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Review Article

Risk in Craniofacial Syndromes

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Abstract

Craniofacial malformations are some of the most prevalent pathologies in children. Some of them, such as cranial malformations, can endanger the child's life or leave irreparable consequences such as intellectual deficit. A comprehensive bibliographic review was conducted on the main risks associated with craniofacial syndromes, which include neurological, sensory, motor and morphophysiological disorders.

Keywords: Craniofacial; Syndrome; Risks; Dysostosis

Introduction

Craniofacial malformations are some of the most prevalent pathologies in children. Some of them, such as cranial malformations, can endanger the child's life or leave irreparable consequences such as intellectual deficit. On the other hand, facial malformations are not usually life-threatening; however, they mark children and their families for life. Most of them will need multiple and complex operations to try to make their facial appearance as appropriate as possible. Etiology The causes are not always well known, but they are grouped in the following box [1,2].

Hereditary	Defects originating as a consequence of the transmission of genetic alterations.
Environmental Nutritional deficiencies	Biological factors: age of the parents and blood incompatibility.
Maternal infections	Mothers with severe low weight during pregnancy
Hormonal	Rubella Toxoplasmosis Syphilis
Physical effects	Effect of androgens
Chemical effects	Radiation
	Medicines or drugs such as anticonvulsants

Table a

The overall risk of developing malformations is around 2% and the risk of developing CNS malformations is 2.66 per thousand. In spontaneous abortions, the percentage of malformations is very high. Preventive measures such as the systematic administration of folic acid supplements to pregnant women during a period prior to pregnancy and throughout pregnancy have greatly reduced the percentage of Central Nervous System (CNS) malformations. Formation of the pharyngeal arches The pharyngeal arches are mainly mesodermal embryological structures, although they are also lined with ectoderm and have a core of endoderm and are located on both sides of the pharynx [1,2].

They are formed by the migration and differentiation of neural crest cells and most craniofacial components originate from here. Understanding the origin and differentiation capacity of the pharyngeal arches; It will help us understand the reparative capacity of craniofacial tissues. First pharyngeal arch It forms the maxillary and mandibular components, the derivatives of the first pharyngeal arch are innervated by the trigeminal nerve; the following originate from this first arch: Maxilla, malar, zygomatic process of the temporal, mandible after the formation of Meckel's cartilage, malleus, incus, sphenomandibular ligament, in addition to the masticatory muscles, anterior belly of the digastric muscle, mylohyoid, tensor veli palatini and eardrum.

Second pharyngeal arch Innervated by the facial nerve, it forms the Reichert cartilage, stapes, temporal styloid process. Muscles of facial expression, stapedius, stylohyoid and posterior belly of digastric. Third pharyngeal arch Innervated by the glossopharyngeal nerve, it forms the greater horn and lower body of the hyoid bone, stylopharyngeus muscle. Causes of craniofacial anomalies Craniofacial malformations are the most frequent congenital malformations in humans, but very little is known about their etiology. In some cases there is a Mendelian genetic transmission, although most are sporadic.

There are authors who discuss the role of hyperthyroidism, some metabolic disorders, teratogenic agents, etc. but the reality is that in most cases the cause is unknown. The starting point and the way in which they progress are also poorly understood. In syndromes associated with premature suture closure, the involvement of certain growth factors or their receptors has been demonstrated. The base of the skull and its growth play a very important role, especially in craniostenosis with delayed facial growth. Recently, more and more authors consider that many of the syndromes with craniofacial involvement have something in common, and that is that the malformations are produced by alterations in the cells of the neural crest and they consider them as neurocrestopathies.

Objective

To describe the main consequences and risks of craniofacial syndromes.

Bibliographic search methods Scientific information was collected through a search using the following descriptors in English: The Medical Subject Headings (MeSH): "craniofacial syndromes, dysostosis, malformation.

Analysis strategy

The search was based solely on craniofacial syndromes.

Development

During the last decade there has been great progress in the identification of the genetic bases for most of the craniofacial syndromes. For those cases or conditions without an identifiable genetic pattern, factors defined as "teratogenic" agents have been demonstrated, environmental conditions that are detailed below

- Radiation. High doses are associated with Microcephaly.
- Infection. Newborns with a history of toxoplasma, rubella or cytomegalovirus have a high incidence of facial fissures.
- Maternal idiosyncrasy. High levels of phenylketonuria increase the incidence of cleft lip and palate, hyperinsulinism is associated with oculoauriculovertebral malformations, and factors such as age and weight are associated with other craniofacial malformations.
- Chemicals. Vitamin deficiencies are associated with increases in the incidence of cleft lip and palate. Drugs such as maternal tobacco and nitrofurantoin are associated with craniosynostosis. Alcohol and anticonvulsants such as phenytoin and valproic acid are associated with an increase in the incidence of cleft lip and palate.

As professionals in the field of stomatology, it is vitally important to know the different normal and genetically altered structures during embryonic development. Due to the different areas of medicine focused on the study of craniofacial alterations, it has led to a thorough search for each of the specialties in order to be able to study and classify these cephalogenic alterations. The American Association of cleft lip and palate and craniofacial malformations (ACPA) proposed in 1981, a general classification for all craniofacial anomalies; which are

- Facial clefts, encephaloceles and dysostosis.
- Atrophy and hypoplasia.
- Neoplasias.

- Craniosynostosis.
- Unclassifiable (1). All of them present craniofacial syndromes and malformations, some of which have a potential risk of presenting obstructive compromise of the airway [2-5].

Committee on Nomenclature and Classification of Craniofacial Anomalies derived from the American Cleft Lip and Palate Association This classification allows us to have a summary and order of the causes and management of the most frequent craniofacial anomalies: Facial clefts/encephaloceles/dysostosis Facial cleft Facial clefts are the most frequent craniofacial anomalies, the most common being those that occur parallel to the philtrum and may or may not involve the palate, also known as cleft lip and palate. Classification.

- Morian 1887 Describes three types Type I: Oculonasal cleft Type II: Oro-ocular cleft in front of the canine with extension to the orbit Type III: Oro-ocular cleft behind the canine with extension to the orbit.
- Karfik 1996 Group A: Malformations of the rhinoencephalic region Subgroup
- A1. Frontonasal prominence malformation Subgroup
- A2. Involves developmental disorders of the nose, including oro-ocular clefts.
- Group B: Includes deformities related to the 1st and 2nd AB, subdivided
- B1. Includes lateral otocephalic disorders, encompasses entities such as hemifacial microsomia and ear malformations.
- B2. Includes malformations of the midline and mandibular processes.
- Group C: Includes otopalpebral malformations
- Group D: Includes craniofacial syndromes (Apert and Crouzon)
- Group E: consists of atypical malformations primarily presenting asymmetry.
- Demeyer Groups midfacial anomalies into 2 categories
- A: anomaly in which the volume of the tissues is deficient or absent
- B: the volume of the tissues is almost normal or is in excess associated with an established malformation. For better orientation, the orbit is divided into two hemispheres, everything below the lower eyelid corresponds to the facial fissures and what is above the upper eyelid to the cranial fissures.

According to Tessier's anatomical classification, the involvement of the soft parts and their relationship with the bone component do not always coincide, and two or more fissures may even coexist. In summary, facial fissures can be numbered from 0 to 14, with lip and palate clefts accounting for 75% of major facial malformations and 80% of all orofacial fissures. These correspond according to the classification described by Tessier numbers 1-2-3 with an incidence in Chile of 1 in every 700 live births. Cleft 0 or middle cleft, rare with an incidence of 0.40-0.70%, is seen in less than every 100 clefts. It has different degrees of expression and corresponds to the non-fusion of the nasal processes at their origin.

The problem with this type of cleft is the possibility of compromising brain development depending on the type, its spectrum being very broad, ranging from a small defect or "notch" in the vermilion to a middle cleft with hypotelorism with holoproscencephaly [4-7].

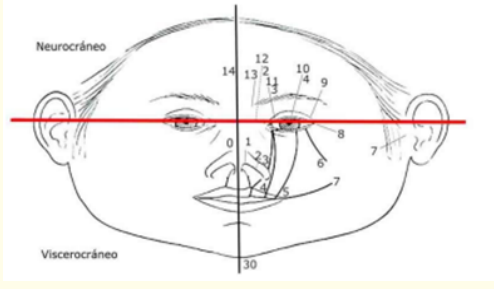

Figure a

Diagram of Tessier facial fissures in soft tissues. Cuban Journal of Stomatology 2013;49(1):2-27.

Diagram of Tessier facial fissures in hard tissues. Cuban Journal of Stomatology 2013;49(1):2-27.

Encephalocele Encephalocele is a rare developmental disease, belonging to the group of defects in the closure of the neural tube (central longitudinal tube of the embryo that originates the brain, spinal cord and other tissues of the central nervous system), which normally occurs during the fourth week of gestation; when these defects in the closure of the neural tube affect the brain, they give rise to anencephaly and encephalocele and if they are located in

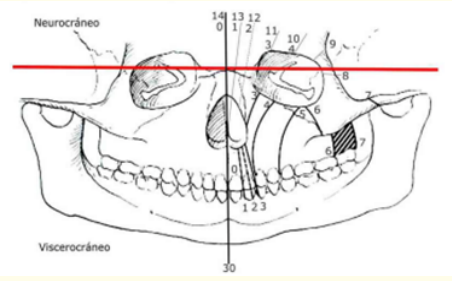

Figure b

the spinal column they cause spina bifida, characterized by herniation or protrusion of part of the brain and the meninges through a cranial defect; if only the meninges protrude it is called cranial meningocele, while if the ventricle protrudes it is called meningohydroencephalocele.

Encephalocele is the least frequent open defect of the neural tube. On average, it occurs in one case in every 2,000 to 6,000 live births, but its incidence varies considerably depending on the different studies. It is apparently more frequent in Mexico, in countries of Celtic origin and in certain countries in Southeast Asia such as Indonesia, Malaysia and Thailand, where it reaches a frequency of one in every 5,000 live births. Although its production mechanism is still unknown, genetic factors are involved and it is estimated that approximately 10% of neural tube defects are caused by genetic mutations or chromosomal alterations, since a high incidence has been seen in siblings of children with this disease [4-7].

The typical content of the herniation is cerebrospinal fluid and neural tissue that connects to the brain through a narrow pedicle; the covering of the hernial sac can vary from a well-formed layer with skin and hair to a thin meningeal layer; therefore the lesion can be completely covered by skin, or alternate with areas devoid of it, leaving the nervous tissue exposed. Encephaloceles are located in the occipital region in 7 5% of cases and, to a lesser extent, around 15%, they can be located in the parietal, frontal and sincipital regions (the sinciput is the upper anterior part of the head). The latter are subclassified by their location into: nasofrontal, nasoethmoidal and nasoorbital. Clinical manifestations depend on the area of the brain herniated, the most frequent being visual disturbances, microcephaly (abnormally small head), mental retardation and seizures; sincipital encephaloceles have, in addition to visual disturbances, nasal and auditory manifestations. Encephalocele can occur in isolation or associated with other abnormalities of the central nervous system: hydrocephalus, myelomeningocele, absence of the corpus callosum and lissencephaly; with other congenital malformations: frontonasal dysplasia, amniotic band syndrome; It has also been described in some chromosomal trisomy 18 and 13 and deletions (13q and 16q) [4-7].

It can be part of polymalformative syndromes such as Walker Warburg, Meckel syndrome, in which the encephalocele is occipital and less frequently Fraser cryptophthalmia, Knobloch syndrome and Warfarin embryofetopathy.

Differential diagnosis should take into account cystic hygroma, in which there is no bone defect, edema of the skull, teratomas (complex mixed tumors in which multiple tissues are arranged in differentiated organs) and other congenital anomalies such as anencephaly, cystic brachial cleft, hemangioma and mesenchymal sarcoma. In cases of frontal encephalocele, it must be differentiated from dacryocystocele (tear duct cyst) or nasal teratoma. The prognosis varies depending on the size, location and type of herniated brain tissue and on the number, type and severity of associated malformations. Infants with encephalocele have a higher risk of developing hydrocephalus (fluid accumulation in the brain) due to stenosis (pathological narrowing of a duct) of the aqueduct, a Chiari malformation, or Dandy Walker syndrome [4-7].

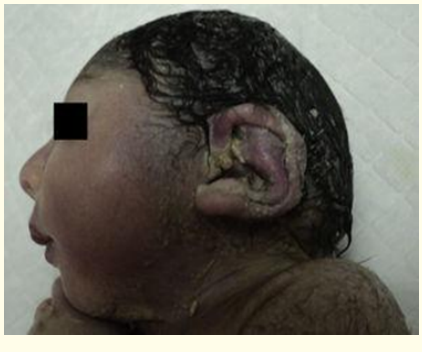

Figure c

Dandy Walker syndrome, microcephaly, low-set and malformed ears, wide nasal root, retrognathia. (Dandy-Walker complex associated with polymalformative syndrome Gonzalo E. Quesada Segura, Carolina Cantos García - Obstetrics and Gynecology Service, Río Hortega Hospital, Valladolid, Spain) The determination of maternal alpha-fetoprotein levels and the performance of prenatal ultrasound allow intrauterine diagnosis that contributes to a more appropriate management of the patient and enables the screening

of other malformations and the planning of treatment. The ultrasound image of the encephalocele consists of a mass of tissue always associated with a bone defect through which the herniation occurs. The treatment is surgical and must be addressed interdisciplinarily. Most encephaloceles must be corrected, even the largest ones, since they can be removed without causing significant functional disability. Urgent surgical correction is necessary when the lesion is open, that is, not covered by skin [6,7].

Types of encephaloceles according to their anatomical location - Mexican Council of Neurosciences.

Figure d

Dysostosis Hemifacial microsomia Also known as first and second arch syndrome, which is directly correlated with Tessier's cleft 7. Hemifacial microsomia is a disorder in which the tissue on one side of the face does not develop completely, primarily affecting the auditory (ear), oral (mouth), and mandibular (jaw) regions. In some cases, both sides of the face may be affected, and even the face and skull may be involved.

The deformity in hemifacial microsomia varies greatly depending on the severity of the disorder, which ranges from mild to severe, and the region of the face involved. Structures that are typically involved to varying degrees include: the middle and external ear, the maxilla and mandible, the teeth, the soft tissues that make up the cheek and branches of the facial nerve that allow facial expressions Pruzandsky classification system (1969) The first classification used in patients with FHM was made by Samuel Pruzansky in 1969, based on x-rays of the jaws of patients with this condition. In his classification, Pruzansky observed three types of mandibular hypoplasia, from a relatively complete jaw (Grade I) to a very small one whose deformity worsened over time (Grade III) This classification only meets the description of the jaw, therefore, when used in patients with FHM, many aspects of the pathology are left out [6-9].

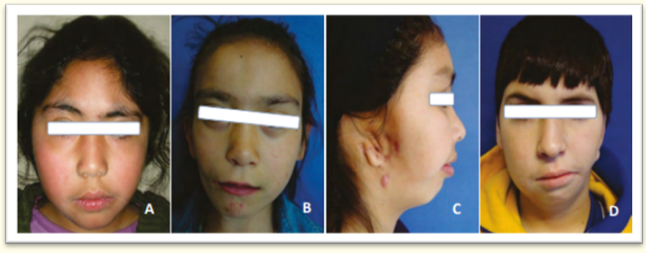

Figure e

Image showing diversity of hemifacial microsomia (Veliz S, Agurto P, Leiva N. Hemifacial microsomia. A literature review. Rev Fac Odontol Univ Antioq 2016) Goldenhar syndrome Goldenhar syndrome, also known as first and second branchial arch syndrome or oculo-auriculo-vertebral spectrum, is a complex of craniofacial and vertebral anomalies. It was originally described by Von Arlt, but was not considered until 1952, when Goldenhar reported three new cases of this complex that has subsequently been referred to with his name. In 1990, Gorlin., *et al.* extended the specifications to a complex of events that included a facioauriculoventricular syndrome, microtia, otomandibular dysostosis [4-7].

These findings can be found alone or usually associated with microtia, mandibular hypoplasia, or congenital vertebral malformations. The incidence is limited and varies between 1 case in 45,000 to 2 in 100,000 inhabitants. Currently, it should be considered a BILATERAL malformation, which would differentiate it from Hemifacial Microsomia.

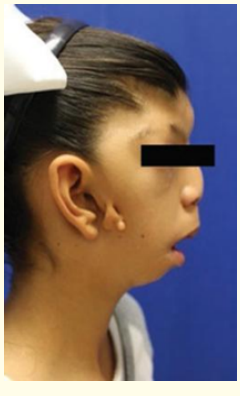

Figure f

Patient with Goldenhar syndrome and preauricular appendages This pathology is characterized by an abnormal development of several craniofacial structures, such as the eyes, which classically present epibulbar cysts and orbital malformations (microphthalmia and orbital dystopia), and the ears, which may or may not have hearing loss, facial asymmetry, macrostoma, facial clefts, presence of epibulbar dermoids, preauricular appendages, hypoplasia of the masticatory muscles (mainly the lateral pterygoid), alteration of the facial nerve, velopharyngeal insufficiency, mandibular and maxillary hypoplasia, and dental lesions [7-10].

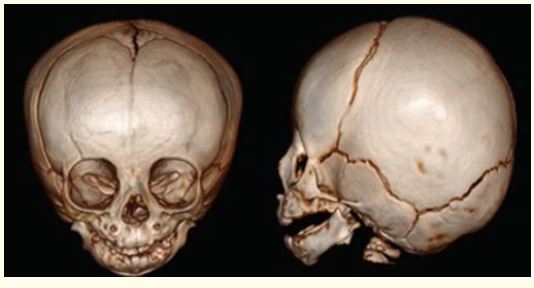

Figure g

Computed tomography with three-dimensional reconstruction. Treacher Collins syndrome Described by Berry in 1889, also known as mandibulofacial dysostosis. It is correlated with Tessier's facial clefts no. 6-7-8. Autosomal dominant with an incidence of 1:10,000 live births. Symmetrical and bilateral anomaly. Genetically, it would correspond to a mutation in chromosome 5 with its locus 5q31.33q33.3. Its etiology is unknown. The characteristics of the syndrome are: anti-Mongolian palpebral fissures and colobomas of the lower eyelid, malar hypoplasia, malformation of the auricle and sometimes of the middle and inner ear, macrostomia, anomalies in the insertion of the hair line, absence of eyelashes in the medial third of the lower eyelid. Airway management in the neonatal period is a major challenge given the marked facial retrusion.

Its treatment is functional and multidisciplinary surgical. The basic facial abnormalities described are; very pronounced downward slanting palpebral fissures are reported in (89%), malar hypoplasia in (81%), micro-retrognathia also extreme in (78%), characteristic cleft in the lower eyelid in (63%), at which level the eyelashes are missing in (69%), and bilateral microtia of variable degree, as with the other anomalies. The dentist may also encounter difficulty in providing adequate and deep anesthesia. This may be due to a large variation in the nerve pathways. Providing dental treatment under general anesthesia may be the best option. Essentially all patients affected by Treacher Collins syndrome show malocclusion and an anterior open bite due to zygomatic and mandibular hypoplasia [4-7].

Often these patients also show effects on the masticatory muscles and temporomandibular joints. Approximately 25% of children born with Treacher Collins syndrome have a cleft palate. Cleft palate is usually repaired around the child's first birthday. Underdevelopment of the jaw can be corrected by a procedure known as bone lengthening, which is the application of a rib graft to the jaw. Deficiencies in the maxilla and mandible often result in the need for nasal surgery. Other dental/oral abnormalities include tooth agenesis (primarily affecting the second premolars), ectopic eruption, and enamel opacity [7-10].

Figure h

Characteristic craniofacial abnormalities. Hypoplasia of the auricle. Slanted palpebral fissure. Maxillary hypoplasia (Mexican Journal of Pediatrics Vol. 77, No. 4 • July-August 2010 pp 159-163) Nager Syndrome Nager syndrome is a rare disease. Facial features include downward slanting palpebral fissures, absence or lack of development of the lower hemimandible, malformations of the middle and external ear with atretic or stenotic auditory canal, cleft hard or soft palate, absent or lower eyelashes, scalp hair extending to the cheek. There are defects in the upper limbs that include lack of development or absence of the thumbs and occasionally, absence of the radial portion of the limb. Other limb abnormalities may exist such as limitations of elbow extension. The toes and legs may also be affected. There are some internal abnormalities including reflux from the kidney or stomach and congenital heart problems. The severity of the syndrome varies. There are approximately 40 documented cases of Nager syndrome [7-10].

Figure i

Low implantation of the auricles and bilateral eyelid coloboma. (Rev Esp Méd Quir Volume 18, No. 1, January-March, 2013) Binder syndrome Binder syndrome is a pathology characterized by nasal-maxillary hypoplasia, flat nasofrontal angle, hypoplastic frontal sinuses, absence of the anterior nasal spine, short columella and acute nasolabial angle. The diagnosis of Binder syndrome is clinical and radiological. The most important clinical characteristics of the syndrome concern the nasal pyramid and dental occlusion. The nose of the Binderian has a flattened and drooping tip due to the premaxillary skeletal defect and the reduced horizontal dimensions of the nasal septum, the nostrils appear triangular, the columella is short and the nasolabial angle is acute. Due to the contraction of the upper jaw due to premaxillary atrophy, the dentoskeletal relationships are always of class III. In the most serious cases, the reduction in the diameter of the nasal cavities in correspondence of the nostrils, in association with the contraction of the upper jaw, can cause neonatal respiratory distress [7-10].

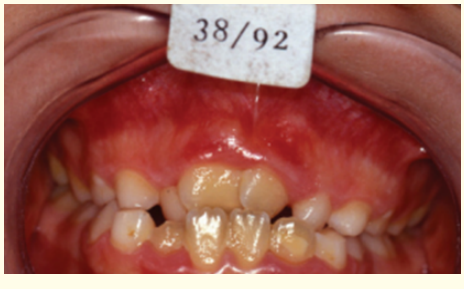

Figure j

Binder Syndrome. Intraoral photography (ODONTOL PEDIÁTR (Madrid) Vol. 12. N.º 2, pp. 93-98, 2004)

Pierre Robin Sequence Pierre Robin Syndrome (PSS) was described in 1923 by the French stomatologist who described the classic triad of micrognathia, glossoptosis and respiratory obstruction.

This respiratory difficulty, characteristic of these patients, especially during the newborn period, is caused by mandibular hypoplasia that causes lingual retroposition, which obstructs the passage of air. Early and effective management is essential for the survival of these patients. The vast majority are managed with positional changes, especially the prone position, which allows the retropharynx to be cleared when the tongue falls by gravity into a more anterior position. Continuous monitoring of O2 saturation during sleep and feeding of these children will determine the effectiveness of the position.

The objective is to ensure that the child grows as his or her mandibular hypoplasia grows. Patients who fail to stabilize or fail to achieve weight growth according to their gestational age must enter a multidisciplinary management protocol between neonatologists and plastic surgeons, which specifies which patient should be intubated, which patient is a candidate for bilateral mandibular distraction, and which patient should be directly tracheostomized.

Figure k

LEFT IMAGE: 1 month old with Pierre Robin Syndrome, low weight gain and obvious respiratory difficulty. CENTER IMAGE: Profile X-ray showing airway interruption due to lingual retroposition; RIGHT IMAGE: 1 year old with adequate mandibular development with weight gain. Patient treated with distraction osteogenesis.

The treatment seeks to achieve an ideally permanent and definitive unblocking of the airway, in order to avoid respiratory and feeding problems, and under this precept, mandibular distrac-

tion osteogenesis is one of the tools that allows this objective to be achieved. When distraction fails, the patient must undoubtedly undergo tracheostomy in order to guarantee a patent and safe airway that facilitates swallowing without risk of aspiration or other complications derived from the underlying condition. In addition, it is important to mention that tracheostomy can cause long-term complications such as tracheomalacia, chronic bronchitis, chronic obstructive pulmonary disease, and recurrent respiratory infections, so avoiding this treatment would objectively have a better outcome for patients. Atrophy/Hypoplasia Parry Romberg Syndrome.

The first description of this disease is attributed to Caleb Parry in 1825, later in 1846, Moritz Romberg made a detailed review of this entity, describing it as a syndrome and in 1871 Eulemberg introduced it as progressive hemifacial atrophy. Almost two centuries after the description of this disease, its etiology has not yet been well established; however, there are several theories, among which the following stand out: persistent autoimmune neurovasculitis, which is secondary to trigeminal neuritis, due to chronic infection caused by a neurotropic virus such as herpes, and due to an increase in sympathetic nervous activity that induces the development of facial atrophy. Other less accepted theories include: alterations in fat metabolism, trauma, myelopathy, vitamin B12 or E deficiency, endocrine diseases, demyelinating neuropathy and intoxication by drugs, alcohol, cisplatin and pyridoxine, although none have managed to specifically explain the clinical manifestations of this disease. Different authors have observed immunological abnormalities in the subcutaneous tissue of patients with this syndrome, although this relationship has not been verified so far. The main clinical characteristic of this disease is the presence of hemifacial atrophy, which is detected in 100% of cases, usually affecting the left side. It can manifest itself from a barely perceptible asymmetry to a severe facial deformity, with neurological and ophthalmological symptoms. Its treatment will depend on the severity of the clinical manifestations, the first line being the replacement of those atrophied structures with camouflage elements such as fatty filler with the aim of recovering volume, which can range from lipoinjection, dermofat graft to a microvascularized free flap [7-10].

Figure l

Deviation of the corners of the mouth and nose (Martínez EV., *et al*. Parry Romberg syndrome or progressive hemifacial atrophy - Rev Cent Dermatol Pascua 2019; 28 (2): 76-81)

Figure m

Atrophy of half of the tongue on the right side (Martinez EV., *et al*. Parry Romberg syndrome or progressive hemifacial atrophy - Rev Cent Dermatol Pascua 2019; 28 (2): 76-81) Neoplasias / Hyperplasias Tumors considered within craniofacial anomalies are

- Fibrous bone dysplasia
- Neurofibromatosis Fibrous bone dysplasia

Fibrous dysplasia (FD) is a benign fibro-osseous disease that consists of the replacement of normal bone with excessive proliferation of fibrous connective tissue with non-functional bone structures. The form of craniofacial FD is rare and not well defined. The most frequent involvement in the craniofacial area occurs in the body of the mandible and posterior area of the maxilla. The authors describe the complete management and functional rehabilitation of an advanced case of fibrous dysplasia of the mandible and review the therapeutic options for this condition.

The etiology of FD is most likely a mutation in the Gsa gene (GNAS1) on chromosome 20q11. This mutation can occur during embryonic development or postnatal life. The mutation of the Gsa gene produces an increase in adenylate cyclase, which increases intracellular cAMP. The high concentration of intracellular cAMP generates an increase in the proliferation and inappropriate differentiation of the mutated cells, causing the formation of an immature and disorganized fibrous matrix, generating the fibrous tissue of dysplasia. The most frequently observed clinical manifestations are those derived from the gradual, painless enlargement of the involved bone, in this case, facial asymmetry, with its corresponding aesthetic deformity. Other symptoms result from constriction of cranial foramina or obliteration of bony cavities: anosmia, diplopia, proptosis, epiphora, strabismus, facial paralysis, tinnitus, nasal obstruction, malocclusion and interference with mastication and speech [7-10].

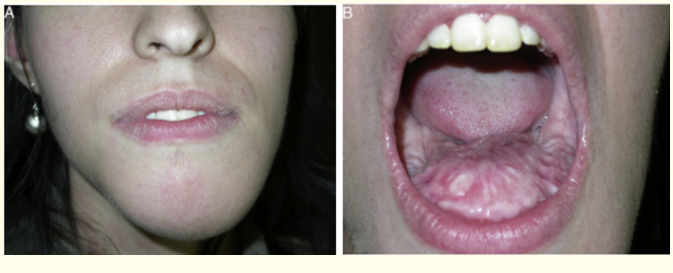

Figure n

Initial clinical examinationΛ A) Extraoral and (B) Intraoral. From a patient diagnosed with fibrous dysplasia - Rev. Oral Maxillofacial Surgery 2014;36(1):32-37 Neurofibromatosis Neurofibromatoses constitute a group of inherited disorders of autosomal dominant transmission, with a prevalence of 1 case per 3,000 births (1), whose expressivity varies and, frequently, in 50% of cases there is no family history of the disease, which represents that it appears as the result of a spontaneous mutation (1, 2).

The gene involved in NF1 is located on the long arm of chromosome 17, exactly in band q11.2; this gene secretes a protein known as neurofibromin which has the function of inhibiting abnormal cell growth. This gene contains approximately 50 exons, which explains the great variability of the disease's penetration, and the great variability of its clinical characteristics can be explained by the numerous mutations detected. On the other hand, the gene responsible for NF2 is located on the long arm of chromosome 22, although it is not yet known which of its bands. Orofacial manifestations Orofacial manifestations of neurofibromatosis type 1 occur in between 4 and 7% of cases. When they affect soft tissues, they appear on the tongue, the floor of the mouth, the alveolar ridge, the palate and the buccal mucosa, following this order of frequency. The most frequent finding, in this case on the tongue, is hypertrophy of the fungiform papillae and what could presumably be called neurofibromas, although these only appear intraorally in 25% of patients. On the floor of the mouth, nodules with a sessile or pedunculated base, of firm consistency, covered with mucosa of normal appearance and consistency can be observed, while on the alveolar ridges, enlargements of firm consistency are usually observed that can cause displacement of the dental organs.

As for the palate and buccal mucosa, they manifest with the same characteristics as those of the floor of the mouth and alveolar ridges. When they affect bone tissues, the radiological findings are basically of three types: 1. As a central lesion that is considered rare. 2. They appear as a result of extraosseous compression, giving rise to lesions such as atrophy or erosion of the cortex with displacement of organs or tooth germs. 3. Deformities similar to dysplasias that appear in other parts of the skeleton. These lesions may or may not be directly associated with neurofibromatous tissue. It is also typical to see radiologically an increase in the size of the mental foramen, as well as the inferior dental nerve canal [9,10].

Neurofibromatous lesion in the alveolar ridge region and anterior third of the tongue Rev Esp Cir Oral y Maxilofac 2008;30,3 (May-June):185-190 © 2008 ergon Craniosynostosis Craniosynostosis corresponds to the premature closure of 1 or more cranial sutures. The term craniostenosis, although sometimes used as a synonym, refers to the space conflict that may be secondary to craniosynostosis. It is estimated that the frequency is 1 in 2000-2500 newborns, being more frequent in men. There is no evidence that positional asymmetries affect the development or neurological condition of

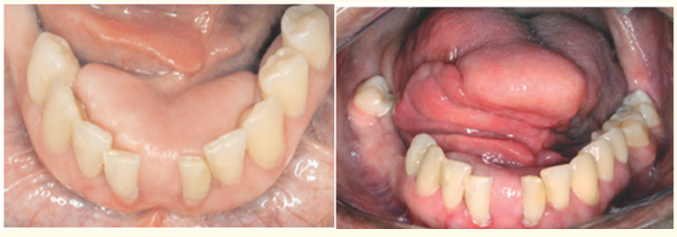

Figure o

individuals and the tendency is for the asymmetry to improve once the child begins to sit up. In these cases, management should be conservative and does not require special measures, except for recommendations regarding changes in position. The possible consequences of synostosis, mainly syndromatic or those in which more than one suture is compromised, include intracranial hypertension, visual defects and decreased motor skills, among others. For this reason, treatment is generally surgical. There are various ways of classifying craniosynostosis: by the shape of the skull, whether there is only one affected suture or several (simple vs complex), when it is associated with another identifiable malformation (syndromatic vs non-syndromatic), and if an underlying cause can be identified (primary vs secondary).

There are some factors related to a higher risk of presenting non-syndromic (or sporadic) craniosynostosis. In a recent study, it was found that multiple pregnancies, cesarean section, breech presentation, gestational diabetes and oligohydramnios are associated with craniosynostosis. Pathophysiology and genetics Sutures are synarthrosis-type joints. The adult has 16 sutures: 4 odd (metopic, sagittal, coronal and lambdoid) and 6 paired (squamous, sphenofrontal, spheno-squamous, spheno-parietal, parieto-mastoid and occipito-mastoid). They are formed by fibrous tissue that, on the one hand, prevent excessive separation of the bones and on the other hand allow the increase in size of the skull. The development of the brain acts as a motor for the growth of the skull. When a suture closes prematurely, the expansion of the skull is restricted in the axis perpendicular to the suture, causing compensatory growth in a direction parallel to the suture.

This is known as Virshow's Law and allows the prediction of skull shape. In addition, there are 4 other principles that explain skull shape patterns

- The bones of the cranial vault adjacent to the synostotic suture act as a single bone plate, with reduced growth potential.
- Asymmetric bone deposition occurs at the cranial vault sutures and along the perimeter of the bone plate. Bone deposition is greater at the periphery, at the margin of the fused bone plate.
- Due to the restriction of cranial vault growth, there is compensatory growth that occurs symmetrically at sutures that are "in line" with the synostotic suture. For example, In right anterior plagiocephaly, there is compensatory growth in the contralateral cranial bone and suture.
- The greatest degree of compensatory growth occurs in the sutures closest to the fused suture, and to a lesser degree in sutures distant from the affected suture.

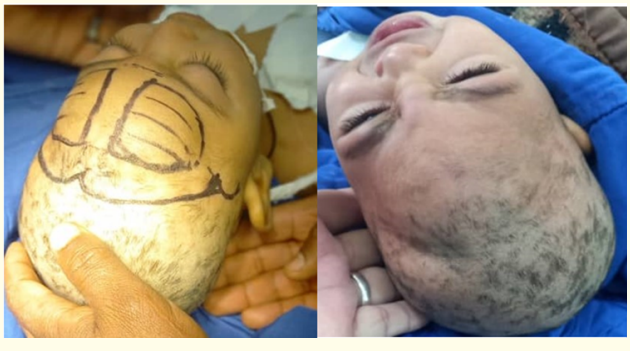

Figure p

Craniosynostosis. Photographs courtesy of Dr Damian Lastra Copello. Neurosurgery Specialist, Dr Miguel Enrique Clinical Surgical Hospital. Havana, Cuba.

In syndromic craniosynostosis (which is associated with other malformations), genetic mutations can be identified in up to 30% of cases. In patients in whom craniosynostosis is the only malformation identified, these mutations are only identified 2-5% of the time. The most frequently mutated genes are the Fibroblast Growth Factor Receptor (FGFR1, 2 and 3) and the homologous human gene of Drosophila TWIST1. These mutations can be found in healthy relatives, which shows that it is not the only causal factor and that there is incomplete penetrance.

Coronal synostosis (uni or bilateral) is the one most frequently associated with a genetic alteration. A Proline-Arginine substitu-

tion (Pro250arg) is found in up to 30% of cases in FGFR3. This point mutation determines Muenke syndrome, even in the absence of other malformations. Other less frequent mutations are: variants of the Insulin-like Growth Factor Receptor 1 (IGF1R), the transcription factor RUNX2, TCF12 (which is found in non-syndromic craniosynostosis) and the SMAD6 mutation, which is related to metopic and sagittal synostosis.

Ridgway EB, Weiner HL. Skull deformities. Pediatr Clin North Am. 2004;51(2):359-87. The types of treatment are: total cranial reconstruction, minimally invasive bone strip craniectomy with use of cranial orthosis, minimally invasive bone strip craniectomy with spring implantation and cranial distraction. In general, for syndromatic and non-syndromatic cases, it is recommended to perform the surgical procedure after nine months, since a lower rate of restenosis and complications (mainly bleeding) has been seen in this age group. For follow-up, the Whitaker scale has been used, which describes the postoperative appearance and the need for surgical reinterventions

- **Category I:** Surgical revisions are not considered advisable or necessary.
- **Category II:** Revision of soft tissues or minor bone contours is suggested.
- **Category III:** Major alternative osteotomies or bone graft procedures are required.
- **Category IV:** Craniofacial procedures are required that duplicate or exceed the original surgery to an extent.

The anomalies of the number of teeth (agenesis, oligodontia or supernumerary), as well as the shape of the tooth, the included tooth and the ectopic eruption (transposition) were marked and specified according to the analysis of panoramic radiographs, plaster models and data obtained from medical records related to dental development. Most of the craniofacial malformations identified in each of the aforementioned paragraphs are part of a number of alterations or pathologies of the human body, which in some way trigger craniobuccomaxillofacial alterations that modify the proper stomatological functioning, so we must not neglect the dental treatment of this type of patients by a multidisciplinary team for the joint treatment of this type of patients. Doctors of stomatology and other specialties must be knowledgeable and not afraid to treat these types of patients.

Conclusion

The main consequences and risks of some craniofacial syndromes were described, where it was shown that important morphophysiological alterations can be detected, affecting the correct development and quality of life of those affected.

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