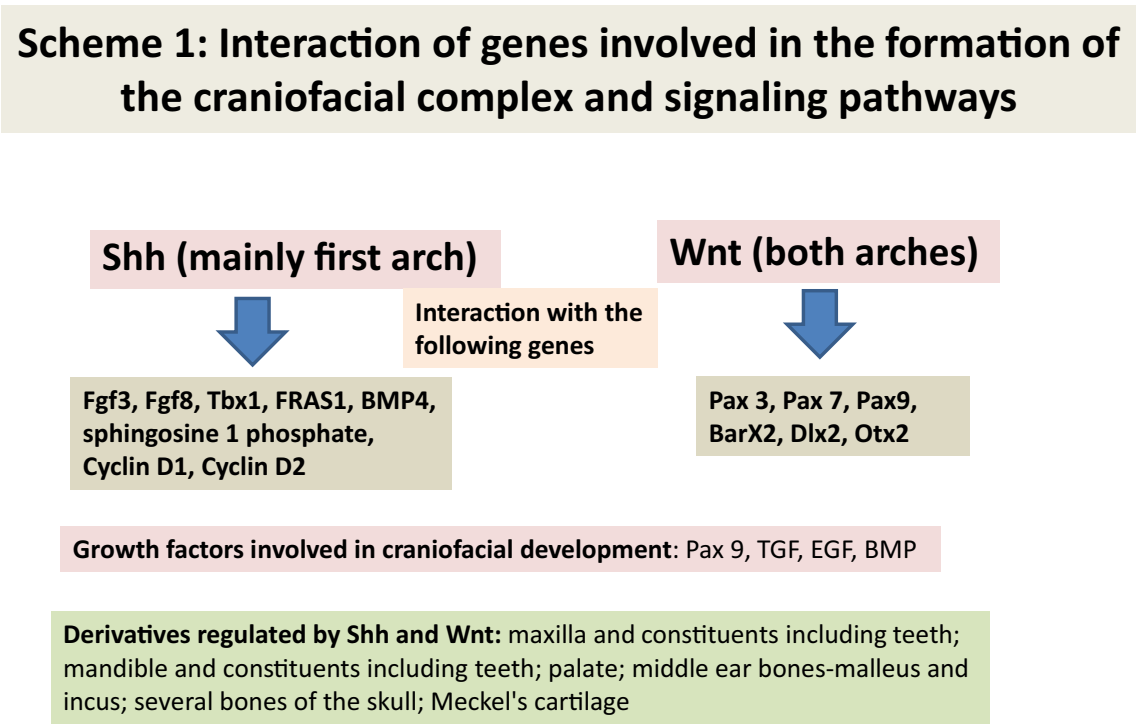
General developmental processes

The craniofacial complex is composed of two main parts. The dorsal—rostral neurocranium that encapsulates the brain; and the ventral—caudal viscerocranium which is basically involved in nutrition and respiration and supports the mouth, pharynx and upper larynx [1, 2]. Two tissues contribute to most of the craniofacial complex—the ectomesenchyme, the mesenchyme that originates from the ectoderm, and the neural crest cells which originate from the neural tube. Cephalic neural crest cells populate both the neurocranium and viscerocranium, while the ectomesenchymal tissue is found only in the neurocranium. The first and second pharyngeal arches and their constituents form most of the viscerocranium [3, 4]. Pharyngeal arch ectoderm and endoderm are involved in the formation of the oral and pharyngeal cavities. Some of the neural crest cells between the cephalic and trunk neural crest (vagal neural crest cells) contribute to the circumpharyngeal region [4]. The two most important signaling regulators in these developmental processes are Sonic hedgehog (Shh) and Wnt [1, 2, 5, 6].

Evolutionarily, the first craniofacial complex in vertebrates (as seen today in some primitive fish) was jawless. Then a jaw—the complex serving both for feeding and respiratory purposes—developed [7]. The development of the craniofacial complex involves complex ectodermal–mesenchymal interactions with various signaling pathways from the anterior visceral endoderm, anterior neural ridge and head mesoderm and the cranial neural crest cells [7]. The interaction of cranial neural crest cells with the other cells in the face is largely dominated by 2 groups of regulatory molecules: growth factors (i.e., FGF, TGFs, EGF) and retinoic acid superfamily [8]. Hence, abnormalities of these regulatory systems might result in craniofacial malformations.

Genes that control craniofacial development (Scheme 1)

Much of the knowledge on the craniofacial development has come from experiments in chicks, using chick



Scheme 1 Interaction of genes involved in the formation of the craniofacial complex and signaling pathways

quail chimera [1, 2]. The high degree of conservation between chicken facial ontogeny and other model organisms including mammals enables us to translate the basic principles from chicks to mammals [2]. These studies were especially helpful in the understanding of the role of neural crest cells in the formation of the craniofacial complex.

The main molecule involved in the interaction between brain and facial development is Sonic hedgehog (Shh). The earliest *Shh* signals come from the prechordal plate, which then "turns on" the expression of *Shh* in the ventral diencephalon between 6 and 8 somite stages, which is the stage of neural crest cells formation [2, 5]. Interference in the expression of Shh will induce facial malformations, such as cleft lip and palate [2]. High levels of retinoic acid may inhibit Shh and will therefore lead to various craniofacial malformations [5]. The role Shh plays in the regulation of craniofacial development is schematized in Scheme 1.

As stated, the cranial neural crest cells form most of the facial skeleton, shaping the face. The rostral neural crest cells that originate from the area of the diencephalon are Hox negative, i.e., no Hox genes are expressed, while the more caudal neural crest cells are Hox positive and are responsible for the formation of the hyoid bone [1]. Defects in the Hox-negative neural crest cells may lead to severe malformations of the brain, demonstrating the close interrelationship in the development of the brain and the craniofacial complex.

Marcucio et al. [9, 10] claim that the brain is the structural platform which influences the position and shape of the face; the neural crest cells originate from the dorsal part of the forebrain and signals from these cells control the growth of the anterior forebrain.

A variety of nervous system developmental genes are also involved in the formation of the craniofacial complex. Examples are Wnt genes (Wnt1, Wnt8b), Shh, Dlx2 and Otx2 ext [1]. The role of Wnt signaling is of special importance as it also plays a crucial role in palate development (Scheme 1), and mutations in Wnt genes are associated with a significant number of craniofacial abnormalities including oral clefts [6]. On the other hand, the non-Shh cephalic neural crest cells are also involved in the formation of the prosencephalon and mesencephalon (forebrain and midbrain). In humans, there are plenty of clinical evidences which demonstrate the close developmental associations between the brain and the face, as in many defined syndromes the brain and the face are both affected in very specific ways [5, 10]. Hence, developmental deviations of the brain often induce typical facial dysmorphism which enables the diagnosis of the underlying brain malformation (i.e., Down syndrome).

Morphological development of the face

The major phases of face development take place during week 4–10 post-fertilization. However, important morphological changes also occur thereafter, shaping the specific facial appearance [11, 12].

The main process is the fusion of five facial prominences that are derived from the frontal process of the early embryo: The frontonasal prominence in the upper middle part of the face is formed by the end of the third week and the beginning of the fourth [13]. An ectodermal invagination forms during the fourth week to establish the primitive mouth. This invagination meets the most cranial part of the foregut that is covered with endoderm, forming the oropharyngeal membrane that disintegrates during the fifth week. During that time, the neural crest-derived mesenchyme from the first pharyngeal arch forms the two maxillary processes and more caudally the mandibular processes [13]. A bilateral ectodermal invagination, the olfactory placode, starts to form during the fourth week and sinks into the mesoderm of the frontonasal prominence forming the two nasal pits and nasal sacs. This invagination will then 'create" in the process two medial and two lateral nasal processes. The olfactory sacs deepen and enlarge to meet the oral cavity. In the meantime, the two maxillary processes and 2 mandibular processes develop in the first pharyngeal arch [11, 12].

With the formation of the nasal processes, there is enhanced growth of the left and right maxillary processes which fuse in the fifth–sixth week with the two lateral nasal processes forming the upper lip [13, 14]. The exact timing of fusion of the different processes that form the face is crucial for its normal development [15]. While the general shape of the face is established in humans during week 4–10 post-fertilization, the upper lip forms during weeks 4–6, more accurately, during days 24–37 [16]. Any deviation in the sequence and timing of these processes may lead to abnormalities of the face, especially cleft lip with or without cleft palate (CL/CP).

Shh is one of the most important signaling pathways in the formation of the upper lip; any abnormality in this signaling pathway may lead to craniofacial anomalies [15]. It is important to note that Wnt signaling is complementary to Shh signaling in completing the process of normal lip fusion. Hence, if these signals do not operate in complete coordination, CL/CP may be the result.

During these early phases, the brain controls the timing and steps of facial development. The effects are due to the physical as well as molecular influences [9]. Later, this control is lost and the further development of the face and its specific shape is controlled by many local genes. The intimate relationship between the brain and face development was demonstrated in mice where slower brain growth was found to produce a more mature-looking face [17].

During the fifth week, the lower jaw is formed by the fusion of the 2 mandibular processes in their ventral parts, as by a forward growth they form the chin. Anomalies of the lower jaw are common, especially in the Pierre Robin sequence where mandibular hypoplasia is an essential phenotype of this syndrome [18]. Often, there is a postnatal mandibular catch up growth with increased age [19].

Development of the palate

By separating the mouth and pharynx from the nasal cavity, the palate enables eating and breathing at the same time; it closes up the nasal airways preventing food from entering while swallowing. The palate develops from 2 parts—the primary palate, anterior to the incisive foramen and posterior to the 4 incisors; and the palatine shelves—two halves of the secondary palate which are maxillary processes composed of neural crest-derived mesenchyme of the first pharyngeal arch covered by the oral epithelium. The palatine shelves merge in the midline around week 9–11 post-fertilization and also fuse superiorly with the nasal septum [20]. The fusion of the palatine shelves is dependent on many surrounding organs such as the tongue, the upper lip and the mandible. Their growth and fusion is controlled by many genes and by complex epithelial–mesenchymal interactions [20]. There are many chromosomal (Trisomy 18) genetic (gene mutations) and environmental (methotrexate during pregnancy) causes that may interfere with the normal development of the palate, resulting in different degrees of cleft palate.

Although the development of the palate in human embryos begins in the fifth week post-conception, it is completed only by the 12th week [16, 21].

Sonic hedgehog protein secreted by the oral epithelium is the most important signal protein for the outgrowth of the palatal shelves [20]. Wnt5a, Pax9 and Osr2 are transcription factors involved in the elevation of the palatal shelves. Several genes are involved in the process of palatal fusion, especially interferon regulatory factor 6 (IRF6); in humans, the loss of function of IRF6 (gene mutations) results in cleft palate [22]. An additional important signaling is the FGF signaling [23].

Craniofacial dysmorphism

Dysmorphology is the study of structural birth defects of prenatal origin affecting the anatomy (morphology) of the individual. It is an important tool in clinical genetics focusing on standardizing the descriptive terminology used to define deviations from the normal structure. Many birth defects affecting the craniofacial complex have a significant and important effect on the appearance of the neck, head and face (facial dysmorphic features), because they generally affect the different derivatives of the embryonic branchial arches [24].

Many abnormal features of the face are continuous, being above or below 2 standard deviations from the mean. Microtia (small auricles) or hypertelorism (increased distance between the pupils) are such examples. Hence, these features can be measured [24, 25]. However, there are also discontinuous features causing facial dysmorphism, for example: pre-auricular ear pits that are not observed in the normal face.

If such deviations are present in isolation, they are considered as minor malformations and have very little clinical importance. However, if there is a combination of several "minor" dysmorphic features, they may be part of a wider clinical entity constituting a specific syndrome with significant clinical importance. For example, the distinct facial dysmorphic features in children with trisomy 21 (Down syndrome) or the craniofacial features of other chromosomal abnormalities [24]. In the last decade, computer-based 3D face shape modeling is being used for a better delineation of facial dysmorphology [26].

The overall prevalence of craniofacial malformations is high, since changes in the craniofacial complex are common not only in isolated craniofacial malformations but also in a large number of systemic malformations. However, the total prevalence is largely unknown, as most studies report on the rate of individual craniofacial malformations. In the USA, for example, when Kirby reported in 2017 the rate of major congenital malformations in the USA, he only reported the prevalence of orofacial defects (cleft lip with or without cleft palate or isolated cleft palate) that was 17/10,000 birth (0.17%) [27]. In Europe, the EUROCAT registry does not include craniofacial anomalies as one group, but includes several major craniofacial malformation, each one as a separate diagnosis.

Malformations of the craniofacial complex: oral clefts

Since there are thousands of different clinical entities with craniofacial dysmorphic features and hundreds of primary craniofacial malformations, it is impossible to discuss each one separately or use a specific classification. We will therefore discuss the more common malformations that constitute specific entities (i.e., oral clefts or craniofacial microsomia), or discuss several more common malformations of genetic, multifactorial or teratogenic etiology.

Cleft lip with or without cleft palate

This is apparently the most common craniofacial malformation, with a prevalence of 1/700–1/600 live birth [27, 28]. Cleft lip can be unilateral or bilateral, complete or

incomplete, accompanied or not with cleft palate [28]. This malformation may be isolated or combined with other malformations as part of defined syndromes, genetic or chromosomal abnormalities. While many craniofacial malformations cannot be diagnosed prenatally, CL/P can be diagnosed during pregnancy by second trimester ultrasonic evaluations [29]. Although diagnosis after birth is straightforward, treatment is complicated and necessitates a teamwork [29–31].

There are several known etiologies for CL/P, although in most cases the etiology is unknown. About one-third of the CL/P cases is a part of specific syndromes, and therefore has also other congenital malformations [30]. Genetic causes are generally related to CL/P as part of specific syndromes (i.e., holoprosencephaly, trisomy 18) or in isolated CL/P-like FGFR2, BMP4 or van der Woude syndrome with a defect in gene IRF6 [30]. Teratogens such as alcohol (heavy drinkers) some antiepileptic drugs, retinoids, methotrexate and others are also frequent etiologic factors (see below). Some maternal diseases such as maternal pregestational diabetes and folate deficiency are also associated with a higher prevalence of CL/P. Dental anomalies are generally observed in children with CL/P and necessitate orthodontic and other treatments [31].

Treatment

Treatment is surgical but due to the complication of the anomaly, it should involve a team as, in addition to the surgical correction of the cleft (lip and palate), there is a need to restore normal dentition, normal speech function and general facial esthetics. There are also additional psychologic, psychosocial and economic effects on the child and family. The team should therefore comprise a plastic (or oral) surgeon, an orthodontist, a speech therapist, a social worker and if possible a child psychologist. The cleft lip is generally corrected around 10–12 weeks of age unless there are contraindications to surgery. If cleft palate is present as well, it is corrected around 1 year of age. Orthodontic treatment and orthodontic devices are generally needed, being an essential part of treatment [31–34].

Cleft palate (isolated cleft palate, CPO)

There are large differences in the prevalence of CPO between ethnic groups, ranging between 1.3/10,000 in Africa to the highest in Europe (14.3/10,000 in Finland) [35]. CPO is rarer than CL/P and is more common in females. About half of the cases are part of a syndrome (i.e., DiGeorge syndrome) or occur together with other malformations such as cardiac or renal. The different types of CPOs are either: unilateral—complete or incomplete; or bilateral—complete or incomplete or submucous. Since cleft palate may also affect speech, dentition and swallowing, there is a need for long-term comprehensive care by a team of professionals, similar to that needed for the treatment of cleft lip [33, 35].

Cranifacial microsomia (CFM)

This is a spectrum of craniofacial malformations characterized by a wide range of phenotypes differing in severity. It is considered to be the second most common of the craniofacial malformations, second in prevalence to oral clefts [33]. Treatment depends on the degree and location of deformities of the facial structures and the presence of other congenital malformations. These facial malformations are genetic and non-genetic (environmental) in origin. The characteristic facial malformations are: microtia and mandibular hypoplasia (micrognathia)—either isolated or combined. These dysmorphic features are found in over 50% of the cases. Less common dysmorphisms are orbital abnormalities and facial soft tissue abnormalities (Fig. 1) [34]. Birkfeld et al. [35] described a method of defining the typical facial dysmorphic features from facial photographs. This is significantly more precise (90%) compared to physical examination. Caron et al. [33] studied 755 patients with craniofacial microsomia.

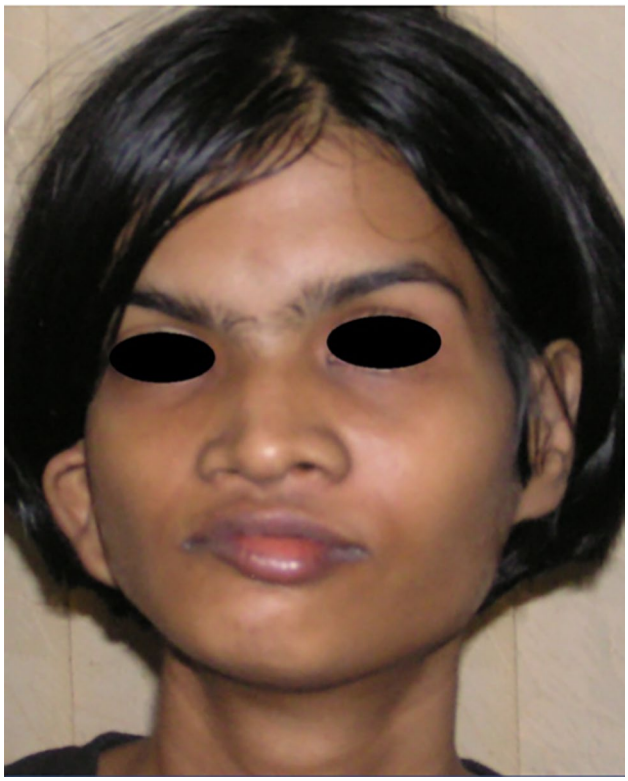


Fig. 1 Photograph of a child with craniofacial microsomia. Low-set auricles, lower in the right side and facial hypoplasia on the same side. Photograph from J Clin Diagn Res Oct 2013, 7:2383-2386 with permission of the authors and publisher

They found various malformations of first and second pharyngeal arch derivatives with unilateral or bilateral distribution and a high rate of extra-facial malformations.

There are several types of classification systems. The commonly used classification is termed "OMENS" considering the orbit, mandible, ear, nerve and soft tissue malformations. A more recent classification system—a modified version of OMENS—has since been published (OMENS PLUS), which is used when noncraniofacial structures are also involved [36, 37].

The mechanism behind CFM is thought to be related to the development of the first two pharyngeal arch structures. Any disruption of the complex interactions in craniofacial development, as well as abnormalities in facial blood supply, can lead to developmental abnormalities of this complex. Among the more common clinical–morphological presentations are mandibular and auricular malformations as well as abnormalities of masticatory muscles [36].

Central nervous system malformations are relatively common in children with craniofacial microsomia occurring in up to 18%. The more common anomalies are neural tube defects, corpus callosum hypoplasia or agenesis, intellectual disability and various neurodevelopmental disorders [38]. Abnormalities of cranial nerves are found in slightly less than half. Other congenital malformations are also common, i.e., cardiovascular, oral clefts and vertebral anomalies [39–41].

Treatment is generally surgical, correcting the facial asymmetries or cosmetic problems and the functional deficits whenever they exist. There is still a debate whether surgery should be carried out early in life, often necessitating several surgical procedures during childhood and adolescence, or later when growth is almost over [33, 36].

Craniofacial anomalies induced by teratogens

Most teratogens that affect brain development may also induce craniofacial malformations. Many of these teratogens also affect neural crest cells, especially cranial neural crest. The more commonly known human teratogens which cause specific syndromes and craniofacial malformations are: folic acid antagonists, especially methotrexate (methotrexate embryopathy), retinoids (retinoid embryopathy), cyclophosphamide (cyclophosphamide embryopathy), mycophenolate mofetil (mycophenolate syndrome), valproic acid and several other antiepileptic drugs (antiepileptic drug syndrome, i.e., valproate syndrome, phenytoin syndrome, carbamazepine syndrome, etc.), alcohol (fetal alcohol spectrum disorder—FASD) and (heavy) smoking. Exposure must occur in the first trimester of pregnancy, during facial organogenesis. These craniofacial anomalies will be discussed according to the responsible teratogenic agent.

Methotrexate embryopathy

Methotrexate is a folic acid analog that inhibits dihydrofolate reductase resulting in a decrease in tetrahydrofolate needed for various metabolic pathways [42]. Hence, its antifolate activity is dose dependent. It is a well-established teratogen affecting most animals [43, 44]. If administered during pregnancy, it may cause dysplasia and a specific pattern of malformation—the methotrexate syndrome, also affecting the craniofacial complex [45]. The typical craniofacial malformations are hypoplasia of skull bones, "clover-leaf" skull with wide fontanelles and a large head, swept-back hair, low-set ears, prominent eyes, wide nasal bridge, micrognathia, maxillary hypoplasia and other facial dysmorphic features (Fig. 2) [42–44]. Additional malformations may be limb defects including absence of ossification centers and CNS abnormalities including anencephaly, hydrocephaly and

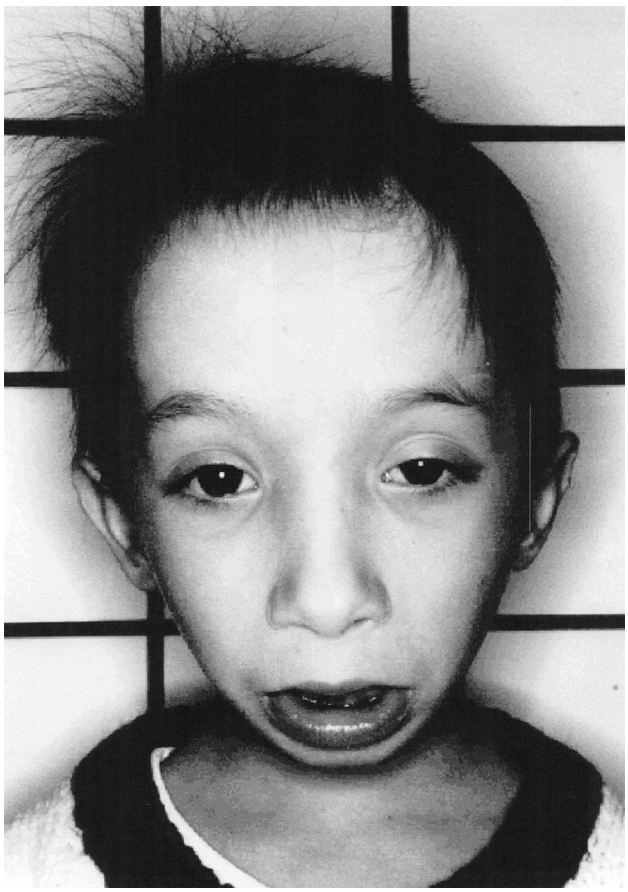


Fig. 2 Photograph of a child with methotrexate embryopathy. Hypertelorism with epicanthal folds, severe micrognathia, elongated thin upper lip and high frontal hair line. Photograph from South African J Child Health 2013, 7:74–76 with permission of the publisher

meningomyelocele. In addition, there are neurobehavioral disorders including mental retardation. Similar anomalies were described following maternal treatment with aminopterin that was used in the 1950s for the termination of pregnancies [42, 43].

Methotrexate is used today to induce embryo lethality in cases of extra-uterine pregnancies and in low doses for immunosuppression in autoimmune diseases. Low doses of methotrexate, less than 10 mg/week, such as that used in the treatment of some autoimmune diseases, are apparently not teratogenic [43, 46]. However, rare cases of methotrexate embryopathy following administration of low doses have been described.

Retinoid embryopathy

Retinoids (13-*cis* retinoic acid and all-trans retinoic acid) are a group of drugs whose teratogenicity was suspected prior to their clinical use as a treatment for acne and for psoriasis and recently for pro-myelocytic leukemia [47, 48]. They are natural derivatives of vitamin A and therefore low levels of 13 *cis* retinoic acid is normally present in the blood, but high levels are highly teratogenic affecting about 30% of the exposed fetuses and often causing retinoid syndrome (embryopathy). Very little retinoid is absorbed in the blood with topical use, and topical use is not associated with retinoid embryopathy [47, 48]. Retinoids may increase malformations of the heart, brain, ears, eyes, face and limbs [47–52]. The typical craniofacial malformations are as follows: microtia and various auricular abnormalities, agenesis or stenosis of the external auditory canal that often leads to hearing impairment and deafness, damage to the middle or inner ear, and facial and palatine abnormalities. They may also affect the brain causing hydrocephalus and a variety of neurological, cognitive and neurobehavioral disorders [52, 53].

Cyclophosphamide embryopathy

This alkylating agent is used for chemotherapy and in small doses as an immunosuppressive agent. As observed from human case reports and case series, first trimester exposure has been associated with embryonic and fetal death, intrauterine growth restriction and various craniofacial malformations including eye anomalies, cleft palate, micrognathia, low-set ears, microtia, hearing defects, craniosynostosis and facial asymmetry, as well as malformations of the brain (hydrocephaly), limbs and eyes [53–60]. Treatment in the second or third trimester of pregnancy is apparently not associated with an increased risk of congenital malformations, but has been associated with increased fetal death. There seems to be no data on the possible effects of low doses of cyclophosphamide in pregnancy, and therefore low doses are as yet contraindicated [61].

Mycophenolate mofetil

This immunosuppressive drug is used in organ transplantation or for the treatment of autoimmune diseases such as lupus and rheumatoid arthritis [48, 62]. This is a relatively "'newly recognized" teratogen, mainly affecting the craniofacial complex [48, 62]. The main anomalies are microtia, anomalies of the external ear and auricles, conductive hearing loss, cleft lip/palate, micrognathia, microphthalmia, cataracts, coloboma of the retina and dental anomalies [63–65]. Often, there are also other malformations such as kidney or cardiac malformations and/or tracheo-esophageal atresia. Various brain anomalies have been reported as well, including meningocele, hydrocephaly and agenesis of the corpus callosum [62]. There is also a high risk for spontaneous abortions and intrauterine death. However, the accurate risk for malformation has not been determined yet, although it may be high [62, 66]. Hence, this drug is contraindicated in pregnancy.

Valproic acid (VPA) and other antiepileptic drugs: antiepileptic drugs syndrome

Antiepileptic drugs are generally used to control seizure disorders. Some of them are also used as mood stabilizers in psychiatric disorders. As a group, many of these drugs are known teratogens inducing a variety of congenital malformations as well as neurodevelopmental problems. Of these drugs, VPA, which is an effective mood stabilizer as well as an antiepileptic drug, seems to be the most teratogenic [67–71]. VPA, if taken during pregnancy, is known to cause neural tube defects (NTD) in 1–2% of the offspring as well as cardiac, skeletal and limb defects and a specific craniofacial dysmorphism—the "fetal valproate syndrome". In addition, VPA may affect development, inducing speech and language delay, reduced cognitive abilities and increased rate of autism spectrum disorder (ASD) [67, 69]. The typical craniofacial abnormalities include long and thin upper lip, shallow philtrum, epicanthal folds, midface hypoplasia with flat nasal bridge, small nose and upturned angles of the mouth (Fig. 3). Intrauterine growth restriction is also common. There are several mechanisms explaining the teratogenicity of VPA, the most important is its effects as a histone deacetylase inhibitor affecting the expression of many genes. These epigenetic effects may also explain the effects of VPA on the brain and the craniofacial complex [69, 70].

Facial dysmorphic features have also been described following maternal use of other antiepileptic drugs, especially phenytoin, phenobarbital and carbamazepine [71–73]. For example, of 47 children prenatally exposed to

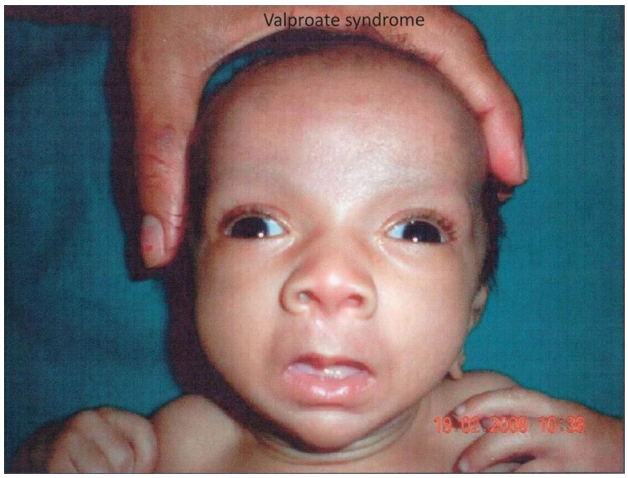


Fig. 3 Photograph of an infant with valproate embryopathy showing the typical facial features of this syndrome. Low-set ears, broad and depressed nasal bridge, long upper lip and shallow philtrum, small upturned nose, thin upper lip, small mouth, and medial deficiency of eyebrows. Photograph from the original publication of Diliberty et al., Am J Med Gent 19:473–481, 1984 [70]

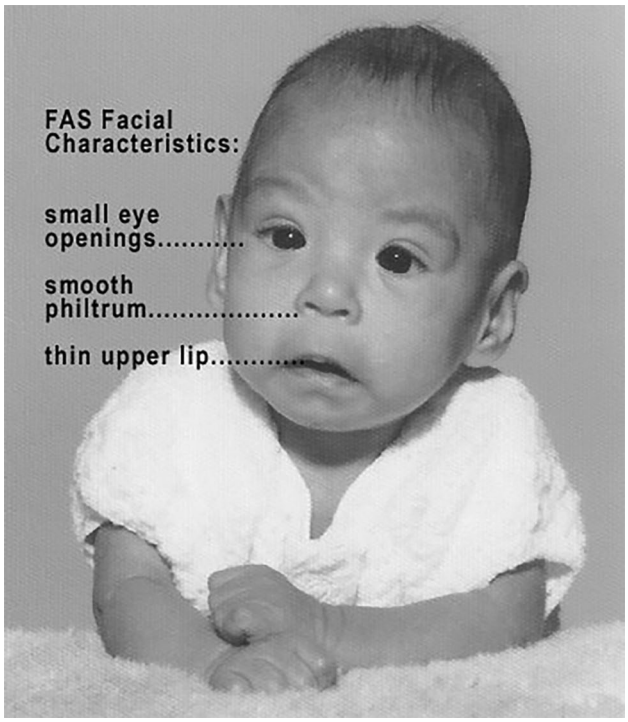


Fig. 4 Typical facial features of FASD. Note small eyes, hypertelorism with epicanthal folds, thin upper lip with smooth philtrum. Obtained with permission from https://upload.wikimedia.org/wikipedia/commons/7/72.FAS.jpg

carbamazepine, we found 6 with typical facial dysmorphism (carbamazepine syndrome) and developmental delay [73]. Many antiepileptic drugs also increase the rate of various congenital malformations as well as the rate of neurodevelopmental disorders. The typical facial dysmorphic features observed in antiepileptic drug syndrome are: hypertelorism, flat nasal bridge, low-set ears, reduced head size and sometimes oral clefts. There are some minor differences in presentation among individual drugs [48, 73, 74].

Alcohol (ethanol) embryopathy

Ethanol is a well-known teratogen affecting a very large number of pregnancies. There seems to be a dose response regarding the extent and severity of symptoms. It is apparently the most important teratogen in the USA and Europe due to the habit of alcohol drinking [48, 75]. The craniofacial abnormalities are generally found in children with the most severe damage induced by alcohol and exhibit the "fetal alcohol spectrum disorder" (FASD). The alcohol-induced abnormalities include prenatal and postnatal growth deficiency and central nervous system dysfunction including mental retardation, hyperactivity, antisocial behavior and increased tendency for substance abuse [75]. The abnormal facial features include small head size (microcephaly), short palpebral fissures, epicanthal folds, hypoplastic smooth philtrum, thin upper lip, flattened maxilla, short nose and low-set ears (Fig. 4) [75]. Some studies also found an increase in cardiac malformations and in oral clefts [76–78]. Due to the variability of the clinical findings it may be difficult to diagnose alcohol-induced abnormalities without a history of alcohol ingestion and therefore several guidelines for the physical examination of children suspected to have FASD have been published [77]. Moreover, as children with FASD age, the facial features become less distinctive making the diagnosis more difficult [75]. The full spectrum of FASD appears in children of mothers who consumed large amounts of alcohol during pregnancy. Drinking lower amounts may result in the fetal alcohol effects, with fewer clinical signs that are more difficult to diagnose [48, 75]. The specific craniofacial dysmorphic features in FASD are explained by the damage to neural crest cells induced by alcohol [79]. A major mechanism of alcohol-induced embryopathy is increased oxidative stress affecting the developing embryo and fetus, mainly due to the poor antioxidant capacity of neural crest cells and brain tissue.

Other well-established mechanisms are the epigenetic effects of alcohol that may induce changes in the expression of various embryonic and fetal genes induced by alcohol [80]. Generally, several studies demonstrated enrichment of H3K9ac, H3K27me2,3 and H3K9me2, and increased expression of histone acetyltransferases and methyltransferases [81].

Smoking and oral clefts

While the damaging effects of maternal smoking on the developing embryo and fetus are generally dose dependent, especially weight reduction and neurodevelopmental problems [82–84], there are inconsistent data regarding congenital malformations. It seems, however, that there is sufficient data to demonstrate that smoking early in pregnancy would increase the rate of CL/CP and of CP. In a recent meta-analysis by Xuan et al. [83] analyzing 29 studies, the OR for CL/CP was 1.368 (95% CI 1.259–1.486) and for CP 1.241 (95% CI 1.117–1.378), both being of statistical significance ($P < 0.05$). Several studies also observed an increase in various cardiac malformations, especially if both parents smoked [85]. No increase in external facial dysmorphism was reported.

Craniosynostoses and primary abnormalities in the shape of the skull

This is a group of entities where the primary morphological manifestations (dysmorphism) are in the shape of the skull. They are characterized by premature closure of one or more of the calvarial bone sutures. Most of these abnormalities are isolated closures of specific sutures, but about 10% constitute specific syndromes (syndromic craniosynostoses). The general occurrence is about 1/2000–1/2500 live-born infants [86]. These disorders generally also affect, in addition to the shape of the skull, important features and shape of the face. They may have imperative effects on the brain, generally interfering with its growth and development, and often also interfere with dentition or cause malocclusion (Fig. 5) [86–88].

Syndromic craniosynostoses

These constitute specific defined syndromes that will be discussed below [87]. All these syndromes have common genetic backgrounds. They are generally either inherited as autosomal dominant diseases or result from de novo mutations [87, 88]. The more common mutations are in the following genes: genes of the FGF receptors (FGFR1, FGFR2, FGFR3 as in Apert, Pfeiffer, Antley–Bixler, Crouzon and Muenke syndromes, all of which have a chromosomal dominant inheritance, or mutations in TWIST1 (Saethre–Chotzen syndrome, autosomal dominant) or EFNB1 (cranio-frontonasal syndrome, X-linked dominant) genes. It is quite certain that more mutations will be found in the future [88].

In syndromic craniosynostoses, there are often also extracranial malformations, especially of the heart, respiratory tract and limbs [87, 88]. Sometimes, neurodevelopmental problems including mental retardation are integral features of the syndrome [88, 89]. A computerized program for the identification of the different craniosynostoses was developed by Shim et al. [90], but the accurate diagnosis is generally carried out by the identification of the affected gene [87, 88]. Prenatal diagnosis is possible by ultrasonography and the use of additional imaging techniques (MRI), and/or by genetic studies of fetal cells.

Treatment is aimed to avoid the possible deleterious effects on brain growth and correct the cosmetic and/or functional facial and skull deformities. In addition, it is aimed to treat any dental and orthodontic problem as well as any interference with mastication, swallowing or respiration. Due to the cosmetic problems, long-term psychosocial support is often needed. Hence, treatment is generally by a team of or professionals from these different disciplines [91].

Specific syndromes

Apert syndrome

This syndrome is characterized by severe syndactyly of the fingers of the hands and feet in addition to the premature closure of multiple calvarial sutures [88, 92, 93]. There are several craniofacial dysmorphic features such as flat forehead, hypertelorism, retracted midface and low-set auricles [88]. There may be severe malformations of other organs, especially the cardiovascular system. There are differences in the severity of the facial dysmorphism related to the specific mutated locus, whether S252W or P253R in the FGFR2 gene [93]. Most cases of Apert syndrome are caused by de novo mutations [92]. The cognitive abilities vary from normal intelligence to moderate–severe mental retardation.

Crouzon syndrome

In addition to coronal suture synostosis there is premature closure of several other sutures. Craniofacial manifestations are: frontal bossing, maxillary hypoplasia and micrognathia. Typical features are shallow orbits, ocular proptosis and strabismus. In about one-third there is development of hydrocephalus and in over half development of hearing loss [94]. Increased intracranial pressure and tonsillar herniation might cause even death if surgery is not performed on time. In the majority of cases, the mutation is in the FGFR2 gene and in a minority in the FGFR3 gene [88].

Pfeiffer syndrome

In addition to craniosynostosis of several cranial sutures, there are broad thumbs and big toes. Often, partial syndactyly is an additional malformation. Sometimes hydrocephalus, ankyloses of the elbows and proptosis are also observed. Mental deficiency may be found in some cases as

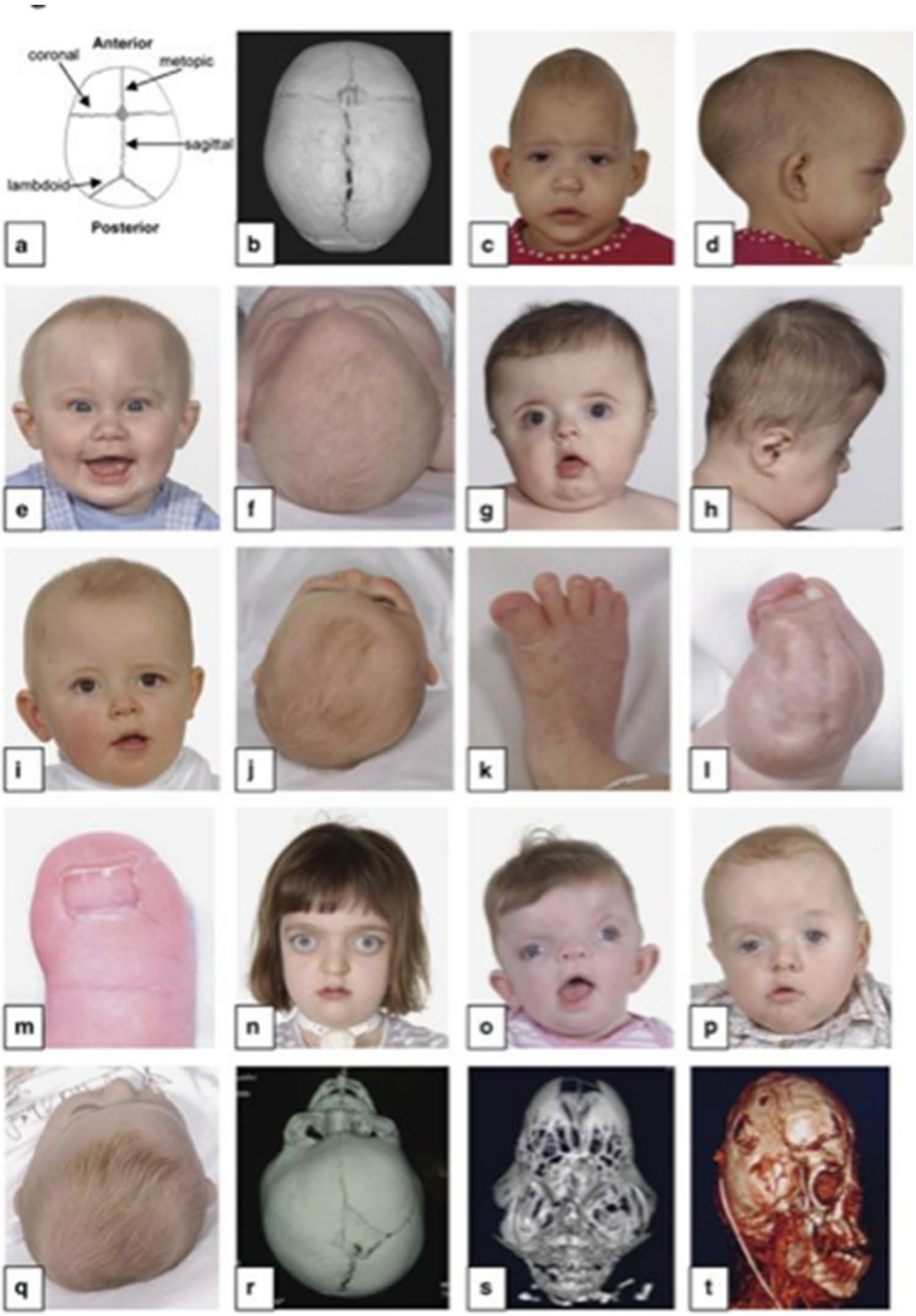


Fig. 5 Photographs of children with different types of craniostenosis. Obtained with permission from the Europ. J Hum Genet. 2011; 19:369–376 [102]

an essential part of this syndrome [88]. The mutation may be on FGFR1 or FGFR2, with complete penetrance, but variability in the clinical expression. Proper prenatal imaging or molecular studies enable prenatal diagnosis [95].

Antley–Bixler syndrome

In addition to synostosis of the cranial bones, there are typical synostoses in other joints as well. While the cranial vault is composed of membranous bones, synostoses are also common in joints between endochondral bones, especially in radio-humeral and radio-ulnar joints. Frontal bossing and midface hypoplasia are prominent features in addition to the synostosis. Cardiac and renal anomalies are also common [88]. Of the two possible affected genes FGFR2 and POR, those with POR mutations also have congenital adrenal hyperplasia and ambiguous genitalia [96]. Prenatal diagnosis is carried out by CT and MRI of the developing fetus [97].

Saethre–Chotzen syndrome (acrocephalosyndactyly type III syndrome)

The coronal suture is generally affected uni- or bilaterally. Additionally, there are limb malformations (generally clinodactyly and partial syndactyly and broad great toes) and sometimes synostosis of additional cranial sutures. The facial abnormalities are low-set ears, hearing loss, ptosis and hypertelorism. Intelligence is generally normal [88, 98]. The affected genes are TWIST1 or FGFR2 [99].

Muenke syndrome

Synostosis is typically in the coronal suture. The facial and extracranial malformations are quite similar to those of Saethre–Chotzen syndrome and include hearing loss, developmental delay, downslanting palpebral fissures, proptosis and limb malformations [88, 100]. The common mutation is in the FGFR3 gene [100].

Cranio-frontonasal syndrome

Both coronal sutures are affected by premature closure. There are typical midfacial malformations including bifid nasal tip, CL/P or at least high arched palate, frontal bossing, hypertelorism and dental anomalies. Limb malformations are common and include syndactyly, clinodactyly, broad thumbs and even abnormal clavicles [101]. The affected gene is EFNB1 on chromosome Xq12. Inheritance is therefore sex-linked dominant.

Nonsyndromic craniosynostosis

These types of craniosynostosis constitute 80–90% of all cases of craniosynostosis [86]. Generally, the sutures that close prematurely will dictate the shape of the head, because the growth of the affected calvarial bones, perpendicular to the suture, is largely inhibited. This, in turn, may cause expansion of the growing brain in other directions causing distortion of the skull and face. In many cases, dentition is affected too. There are multiple etiologies including genetic, environmental and intrinsic bone abnormalities but in many cases the etiology is unknown [86, 102, 103]. Treatment and prevention of complications is similar to that of the syndromic craniosynostoses. Prenatal diagnosis is possible in some cases depending on the intrauterine changes in calvarial shape or other anomalies observed by routine prenatal ultrasonographic screening. Optimal treatment is by a multidisciplinary team [86, 102, 103]. Such a multidisciplinary team should comprise, in addition to dental discipline professionals (a pediatric dentist and an orthodontist), also a neurosurgeon or plastic surgeon, a social worker and a pediatric psychologist.

Other genetic or multifactorial craniofacial malformations

As discussed above, many cases of craniofacial abnormalities are of genetic or mixed genetic and environmental origin (multifactorial). Often, they are part of a genetic syndrome with variable clinical manifestations. A comprehensive description of all these anomalies is beyond the scope of this review. We will, however, discuss shortly two examples: one with a multifactorial etiology or induced by a chromosomal microdeletion and the other will be an example of a genetic autosomal dominant mutation. They are both very serious anomalies that need the attention of a variety of disciplines.

Goldenhar syndrome (oculo-auricular–vertebral syndrome)

It affects about 1 in 5000 births. The etiology of this syndrome is generally unknown. Sometimes, it may result from a microdeletion of chromosome 22 (22q11.21 microdeletion) or, in rare cases, it results from an autosomal recessive or autosomal dominant gene mutation [104, 105]. The basic clinical presentation of this syndrome is unilateral (in 85%) or bilateral (15%) facial microsomia with involvement of the eye (epibulbar dermoids, coloboma, microphthalmia). In addition, there may also be non-facial abnormalities, often cardiovascular and of the brain [105]. Hence, this craniofacial malformation is just an example of many additional craniofacial abnormalities that will not be further presented in this review.

Treacher Collins syndrome (mandibulofacial dysostosis)

This is an example of an autosomal dominant syndrome with a mutation in the TCS gene—TCOF1 on chromosome 5q32 and severe craniofacial manifestations. In this rare syndrome (about 1/50,000), the abnormalities are in derivatives of the first and second branchial arches manifested by hypoplasia of facial bones, micrognathia, antimongoloid slant, coloboma of the lower eyelid and auricular abnormalities [106, 107]. In addition, there are abnormalities of dentition and orthodontic problems, conductive hearing loss, narrow nasal cavity, microcephaly and neurodevelopmental delay. Treatment is generally by a multidisciplinary team.

There are many genetic syndromes with craniofacial involvement, but they will not be discussed here. However, the following is a list of the more common syndromes with craniofacial manifestations [24]. These are: most chromosomal trisomies, triploidy, most chromosomal deletions and microdeletions, ataxia–telangiectasia, Carpenter syndrome,

cleidocranial dysplasia (dysostosis), ectodermal dysplasias, Golge syndrome, Gorlin syndrome, Hallermann Streiff syndrome, Miller syndrome, Moebius syndrome, Nager syndrome, neurofibromatosis 1, Stickler syndrome and velocardiofacial syndrome. This partial list emphasizes the importance of craniofacial dysmorphology in the diagnosis and treatment of many genetic disorders. Moreover, in many of them there are also distinct dental anomalies that will not be discussed further in this review.

Anomalies of dentition and craniofacial malformations

The development of the teeth is intimately connected with the development of the craniofacial complex. It involves reciprocal inductive interactions between epithelium and mesenchyme with cranial neural crest cells playing a crucial role as progenitors of the teeth [108, 109]. Shh and Wnt signaling are responsible for many of the developmental phases of dentition in combination with bone morphogenetic proteins (BMP) and fibroblast growth factor (FGF) [108, 110, 111]. Shh signaling plays an important role in the initiation of dental lamina formation and tooth number and continues into more advanced steps of the morphogenesis of individual teeth, especially in the epithelial–mesenchymal interactions [111]. As Shh also plays a crucial role in craniofacial development [112], disruption of the Shh signaling may cause abnormalities in teeth number, shape and position as well as craniofacial and brain malformations [113].

Abnormalities of dentition and of the jaws can be isolated, but are more often just one of the additional clinical signs of defined syndromes affecting the craniofacial complex and/or the brain [32, 114]. One of the most important and relatively common craniofacial malformations is oral clefts which are generally accompanied by orthodontic and dental anomalies as well [32]. However, this review deals primarily with craniofacial malformations, hence the involvement of dentition will not be further discussed. It only stresses the importance of dentists in the multidisciplinary team that is mandatory for comprehensive treatment of these malformations.

Conclusions

This review highlights the importance of craniofacial anomalies among the large group of congenital malformations. These anomalies impose not only a cosmetic problem presenting craniofacial dysmorphic features, but may also interfere with important functions such as chewing, swallowing and respiration. In addition, craniofacial malformations quite often also involve teeth and dentition. Moreover, the close relation between the development of the brain and the craniofacial complex induce various, but specific, craniofacial changes in a variety of brain disorders. Moreover, craniofacial malformations sometimes serve as a tool for the identification of the brain abnormalities. In addition, primary anomalies of the craniofacial complex might secondarily affect the brain, as occurs in the various craniosynostoses. As many craniofacial malformations can be visualized by imaging techniques in utero, or by genetic molecular studies, it is important to be aware of these possibilities and pay meticulous attention to possible craniofacial malformations during routine ultrasound examinations in pregnancy, especially in the second and third trimesters. The dentist is a key person in all multidisciplinary teams that treat the different craniofacial malformations. He should therefore be very mindful of the large and important group of these anomalies.

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Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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