Craniosynostoses

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Abstract

Craniosynostoses are serious abnormalities of infancy and childhood. The term craniosynostosis (CS) indicates a cranial or craniofacial dysmorphism characterized by the premature closure of one or more sutures of the cranial vault and/or base. Classification is based on etiology, number of involved sutures, and association with other malformations or developmental defects. Among radiological methods, three-dimensional computerized tomography (3DCT) plays a major role in the characterization of these disorders and in the evaluation of surgical results, with a growing role for magnetic resonance imaging (MRI) especially in patients with neurological disorders, raised intracranial pressure, or syndromic craniosynostoses. This chapter highlights the pathophysiology of normal and abnormal skull growths, the rationale and indications for radiological studies, and the imaging features of the principal nonsyndromic and syndromic craniosynostoses.

Introduction

Craniosynostoses are serious abnormalities of infancy and childhood. The term craniosynostosis (CS) indicates a cranial or craniofacial dysmorphism characterized by the premature closure of one or more sutures of the cranial vault and/or base.

While already in 100 BC Hippocrates had described infants born with an abnormal head shape, the introduction of the term “craniosynostosis” is credited to Otto in 1830 and Virchow in 1851 (Kirmi et al. 2009; Virchow 1851). Virchow codified the general rules to explain cranial deformities, based on a concept of growth interruption of the skull perpendicular to the suture involved and consequent compensatory growth of the cranium parallel to the “pathological” suture. This concept, widely known as “Virchow law,” remains valid after 150 years, even though knowledge concerning the epidemiology, etiology, pathogenesis, and clinical/surgical therapy has dramatically changed and increased, especially during the last 20 years. Recently acquired genetic notions indicate that the basic concepts, as well as the medical–surgical approach to these pathologies, will radically change in the future.

The suspicion of CS is usually clinical, based on a cranial deformity. The diagnosis has always been almost exclusively radiological and was recently revolutionized by the introduction of digital techniques, above all computed tomography with three-dimensional reconstruction (3DCT). The aim of imaging-based evaluation is to define the suture(s) involved, to image the deformity of the skull vault and base (required for planning surgical correction), and to exclude intracranial and/or brain alterations (which could be either a consequence of or associated with CS). The neuroimaging workup is also important in monitoring the results of treatment and the “natural” evolution of the disease.

In this chapter, we will define the indications, applications, and limits of neuroimaging procedures in the diagnosis of CS. First, the epidemiology, etiopathogenesis, and classification of CS will be delineated.

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Then, we will attempt to explain the evolution of neuroimaging as applied to CS, review all applicable imaging methods, and, above all, define the rational indications for the various imaging procedures in terms of cost-effectiveness. In a more detailed discussion of 3DCT, we will then present the available techniques, their semiotics, and the results obtainable, taking into account the most recent technological advances. The most common and significant clinical–radiological presentations of CS will then be illustrated in order to emphasize the optimal use of 3DCT and, when necessary, MRI. The last section will be dedicated to neuroimaging follow-up, especially after surgery.

**Epidemiology**

Generally, the deformities that result from CS are recognized in infancy. Reported incidence rates of all forms of CS range from 1:1,900 to 1:4,000 births, with an average incidence of approximately 1:2,500 births (Boulet et al. 2008). The prevalence of CS in the general population ranges from 34 to 48 per 100,000 live births, with syndromic cases being less common than nonsyndromic ones (Lajeunie et al. 1995; Cohen 2000).

Craniosynostosis is classified according to the suture or sutures involved and whether it occurs as an isolated defect, as one of multiple major unrelated defects, or as part of a syndrome; CS has been reported as a clinical feature in more than 100 genetic syndromes, the most common of which include Crouzon, Apert, and Pfeiffer syndromes. Numerous studies have evaluated the association between craniosynostosis and risk factors such as infant sex, breech presentation, plurality, parity, preterm birth, advanced maternal or paternal age, maternal race/ethnicity, prepregnancy obesity, smoking, alcohol use, parental occupation and education, high-altitude exposure, medication use, and infertility/use of assisted reproductive technology; however, the data from these studies are largely inconclusive (Boulet et al. 2008).

Since 1992, there has been an increase in the number of infants seen with deformational posterior plagiocephaly. The most likely explanations for this phenomenon was the application of the American Academy of Pediatrics recommendation that infants slept in supine position to decrease the risk of sudden infant death syndrome and the increased awareness of plagiocephaly among pediatricians and other primary care providers (American Academy of Pediatrics AAP task force on infant positioning and SIDS: positioning, SIDS 1992).

**Classification**

The classifications of CS and, generally speaking, of the craniofacial anomalies are various, complex, and sometimes contradictory. There are multiple classification schemes, among which are the Virchow, Greig, Gunther, Simmone–Peyton, Fairman–Horrax, Laitinen, and Tessier classifications, as well as classifications determined by anatomy, genetics, and several other considerations (Branson and Shroff 2011). The different types of craniosynostosis have traditionally been classified according to:

- **Etiology**: primary (caused by a primary defect of ossification) or secondary to mechanical causes, systemic disorders, or iatrogenic causes (see below).
- **Number of the involved sutures**: simple (involving one suture) or complex (involving two or more sutures). In isolated forms, the condition is named according to the morphology of deformities consequent to the synostosis/es. These include dolichocephaly/scaphocephaly (synostosis of the sagittal suture), trigonocephaly (synostosis of the metopic suture), brachycephaly (bilateral synostosis of the coronal sutures), plagiocephaly (asymmetry of the neurocranium due to synostosis of a single
coronal suture, or monolateral lambdoid suture in the case of posterior plagiocephaly), and oxycephaly (bilateral synostosis of the coronal sutures + other suture involvement, if metopic and sagittal: turricephaly). The synostosis of multiple sutures leads to various cranial morphologies resulting from the combined effects of interruption and increased compensatory growth. The term kleeblattschädel, or a cloverleaf cranium, is used to describe a deformity resulting from the involvement of all sutures, i.e., sagittal, bicornal, and bilambdoid synostosis (Badve et al. 2013).

Association (or lack thereof) with other dysmorphic features or developmental defects: isolated/idiopathic (nonsyndromic) CS versus syndromic CS. Nonsyndromic CS occurs more commonly with the premature closure of a single or two sutures, and sagittal CS is the most common form comprising approximately 40–60 % of cases (Kolar 2011). Syndromic CS more frequently involves the fusion of several sutures and is often associated with facial deformities and brain anomalies. This difference is of utmost importance for clinicians and radiologists alike, because while nonsyndromic CS represents almost exclusively as a cosmetic problem, in syndromic CS, neurological impairment is more commonly encountered due to associated intracranial anomalies and/or raised intracranial pressure. Therefore, the radiological workup of syndromic CS should routinely always include MRI evaluation (see below). The more common and clinically significant syndromes that include CS are Apert, Crouzon, Saethre–Chotzen, Pfeiffer, Carpenter, and mixed Apert–Crouzon syndromes. In most of these syndromes, synostosis is found bilaterally in vault and skull base sutures, but all the sutures may be involved. The so-called cloverleaf anomaly, probably the most impressive craniofacial deformity due to CS, is not to be considered a specific syndrome, as it represents an anomaly that may be found in several different syndromes. A precise differential diagnosis between the various forms of syndromic CS is mainly based upon the associated facial and extremity features; despite these criteria, a precise distinction may not be feasible in individual cases (Ciurea and Toader 2009).

Etiology

According to their etiology, CS can be categorized into primary and secondary.

In primary craniosynostosis, the premature fusion of one or more sutures is believed to be due to a developmental error during embryogenesis; the condition may be caused by various genetic mutations. The process, involving one or more sutures, usually begins in utero or shortly after birth, although it is usually diagnosed in infancy due to the resulting skull deformities.

In secondary craniosynostosis, the premature suture fusion is due to mechanical causes (such as intrauterine fetal head constraint during the last months of pregnancy), metabolic causes (i.e., hypophosphatemia, hypercalcemia, hyperthyroidism, and mucopolysaccharidosis), systemic disorders (bony dysplasia, hematological diseases), and teratogens (such as retinoic acid, diphenylhydantoin, and valproic acids) (Cohen 1991; Nagaraja et al. 2013; Slater et al. 2008; Coussens et al. 2007). In secondary forms, the synostosis is a consequence of an interruption in the growth of the brain or a reduction of the cranial volume content (Hui and Joyner 1993; Wilkie et al. 1995).

Until the recent past, little was known about the causes of craniosynostosis. The discovery of genetic mutations in both syndromic and nonsyndromic cases has led to considerable insight into the etiology, classification, and developmental pathology of these disorders (Morriss-Kay and Wilkie 2005).

Approximately 85 % of cases of CS are believed to be nonsyndromic, with no identifiable gene mutation. When associated anomalies or delays are present, the possibility of a syndrome should be considered. There are greater than 100 syndromes that include craniosynostosis, and significant progress has been made in the understanding of their clinical and molecular aspects. Genetic factors involved in the pathogenesis of syndromic (and nonsyndromic) CS include activating mutations in the fibroblast growth
expression. The development of the skull is divided into the neurocranium, i.e., the protective casing around the brain, and the viscerocranium, i.e., the skeleton of the face. The neurocranium is further divided into the membranous part that forms the skull vault (frontal, parietal, squamous temporal, alisphenoid, and squamous occipital bone) and the cartilaginous part that forms the skull base (basilar and lateral occipital, sphenoid, ethmoid, and mastoid and petrous parts of the temporal bone) (Kirmi et al. 2009). Construction of the skull from a number of separate bones enables growth to take place at the margins of the bones for as long as the skull is required to expand around the growing brain. The adjacent margins of membranous bones form the sutures, where growth of the skull vault takes place; the growth regions between the bones of the skull base are cartilaginous and are referred to as synchondroses (Morriss-Kay and Wilkie 2005).

All the flat bones of the mammalian skull vault (the paired frontals and parietals and the unpaired squamous occipital) are formed by intramembranous ossification within a layer of mesenchyme, the skeletogenic membrane, between the dermal mesenchyme and the meninges surrounding the brain. Between the interparietal bone and the foramen magnum (outlet for the spinal cord), the cartilage derived from the sclerotomal components of the occipital somites ossifies to form the supraoccipital bone, which fuses with the membranous interparietal to complete the skull vault posteriorly (Morriss-Kay and Wilkie 2005). During the embryonic period (4–10 weeks of gestation), the ossification centers of the skull bones form; membranous centrifugal ossification continues during the fetal period (weeks 10–40). Brain development precedes the ossification of the calvarium; at gestational week 13, the ossification centers mineralize and at week 18 those mineralizing bones have expand sufficiently for their borders to approach each other, forming nonossified zones: the sutures. At birth, most of the skull bones (neurocranium) are ossified and separated by the sutures (Kirmi et al. 2009). At the points where three adjacent bones meet, the sutures remain wide and are called fontanels (Nagaraja et al. 2013). The sutures are fibrous bands of tissue connecting the bones of the skull and allowing their growth during development, whereas the fontanels are membranes covering parts of the skull where the bones have not yet settled, allowing the

**Structure and Growth of the Skull**

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skull bones to adapt to brain expansion and providing “functional mobility” during birth and the first year of life (Calandrelli et al. 2014).

The sutures normally fuse from back to front and lateral to medial, with the exception of the metopic suture that closes in the opposite direction, from the glabella (front) to the anterior fontanel (back). Normally, sutures and fontanels ossify at different times after the birth: the metopic suture is the only suture which normally closes during infancy. Its physiologic closure can occur as early as 2 months of age (Birgfeld et al. 2013). The sagittal suture begins to close after the age of 22 years, the coronal suture after 24 years, and the lambdoid suture after 26 years. Incomplete closure until the age of 40 years is normal (Kirmi et al. 2009). The anterior fontanel (bregmatic fontanel) typically ossifies within the second year of life, the posterior fontanel (lambdoid fontanel) is no longer palpable after the first 3 months of life, the sphenoid fontanels (pteric fontanels) close after the first year of life, and the mastoid fontanels (asteric fontanels) ossify more often within the first 18 months of life (Kirmi et al. 2009; Monteforte and Giannoni 2013).

According to the Virchow law, the direction of the cranial growth is perpendicular to the direction of each suture, and premature fusion causes restricted growth perpendicular to the affected suture with compensatory overgrowth along other patent sutures; synostosis of one or more sutures is accompanied by compensatory growth, both in other sutures and by the remodeling (appositional growth) of other parts of the skull.

In craniosynostosis, premature fusion of the skull sutures, often associated with premature closure of the fontanels, occurs in the prenatal period, perinatal epoch, or during early infancy (Nagaraja et al. 2013). The synostotic process progresses over time along the four “sutural arches” of the skull. These “arches” are formed by the sutures of the vault and the base (“major” and “minor”) as well as three of the seven synchondroses of the skull base. The sagittal arch is composed of the sagittal and metopic sutures (major sutures) and of the ethmoido-frontal sutures (minor sutures). The coronal arch consists of the coronal sutures of both sides (major sutures); the extension of each coronal suture toward the skull base is divided into an anterior and a posterior branch. The anterior branch is composed of the frontosphenoidal suture (minor suture) and the ethmoidosphenoidal synchondrosis, whereas the posterior branch consists of the sphenoparietal and sphenosquamous sutures (minor sutures) as well as sphenopetrosal synchondrosis. The lambdoid arch consists of the lambdoid suture (major suture) extending to the minor sutures of the skull base, including the occipitopetrosal or occipitomastoid suture and the spheno-occipital synchondrosis. The parietosquamosal arch represents the joint between the coronal and lambdoid arches and consists of the parietosquamous and parietomastoid sutures (Calandrelli et al. 2014; de Ribaupierre et al. 2007).

Severe CS, characterized by the involvement of a larger number or even all cranial sutures, may impair brain growth and cause seizures, mental retardation, increased intracranial pressure, and visual loss (Denis et al. 1994; Di Rocco and Velardi 1988). The growing brain generates forces that cause compensatory growth at the sutures causing them to remain open, which results in deformity of the calvarium that progresses over time.

Pathophysiology

Brain development precedes the ossification of the calvarium. Several factors such as optimum tensile force caused by brain expansion; tissue interaction between the dura, perioisteum, and skull bones; and molecular and genetic interactions are critical for appropriate fusion of the cranial sutures (Badve et al. 2013).
Skull Base/Vault and Facial Growth in CS

Calvarial growth in the infant requires rapid and symmetrical displacement of each of the large bones (frontal, parietal, and occipital) of the skull along with osseous deposition along the sutures and within the bone matrix. Skull base and facial growth follows closely and symmetrically behind calvarial growth. In the growth sequence, the anterior fossa completes its growth first, followed by the posterior and middle fossae. The anterior fossa relies on the growth at the sphenoid, ethmoid, and frontal bones using primarily growth at the frontosphenoidal and ethmoidosphenoidal sutures. Growth is rapid in this area up to about 7 years of age. The middle fossa continues its growth for an even longer period, into the teenage years, with the sphenopetrosal synchondrosis and occipitopetrosal suture being most involved. The posterior fossa also continues an active growth pattern into childhood and adolescence. The intraoccipital synchondroses complete their growth in childhood, with the spheno-occipital synchondroses remaining active into adolescence. Concomitant to this skull base growth pattern is the growth rate of the facial skeleton that continues until well into the adolescence era, with a spurt that occurs during puberty. As a result, any form of premature fusion of any of the skull base sutures and synchondroses can lead to significant alterations of skull and facial alignment, resulting in any of a number of different craniofacial anomalies.

Since the work of Virchow, there has been much discussion on whether skull base anomalies in craniosynostosis are the primary or secondary result of craniosynostosis. Virchow felt that the premature closure of a skull suture was the primary cause, while skull base deformation followed. The work by Melvin Moss and his team has argued the opposite, in that the skull base attachments of the dura develop aberrant tensile forces that are transmitted upward to the skull, resulting into the synostosis of the cranial suture. The key concept in both views is the interrelationship of the calvarium, the skull base, and the facial complex: alteration of growth direction in one leads to an alteration in the other (Goodrich 2005).

Moss (1962) in 1962 proposed that the skull should be viewed as consisting of independent but coordinated functional components which are based on the major functions of the head, such as sight, speech, etc. The various bones that comprise the skull should be viewed as components of their functional groups. Moss also demonstrated that the growth of the neural skull is primarily a growth of the neural functional matrix and that calvarial bone growth is secondary to matrix (brain) growth (Moss 1954; Young 1959). He then proposed the theory called “neurocranial capsule” which, applied to the neural skull, implies that the calvarial bones lie within the neurocranial capsule. The composition of the neurocranial capsule in the adult includes five layers of the scalp (skin, dense connective tissue, aponeurotic layer, loose connective tissue layer, and periosteum), then the bone and contiguous skeletal units (outer table, inner table, diploic space, and variable sinuses), and the layers of the dura mater.

In the late 1970s, the introduction of computerized tomography (CT) and, later, three-dimensional reconstruction (3DCT) offered a new tool for visualizing the anatomical deformities more accurately and detailed than plain radiographs. This gave rise to a new perspective of skull growth and resulted in the concept of a three-dimensional skull growth deformity, thus amalgamating the views of Virchow and Moss (Sgouros 2005). On the other hand, it is demonstrated that modifications of the base and relative sutures could be the consequence of alterations of the vault (Sgouros et al. 1999) in different forms of craniosynostosis.

In single-suture synostoses (e.g., scaphocephaly), the involvement of skull base sutures is rare, but there are at least two potential exceptions to this rule: plagiocephaly and trigonocephaly. In plagiocephaly, premature closure of one of the coronal sutures occurs with the possible involvement of the sutures of the anterior or posterior branch of the coronal arch, while in trigonocephaly, premature closure of metopic suture occurs with possible involvement of the sutures of the coronal arch. Children with syndromic craniosynostoses (e.g., Crouzon, Apert, etc.) exhibit progressive and sometimes relentless synostosis of multiple sutures, including both sutures and synchondroses of the vault and the skull base. Although the
skull base synchondroses are not primarily involved, it is generally recognized that skull vault sutural
synostosis alters significantly the growth pattern of the cranial base, which can then present hypoplasia or
deformation even in the absence of synchondrosal synostosis. The disharmony that occurs between the
calvarium, skull base, and facial skeleton is progressive and continues well into puberty (Goodrich 2005).

Although considerable scientific work has been published on the role of the skull base in CS, the
changes that occur throughout childhood have not been fully studied. Sgouros et al. (Sgouros et al. 1999)
investigated the role of skull base growth in CS using a computer-based image analysis study of the three-
dimensional anatomy. These authors quantified the growth of the skull fossae with age by identifying
34 points of the skull base on CT scans of 50 children (ages ranged from 1 month to 5 years) with various
types of CS and by measuring various distances and angles between these points. Comparisons were made
with normal controls. The results of this study indicated that, during the first 2 years of life of children with
CS, the anterior cranial fossa was overdeveloped in males and underdeveloped in females, the sphenoid
body was moderately underdeveloped in both sexes (though the effect was more prominent in the males),
the middle fossa was overdeveloped in both sexes, and the posterior fossa was underdeveloped in both
sexes (more pronounced in females). Overall, CS affects both sexes to a similar degree, despite regional
differences in the growth patterns.

A better understanding of the normal growth pattern of the skull base and the alterations from normal
growth that occur in CS may assist our approach to surgical treatment, particularly regarding the role of
anterior and posterior skull expansive surgery.

**Intracranial Pressure and Venous Drainage in CS**

The modifications of the skull base in CS, in particular of the posterior cranial fossa, are also a key point to
understand the establishment of intracranial hypertension and its clinical implications, playing a causal
role on the abnormalities of the venous drainage and of the cerebrospinal fluid (CSF) flow and for caudal
displacement of the hindbrain. The premature fusion of multiple sutures prevents cranial growth in
response to normal brain growth. As a result of continued brain growth within the confines of a fixed
skull, the Monro–Kellie doctrine predicts that intracranial pressure will rise.

The incidence of elevated intracranial pressure is significantly higher in the case of multiple sutural
fusions than with single-suture synostosis; as such, the symptoms of elevated intracranial pressure are
more commonly seen in cases of pansynostosis. The sequelae of prolonged intracranial hypertension may
include cognitive impairment, visual and sleeping impairment, ataxia, spasticity, and, in some cases,
cranial nerve neuropathy.

Taylor et al. (2001) analyzed the patterns of venous drainage as seen with angiographic studies of
23 patients (18 with a CS-related syndrome and 5 with nonsyndromic multisutural synostosis). They
concluded that in children with complex forms of CS, in whom other factors such as hydrocephalus are
absent, abnormalities of the venous drainage that affect the sigmoid–jugular sinus complex produce a
state of venous hypertension that, in turn, is responsible for the majority of cases of raised intracranial
pressure. The period of greater vulnerability to the effects of venous hypertension lasts until the affected
child is approximately 6 years old, after which the collateral venous drainage through the stylomastoid
plexus usually becomes adequate. On the other hand, Rollins et al. (2000) studied 17 patients aged
4 months to 34 years (mean 7.3 years) with various forms of complex CS with MR venography (MRV).
Overall, jugular vein obstruction was seen in 71 % patients, and the predominant collateral drainage
pathway was via the posterior condylar veins. Hydrocephalus was present in 75 % of patients with
abnormal MRV. Two patients had hydrocephalus with normal MRV. In ten patients with tonsillar
herniation, seven had associated shunted hydrocephalus. Almost all patients with tonsillar herniation
had an abnormal MRV. The authors concluded that the posterior condylar veins play an important role in
maintaining venous drainage in patients with occlusion of the jugular bulbs, but venous outflow
obstruction seen with MRV does not necessarily indicate the presence of a significant intracranial venous hypertension. Therefore, knowledge concerning the anomalies of venous drainage is extremely important for presurgical management. In fact, in syndromic cases with severe modifications of skull base, the sigmoid–jugular sinuses can be bilaterally occluded, resulting in the development of large superficial compensatory veins over the cranial vault surface whose inadvertent closure during surgery may lead to postoperative venous outflow impairment and raised intracranial pressure.

**Chiari Malformation (CM) in CS**

Premature fusion of cranial vault and/or cranial base sutures may cause cephalocranial disproportion leading to the overcrowding of the posterior fossa and hindbrain herniation, i.e., Chiari I malformation (CM). Other mechanisms such as congenital anomalies of the cerebellum and brain stem, brain turgor, hydrocephalus, and venous hypertension have also been reported to play a role in the pathogenesis of hindbrain herniation.

CM is a frequent finding in multisutural and syndromic craniosynostosis, occurring in 70% of patients with Crouzon syndrome, 75% with oxycephaly, 50% with Pfeiffer syndrome, and 100% with the kleeblattschädel deformity (Cinalli et al. 2005), other than in some cases of nonsyndromic complex craniosynostosis involving the lambdoid suture and in some rare cases of scaphocephaly; its pathogenesis is still controversial as well the rationale for the treatment. Several factors have been cited to play a role in inducing CM. More than one-third of patients with hindbrain herniation become symptomatic or develop hydrosyringomyelia.

Thompson et al. in 1997 used MRI to evaluate the herniation of the hindbrain in a population of children with CS (Thompson et al. 1997). They also assessed the roles of intracranial pressure, posterior fossa size, and hydrocephalus in the development of this deformity. MRI was performed in 27 cases of CS without previous cranial vault surgery. Herniation of the hindbrain below the plane of the foramen magnum occurred in 10 of 27 cases (37%), and all hydrocephalic patients also had hindbrain herniation. The authors did not find a correlation between hindbrain herniation and age and concluded that herniation of the hindbrain in CS was not a primary malformation of brain development, but rather a consequence of brain deformation that occurred in response to the physical forces resulting from a combination of anatomical skull base deformity and intracranial hypertension.

According to Thompson and others (1997), the role of congenital anomalies of the cerebellum and brain stem in the pathogenesis of CM in craniosynostosis appears not to be crucial. The observation that in most cases of craniosynostosis hindbrain herniation is not present at birth, but develops in parallel with skull shape modifications secondary to premature closure of the cranial base sutures (particularly of the posterior cranial fossa sutures), further supports the hypothesis that the overcrowding of the posterior fossa is secondary to premature sutural fusion (Cinalli et al. 1995a). Some authors (Mulliken et al. 1999; Fujisawa et al. 2002) also tried to find a correlation between the observed gene mutation and the presence or not of CM, particularly suggesting the involvement of exons IIIa and IIIc of FGFR2 in Crouzon’s patient with CM. Nevertheless, the cascade of events from the nucleotidic mutation to the final phenotype is largely unknown.

In Crouzon syndrome, the skull base synchondroses are in several cases completely fused in the first year of life, while in the Apert syndrome, they never are. This results in significant differences in the final anatomy of the skull base, especially concerning the posterior cranial fossa. Moreover, premature fusion of the occipitopetrosal suture may lead to stenosis or atresia of the jugular foramen, and lambdoid suture synostosis was observed to occur significantly earlier in the cases of Crouzon syndrome associated with CM compared to those without CM. The interpretation of these data would be that the conflict between neural and skull growth is most dramatic at the level of the posterior fossa if the lambdoid suture closes during the first 2 years of life, when cerebellar growth is especially accelerated. Consequently, a patient
with craniosynostosis characterized by an early closure of the lambdoid suture (and of the synchondroses of the cranial base) would be at a higher risk of CM.

In the first 2 years of life, progressive fusion of the lambdoid suture (associated or not with closure of cranial base synchondroses) produces alterations in the skull base and, if the petro-occipital synchondroses are primarily involved, stenosis of the jugular foramina. This results in a small posterior fossa with consequent herniation of the cerebellum into the cervical canal during the phase of rapid neural growth in the very first months of life. Also, venous hypertension results from both jugular foramen stenosis and the crowding of the posterior fossa, with consequent compression of the sigmoid sinus. The crowding of the posterior fossa can also alter cerebrospinal fluid (CSF) hydrodynamics, impairing CSF circulation and reabsorption. To summarize, interactions between synostosis of the lambdoid suture and skull base synchondrosis, the crowding of the posterior fossa, venous sinus hypertension, and increased CSF outflow resistance all give origin to complex pathophysiological mechanisms inducing CM, with or without hydrocephalus.

CM malformation can occur also in cases of CS without involvement of posterior cranial fossa sutures. When closure of sagittal and coronal sutures occurs in utero, cephalocranial disproportion in the supratentorial compartment occurs early. Thus, neural growth is forcibly directed posteriorly and inferiorly, pushing down the tentorium with subsequent reduction in posterior fossa size (Loukas et al. 2011). Thereby, the risk of CM and of hydrocephalus is increased, especially if premature lambdoid synostosis also occurs.

**Hydrocephalus in CS**

The association between hydrocephalus and craniosynostoses has been well documented, and the incidence of hydrocephalus has been found to be between 4 % and 10 %. The incidence is significantly higher for syndromic craniosynostoses than for nonsyndromic craniosynostoses. In syndromic craniosynostoses, CM is observed in the majority (88 %) of children affected by hydrocephalus. CM seems to be a condition necessary but not sufficient for the onset of hydrocephalus, and CM itself cannot be considered to be the simple result of chronic intracranial hypertension induced by hydrocephalus.

Sinovenous hypertension has been evoked as a possible pathophysiological factor in the origin of CM. The driving force for CSF reabsorption is the difference between CSF pressure and sagittal sinus pressure. Venous hypertension induced by jugular foramen stenosis increases sagittal sinus pressure, resulting in higher CSF pressure in order to maintain CSF balance. The effects of this mechanism depend on the degree of jugular foramen stenosis, the effectiveness of collateral circulation, and the degree of craniocerebral compliance. In children with closed sutures, intracranial pressure may rise up to very high levels, overcoming the high sagittal sinus pressure and permitting CSF absorption, with normal-sized or small ventricles; in contrast, in children with open sutures (or in craniosynostotic patients following cranial suture release), increased CSF pressure induces progressive head enlargement and dilatation of the ventricles and subarachnoid spaces: if the venous obstruction is not compensated by the development of collateral venous pathways, the rise in CSF pressure may result in progressive hydrocephalus and intracranial hypertension (Sainte-Rose et al. 1984).

It is also important to remember that hydrocephalus is not a necessary factor in the pathogenesis of CM and that in hydrocephalic patients, CM is already present at the time of the diagnosis of hydrocephalus. In patients with CS and CM, posterior cranial vault expansion should be the first surgical procedure in order to release intracranial hypertension, while fronto-orbital advancement should be delayed (Cinalli et al. 2005).
Radiological Evaluation: History, Methods, Techniques, and Rational Indications

Because the brain doubles in weight during the first months of life and triples in weight during the first 2–5 years, an early detection and prompt treatment of CS are of utmost importance. When an abnormal calvarial configuration is present, a radiological evaluation is necessary to better characterize the deformity and to plan a correct surgical procedure (Di Rocco and Velardi 1988; Barkovich 2000). Radiological evaluation has traditionally played an important role in the diagnosis and characterization of craniosynostosis. Imaging techniques have evolved rapidly from skull radiography to highly sophisticated CT scans with 3D reconstructions of the skull. Neuroimaging methods are essential to assess the severity of the disease, identifying eventually coexistent anomalies and complications associated with these deformities, for the surgical planning and posttreatment evaluation (Badve et al. 2013).

X-Rays
Historically, radiography has served as an initial imaging modality in children with abnormal head shape (Badve et al. 2013). On plain X-ray films, findings of CS have been described as primary (direct demonstration of the pathological suture) or secondary (craniofacial deformity as a direct consequence of suture synostosis) (Mulliken et al. 1999). A normal unfused suture on a radiograph is lucent, serrated, and nonlinear. On the other hand, a prematurely fused suture shows perisutural sclerosis, linearity, bony bridging, or complete nonvisualization (Badve et al. 2013). The radiological demonstration of CS could be difficult in the early stage of the disease because the shape of the head may not be altered. In order to evaluate all sutures, a minimum of four views of the skull used to be required in children with suspected CS; additional views were required when one suspected that only a segment of the suture was fused. Ultimate demonstration of the fused suture was obtained by positioning the X-ray beam tangentially to the surface of the skull, pointed along the line of the affected suture. Early detection and correct evaluation of complex cases were often unsatisfactory. Nowadays, plain X-ray films have been completely replaced by CT, which has been proven to be more accurate in the early diagnosis and presurgical assessment of the disease (Gates and Dore 1975).

Scintigraphy
Bone scintigraphy was also used in the past for the diagnosis of CS. Early diagnosis was based on findings of increased activity of a suture before its expected time of closure (Di Rocco and Velardi 1988; Gates and Dore 1975). Late diagnosis depended upon changes in head shape coupled with decreased activity along a given suture (Tait et al. 1979). Interpretation of scintigrams required knowledge of the normal activity at each suture or segment. Scintigraphy was not as successful as plain X-ray films in some later studies (Di Rocco and Velardi 1988; Gates and Dore 1975) and never replaced them.

Ultrasound
Sonography is an inexpensive, radiation-free modality that can confirm synostosis versus molding or underlying intracranial lesion as a cause of skull deformity. High-resolution sonographic images also provide a relatively easy means to assess sutural width and may provide information regarding increased intracranial pressure (Soboleski et al. 1998).

At ultrasound (US) examination, normal sutures show an uninterrupted hypoechogenic gap between the two hyperechoic bone plates, while synostotic sutures show loss of this hypoechogenic space. Less specific signs include irregular thickened margins, loss of beveled edges, and asymmetry of the fontanels. Secondary signs of raised intracranial pressure including diastatic sutures and hydrocephalus can also be identified on US images (Badve et al. 2013). Miller et al. (2002) retrospectively evaluated 26 prenatal
US studies of 19 patients with postnatal diagnosis of metopic or coronal suture synostosis. The US examinations were compared with normal images and gestational tables. They concluded that US is not able to diagnose CS before the second trimester of life.

The introduction of transcranial color Doppler (TCD) in 1982 provided a noninvasive technique for the investigation of intracranial arteriovenous vascular diseases (Aaslid et al. 1982). Rifkinson-Mann et al. (1995) first used TCD to noninvasively monitor intracranial pressure, blood flow velocities, and resistive index (RI) in patients with CS. Their results demonstrated that TCD-US is a fast, convenient, accurate, and reproducible method to measure intracranial pressure. Therefore, it is an integral part of a preliminary evaluation of the patient before surgical treatment. Westra et al. (2001) used TCD to measure the RI of basal cerebral arteries with a pressure provocation test, in order to identify abnormal intracranial compliance in infants and children with CS before and after surgery. They performed TCD-US through the temporal squama, fontanels, and existing skull defects prior to and immediately following cranioplasty. A total of 24 studies were performed in six patients with multisutural synostosis, 61 studies were performed in 26 patients with single-suture synostosis, and 23 control studies were performed in 23 control subjects. Six of the nine preoperative TCD-US studies were abnormal in multisutural synostosis. Three recurrences were observed during the postoperative follow-up period, only one showing a TCD-US finding. In single-suture synostosis, seven of the 26 preoperative TCD studies were abnormal, and all occurred in young infants with sagittal and unicoronal synostosis. The immediate effects of surgery were variable. Increases in RI were observed in all patients with sagittal synostosis immediately after surgery, though they normalized during the subsequent follow-up. No significant differences in RI were reported between patients with successfully treated CS and control subjects. The authors concluded that TCD-US is a suitable noninvasive test to monitor the effects of surgery on compliance, especially for periodic noninvasive screening of patients with mild skull deformities, where intracranial pressure variations are a clear indicator for surgery.

Cranial sutures can also be assessed prenatally with ultrasound; both 2D and 3D techniques can be used, although 3D better visualizes the sutures. Documentation of intrauterine craniosynostosis by fetal US and magnetic resonance imaging (MRI) (see below) is possible during and after the second trimester (Blaser 2008).

Initial imaging evaluation after clinical assessment may include high-frequency ultrasound (US) of the sutures. Anyway, in case a syndromic/complex CS is suspected, it is mandatory to use CT to better delineate the extension of the synostotic process.

CT

It is generally accepted that computed tomography with three-dimensional reconstruction (3DCT) optimally evaluates the presence and degree of sutural involvement, assessing associated facial and intracranial abnormalities. Vannier et al. (1994) in 1994 first reported on the diagnostic accuracy (ranging from 85 % to 91 %) of 3DCT in the assessment of single-suture CS. Subsequent studies have confirmed these high scores of accuracy for 3DCT in the diagnosis of CS.

CT findings for craniosynostosis include absence of a suture, an indistinct suture, parasutural sclerosis and bridging, narrowing of a suture, and bone beaking (Branson and Shroff 2011). 3DCT images provide additional information of depth perception, contours, volumes, and extent of abnormalities. This is especially important and useful in the assessment of complex anomalies and in preoperative planning. 3DCT scans also allow to perform a morphometric analysis of the skull base to evaluate the symmetry between the two hemibases, angles, and lengths of the cranial hemifossae. 3DCT also is useful to identify early restenosis after surgical correction, helping in patient follow-up.

Shaded surface display (SSD) or surface display (SD) 3DCT images are essential for preoperative assessment, enabling the detection of the specific sutures fused and the extent of fusion. The major cranial
sutures can be shown in their entirety, which is a crucial information to obtain as bony fusion or bridging at even one point along the suture may result in functional closure and require surgical correction. Medina et al. (Medina 2000) demonstrated the importance of 3DCT with maximum intensity projection (MIP) to depict suture patency, extent of synostosis (i.e., complete versus incomplete), bone bridging, and calvarial deformity in children with suspected CS. Because the quality of spiral 3D images is higher than that of images obtained by conventional (sequential) CT and scan times and radiation dose to the patient are considerably lower, spiral CT is indicated as the technique of choice for the study of CS. Craven et al. (1995) in 1995 described the advantages of spiral CT over conventional CT in the investigation of CS: the faster scan time, enabling reduction of artifacts related to patient motion and, thus, the need of anesthesia, and the reduction of the patient dose. In addition, spiral CT technique enables reconstruction of overlapping images at arbitrary intervals after the acquisition of a spiral volume data set.

In the past decade, there has been growing awareness and concern about radiation exposure in children, whose tissue is up to ten times more radiosensitive than that of adults (Schweitzer et al. 2012), and the resultant cancer risk (Brenner et al. 2001). Brenner et al. also demonstrated that this risk dramatically decreases with increasing age, especially during the first year of life. Since the application of the ALARA (as low as reasonably achievable) concept to pediatric CT imaging, significant efforts have been made to reduce CT radiation doses in children, especially in the younger age groups (Badve et al. 2013). For this reason, the use of CT for the evaluation of patients with single-suture craniosynostosis is controversial. In most craniofacial centers, at least one 3DCT scan is obtained in every case of suspected craniosynostosis, although it has been proved that CT scan adds little information beyond the findings of a careful clinical examination. Some authors have suggested alternative techniques, such as ultrasound and conventional radiography of the skull, in children with cranial deformities associated with a lower clinical suspicion of craniosynostosis or in children with the clinical suspicion of simple monosutural craniosynthesis (Schweitzer et al. 2012). Nevertheless, other authors underline the high sensitivity (96.4 %) and specificity (100 %) of low-dose CT with 3D MIP reconstructions for the identification of synostosis of the vault sutures in newborns with craniosynostosis associated with serious skull and facial deformities (complex craniosynthesis) (Medina et al. 2002; Vannier et al. 1989).

Apart from that, all CT protocols should be designed using the mA reduction factors provided by the Image Gently initiative of the Alliance for Radiation Safety in Pediatric Imaging. In this regard, almost all of the modern MDCT scanners are currently equipped with some type of automatic exposure control (AEC) or automatic tube current modulation (ATCM) technique (Strauss et al. 2010; Strauss and Goske 2011). Badve et al. suggested a full-dose protocol for the initial assessment of a patient with CS and half-dose protocols for postsurgical patients; in the latter, full-dose protocol should be employed only after discussion with the neurosurgical team, to address specific concerns (Badve et al. 2013).

Two different algorithms are generally used for image reconstructions. A first set of images is reconstructed using the soft tissue algorithm; these images are used for both brain evaluation and 3D reconstructions. A second set is reconstructed using a bone algorithm for visualization of sutures on the axial plane. 3D reformatted images can easily be obtained using a surface rendering software. The threshold chosen for 3D reconstructions should be set to the lowest level that permits avoidance of soft tissue visualization from the thinnest structures of the facial bones. The width of a suture on 3D reconstruction may be considerably altered when different thresholds are selected. An increase in threshold value can artifactually “open” the sutures and enlarge the pseudo foramina. Generally, threshold values ranging from 120 HU for younger patients to 150 HU for older patients are adequate.

According to Tartaro et al. (1998), the standard 3DSCT examination of the skull (Fig. 1) consists of eight views rotated at 45° intervals on the z-axis, including left and right lateral views, anterior and posterior left and right oblique views, and frontal and posterior views. In addition, the 3DSCT examination should include the vertex and bottom views as well as the electronic “cutaway” of the calvaria for the
view of the skull base from the vertex. More recently, new softwares for 3D image reconstruction have been used for the imaging of CS; modern softwares actually permit rotational images from left to right and from up to down. Reported diagnostic accuracy values of 3DSCT for each suture synostosis are sagittal 90.7%, metopic 100%, right lambdoid 93.9%, left lambdoid 90.9%, right coronal 91.1%, and left coronal 85.7% (Blaser 2008). Typical artifacts of 3DSCT have been described by Craven et al. (1995). They principally include the “chainsaw” artifact, resulting from slices missing from the 3D reconstruction, and the “Lego effect,” appearing in 3D reconstructions when the profile of the skull changes quickly, such as at the top of the head. Because of their limitations, the 3D images should always be evaluated in conjunction with axial images.

**MRI**

When MRI began to be widely available in the neuroradiological practice in the late 1980s, 3DCT was already considered the diagnostic gold standard in the diagnosis of CS. At that time, the use of MRI in this condition was limited to the evaluation of the intracranial anatomical relationships between the brain and the skull. During the decade following its first applications, a better definition of the role of MRI was felt to be necessary. Generally, in patients with isolated or idiopathic CS without neurological symptoms or evidence of increased intracranial pressure, MRI is not required. On the contrary, in patients with isolated/idiopathic forms who show neurological impairment and/or signs of raised intracranial pressure and in those with syndromic CS, a large body of experience indicates the need for an integrated approach based on an association of 3DCT and MRI. In syndromic patients, the incidence of brain and/or craniocervical junction abnormalities detected on MRI is high (Cinalli et al. 1995b). In neurologically symptomatic or syndromic patients, MRI should include not only a standard study of brain but also specific sequences in order to completely answer all clinical questions, especially during the presurgical stage. Fetal MRI is possible during and after the second trimester of pregnancy (Fig. 2). Craniosynostosis with onset in utero is often syndromic and results from aneuploidy or denotes an underlying brain malformation (Blaser 2008).

![Fig. 1 3D surface display (SD) standard spiral CT reconstructions of a normal skull (1-month-old child).](image)

(a) Frontal view, (b) anterior oblique view, (c) lateral view, (d) posterior view (note wormian bone at the lambda), (e) vertex view, (f) skull base view from the vertex after electronic “cutaway” of the calvaria, (g) inferior view
Other than demonstrating the various forms of hydrocephalus, MRI must also precisely depict the anatomy of the posterior cranial fossa and craniocervical junction. The Chiari I malformation (CM) and similar anomalies, in which there is a disproportion between the capacity of the infratentorial compartment and its contents, are frequently associated with multiple CS, especially in the syndromic forms. MRI also enables evaluation of CSF circulation, which completes the diagnosis of hydrocephalus. When CM is associated with hydrocephalus, the MRI evaluation should include the entire spine to rule out hydroxy-syringomyelia. The high frequency and the significance of chronic tonsillar herniation in syndromic CS were well demonstrated by Cinalli et al. (1995b).

In the presurgical workup, particularly in syndromic CS, the dural venous sinuses and the jugular venous drainage should be studied. Alterations of venous drainage can result from encroachment of basal foramina, and the impaired venous drainage may induce increased venous pressure and secondary raised intracranial pressure and/or a hydrocephalic state. On axial CT slices, as well as on 2D sagittal/coronal and 3D reconstructed images, particular attention must be directed toward the jugular foramina. The use of MR venograms is a reliable and noninvasive alternative to catheter angiography to demonstrate anomalies of venous drainage, representing a potentially serious intra- and postoperative risk. As previously cited, in the absence of the physiological pathways of venous outflow, superficial/extracranial veins may develop and play an important role in venous drainage rerouting. The MRI-based recognition of these anomalies should alert the neuroradiologist, thus enabling preservation of such critical veins. Therefore, an MRI study of a patient with craniosynostosis should always include, in addition to the sequences of a standard study, a 3D T1 volumetric sequence for the study of eventually associated parenchymal abnormalities and a venous angiographic sequence preferably after Gd administration.

More recently, new sequences such as “black bone” MRI were introduced. “Black bone” MRI employs novel gradient echo parameters that minimize soft tissue contrast in order to enhance the bone–soft tissue contrast.
boundary. This is achieved by using 3D volume acquisition, with a short TE, TR, and low flip angle. As a result, imaging times are short. In children with craniosynostosis, patent sutures are seen as areas of increased signal intensity, with these features being absent at the site of synostosis. Eley et al. compared “black bone” data sets to CT and clinical findings to determine the potential of “black bone” MRI as a potential nonionizing alternative to CT in the identification of normal and prematurely fused cranial sutures both in 2D and 3D imaging; the main sutures (sagittal, metopic, left and right coronal, and left and right lambdoid sutures) were evaluated both on MR and CT scans. They found that the findings on “black bone” MRI were consistent with both the clinical diagnosis and the CT findings, demonstrating considerable clinical potential as a nonionizing alternative to CT (Eley et al. 2014).

While MRI eliminates the risks of ionizing radiation, it has limitations, including the increased scanning time, requiring general anesthesia or sedation in young children, and the incomplete or insufficient evaluation of air–bone interfaces, such as the mastoid region and paranasal sinuses.

Recent studies applied fMRI techniques to the analysis of brain connectivity and function in patients with CS. Beckett et al. collected DTI and resting-state functional connectivity MRI data sets in adolescent patients with sagittal nonsyndromic CS (sNSC) that had been previously corrected via total vault cranioplasty and compared them with data from control adolescent patients without CS. They demonstrated altered neocortical structural and functional connectivity in sNSC that may underlie the neuropsychological deficits commonly reported in this population (Beckett et al. 2014). Future studies combining multimodal MRI and neurocognitive characterization may allow a better understanding of brain development of children with syndromic and not syndromic CS.

**Radiological Findings**

Primary radiological signs of CS (Benson et al. 1996) basically involve narrowing or indistinctness of the whole suture; bony bridging or presence of a bony “spur” along the suture can be associated. Basically, these alterations are visible on both X-ray films and 3DCT images. Sometimes, these findings may be detected over a few millimeters along the suture. When a fibrous union affects the pathological suture, no primary radiological changes can be noted, despite marked secondary signs.

3DCT and high-resolution planar images can easily detect the course and width of the sutures (Tartaro et al. 1998; Cinalli et al. 1995b; Eley et al. 2014; Beckett et al. 2014; Benson et al. 1996; Fernbach and Feinstein 1991). On planar CT images, affected sutures show evidence of sclerosis along the inner and outer tables. Suture closure or narrowing is revealed on 3DCT images by partial or complete disappearance of the suture, sometimes with the presence of a bony spur along the suture line. Multiple 3D views allow a more appropriate analysis of individual sutures. Secondary signs include altered calvarial shape, changes in shape and timing of closure of the fontanels, and facial anomalies. Normal skull growth occurs in a perpendicular direction to the major sutures. Synostosis inhibits the elongation at right angles of the affected sutures; compensatory growth occurs perpendicular to the patent sutures, resulting in characteristic deformities depending on what sutures are fused (Fig. 3). The lack of growth across a suture often results in effacement of the underlying subarachnoid spaces, implying a restriction on brain growth. Patients with CS may have an enlarged subarachnoid space beneath regions of compensatory skull growth.

As previously stated, premature fusion of cranial sutures leads to characteristic craniofacial deformities, which frequently require surgical correction for cosmetic concerns; neurological complications due to the disproportion between the growing brain and the limited intracranial space can be associated.
Fig. 3 The main craniostenoses. Dotted lines indicate the pathologic sutures. (a) Scaphocephaly: increase of the anteroposterior diameter of the skull, with the relative reduction of the lateral diameters; (b) anterior plagiocephaly: unicoronal synostosis with asymmetric skull growth; (c) posterior plagiocephaly, unilambdoid synostosis with asymmetric skull growth; (d) brachycephaly, reduced anteroposterior diameter and increased biparietal distance; (e) oxycephaly (turricephaly), generalized reduction of skull growth; and (f) anterior trigonocephaly, symmetric reduction of frontal bone growth with keel-like triangular shape of the frontal bones.
Scaphocephaly, or dolichocephaly, is classically considered the most common form of CS. It is caused by partial or complete premature closure of the sagittal suture, accounts for 50% of all cases, and is usually an isolated finding (Benson et al. 1996), although genetic and syndromic cases do occur. TWIST1 mutations have been identified. Familial cases with dominant transmission represent 6% of sagittal synostosis cases. Males (3.5:1) and multiple births are overrepresented (Blaser 2008).

Skull growth is inhibited perpendicularly to the sagittal plane, and compensatory growth of the coronal sutures results in an elongated skull associated with frontal and occipital prominence due to compensatory growth patterns along the metopic, coronal, and lambdoid sutures (Naidich et al. 1996). The increase of the anteroposterior diameter of the skull, with the relative reduction of the lateral diameters, also lengthens the posterior cranial fossa. The sphenoid wings and the orbits are normally not involved. Axial and 3DCT images show the sclerosis of the posterior portion of the sagittal suture with a prominent bony spur (Fig. 4).

Fig. 4 Scaphocephaly: different patients. (a) Slightly posterior oblique 3DSCT view, (b) vertex 3DSCT view, and (c) corresponding vertex view of patient’s head show disproportionate sagittal elongation and transverse narrowing of the skull. The hyperostotic crest of the fused sagittal suture is visible both on CT renderings (arrowheads, a and b) and on clinical inspection (c). (d) Axial bone-window CT also shows the hyperostotic crest (arrowhead, d). (e) Sagittal MPR CT scan and (f) sagittal T2-weighted image from another patient show disproportionate sagittal elongation, associated short clivus for premature synostosis of the sphenop-occipital synchondrosis (arrowhead, e), enlarged cisterna magna, and mild tonsillar herniation (f). (g) Slightly posterior oblique 3DSCT shows result of multiple craniotomies to expand the supratentorial compartment

Single-Suture Synostoses

Scaphocephaly
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Partial involvement of other sutures introduces variants to the baseline picture, such as:

1. Bathrocephaly: synostosis of the posterior two-thirds of the sagittal suture associated with bilateral lambdoid suture fusion (Fig. 5)
2. Leptocephaly: association with moderate degree of metopic suture synostosis (Fig. 5)
3. Clinocephaly: presence of marked prominence of the frontal convexity, retrobregmatic depression, and, sometimes, compensatory temporal prominence
Scaphocephaly is the least functionally severe form among single-suture CS and the least complex one from a surgical perspective. Early cranioplasty for scaphocephaly has become routine. It has a double goal, i.e., to normalize the shape of the skull and to prevent intracranial hypertension. Despite early surgical correction of skull shape, neurocognitive performances of scaphocephalic patients do not improve significantly. This implies that impairment of brain function has already taken place in utero. Nevertheless, surgical correction performed in the first month of life seems to decrease developmental delay (Virtanen et al. 1999; Barritt et al. 1981; Aviv et al. 2002). As previously reported, Beckett et al. collected DTI and resting-state functional connectivity MRI data in adolescent patients with nonsyndromic scaphocephaly that had been previously corrected via total vault cranioplasty, demonstrating altered neocortical structural and functional connectivity that may underlie the neuropsychological deficits in this group of patients (Beckett et al. 2014).

Plagiocephaly
The term plagiocephaly (flattening) literally refers to skull asymmetry; two mechanisms can be distinguished:

(i) Malformational plagiocephaly secondary to premature synostosis of a cranial suture
(ii) Deformational plagiocephaly without synostosis, positional or functional (Captier et al. 2003)

Anterior Plagiocephaly
Anterior plagiocephaly can be pathogenically categorized as either deformational or synostotic. Both conditions present with ipsilateral flattening and contralateral bulging of the forehead (Rogers et al. 2002). Yet, on physical examination, there are clear differences that permit accurate diagnosis: clinically, positional plagiocephaly and synostotic plagiocephaly differ by a rhomboid versus trapezoid head
shape (Plooij et al. 2009); the differential diagnosis is important, as synostotic frontal plagiocephaly requires operative correction to achieve facial symmetry while surgical correction is almost never indicated in positional plagiocephaly.

Unilateral frontoparietal (unicoronal) synostosis (Fig. 6) is the most common cause of synostotic frontal plagiocephaly, occurring in approximately 1:10,000 live births. Most cases are sporadic and nonsyndromic, although this deformity can occur in association with the Saethre–Chotzen syndrome, craniofrontonasal syndrome, and Muenke syndrome (Rogers et al. 2002). TWIST1 and pro250arg FGFR3 gene mutations, among others, have been implicated in some unilateral coronal synostosis cases. There is a more marked phenotype in girls (Blaser 2008). Synostotic anterior plagiocephaly may also be caused by other fusions along the coronal hemi-ring (frontosphenoidal suture and sphenoothmoidal synchondrosis), with or without the involvement of the frontoparietal suture, resulting in frontal asymmetry which may be difficult to clinically differentiate from frontoparietal synostosis (Marucci et al. 2009). The concept of “coronal ring” was postulated first by Bertelsen (1958), who noted that the coronal suture extended bilaterally to the frontosphenoidal sutures and to the sphenoothmoidal synchondroses. Burdi et al. (1986) demonstrated that although the articulations form a complete ring, the ring is not entirely sutural since it includes the cartilaginous sphenoothmoidal synchondrosis (Dundulis et al. 2004). The frontozygomatic suture has also been implicated as a cause of frontal plagiocephaly (Currario 1985).

Frontoparietal synostosis usually begins in the middle of the suture and then extends superiorly and inferiorly and may extend to involve the adjacent lateral part of the frontosphenoidal suture (Marucci et al. 2009). According to Rogers and Mulliken (2005) “classical” plagiocephaly, in its later stage, does
not only involve the coronal suture but also the frontosphenoidal, sphenopetrosal, and sphenosquamosal sutures. There is an age-dependent, progressive involvement of the lateral frontosphenoidal suture. The frontosphenoidal suture begins in the anterior/inferior temporal fossa as the caudal extension of the frontoparietal suture, continues inferiorly and medially across the anterior cranial base and the orbital roof, and is confluent with the ethmoidosphenoidal suture in the middle of the anterior cranial fossa, posterior to the cribriform plate. Synostosis anywhere along the coronal hemi-ring can restrict growth at other, adjoining collinear sutures. Thus, fusion of the frontosphenoidal suture can impair growth at the ipsilateral frontoparietal suture, resulting in frontal flattening. Observations in animal models have suggested that fusion of the coronal suture is progressive and may have a “cascading” effect on adjacent contiguous sutures (Rogers and Mulliken 2005). Synostosis in the coronal ring restricts growth and ventral expansion of the anterior cranial fossa with secondary effects on orbital and midfacial growth (Rogers et al. 2002).

Isolated frontosphenoidal synostosis (Fig. 7), with a patent coronal suture, would have a different starting point and has been described in few cases; its recognition is important to ensure the child receives proper surgical treatment. Prior studies have attempted to define phenotypic differences between isolated frontosphenoidal synostosis and unilateral coronal synostosis (de Ribaupierre et al. 2007; Rogers et al. 2002; Plooij et al. 2009; Marucci et al. 2009; Dundulis et al. 2004; Rogers and Mulliken 2005; Francel et al. 1995; Kane et al. 2002). Complicating these studies, however, is the fact that there is no standard phenotype for frontosphenoidal synostosis (Dundulis et al. 2004). Clinically, frontosphenoidal synostosis seems to have a weaker phenotype than coronal synostosis. As in coronal synostosis, a unilateral frontal flattening is always seen. The position of the nasal root in frontosphenoidal synostosis

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**Fig. 7** Anterior plagiocephaly: unilateral frontosphenoidal synostosis. (a) Axial CT scans of a 9-month-old boy shows synostosis of the right frontosphenoidal suture, sclerotic *(arrowhead)*, while the left one is patent. (b, c) Slightly anterior right and left oblique 3DSC views demonstrate that both coronal sutures and the left frontosphenoidal suture *(arrowhead, c)* are patent, while right frontosphenoidal suture is not visible. (d) Frontal 3DSC view shows depression of the superior orbital rim on the side of the synostosis (no harlequin deformity) and mild rightward deviation of the nasal root. (e) Vertex and (f) cranial base 3DSC views demonstrate flattening of the right portion of the frontal bone with compensatory contralateral frontal expansion; the ethmoidal axis *(black line, f)* is deviated leftward (contralateral deviation)
is variable (Dundulis et al. 2004), occurring either midline or contralaterally deviated (Francel et al. 1995), while in all cases of isolated coronal synostosis, the nasal root is always ipsilaterally deviated (Dundulis et al. 2004; Francel et al. 1995). Kane et al. also described additional bony abnormalities of the patients with frontosphenoidal synostosis, including a contralateral deflection of the anterior cranial base (de Ribaupierre et al. 2007; Rogers et al. 2002; Marucci et al. 2009; Francel et al. 1995; Kane et al. 2002), while many reports of endocranial morphology have documented that, in unilateral coronal synostosis, the anterior fossa midline (“ethmoidal axis”) is always deflected toward the synostosis (Lo et al. 1996). Dundulis et al. found that the endocranial base deflections were more acute in unilateral coronal synostosis with frontosphenoidal synostosis; they hypothesized that increased cranial base deflection in unilateral coronal synostosis with frontosphenoidal synostosis results from the additional compensation for the extended synostosis, so that the extensions of the synostosis along the coronal ring (coronal plus frontosphenoidal) produce greater angulation of the cranial base (Dundulis et al. 2004).

Verticalization of the orbit (“harlequin deformity”) (Fig. 6) is one of the pathognomonic dysmorphic features of unilateral coronal synostosis; it is due to the relative elevation of the greater sphenoid wing. Dundulis et al. (2004) proposed that the harlequin deformity associated with isolated frontoparietal synostosis results from a compensatory response at the patent frontoparietal suture. If, however, the frontosphenoidal suture is synostosed, such compensation is prevented and orbital elongation is minimized. For this reason, in patients with isolated frontosphenoidal synostosis, the ipsilateral superior orbital rim has been described as elevated but with minor elevation of the lesser sphenoid wing and the ipsilateral orbit than in patients with coronal synostosis (Francel et al. 1995) or depressed, with no evidence of the harlequin deformity (de Ribaupierre et al. 2007; Rogers et al. 2002).

**Fig. 8** Deformational versus synostotic posterior plagiocephaly. Deformational plagiocephaly: (a) axial CT scan, (b) posterior, and (c) vertex 3DSCT views show left parieto-occipital flattening. All sutures are patent, including the lambdoid suture bilaterally (black arrows, a). The cranium shows a parallelogram configuration. (c) Posterior plagiocephaly: (d) axial CT scan, (e) posterior, and (f) vertex 3DSCT views show left parieto-occipital flattening and contralateral bossing. Left lambdoid suture is synostotic, while the right one is patent (arrowhead, d). The cranium shows a trapezoidal configuration (f).
3DCT studies are indicated in infants with frontal plagiocephaly who fail to improve despite position-
ing and/or helmet therapy. If standard CT demonstrates an open frontoparietal suture, it is recommended
 to focus the examination on the basilar coronal ring sutures (Rogers et al. 2002); a careful assessment of
 the 3DCT scan may reduce treatment delay. As in unilateral coronal synostosis, also in frontosphenoidal
 synostosis, bilateral orbital advancement is recommended (early surgery, between the ages of 6 and 9);
 however, in this case, the correction of the dimensions of the orbit on the side of the frontosphenoidal
 suture (usually smaller) is of particular importance (de Ribaupierre et al. 2007).

Posterior Plagiocephaly
Posterior plagiocephaly is a common presentation in pediatric patients. As for anterior plagiocephaly,
distinguishing synostotic posterior plagiocephaly, which requires complex surgery, from deformational
posterior plagiocephaly, well responding to conservative management, is critical. Over the years, there
has been an increase of children with positional posterior plagiocephaly (Fig. 8) because of the American
Academy of Pediatrics recommendation in 1992 to place sleeping infants on their side or back to reduce
the risk of sudden infant death syndrome (American Academy of Pediatrics AAP task force on infant
positioning and SIDS: positioning, SIDS 1992); true lambdoid fusion occurs in only 2–3 % of patients
with posterior plagiocephaly.

A craniofacial specialist can make the diagnosis in most patients by means of clinical examination,
showing a parallelogram shape of the skull in deformational plagiocephaly and a characteristic trapezoid
shape with convergence of frontal and posterior convexities toward the side of synostosis in synostotic
plagiocephaly; however, in unusual cases or in patients with a high likelihood of having synostosis, CT
scan is mandatory (Sze et al. 2005).

In synostotic posterior plagiocephaly, patients have ipsilateral flattening of the occipital and parietal
bones and contralateral parieto-occipital expansion. On the endocranial skull base view, there is deviation
of the posterior fossa axis (basion–opisthion) ipsilateral to the synostosis (Fig. 8). Compensatory growth
occurs along the sagittal, contralateral lambdoid, and ipsilateral squamosal sutures (Vannier et al. 1989).
Generally, facial dysmorphisms are not associated. This synostosis may result in functional disturbances,
including increased intracranial pressure and visual impairment (Thompson et al. 1995).

Sze et al. (2005) described three unusual cases of posterior plagiocephaly. The first patient had right
lambdoid fusion with prominent patent mendosal sutures; the consequence was a prominent bulge over
the right mendosal suture and only a minimal deviation of the endocranial skull base toward the synostotic
side. The other patients showed skull base and calvarial changes typical for unilateral lambdoid synostosis
but had bilaterally patent lambdoid sutures while premature fusion of the posterior intraoccipital
synchondrosis or anterior intraoccipital synchondrosis was present. Identifying the suture involved in
the craniostenotic process is obviously critical to plan surgery.

Brachycephaly
Bilateral closure of the coronal suture determines a characteristic deformation of the skull known as
brachycephaly. The skull deformity is characterized by an abnormal expansion of the skull with reduced
anteroposterior diameter, increased biparietal distance, and compensatory vertical development. The
orbits and anterior cranial fossa are short, causing exorbitism and hypertelorism (Fig. 9). The
frontosphenoidal sutures are involved in 85 % of cases. This anomaly can be isolated, but is more often
present in Apert, Crouzon, and other craniofacial syndromes (Fernbach and Feinstein 1991; Kaplan

Bilateral synostosis of the lambdoid suture causes the less common posterior type of brachycephaly.
The skull deformity is characterized by flattening of the occipital bone with a shallow posterior fossa.
Increased bone growth occurs along both squamosal sutures and sagittal sutures. As a consequence of the bony expansion, the vertex elevates.

**Oxycephaly**

Oxycephaly results from bilateral synostosis of the coronal sutures and of other sutures of the skull vault and base. This malformation causes circumferential constraint of the skull, shortening of the anterior and middle cranial fossae, and prominence of the frontal and temporal eminences. Raised intracranial pressure, Chiari malformation, and hydrocephalus are often associated, and optic atrophy, psychomotor delay, and seizures often ensue in untreated cases. Depending on the severity of the dysmorphism and the association with other synostoses, three variants can be identified:
Type 1: pure bicoronal and sagittal suture synostosis. The skull has a pointed configuration and the forehead is shallow.

Type 2 or turricephaly: due to concurrent metopic and sagittal (Nagaraja et al. 2013) suture synostosis, the skull has an exaggerated upward growth in the fronto-bregmatic region (Figs. 10 and 11).

Type 3: bilateral coronal and lambdoid synostosis. In this case, the conformation of the head can be less disharmonious.

Furthermore, complex forms, due to asymmetric involvement of the coronal and lambdoid sutures, can rarely be found (Fig. 12).

Surgical correction can be complex as it involves, other than craniotomy and bilateral fronto-orbital advancement, also remodeling of the fronto-naso-glabellar region, which is usually hypoplastic and flattened.

**Trigonocephaly**

The term trigonocephaly refers to a triangular conformation of the skull. Two forms, i.e., anterior and posterior, can be identified, of which the anterior one is much more frequent.
Anterior Trigonocephaly

Synostosis of the metopic suture determines a keel-like triangular shape of the frontal bones (Fig. 13). Radiographic signs include a median frontal bony spur, hypotelorism (intercanthal distance less than 15 mm in infants less than 1 year old), hypoplastic ethmoid sinuses, and anterior bowing of the coronal sutures with reduction in size of the anterior cranial fossa (Benson et al. 1996; Fernbach and Feinstein 1991; Kaplan et al. 1991). Brachycephaly can sometimes be associated with the possible involvement of the sutures of the coronal arch.

Metopic CS accounts for approximately 3–10 % of cases of single-suture craniosynostosis (Birgfeld et al. 2013). The majority (64–75 %) of cases identified postnatally are isolated and nonsyndromic. As many as one-third of patients, therefore, are syndromic or have associated malformations. Syndromes known to be associated with metopic synostosis include Jacobsen/11q23 deletion, chromosome 9p deletion, Opitz C syndrome, and various aneuploidies (Boulet et al. 2008). Familial cases occur in 6 %. Males and multiple births are overrepresented in series of metopic synostosis, as they are in sagittal synostosis (Blaser 2008).

The metopic suture is the only calvarial suture that normally closes during infancy. Its physiologic closure can occur as early as 2 months of age; therefore, identification of a closed metopic suture on a CT scan in a 3-month-old does not necessarily indicate premature closure, and other factors must be taken into consideration. Moreover, upon closure, a palpable and visible ridge often forms, which can be confused with metopic craniosynostosis. Metopic ridging is treated nonsurgically while metopic craniosynostosis is treated surgically, so the differential diagnosis is fundamental (Birgfeld et al. 2013).

Surgery involves bilateral frontal craniotomy, removal of the hyperostotic midline crest, and bilateral orbito-pterional osteotomy. Rotation of the remodeled frontal opercula, bilateral advancement of the

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Fig. 11  Multiple-suture synostosis (assimilated to type 2 oxycephaly). (a) Frontal and (b) lateral 3DSCT views in a 4-year-old child show a conical appearance of the cranial vault (turricephaly). (c) Sagittal T1-weighted image of the same patient shows associated Chiari I malformation (arrowhead) due to the small posterior cranial fossa because of the premature closure of lambdoid sutures. (d) MR angiography, axial projection, shows hypertrophic suboccipital venous plexus (arrowheads)
Fig. 12 Unclassified form of oxycephaly. (a) Profile photograph of the patient and (b) lateral X-ray film show disproportionate anteroposterior shortening of the skull and vertical development at level of the fronto-bregmatic region. Also, notice large, irregular skull lucencies on X-rays (b). (c) Anterior oblique 3DSCT view shows large skull lacunae to the right. (d) Axial CT scan shows irregular hyperostotic spurs projecting inward from a thinned, partly interrupted vault; (e) axial T2-weighted image shows the right hemisphere convolutions are tightly pressed against the inner table of the skull. (f) Surgical features: the inner surface of the skull shows large convolutional markings resulting from the pressure exerted by the underlying brain within the closed skull cavity.

Fig. 13 Anterior trigonocephaly. (a) Vertex and (b) slightly anterior oblique 3DSCT view show the trigonocephalic shape of the head with an hyperostotic spur (arrowhead) along the course of the synostotic metopic suture; the coronal and sagittal sutures and the bregmatic fontanel are widely patent. (c) Axial CT scan shows the triangular shape of the forehead and the hyperostotic spur (arrowhead). (d) Axial T2-weighted image shows slight dilatation of the frontal subarachnoid spaces. (e) Postoperative X-ray at 6 months shows results after multiple craniotomies along the metopic suture. (f) Vertex photograph of a different patient’s head showing the trigonocephalic shape of the head.
supraorbital arches, and reconstruction of the zygomatic angles enable reconstitution of a satisfactory fronto-orbital convexity.

Posterior Trigonocephaly
The skull has a triangular shape pointing posteriorly (Fig. 14) due to synostosis of the posterior third of the sagittal suture as well as of both lambdoid sutures. As such, it can be viewed as a minor form of bathrocephaly (see above). A hyperostotic spur is often depicted at the level of the posterior portion of the sagittal suture. Surgical correction requires bilateral osteotomy.

Complex Synostoses
Most multiple-suture synostoses are rare and more often syndromic. Several patterns arise because of involvement of various combinations of sutures. The most severe deformity, called kleeblattschädel (Fig. 15), arises from premature fusion of sagittal, coronal, and lambdoid sutures. The cranium resembles
a cloverleaf, with bulging temporal regions and severe proptosis, and there is severe neurological impairment. Premature fusion of sagittal, bilateral coronal, and metopic sutures results in an anteriorly tall cranium. Bilateral lambdoid fusion with sagittal suture synostosis is called Mercedes-Benz synostosis (Badve et al. 2013). Pansynostosis can also be seen following severe hypoxic/ischemic injury as a result of lagging brain growth, leading to premature fusion of the sutures. The presentation of infants can be variable depending on the phenotype, with some being seen incidentally, whereas others present with a microcephalic head raised intracranial pressure and proptosis (Nagaraja et al. 2013).

Syndromic Craniosynostoses

CS is found in a wide variety of syndromes: to date, more than 100 syndromes have been reported. The most common syndromes that include CS are Apert, Crouzon, Vogt, Pfeiffer, Saethre–Chotzen, Jackson–Weiss, Carpenter, and Muenke syndromes. Different sutures are affected in individual syndromes. Although there is a general tendency to symmetric involvement, a wide range of findings are encountered, ranging from single suture to generalized suture involvement and cloverleaf deformity. As previously mentioned, the most significant radiological feature is the high incidence of raised intracranial pressure and/or associated brain malformations in syndromic patients with CS. Many of these syndromes also have characteristic involvement of the face and extremities.

Classification of these entities is difficult in view of the heterogeneity of the clinical pictures. In the past, broad groups were identified, i.e., craniofacial dysostosis, acrocephalosyndactyly (ACS), and acrocephalopolysyndactyly (ACPS). However, advances in the understanding of the genetic basis of these syndromes, especially regarding the role of genetic factors (FGFR, TWIST1, TGFβ, MSX2, EFNB1, RAB23, POR, GLI3, and RECQL4) in the pathogenesis of several of these disorders, have led to a reappraisal of these entities and may possibly result, in the future, in a new classification.

Diagnosis requires both genetic and radiographic evaluation. FGFR1-R3 gain-of-function mutations are seen in Apert (FGFR2), Crouzon (FGFR2), Crouzon with acanthosis (FGFR3), Muenke (FGFR2 P250R), and Pfeiffer (FGFR2 > FGFR1) syndromes. Different syndromes may result from identical mutations in FGFR2, whereas mutations in FGFR1 and FGFR2 are able to cause the same clinical phenotype. Mutations in Pfeiffer (FGFR1 variant), Apert (FGFR2), and Muenke (FGFR3) syndromes involve the identical Ig II–III linker region domain of their respective FGFR genes. Mutations in Crouzon and Pfeiffer (FGFR2 variant) are within the Ig III domain of FGFR2c. Saethre–Chotzen most commonly exhibits TWIST1 loss-of-function mutations, while Boston-type craniosynostoses is due to an MSX2
mutation. Association with malformations of the extremities aids in clinical and radiological classification (Blaser 2008).

**Crouzon Syndrome**
Louis Edouard Octave Crouzon, a neurologist, first described this syndrome in 1912 (Badve et al. 2013). The syndrome is also named type 1 craniofacial dysostosis; it is a congenital autosomal dominant disorder caused by mutations in the gene encoding fibroblast growth factor receptor-2 (FGFR2) located on 10q26 and is therefore allelic with Apert syndrome. Several mutations have been identified in the FGFR2 gene, some of which are identical to those seen in Pfeiffer and Jackson–Weiss syndrome; Crouzon syndrome with acanthosis nigricans (Crouzonodermoskeletal syndrome) has been described with Ala391Glu mutation in FGFR3 on 4p16.3. It has been estimated that Crouzon syndrome represents approximately 4.8 % of cases of craniosynostosis at birth; the birth prevalence was estimated to be 16.5 per million births (Tartaro et al. 1998).

The most common deformity is acro-brachycephaly (Fig. 16); exophthalmos is usually pronounced, with mandibular prognathism and a beaked nose. Patients are usually slightly to moderately retarded mentally and have airway obstruction. All sutures may be involved, and the cloverleaf deformity may also be found. Basilar kyphosis is the rule. The orbits are shallow and show upward tilting of their roofs with proptosis, and hypertelorism results from the expanded and ballooned ethmoid. The palate is very short and high. There is a variable degree of maxillary hypoplasia and malocclusion (Carr et al. 1992). The nasopharynx has a reduced anteroposterior diameter, predisposing to obstructive sleep apnea that can be life threatening and has been described to cause sudden death (Cinalli et al. 1995b). Other craniofacial findings include atresia of the external auditory canals and premature calcification of the stylohyoid
ligament (Badve et al. 2013). Brain malformations are common, especially midline anomalies (corpus callosum hypoplasia/aplasia). The Chiari I malformation is frequent and may be found in association with cloverleaf deformity and hydrocephalus.

**Apert Syndrome**

Dr. Eugène Apert, a French pediatrician, first described a case series of patients with acrocephaly and syndactyly in 1906 (Badve et al. 2013). Apert syndrome (Eley et al. 2014; Beckett et al. 2014; Benson et al. 1996; Fernbach and Feinstein 1991) is the most important of the ACS. In some cases, there is an autosomal dominant inheritance, but most cases are sporadic. A paternal age effect in de novo mutations in *FGFR2* has been recently shown (Kimonis et al. 2007). Apert syndrome also results from mutations in the gene encoding *FGFR2*, located on 10q25–26 (Warren and Longaker 2001). Recent advances have shown that nearly all patients with Apert syndrome have been implicated with one of the 2 mutations in *FGFR2*, involving Ser253Trp and Pro253Arg, two adjacent amino acids (Kirmi et al. 2009).

Apert patients have a craniofacial appearance that has been likened to that seen in Crouzon but with a generally more severe deformity characterized by skull malformation (acrocephaly or brachycephalic type), hypertelorism, proptosis, midface hypoplasia, and complex syndactyly of the hands and feet (complete distal fusion with a tendency to fusion also of the bony structures) (Fig. 17). Synostosis constantly involves the coronal sutures bilaterally, but more sutures may be obliterated up to the cloverleaf deformity. The orbits are shallow and the maxilla is hypoplastic. Congenital or acquired intracranial abnormalities are frequently found (Fig. 18). The corpus callosum may be partially or completely absent and, especially after craniectomy, significant hydrocephalus may develop, sometimes requiring shunting.

Fig. 17 Apert syndrome. (a) Photograph of a patient with Apert syndrome shows marked frontal prominence and severe hypoplasia of the orbital arch. (b) Lateral X-ray film shows marked acro-brachycephalic deformity of the skull with marked hypoplasia of the anterior cranial fossa and maxilla. (c) Anterior 3DCT view shows absence of the coronal and metopic sutures. (d) Profile photograph of another patient with Apert syndrome shows the skull is brachycephalic but lacks a marked frontal prominence. (e) Anterior 3DCT view shows that only the coronal sutures are synostotic, whereas there is wide enlargement of the metopic suture, as well as of the other major sutures, explaining the peculiar shape of the head in this patient. Notice hypertelorism and marked hypoplasia of the maxilla bilaterally. (f) Hand X-rays in a different case show bony syndactyly bilaterally, resulting in the so-called spoon deformity.
Altered CSF flow and/or reabsorption is frequently associated with a Chiari I malformation, reflecting the abnormal development of the skull base and cranio-vertebral junction.

Fig. 18 Intracranial abnormalities in Apert syndrome. (a) Anterior and (b) lateral 3DCT views show brachycephaly with hypertelorism, dysmorphic orbits, and marked hypoplasia of maxilla. (c) Sagittal T1-weighted image shows corpus callosum hypoplasia. (d) MR angiography shows hypoplasia of the left transverse-sigmoid sinuses.

Fig. 19 Cloverleaf deformity in a 3-month-old boy with Vogt syndrome (mixed Apert–Crouzon syndrome). (a) Axial, (b) sagittal, and (c) coronal CT reformats show the cloverleaf deformity and the bony bands of constriction that cause the skull deformity. (d) Axial T1-weighted, (e) sagittal T1-weighted, and (f) coronal T2-weighted images on corresponding planes show ventricular dilatation but otherwise normal brain tissue despite the marked deformation caused by the complex craniostenosis. (g) MR angiography shows that the transverse sinuses are not seen; instead, there is a prominent subcutaneous venous vessel (arrowheads) representing the main venous outflow that drains in the jugular vein. This vessel had to be spared during surgery, in order to avoid venous obstruction, venous hypertension, and possible impairment of CSF absorption.
Varying degrees of mental deficiency are associated with the syndrome; however, individuals with normal intelligence have been reported. Individuals who have craniectomy early in life may have improved intelligence (Virtanen et al. 1999).

Other abnormalities in Apert syndrome affect the remaining body systems (mainly cardiac and genitourinary), but they occur less frequently (10 %) (Kirmi et al. 2009).

**Vogt Syndrome**

It is characterized by brachycephaly or turricephaly, maxillary hypoplasia, exophthalmos, and syndactyly (Vogt 1933). This syndrome is characterized by hand and foot malformations characteristic of Apert disease together with the facial characteristics of Crouzon disease with a very hypoplastic maxilla (Fig. 19). The syndactyly is less severe than in Apert disease and the thumbs and little fingers are usually free. This entity has also been called Apert–Crouzon disease, indicating the similarity to both abnormalities.

**Saethre–Chotzen Syndrome**

Previously called acrocephalosyndactyly type III, this autosomal dominant condition was first described by Saethre and Chotzen in the early 1930s (Flores-Sarnat 2002). Most patients with Saethre–Chotzen syndrome harbor mutations in the TWIST1 transcription factor gene on 7p21.1 (Aviv et al. 2002). Craniosynostosis most often involves the coronal and lambdoid and occasionally sagittal sutures, resulting in mild acrocephaly and asymmetry of the skull. There is an underdeveloped midface with small ears and a high-arched palate that may predispose to upper airway obstruction. Ocular findings include proptosis due to shallow orbits, crossed and/or wide-set eyes, bilateral congenital upper eyelid ptosis, and nasolacrimal duct abnormalities. Syndactyly is partial, only involves the soft tissues, and affects the intermediate fingers (Captier et al. 2003). Brachydactyly and bifid halluces may also be present (Kirmi et al. 2009). Although a mild to moderate developmental delay and mental retardation have been reported (especially with deletion of entire TWIST1 gene), intelligence is typically normal (Kimonis et al. 2007).

**Waardenburg Syndrome**

In 1961, Waardenburg et al. described asymmetry of the skull and orbits (plagiocephaly), strabismus, and a thin, long, pointed nose in six generations of a kindred (Waardenburg et al. 1961). Some affected persons had bifid terminal phalanges of digits two and three and absence of the first metatarsal. Cleft palate, hydrophthalmos, cardiac malformation, and contractures of elbows and knees were present in some. This syndrome is today assimilated to Saethre–Chotzen syndrome.

**Pfeiffer Syndrome**

Pfeiffer syndrome (Lyu and Ko 2000) was originally described by Pfeiffer in 1964 and is differentiated from Apert syndrome mainly on the basis of the anomalies involving the extremities; syndactyly is limited to the soft tissues, and both toe and thumbs are short and broad. The majority of patients with Pfeiffer syndrome have mutations in FGFR2 on 10q26, similar to Apert and Crouzon syndromes (several mutations of FGFR2 have been described), although a small number have also been identified in FGFR1 (<5 %)(Pro252Arg) on 8pll.2 (Kimonis et al. 2007). It is inherited as an autosomal dominant trait with sporadic cases, presumably due to fresh mutations.

Congenital brain anomalies are less common than in Apert or Crouzon syndromes, but the postoperative evolution is very similar to that of Apert patients. In most cases, craniosynostosis involves the coronal and sagittal sutures (Fig. 20), with an intracranial bony crest resulting from sagittal synostosis. The cloverleaf deformity is not uncommon, with a variable degree of severity. In our experience, the
Chiari I anomaly is frequently found, due to altered relationships between the posterior fossa, foramen magnum, and their contents (Fig. 20).

Pfeiffer syndrome can be further delineated into three subgroups, although there is overlap particularly between types 2 and 3:

- **Type 1** is the most common and has a good prognosis; impairment of intellect is unlikely without other associated malformations, such as hearing loss or hydrocephalus.
- **Type 2** is more severe and associated with a poor prognosis; presentation is at birth or prenatally with cloverleaf skull, severe ocular proptosis, and broad thumbs and great toes with medial deviation. Additional malformations may include choanal stenosis or atresia, laryngotracheal abnormalities, elbow ankylosis/synostosis, hydrocephalus, seizures, and intellectual disability.
- **Type 3** has a similar facial appearance to type 2 but without the cloverleaf skull; intellectual disability is common (Kimonis et al. 2007). Generally, patients with type 2 and 3 die early.

**Carpenter Syndrome**

Acrocephalopolysyndactyly (ACPS) differs from Apert syndrome in the presence of polydactyly as an additional feature. ACPS was previously classified into type I, or Noack syndrome (dominant), and type II, or Carpenter syndrome (recessive). Only the latter is presently believed to exist as an autonomous entity.

Carpenter syndrome is very rare, with approximately 40 reported cases to date, occurs as an autosomal recessive inherited condition, and it is associated with RAB23 mutation. It is characterized by the association of craniofacial anomalies (including craniosynostosis), lateral displacement of inner canthi (Melville et al. 2010), hypogenitalism, brachysyndactyly of the hands (involving the third and fourth
fingers), and polysyndactyly of the feet. Most patients are mentally retarded, and obesity and short stature are reported. No specific cranial deformity is found, although the cloverleaf skull has been described. The Chiari I malformation may be demonstrated on MRI (Fig. 21).

Muenke Syndrome
First described by Muenke in 1995, Muenke syndrome is characterized by unicoronal or bicoronal CS with midfacial hypoplasia and ocular hypertelorism. Limb involvement may include brachydactyly, carpal bone fusion, and coned epiphyses. Intelligence is usually normal. Extreme clinical variability and significant phenotypic overlap with other craniosynostosis syndromes are described. A single mutation in FGFR3 (Pro250Arg) on 4p16.3 is the defining molecular characteristic of Muenke syndrome, and inheritance is autosomal dominant (Kimonis et al. 2007). Other mutations of FGFR3 cause skeletal dysplasias that have severe effect on the long bones (achondroplasia has identifiable FGFR3 mutations), while long bone anomalies are not a feature of Muenke syndrome. The hands and feet are affected in some cases, but most abnormalities are not clinically significant. The identification of limb anomalies, such as thimble-like middle phalanges, carpal or tarsal coalition, and coned epiphyses, in combination with coronal synostosis strongly suggests the diagnosis of Muenke syndrome (Kirmi et al. 2009).

Boston-Type Craniosynostosis
This is an autosomal dominant disorder caused by a gain-of-function mutation in MSX2 (5q34-q35) and identified in 19 affected individuals in one family; variable phenotypes were reported including fronto-orbital recession, frontal bossing, and turribrachycephaly as a result of coronal craniosynostosis, a cloverleaf skull, and asymptomatic individuals (Lyu and Ko 2000). Further families have not been identified, and mutations in MSX2 were not found in 211 individuals with craniosynostosis in whom mutations in the major genes were excluded (Kimonis et al. 2007).
Although the diagnosis of CS is primarily based on clinical observations, the neuroradiological evaluation is of utmost importance in order to establish a precise diagnosis of the affected suture, to quantify the degree of craniofacial deformity that may ensue, and to adequately plan surgical treatment. The difficulty in the diagnosis of CS varies according to the number of sutures involved. In single-suture synostosis, the diagnosis is easier, whereas in complex abnormalities, the diagnosis may be complicated because the cranial deformity may not be characteristic. The latest technological imaging advancements have improved the diagnostic accuracy in cases of CS. The pre- and postoperative evaluation of patients with CS using 3DCT has become routine.

Selection of the surgical correction technique depends on several factors such as number of sutures involved, type of synostosis, the resultant deformity, and the presence or absence of associated complications. Surgical correction is achieved through various techniques, and multistage corrections are often undertaken. Familiarity with some of the basic surgical procedures used in these patients is necessary when evaluating these studies.

In strip craniectomy, the fused suture is selectively resected, while in barrel-stave osteotomies, the cranial vault is expanded using multiple parallel osteotomies; recently, minimally invasive endoscopic techniques have been introduced for correction of specific synostoses. Various types of metallic and nonmetallic implants are often used, and reference to operative notes is helpful while reading postsurgical scans (Badve et al. 2013).

The time interval between craniotomy and neuroimaging evaluation should be around 3–6 months, while immediate postoperative imaging should be restricted to patients with an eventful perioperative period and high probability of complications, such as hematoma, parenchymal injury, hydrocephalus, or

Radiological Follow-Up

Although the diagnosis of CS is primarily based on clinical observations, the neuroradiological evaluation is of utmost importance in order to establish a precise diagnosis of the affected suture, to quantify the degree of craniofacial deformity that may ensue, and to adequately plan surgical treatment. The difficulty in the diagnosis of CS varies according to the number of sutures involved. In single-suture synostosis, the diagnosis is easier, whereas in complex abnormalities, the diagnosis may be complicated because the cranial deformity may not be characteristic. The latest technological imaging advancements have improved the diagnostic accuracy in cases of CS. The pre- and postoperative evaluation of patients with CS using 3DCT has become routine.

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The time interval between craniotomy and neuroimaging evaluation should be around 3–6 months, while immediate postoperative imaging should be restricted to patients with an eventful perioperative period and high probability of complications, such as hematoma, parenchymal injury, hydrocephalus, or
displacement of bone graft material. The site of the osteotomy and the position of bony flaps and grafts must be defined on the 3DCT reconstruction. Moreover, the improvement of the skull shape should be assessed. Finally, a long-term follow-up with 3DCT can be used to evaluate the stability of the postoperative skull shape (Fig. 22).

References


