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Research Article

Crouzon Syndrome (Congenital Craniofacial Dysostosis): from the Clinical Case to the Review of Craniosynostosis

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Abstract

Crouzon disease or Crouzon syndrome (CS) is a rare congenital anomaly that is caused by intrauterine premature closure of the coronal, sagittal and lambdoid sutures causing abnormal growth of the skull. It is considered an ultra-rare (ultra-orphan) disease, with an incidence of 1/50,000-60,000 neonates. We present the case of a 78-year-old woman with CS who presented congenital craniosynostosis with turricephaly, hypertelorism, external strabismus with bilateral exophthalmos and blindness (due to atrophy of the optic nerve of the right eye), maxillary hypoplasia, hearing loss, narrow palate, mandibular prognathism, malocclusion with crossbite, anosmia, parrot-beak nose, thin upper lip and facial asymmetry. It is a genetic disease with autosomal dominant inheritance, complete penetrance and variable expressivity. It is caused by mutations in the FGFR2 gene (chromosomal locus 10q25-10q26). From 30 to 60% of the cases are sporadic because they are new mutations (de novo mutations). The prenatal diagnosis of this entity is difficult, since the early welding of the sutures generally begins after birth. The diagnosis is fundamentally clinical, which must be complemented with imaging studies. Appropriate genetic counseling is necessary. In the future, with advances in clinical genetics, most craniosynostoses could be avoided if we incorporate the genetic study of the different genes involved (already known) to carrier screening. For this, it is necessary to promote assisted reproduction techniques (preimplantation genetic diagnosis). The cases that correspond to de novo mutations cannot be avoided through these strategies. Regarding treatment, an early diagnosis is required to plan a highly specialized surgery that allows the remodeling of the skull and face so as to achieve good aesthetic and functional results, and avoid some of the auditory and visual complications. In this article we review the embryology of the skull, craniosynostosis, and more specifically of CS.

Keywords: Crouzon disease; Crouzon syndrome; Craniosynostosis; Ultra-rare genetic disorder; Craniofacial dysostosis; FGFR2 gene.

Introduction

Craniosynostosis is defined as premature partial or total fusion of one or more of the cranial sutures. If these disorders are premature and pronounced, they can cause abnormal skull development. This concept groups several types according

to the sutures affected and the associated malformations.

The term *craniosynostosis* derives from the Greek *synostosis* which means "closure". In 75% of cases only one or part of a suture is fused. The prevalence at birth of isolated craniosynostosis is 2-4 cases per 10,000 live births. It is more frequent in boys than in girls (2-3 boys: 1 girl). 85% of the cases are sporadic, mostly involving a single suture: sagittal 56%, multiple 14%, unilateral coronal 11%, metopic 7% and lambdoid 1-0.003% (1). Recent studies point to a higher incidence of synostosis of the metopic suture, placing it as the second most frequent cause (28% of the total), possibly due to a better clinical diagnosis rather than a real increase in its incidence (2).

Crouzon disease or Crouzon syndrome (CS) was first described by the French surgeon Octave Crouzon (1874-1938) as a genetic disorder, characterized by premature fusion of the coronal and frontosphenoidal sutures and the sphenoethmoidal synchondrosis. In figure 1 we show the images of the original article published by Crouzón in 1912 (3). CS is included in the group of congenital defects or alterations that cause abnormal fusion between the bones in the skull and face and is classified within the group of craniosynostoses.

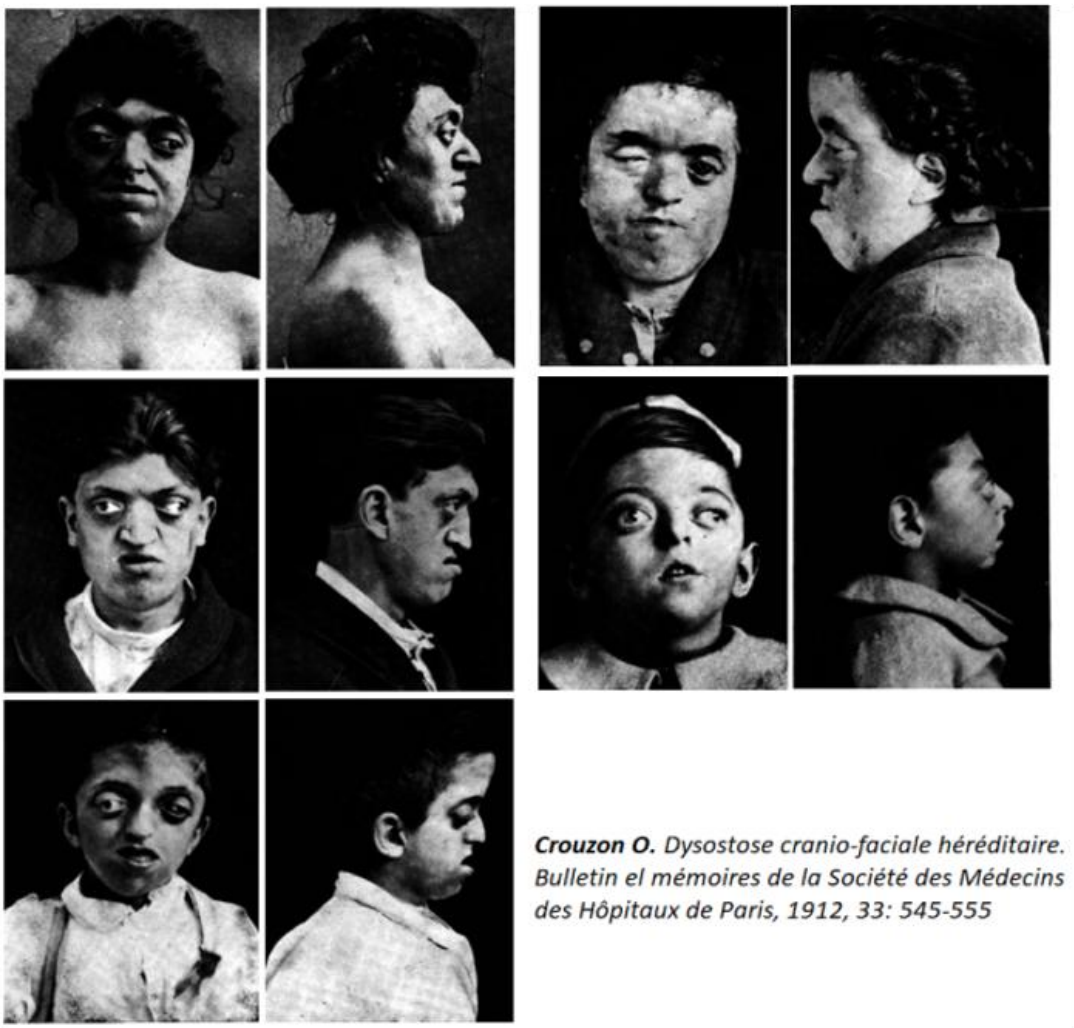

Figure1. Images from the original article by the French surgeon Octave Crouzon

Case Report

We present the case of a 78-year-old woman with CS who presented with congenital craniosynostosis with turricephaly, hypertelorism, external strabismus with bilateral exophthalmos and blindness (due to atrophy of the optic nerve of the right eye), maxillary hypoplasia, fluctuating hearing loss, narrow palate, mandibular prognathism, malocclusion with crossbite, anosmia, parrot-beak nose, thin upper lip and facial asymmetry (Figure 2).

Figure2. Front and head profile of 78-year-old woman with CS

In the oral cavity, an ogival palate is observed, V-shaped, due to the swelling of its lateral parts. Due to age, among other causes, a significant loss of dental pieces is observed (Figure 2a).

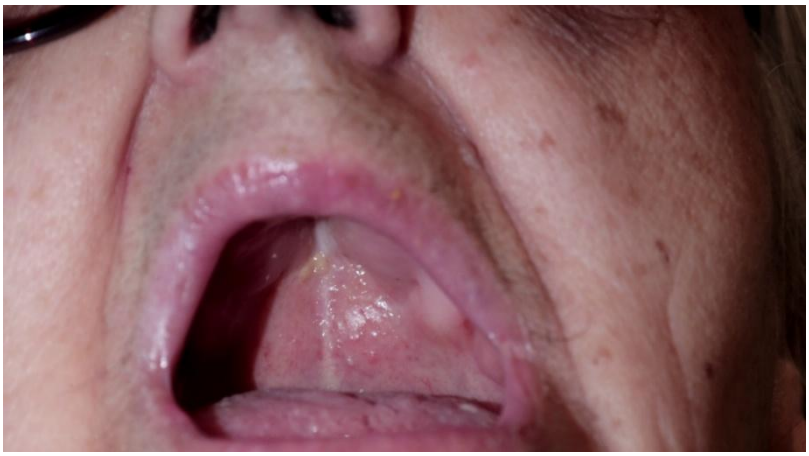

Figure 2a. Ogival palate with loss of most of the teeth

Plain radiographs of the skull can show the consequences of premature closure of the cranial sutures: cranial deformity secondary to synostosis with a prominent front, a short anterior cranial fossa and deep median and posterior compartments, as well as protrusion at the level of the anterior fontanelle; highly accentuated digital prints giving the image of a cloudy skull. Maxillary hypoplasia with flattening of the midface, nasal septum deviation, shallow orbits with decreased anteroposterior size, and lower mandibular prognathism. Calcification of the stylohyoid ligament is also observed (Figure 3).

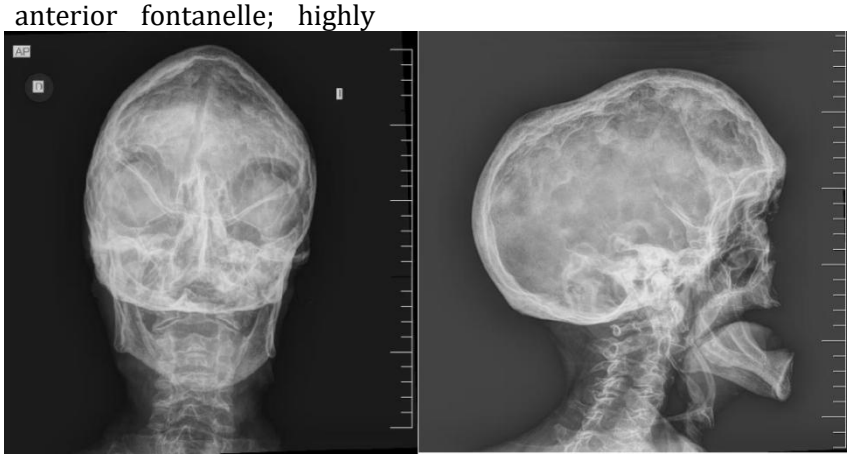

Figure 3. Plain radiographs (anteroposterior and profile) of the 78-year-old woman with CS

Our 78-year-old patient could not benefit from the advances in current medicine at the time of her birth, given the state of the art of surgery at that time. Although she already showed a Crouzon phenotype at birth, her morphological traits became more pronounced as she grew older. She began to walk at 20 months (normal between 12 and 18 months).There is no family history related to this syndrome or other craniosynostosis.

Despite his poor schooling, her intellectual development has been normal. During her school years, she suffered harassment (bullying) due to her physical appearance, which led her to a certain degree of social isolation. She dropped out of school at the age of 14. Unfortunately, as an adult, she continued to suffer the humiliation of a society that is not very tolerant of those who are different. A society that at that time allowed details such as that the label "subnormal or useless" officially appear on her Spanish identity card.

She reports fluctuating hearing loss and visual limitation(bilateral optic atrophy with exotropia and blindness in the right eye). At the age of 39, he was admitted to the hospital due to pneumococcal meningitis that resolved without sequelae. At the age of 76, she was diagnosed with low-grade urothelial (transitional cell) carcinoma, treated with a transurethral resection and with a good evolution. Currently, at the age of 78, she maintains intelligent conversations, retains an exceptional memory to remember dates and events, and is totally independent for the basic and instrumental activities of her daily life.

Skull Embryology (4-10)

The skull is divided into two parts: the NEUROCRANIUM (protective covering around the brain) and the Viscerocranium (skeleton of the face).

The child's brain develops at a rapid rate in the first months of life. Brain volume doubles in the first six months of life, doubling again when it reaches one year of life. By the age of two and a half years, 80-85% of all brain growth will have occurred. The skull grows and remodels itself as a result of this rapid growth. Minimal pressure (approximately 5 mmHg) from the developing brain is required to stimulate new bone formation at the margins. The most significant growth of the skull occurs at the expense of the sagittal suture and coronal sutures.

Initially the face is small in comparison with the neurocranium. In fact, the neonatal face occupies approximately one eighth of the total skull. This initial disproportion derives from the virtual absence of air in the sinuses and the small size of the mandible and maxilla. With the appearance of the dental pieces and the pneumatization of the paranasal sinuses, the face loses its infantile characteristics.

The NEUROCRANIUM (Figure 4) is divided into two parts, the vault and the base: 1) Membranous Portion (forms the flat bones that surround the brain like a vault) and 2) Cartilaginous Portion or Chondrocranium (forms the bones of the base of the skull).

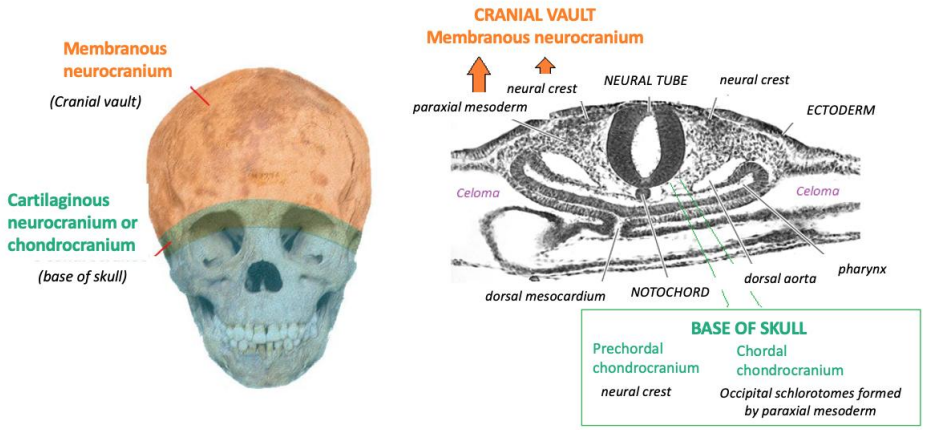

Figure 4. Embryological origin of the Membranous and Cartilaginous Neurocranium

Membranous Neurocranium: The membranous portion of the skull is derived from neural crest cells and paraxial mesoderm. It covers the brain and undergoes intramembranous ossification.

The areas that require faster development have intramembranous ossification, generating bone directly from the mesenchymal tissue, without going through the cartilaginous phase. The consequence is the formation of various flat and membranous bones that are characterized by the presence of bone spicules. These bone spicules radiate progressively from the centers of primary ossification toward the periphery. These "primary ossification centers" are made up of multipotent mesenchymal cells. Cell proliferation and subsequent differentiation into osteoblasts occur at the margins producing radial bone growth until the osteogenic fronts of two bones approach and sutures form.

With growth during fetal and postnatal life, membranous bones gain size through the apposition of new layers on their outer surface as well as simultaneous osteoclastic resorption on their inner surface.In the child, the cranial bones are unilaminar, without diploe, from birth to about four years of age. Thereafter and throughout adulthood, two layers of compact bone become apparent, the internal and external diploes, with an intervening layer of trabecular bone tissue.This bone container (frontal bone, parietal bones, squamous portion of the temporal and occipital bones, and nasal and lacrimal bones) protects the brain, but at the same time it has to allow its growth and, after it has finished, be as hermetic as possible to increase its protective function. The cranial vault is made up of the flat bones of the skull (frontal, parietal, occipital, and the squamous portion of the temporal bone). They are lined by periosteum, which is firmly attached to the dura on the intracranial surface. At birth, these flat bones are separated by SUTURES (narrow bands of mesenchymal-type connective tissue) and where more than two bones meet, the sutures are wide and are called FONTANNELLES (Figure 5). Sutures and fontanels allow for head molding (overlapping) during birth. Shortly after delivery, the membranous bones return to their original position and the skull appears large and round.

There are six main sutures (metopic, sagittal, 2 coronal and 2 lambdoid sutures) and the six fontanelles (anterior/ major/ bregmatic fontanelle - rhomboid -, posterior / lamboid fontanelle - triangular -, 2 anterolateral /pteric fontanellesand 2 posterolateral/ asteric fontanelles) (Figure 4).

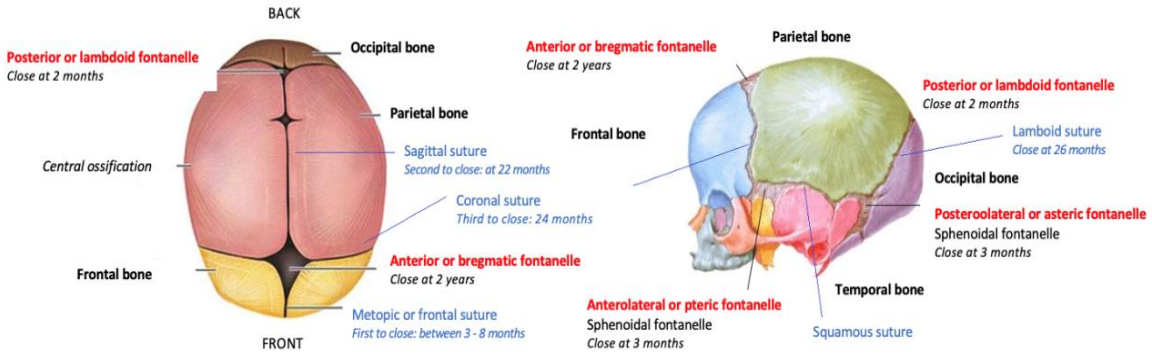

Figure 5. Skull of a newborn. Side and top view

The palpation of the fontanelles gives us very valuable clinical information regarding whether the ossification of the skull is normal or if the intracranial pressure is normal. Various sutures and fontanelles remain membranous for a considerable period after birth to accommodate postnatal growth of the brain. Regarding the closure of the fontanelles, some normal ranges have been calculated: The anterior or bregmatic fontanelle is the largest and is diamond-shaped, measures approximately 2.5 cm and the skin located on it beats. At 3 months after birth, this

fontanelle begins to obliterate due to the growth of the edges of the membranous bone and closes completely at 18 months, before the second year of life. The posterior or lambdoid fontanelle closes between the first and second month of life.

Between 6 months and the first year of life, there is indentation of the cranial sutures, the irregular edges become interdigitalized, are juxtaposed but do not fuse. Although a 5- to 7-year-old child has nearly reached his full cranial capacity, some sutures remain open into adulthood. The sutures fuse, usually from back to front and from the lateral to the medial area, with the exception of the metopic (frontal) suture which fuses in the opposite direction, from the glabella to the anterior fontanelle. The metopic (frontal) suture is the first to fuse, around ten months. The coronal, lambdoid, and sagittal sutures remain patent until the fourth decade of life, with the sagittal suture being the last to fuse. Around 10-13 years of age, the sutures are functionally occupied by fibrous tissue, which is why it is said to have closed; but true ossification occurs between the fourth and fifth decade of life.

Cranial sutures are a form of flexible fibrous joint between the flat bones of the skull. They perform two different functions: firstly, they allow the deformation or overriding molding of the cranial bones during passage through the birth canal; and secondly, they allow the growth and change of shape of the skull, adapting it to brain growth.

Cartilaginous Neurocranium or Chondrocranium (occipital, body and lesser wings of the sphenoid, body of the ethmoid, auditory capsules, nasal capsules, and the petrous and mastoid portions of the temporal bones): At first it is made up of a series of independent cartilages. Two different parts:

1) Caudal chondrocranium: Those located in front of the rostral limit of the notochord, which ends at the level of the pituitary gland in the center of the sella turcica, derive from the neural crest.

2) Chordal chondrocranium: Those located in the posterior region of the notochord originate from the occipital sclerotomes formed by the paraaxial mesoderm. The base of the skull is formed when the cartilages of the caudal chondrocranium and the chordal chondrocranium fuse and undergo endochondral ossification.

The VISCEROCRANIUM (SPLACNOCRANIUM): Includes from the lower edge of the orbits to the mandible. Contains and protects the organs of vision, smell and taste. It corresponds to the bones of the face and derives mainly from the first two pharyngeal arches. The mesechyme for the formation of the facial bones, including the nasal and lacrimal bones, is derived from neural crest cells.

First pharyngeal arch (Figure 6): It gives rise to the dorsal portion, the maxillary process, which extends forward below the region of the eye and gives rise to the maxilla, the zygomatic bone and part of the temporal bone. The ventral portion, the mandibular process, contains Meckel's cartilage. The mesenchyme around the cartilage condenses and presents intramembranous ossification to give rise to the mandible. Meckel's cartilage disappears, except in the sphenomandibular ligament.

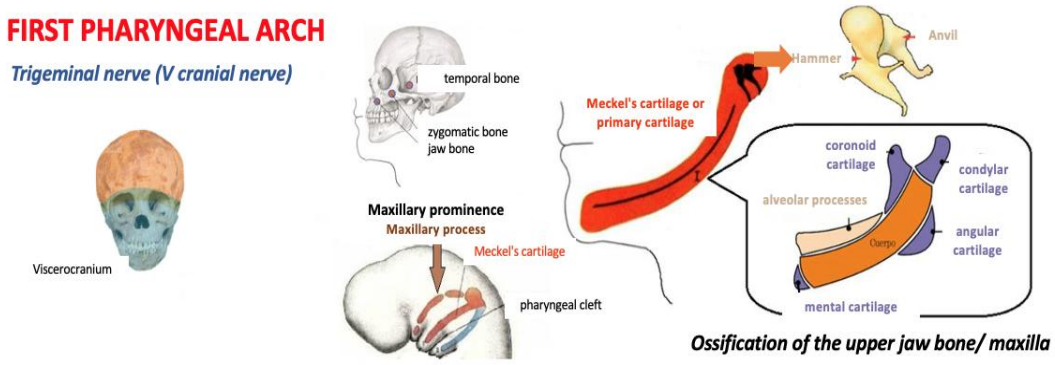

Figure 6. Embryological origin of the Viscerocranium. Structures derived from the first pharyngeal arch

Second pharyngeal arch (Figure 7). From the dorsal end of the mandibular process together with the second pharyngeal arch, it later gives rise to the incus, the hammer and the stirrup. Ossification of the three ossicles begins in the fourth month, making them the first bones to reach complete ossification.

The mastoid process does not develop until the second year of life, and the facial nerve (VII nerve) is relatively exposed and unprotected when it emerges from the mastoid foramen. In an instrumental delivery with forceps, this nerve can be damaged. The two frontal bones unite around 6-8 years of age and their suture rarely appears in adults. The frontal sinuses are absent in the newborn, and invade the bone by 2 years of age.

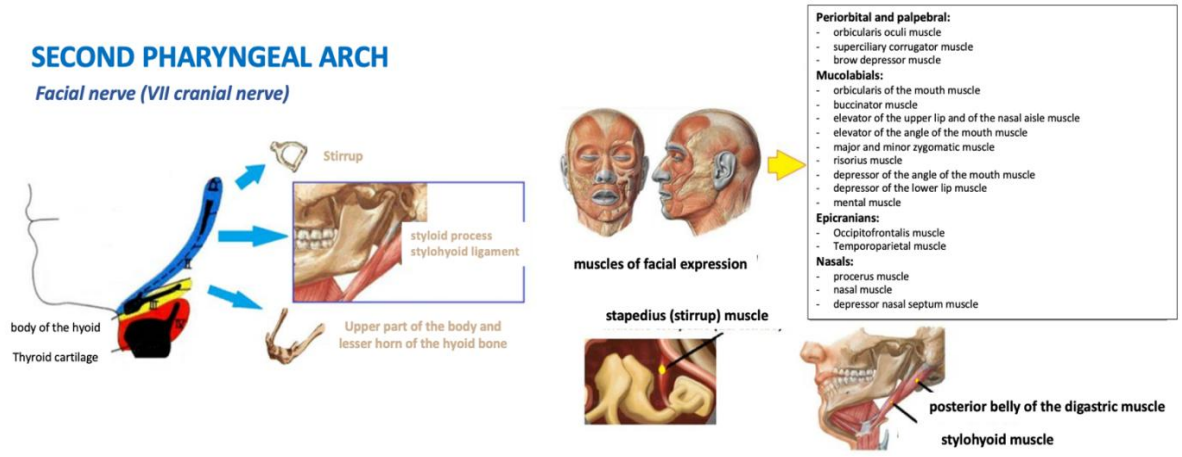

Figure 7. Embryological origin of the Viscerocranium. Structures derived from the second pharyngeal arch

Craniosynostosis or Craniostenosis (11)

In the full-term infant, the cranial bones are well formed and separated by fontanelles and sutures. The alteration of these processes can result in the premature fusion of the cranial sutures, a process that is known as "craniosynostosis". "Craniosynostosis" or "craniostenosis" (Figure 8) is the premature closure of one or more skull sutures.

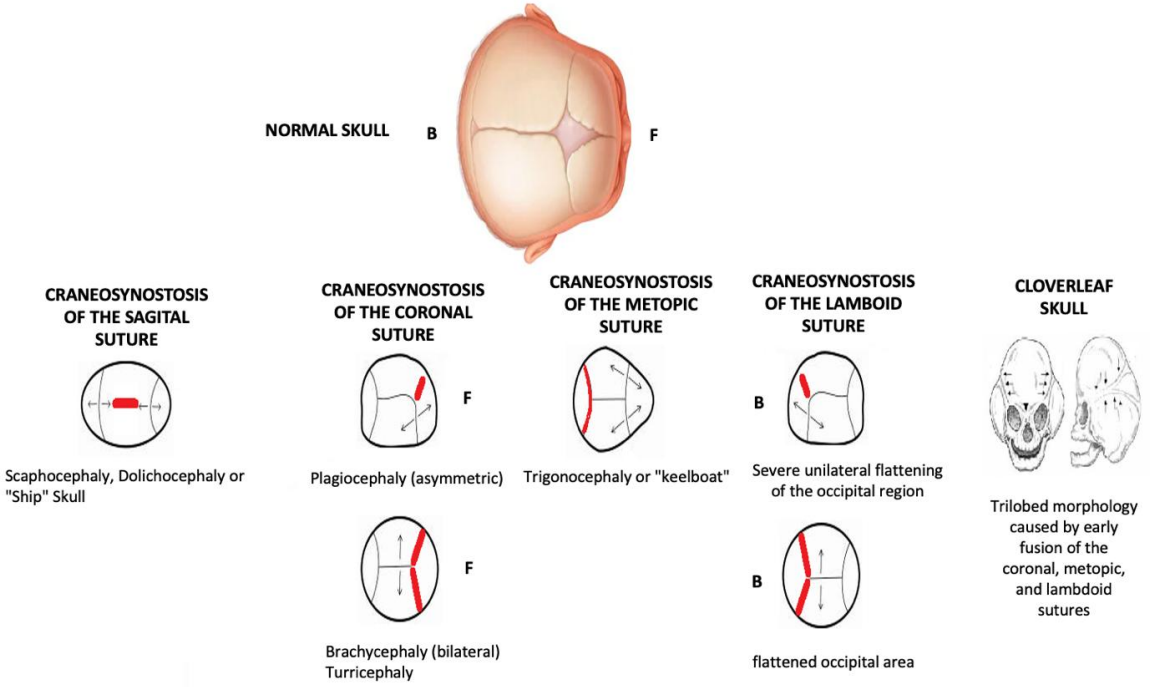

Figure 8. Types of Craniosynostosis

Early diagnosis is essential for management, prevention of complications, and early surgical correction. Craniosynostoses are classified as primary and secondary (Table 1). At present, the treatment of this syndrome requires a multidisciplinary approach as well as early complex orthopedic surgery: it usually requires multiple surgical procedures with complete cranial disassembly and remodeling, treatment of intracranial hypertension, and multiple maxillofacial surgeries for midface advancement using osteotomies and distractors.

It should be suspected when, in a newborn, when palpating the sutures instead of slight depressions, we observe more or less hard elevations (ridges) and/or when the fontanelles are not palpable or they are very small. Together they affect 1 in 2,500 newborns. They can be PRIMARY: 85% non-syndromic primary (alterations in development during the prenatal period) and 15% syndromic primary (alterations develop progressively during the postnatal period); o SECONDARY to metabolic or hematological disease, bone dysplasia, prematurity, external compression of the skull, brain growth failure, or decreased intracerebral pressure.

Table 1. Classification of Primary and Secondary Craniosynostoses

<table>
<tr><td rowspan="6">PRIMARY craniosynostosis</td><td colspan="2">85% NON-SYNDROMIC
Developmental disturbances during the prenatal period</td><td>70-85% SIMPLE
30-15% MULTISUTURE</td></tr>
<tr><td rowspan="5">15%
SYNDROMICAL
The alterations develop progressively during the postnatal period</td><td colspan="2">APERT syndrome (12) (1/100,000-160,000 live births): Craniosynostosis (acrocephalosyndactyly), midface hypoplasia, and anomalies of the fingers and toes with/without syndactyly.</td></tr>
<tr><td colspan="2">CARPENTER syndrome (13) (< 1/1,000,000 live births): Craniosynostosis, intellectual disability, characteristic facies, abnormalities of fingers and toes (brachydactyly, polydactyly and syndactyly), short stature, congenital heart disease, skeletal defects, obesity, genital abnormalities and umbilical hernia.</td></tr>
<tr><td colspan="2">CROUZON syndrome (1/50-60,000 live births)(14): Craniosynostosis, characteristic facies (flattening of the middle third of the face, hypertelorism and exophthalmos, maxillary hypoplasia, parrot-beak nose and facial asymmetry).</td></tr>
<tr><td colspan="2">PFEIFFER syndrome (6, 15) (1/100,000 live births): Craniosynostosis (mainly bicoronal) and associated functional disorders. 3 types have been described. Type 1 ("classic PFEIFFER syndrome") is the least severe form and is characterized by: mild to moderate midfacial hypoplasia, minimal anomalies of the hands and feet, mild or absent ocular proptosis. Types 2 and 3 are associated with more severe manifestations such as extreme proptosis and choanal stenosis or atresia, anomalies in the fingers and toes, ankylosis or synostosis of the elbow and some complications (hydrocephalus and epileptic seizures). Other associated complications include developmental brain disorders, exposure keratopathy, exorbitism, bilateral and symmetric hearing loss, airway obstruction and obstructive sleep apnea. Type 2, the most severe form, is distinguished from type 3 by the presence of a "cloverleaf" or trilobed skull. Types 2 and 3 have only been described in sporadic cases, with an increased risk of premature death due to severe neurological involvement and respiratory problems.</td></tr>
<tr><td colspan="2">SAETHRE-CHOTZEN syndrome (16) (1/25-50,000 live births): Coronal (or, less commonly, sagittal, metopic or lambdoid) suture synostosis, facial asymmetry, low frontal hairline, ptosis, strabismus, lacrimal duct stenosis and small ears with prominent crus. Other frequent manifestations are malformations of the fingers and toes.</td></tr>
</table>

		MUENKE syndrome (17) (1/30,000 live biths**):** Varied phenotype of clinical findings, even within a single family. Most present with coronal synostosis (most often bilateral), although synostosis of other sutures may be seen (turribrachycephaly/cloverleaf skull possible). More than 15% of individuals with the mutation do not have premature skull fusion. More than 70% of patients have some type of hearing loss. They may also present with increased intracranial pressure and hydrocephalus, brachydactyly, broad toes and thumbs, clinodactyly, developmental delay, intellectual disability (often mild), epilepsy, and/or increased risk of behavioral problems, including adaptive behavior.
		NON-SPECIFIC MULTISUTURE CRANEOSYNOSTOSIS: They include clinical entities formerly classified as **KLEEBLATTSCHÄDEL syndrome**(18) (cloverleaf skull and multiple congenital anomalies) or **JACKSON-WEISS syndrome**(19) (foot malformations and, in some patients, craniosynostosis with facial anomalies); others: **BOSTON-TYPE CRANIOSYNOSTOSIS** (prominent forehead, turri-brachycephaly, and cloverleaf skull).
SECONDARY craniosynostosis	*Alteration in brain growth. Intrauterine compression of the skull. Teratogens. Rapid hydrocephalus decompression by valve shunt. Rickets, hypophosphatasia, hypercalcemia, hyperthyroidism.*	

It is important to clarify the differences between the terms *craniosynostosis* (fusion of the cranial sutures) and *plagiocephaly* (from the Greek *plagios* and *cephaly*, which means "oblique head"). The term *plagiocephaly* is used to define cranial deformations due to flattening of the cranial vault caused by the position adopted during sleep, by torticollis or by space restriction in the uterus (20). Currently, when placing babies on their backs to sleep, a posterior secondary flattening is more frequently observed (21). It is impossible to calculate the true incidence of positional plagiocephaly, as it depends on the criteria used to establish the diagnosis: the incidence could be as low as 0.33% (1 in 300 live births) and as high as 48% in healthy children under one year of age (22).

The term *oxycephaly* is used when all the sutures are closed. It can be a *harmonic oxycephaly* (when they all merge at the same time, presenting with a small skull always accompanied by intracranial hypertension syndrome) or a *disharmonic oxycephaly*(when the sutures close slowly). Poorly developed bone canals can cause anosmia, blindness, deafness, and ophthalmoplegia.

In the phenotype of patients with *Primary Syndromic Synostosis*, the cranial shape, the secondary facial mass alterations, as well as the growth of the skull base will depend both on the order and on the number of sutures that close early and on the moment in which they occur. for said closure to occur. On the other hand, the clinical characteristics that most differentiate them are: the presence or absence of anomalies in the extremities, more specifically, syndactyly and/or polydactyly.

In the phenotype of patients with *Primary Syndromic Synostosis*: the cranial shape, the secondary facial mass alterations and the growth of the skull base will depend on the number and type of sutures that are closed early and also on the moment and order of closure. On the other hand, the clinical characteristics that most differentiate them are: the presence or absence of anomalies in the extremities, more specifically, syndactyly and/or polydactyly.

There are around 100 syndromes described with fusion of one or several cranial sutures, and many of them also present alterations in the extremities. Since their clinical manifestations are very similar (23), sometimes genetic analysis is decisive for a reliable diagnosis (Table 2).

Table 2. Genes related to Craniosynostosis

GEN	CHROMOSOME REGION	TYPE OF INHERITANCE	CRANIOSYNOSTOSIS
FGFR2	10q25.3-10q26	Autosomal dominant	*Apert syndrome*
RAB23 MEGF8	6p12.1 19q13.2 (lower frequency)	Autosomal recessive	*Carpenter syndrome*
FGFR2	10q26	Autosomal dominant	*Crouzon syndrome*
The association of Acanthosis Nigricans + Crouzon Syndrome corresponds to a FGFR3 mutation			
FGFR1 /FGFR2	8p11.23 / 10q26.13	Autosomal dominant	*Pfeiffer Syndrome Type I* *Pfeiffer Syndrome Type II* *Pfeiffer Syndrome Type III*
TWIST1	7p21	Autosomal dominant	*Saethre-Chotzen syndrome*
FGFR3	4p16.3	Autosomal dominant	*Muenke syndrome*
MSX2	5q35		*Boston craniosynostosis*
FGFR2	10q26	Autosomal dominant	*Jackson-Weiss syndrome*
EFNB1	Xq12	X-linked	*Craniofrontonasal dysplasia*

Table 2 shows the genes related to the different *Craniosynostosis Syndromes*. The most frequent mutations found affect the genes of fibroblast growth factor receptors 1-3 (Fibroblast Growth Factor Receptors, FGFRs). FGFR1, FGFR2 and FGFR3, located on chromosomes 8p11.2-p11.1, 10q26 and 4p16.3, respectively. FGFRs are membrane receptors that mediate the signal translation of fibroblast growth factors in the cytoplasm. These factors regulate cell proliferation, differentiation, migration, and apoptosis through various complex metabolic pathways. The mutations identified in the FGFRs produce an increase in the function of the gene product, through different mechanisms depending on the type of mutation. This effect, in turn, induces a decrease in the number of FGFRs on the cell surface (24), which can alter the regulation of cell proliferation, differentiation, and apoptosis. However, very little is still known about the intracellular cascade of molecular interactions related to the premature fusion of the bones of the skull and extremities.

The regulation of growth and closure of the sutures are still not precisely known. Molecular signaling at these boundaries regulates cell proliferation and differentiation. The EFNB1 gene encodes ephrin B1, a ligand for EphB receptors, which causes cells to repel each other (anti-adherent activity). Loss-of-function mutations of the EFNB1 gene induce ***craniofrontonasal dysplasia***, a rare X-linked malformation syndrome characterized by craniofacial anomalies, ridged nails, intellectual disability, and various skeletal and soft tissue abnormalities.

Crouzon Disease or Syndrome

CROUZON Disease or Syndrome (1/50-60,000 live births) (25-28): This disorder is characterized by the presence of premature craniosynostosis (early fusion of the coronal and sagittal sutures), hypoplasia of the middle part of the face, with shallow orbits and ocular proptosis. Premature and progressive craniosynostosis usually begins during the first year of life, and is generally complete by 2 or 3 years of age. Headaches occur in 30% and seizures in 10%.

It affects men equally as women and exclusively the craniofacial skeleton. It represents about 5% of craniosynostosis. Inheritance is autosomal dominant, but in more than 50% of cases they are de novo mutations (29,30). The most affected chromosomal position is 10q25-10q26 of the FGFR2 gene (31).

The association of CS with acanthosis nigricans (32) is a very rare form of faciocraniostenosis. Its clinical presentation is variable and consists of Crouzon-like features and premature synostosis of the cranial sutures associated with acanthosis nigricans. It is caused by a specific mutation, p.Ala391Glu, in the FGFR3 gene (fibroblast growth factor receptor 3) located on chromosome 4p16.3, which is involved in the regulation of cell proliferation, differentiation and apoptosis. Its prevalence is 1/1,000,000 births, with a ratio of women to men of 2.4:1.

The term Crouzon pseudosyndrome is used by some authors to designate attenuated cases, without prognathism or

hooked nose, but with involvement of the sutures.

Anomalies of the skull and facial mass are hallmarks of CS: brachycephaly, turricephaly, with a bulging forehead, hypoplasia of the midface, with relative prognathism of the lower jaw. The nasal bridge is often flattened, the nose is large and hooked (parrot-beak nose). There is often a deviation of the nasal septum.

In the oral cavity, an ogival, V-shaped palate is observed, due to the swelling of its lateral parts, grouping of the upper teeth due to hypoplasia of the upper jaw and malocclusion. Sometimes the uvula is bifid. Lower lip drooping and upper lip short; sometimes a cleft palate or cleft lip occurs.

Exophthalmos is a constant finding and is due to the shallowness of the orbits, which in some cases can be complicated by: exotropia or divergent squint (deviation of the eyes outward), exophthalmia due to flattening of the orbits (eyes protruding from their normal position), conjunctivitis or exposure keratitis, visual loss, optic atrophy, hypertelorism (distance between the eyes that is greater than normal due to the position of the bony orbits), and nystagmus.

Atresia of the external auditory canals and malformation of the ossicular chain of the inner ear are accompanied by conductive hearing loss, which is seen in more than half of patients.

Radiologically, the coronal and sagittal sutures are almost always fused and the lambdoid suture in 80%. Calcification of the stylohyoid ligament is observed in 85% of cases.

Intelligence quotient is usually normal, although intracranial hypertension and intellectual deficit have been observed in some cases.

In relation to the prognosis, both the craniofacial deformity and the possible complications (optic atrophy and conduction deafness, atresia of the auditory canal, the ocular alterations already described, intellectual disability, intracranial hypertension, headaches, convulsions) depend on the intensity and the early suture fusion.

The prenatal diagnosis of this entity is difficult, since the early fusion of the sutures generally begins after birth.

The diagnosis is fundamentally clinical, which must be complemented with imaging studies. Appropriate genetic counseling is necessary as it is a hereditary disease (autosomal dominant inheritance) and we know the gene involved (related to an alteration in fibroblast growth factor receptor 2, FGFR2). Although we have to take into account that in a percentage of cases these are de novo mutations. The differential diagnosis should include all craniosynostoses, especially if there is frontal bossing.

Regarding treatment, an early diagnosis is required to plan a highly specialized surgery that allows the remodeling of the skull and face that can achieve good aesthetic and functional results and avoid some of the auditory and visual complications.

Other Primary Syndromic Synotoses (33)

APERT Syndrome (12) (1/100,000-160,000 live births): Presents an autosomal dominant pattern of inheritance and shows complete penetrance. A mutation in the FGFR2 gene (10q25.3-10q26), involved in cell signaling during embryonic development, is the cause of Apert syndrome. The risk of recurrence of affected children for unaffected parents is low, but the risk of an affected patient transmitting the disease to their offspring is 50%. Genetic counseling should be provided to affected families. Advanced paternal age has also been associated with de novo mutations, which are identified in the majority of cases.

CARPENTER Syndrome (13) (<1/1,000,000 live births): presents an autosomal recessive pattern of inheritance. Genetic counseling should be offered to risk couples (both individuals are carriers of a disease-causing mutation) informing them that the probability of having a diseased child is 25% in each pregnancy. The phenotypic expression varies considerably, even within the same family. It is recommended to provide genetic counseling to affected families. The

syndrome is caused by truncating, missense, and loss-of-function variants of two different genes, the RAB23 gene (6p12.1) and, less commonly, the MEGF8 gene (19q13.2). MEGF8 mutations are associated with lateralization defects and less severe craniosynostosis (usually involving only the metopic suture) compared with individuals with RAB23 gene mutations.

PFEIFFER Syndrome (6, 15) (1/100,000 live births): autosomal dominant inheritance with complete penetrance and variable expressivity in terms of syndactyly. It is commonly caused by mutations in the FGFR2 gene (on chromosome 10q26.13). Pfeiffer syndrome type I is associated with mutations in FGFR1 and FGFR2. Pfeiffer syndrome types II and III are associated with mutations in FGFR2. Mutations in the FGFR1 gene (on chromosome 8p11.23) only cause a small percentage of cases of Pfeiffer syndrome type I.

SAETHRE-CHOTZEN Syndrome (16) (1/25-50,000 live births): presents an autosomal dominant pattern of inheritance. Genetic counseling is important. Genetic counseling should be proposed to people with the disease-causing mutation, informing them that there is a 50% probability of transmitting the mutation to offspring. It is caused by point mutations or deletions affecting (or completely deleting) the TWIST1 gene (7p21), which encodes a basic helix-loop-helix (bHLH) transcription factor responsible for cell lineage determination and differentiation. Loss-of-function mutations in this gene cause the induction of premature fusion of the cranial sutures. Gene deletions cause more severe phenotypes, usually associated with significant neurocognitive delays. Prenatal testing for a TWIST1 mutation is rare, but may be performed in families with a known mutation or when ultrasonography shows craniosynostosis of unknown etiology. ROBINOW-SORAUF syndrome is now considered to be part of the spectrum of Saethre-Chotzen syndrome, generally with milder features. Mutations in FGFR3, FGFR2, TCF12, RECQL4, and EFNB1 have been described that cause synostosis-associated disorders that overlap phenotypically with Saethre-Chotzen syndrome. This is not surprising, as there is evidence that FGFR and TWIST1 may be involved in overlapping pathways, including osteoblast differentiation. In addition, mutations in TWIST1 have been detected in some cases of isolated craniosynostosis of a single suture, including sagittal and unicoronal synostosis.

MUENKE Syndrome (17, 31) (1/30,000 live births): presents an autosomal dominant pattern of inheritance. Genetic counseling allows parents to be informed that they have a 50% probability of transmitting the pathogenic variant to their future offspring. It is caused by a mutation in the FGFR3 gene (4p16.3), which codes for fibroblast growth factor receptor 3, necessary for normal skeletal development.

Conclusions

CS is characterized by the presence of premature craniosynostosis, hypoplasia of the middle part of the face, with shallow orbits and ocular proptosis. It represents about 5% of craniosynostosis. Its inheritance is autosomal dominant, but in more than 50% of the cases they are de novo mutations.

The prenatal diagnosis of this entity is difficult, since the early fusion of the sutures generally begins after birth. The diagnosis is fundamentally clinical and must be complemented with imaging studies. Appropriate genetic counseling is necessary.

In the future, with advances in clinical genetics, most craniosynostoses could be avoided if we incorporate the genetic study of the different genes involved (already known) to carrier screening. For this, it is necessary to promote assisted reproduction techniques (preimplantation genetic diagnosis). The cases that correspond to de novo mutations cannot be avoided through these strategies.

Regarding treatment, an early diagnosis is required to plan a highly specialized surgery that allows the remodeling of the skull and face so as to achieve good aesthetic and functional results, and thus be able to avoid some of the auditory and visual complications.

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