Syndromic Craniosynostosis

67

José Hinojosa Mena-Bernal

Contents

Introduction and Pathogenesis of Craniosynostosis

Cranial sutures are essential components in the development of the skull. Nonfunctional sutures during the evolution of the cranial vault and the skull base lead to evolving deformities that may

J. H. Mena-Bernal (✉)
Servicio de Neurocirugía Pediátrica, Hospital Infantil Universitario Niño Jesús, Madrid, Spain
e-mail: jose.hinojosa@salud.madrid.org

C. Di Rocco et al. (eds.), *Textbook of Pediatric Neurosurgery*,
https://doi.org/10.1007/978-3-319-72168-2_63

end in neurological sequel. Although craniosynostosis was a term first used by Bertolotti in 1914, referring to the premature closure of a cranial suture, it was Sommerring who described in 1791 the anatomy of the sutures and postulated not only its role in normal skull growth but also the effects of early closure (Sömmering 1800). In nineteenth century Otto (1830), and later, Virchow asserted that premature closure of sutures (craniostenosis) prevented growth perpendicular to the suture and was accompanied by secondary compensating deformities (Virchow 1851). Premature closure may affect one single suture, but several sutures may also be involved and then, severe deformities will develop in the process including the orbits and anterior fossa. This is even more evident in craniofacial syndromes where the main difference with other single suture and nonsyndromic craniosynostosis is the alteration not only in neuro- but also in viscerocranium that result in anomalies in the midface skeleton.

The true incidence of craniosynostosis is not known, but it is estimated to occur in 1/2500 newborns (Cunningham et al. 2007). Sagittal synostosis is the most frequent (40–60% of all the cases) followed by metopic, coronal, and lambdoid which is relatively unusual (Cohen 2000; Van der Meulen et al. 2009). Over 150 syndromes associated have been described, but in most of the cases, craniosynostosis is an isolated phenomenon. Several theories have been postulated to explain premature synostosis and posterior deformities. Virchow was the first to suggest in 1852 that the early closure of the suture was the primary event, while the vault deformity was a consequence of this closure. In 1959, Moss suggested that the deformity in the cranial base was the primary event (Moss 1959). For this author, dura mater is an important regulator in the activity of the sutures and vault development and the main factor for the alteration in the cranial growth and sutures dysfunction. The abnormal mechanical strengths driven through dural structures from certain maldeveloped points at the skull base (crista galli, petrous pyramids, or sphenoidal wings) would be responsible for cranial deformities and suture dysfunction (Moss 1959). Park and Powers referred to mesenchymal abnormalities in bone structures, related to genetic anomalies, that would explain more thoroughly hypoplasia affecting the craniofacial region in syndromic cases.

Mechanical restraint could explain a number of isolated craniosynostosis, as in some cases of scaphocephaly, lambdoid synostosis, or trigonocephaly. However, genetic abnormalities have been increasingly described as a determinant factor in many craniosynostosis. This is particularly true in craniofacial syndromes where mutations in six main genes have been related to a constant presence in different syndromes. These genes are mainly FGFR1, 2, and 3, MSX2, TWIST, and EFNB1.The identification of these mutations will lead in the future to a new classification of the craniofacial syndromes, based in molecular changes instead of phenotype.

EFBN1 encodes a structural protein, fibrillin. MSX2 and TWIST are transcriptional factors that control and mediate the expression of other genes. TWIST encodes a transcriptional factor type II that gathers as heterodimers, representing the active functional factor joining DNA. Most mutations in this gene produce a lack of union to DNA resulting in an abnormal expression of the gene and a loss of function in protein TWIST. FGFRs are a subgroup of the family of tyrosine kinase receptors. They are constituted by an extracellular domain (glycoside acidic box, Ig-like domain, and CAM-like domain), a transmembrane domain, and an intracellular tyrosine kinase domain. Its active form is the dimer that provokes phosphorylation of the tyrosine intracellular endings. This promotes activation of intracellular events that lead to Ca + 2 release, protein kinase C activation, and kinases phosphorylation that end with activation of transcription factors. FGFR 1, 2, and 3 interact in the cell-to-cell signaling process. They have a complex function intervening in the activation of proliferation, the end of the cellular cycle, cellular migration, differentiation, and apoptosis. FGFR2 promotes proliferation, while FGFR1 acts in the differentiation of cranial sutures. A mutation in any of these genes promotes a lengthening of the signal, which causes an early maturation of bone cells in developing embryo and a premature fusion of sutures, hands,

and feet. FGFR3 is an inhibitor of proliferation during chondrogenesis.

In the end, all these mechanisms and changes will produce a deformity, aesthetic, but also an incompetence of the cranial and facial structures, unable to contain properly the organs inside the vault (brain, cerebellum), and the orbits (optic nerves, eye balls), and hypoplasia of the midface and oropharyngeal region. All these factors are related, and depending on the affected region there will be a predominance of one or another abnormality. However, in craniofacial syndromes the situation is more complex. The presence of raised intracranial pressure (multiple sutures closure), hydrocephalus and CSF circulation abnormalities, venous hypertension (skull base sutures closure affecting jugular foramina drainage; genetic factors including endothelial proliferation in dural venous sinuses), chronic hypoxia and hypercapnia (obstructive airway in relation to midface retrusion and amygdalar hyperplasia), chronic tonsillar herniation, etc. all these factors lead to a unstable clinical condition. Staged treatment is needed after careful and proper understanding of the physiopathology underlying these cases and always in a multidisciplinary team basis.

Multiple Suture Craniosynostosis

Brachycephaly

Brachycephaly results commonly after premature closure of both coronal sutures. The anterior fossa adopts a characteristic deformation, broad and short, and there are retruded frontal bones and orbital rims with a vertical, broad, flat forehead and a high bregmatic point. Brachycephaly may appear as an isolated synostosis and has then a favorable prognosis. Often, it is the common result of different syndromic craniosynostoses that share a premature closure of bicoronal sutures and similar phenotype (like cases of Saehtre-Chotzen or Pfeiffer type I). All patients with brachycephaly should be evaluated by a clinical geneticist (Fig. 1) in order to exclude a syndromic craniosynostosis.

Oxycephaly

The premature and synchronous closure of both coronal and metopic sutures gives the head a pointed appearance (*oxis* is the Greek for "arrow-head"). The sagittal suture may be involved to a variable degree, resulting in a cone-shaped head with a high bregma. It is commonly associated with intracranial hypertension when left untreated (Fig. 2). Oxycephaly is a common aspect in some syndromic craniofacial patients like in Crouzon's.

Crouzon Syndrome

Crouzon syndrome is an autosomal dominant disorder characterized by craniosynostosis that causes secondary alterations of the facial bones and facial structure. Common features include hypertelorism, exophthalmos and external strabismus, parrot-beaked nose, short upper lip, hypoplastic maxilla, and a relative mandibular prognathism. First described by Crouzon in 1912 (Crouzon 1912), it was not until 1959 that Shiller observed an autosomal dominant transmission (Shiller 1959). Crouzon syndrome represents approximately 4.8% of cases of craniosynostosis at birth, and the prevalence is estimated to be 16.5 per million births. Crouzon craniofacial dysostosis is linked to a high number of different mutations, but most of them are located on IgIII of FGFR2 (exons 7 and 9) on chromosome 10q (Reardon et al. 1994). An association between Crouzon syndrome and acanthosis nigricans has been described and is related to an A391E mutation in the FGFR3 gene on chromosome 4p (Meyers et al. 1995).

Crouzon syndrome is characterized by a premature synostosis of both coronal sutures, with a resultant brachycephalic shape of the skull. Sagittal, metopic, or lambdoid sutures may be also prematurely affected, alone or combined (Fig. 3). The cranial base and upper facial sutures are involved with a variable degree of midface hypoplasia and dental malocclusion. The orbits are hypoplastic, and the orbital floor is hollow, resulting in proptosis and additional orbital dystopia that produce mild to moderate orbital

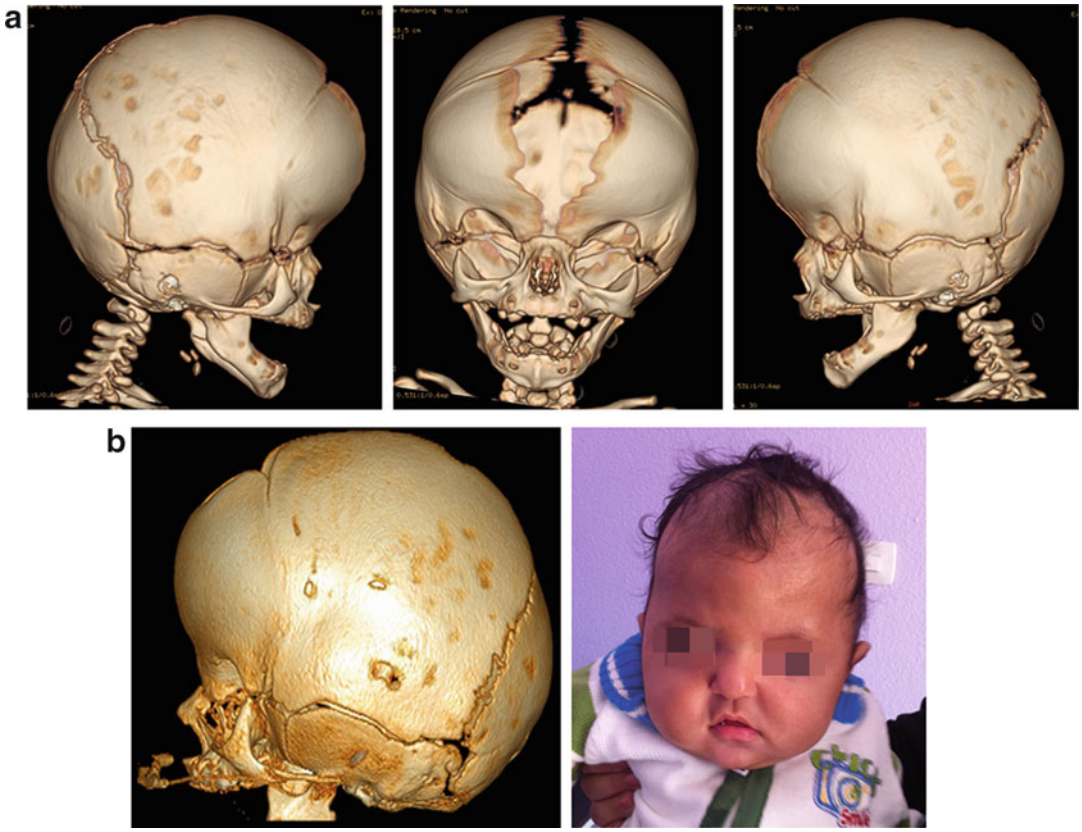

Fig. 1 (**a**) Brachycephaly in a patient with Pfeiffer syndrome; (**b**) brachycephaly with coronal suture involvement in patient with Apert syndrome

hypertelorism and divergent strabismus. Maxillary hypoplasia produces characteristic pseudoprognatism. Nasal septum deviation, together with maxillary hypoplasia, may originate a chronic obstruction to respiratory flow and be associated with choanal atresia, velopharyngeal incompetence, and relative macroglossia. All these malformations will lead finally to more or less severe respiratory obstructions and apneas. They may end in a chronic raised intracranial pressure (ICP) by an increase in venous pressure after hypercapnia and even contribute as an etiopathogenic mechanism in the development of hydrocephalus. Cinalli et al. (1995) reviewed the neurosurgical complications of Crouzon syndrome in a series of 68 patients. Nineteen of these patients required treatment for progressive hydrocephalus and 72.7% of these patients had chronic tonsillar herniation, which was symptomatic in six individuals. Four individuals had syringomyelia and another had a respiratory standstill, whereas the remaining patient had painful torticollis.

The initial treatment for Crouzon syndrome usually requires cranio-orbital decompression, including bicoronal suture release and osteotomies of the anterior cranial vault and upper orbits with reshaping and advancement. They are usually performed by the age of 8 to 11 months unless severe proptosis or signs of increased ICP are present earlier (Marchac et al. 1994; Persing et al. 1990; McCarthy et al. 1995). Sometimes, it is necessary to perform a combined approach, including midface advancement (Meling et al. 2004; Bradley et al. 2006; Cohen et al. 1999; Kubler et al. 2004; Nadal et al. 2000). When Chiari malformation (CM) is present early in life, an occipital–parietal calvarial decompression

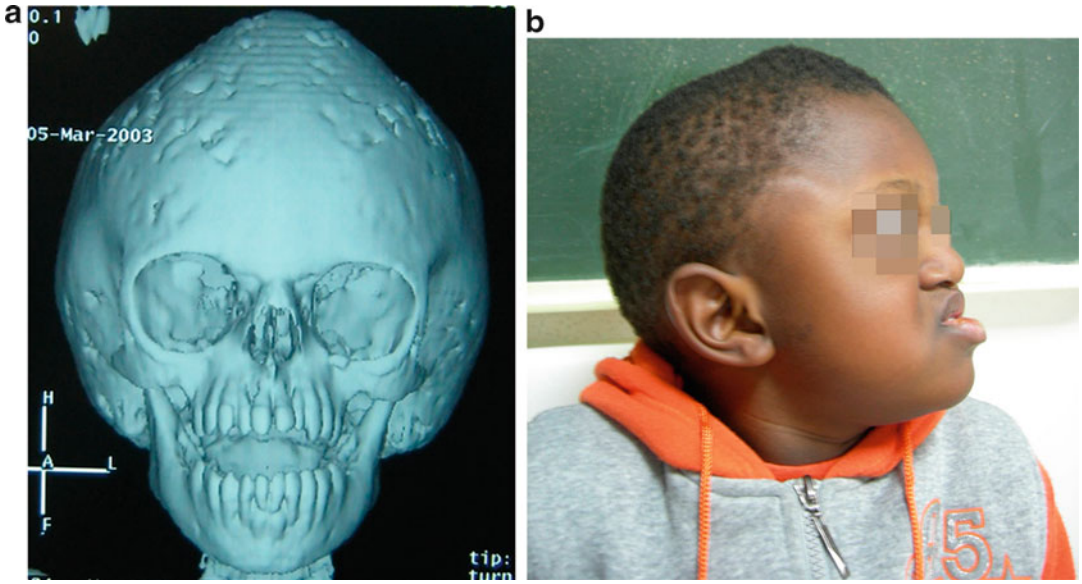

Fig. 2 Patient with Crouzon syndrome and oxycephaly. Note the complete closure of coronal and metopic suture and extreme retrusion of midface

may be preferable to achieve a bigger expansion of the intracranial volume, with or without suboccipital decompression (Rich et al. 2003; Pollack et al. 1996a; Cinalli et al. 1998a, 2005; Sgouros et al. 1996; Hirabayashi et al. 1998). After proper release of the ICP, fronto-orbital remodeling can be achieved via an anterior approach (McCarthy et al. 1995; Hirabayashi et al. 2002; Whitaker et al. 1987).

Apert Syndrome

Apert syndrome, also known as acrocephalosyndactyly type I, is a congenital disorder characterized by multiple suture synostoses, facial hypoplasia, and osseous syndactyly of the hands and feet. It is caused by heterozygous mutation in the FGFR2 gene on chromosome 10q26. Approximately 1 in 65,000 to 165,000 of live births is affected. It is usually classified among a group of craniofacial syndromes with Crouzon, Pfeiffer, and Saehtre-Chotzen syndromes, all of which are allelic disorders with similar clinic manifestations and common genetic background. Wheaton (1894) first noted the coincidence of craniosynostosis and syndactyly (1894), but it was Apert who fully characterized the syndrome in 1906 (31) and characterized it by acrocephaly of brachysphenocephalic type and syndactyly of the hands and feet with complete distal fusion and a tendency to fusion of bony structures.

In Apert syndrome there is a craniosynostosis due to the premature closure of several cranial sutures, typically coronal sutures, and later on those of the anterior cranial base and posterior fossa which originates a brachycephaly (acrocephaly). The sagittal suture is typically widened and opened. It is always accompanied by osseous syndactyly of hands and feet and fusion of the distal phalanxes. There is usually severe hypoplasia of the midface with an ogival-fissured hard palate. The orbital rims are retruded and elevated, and the skin possesses a characteristic acneiform appearance, mostly over the nasal bridge, shoulders, and back. Midface anomalies and anterior fossa craniosynostoses produce a decrease in the orbital volume that may lead to proptosis, strabismus (V syndrome), hypermetropia, or astigmatism. The hands, when all the fingers are webbed, have been compared to a spoon

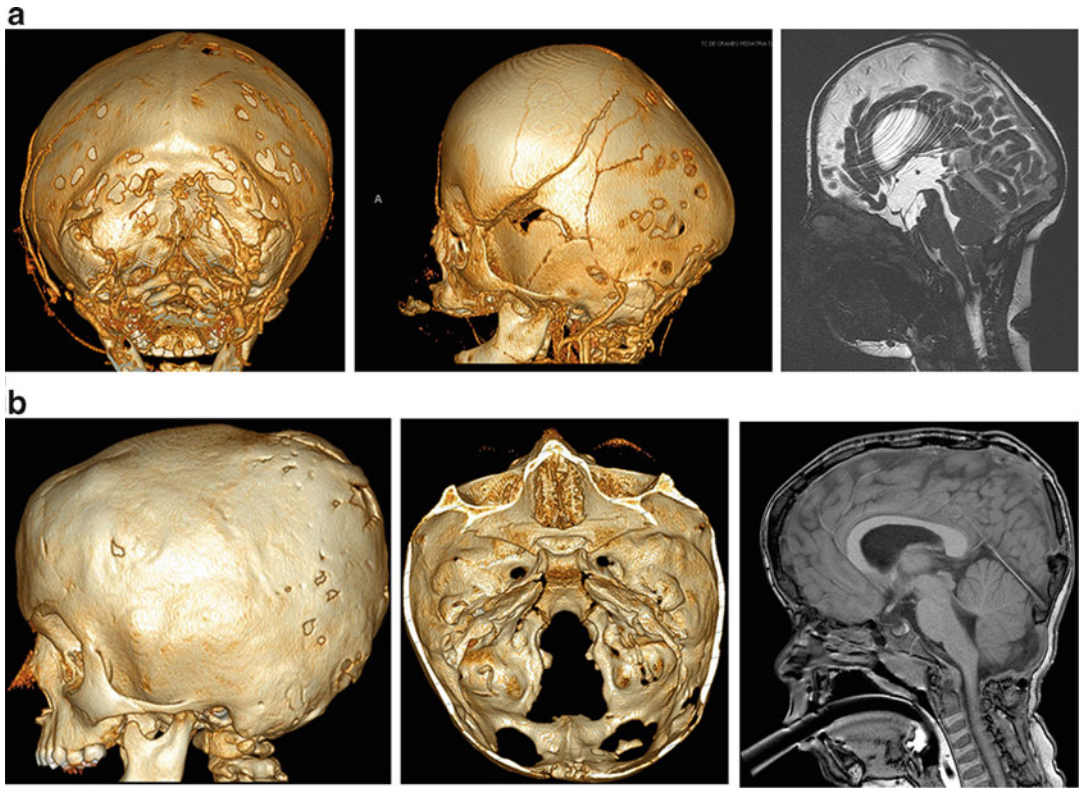

Fig. 3 Crouzon syndrome. (**a**) Complete closure of petrous-occipital synchondrosis and lambdoid suture precludes an acquired Chiari malformation; (**b**) aspect of the same patient after posterior vault expansion with synchronous suboccipital decompression

and, when the thumbs are free, to an obstetric hand. Most of these patients present with central nervous system anomalies, including hypoplasia of the corpus callosum and limbic and mesial temporal structure malformations. Approximately 10% of these children develop hydrocephalus, but only 2% of them suffer from a CM, in contrast to Crouzon syndrome, where 75% of the patients develop a hindbrain herniation (Cinalli et al. 1995). If left untreated, the incidence of raised ICP has previously been reported as 45% (Cinalli et al. 1998a; Marucci et al. 2008). Untreated intracranial hypertension may result in insidious optic atrophy, visual loss, and developmental delay.

Antenatal diagnosis is possible (Leonard et al. 1982), but the majority of the patients are diagnosed at the time of delivery. The possibility of a dominant autosomal inheritance has been described (Roberts and Hall 1971), but most cases are sporadic. Advanced paternal age has been reported to have a role in its pathogenesis. The genetic failure occurs over the long arm of chromosome 10 (10 g26 region) due to a mutation of exon 7, which codifies for FGFR2. In most cases, a S252 W or P253R mutation is present. Slaney et al. (1996) found differential effects of the two FGFR2 mutations on syndactyly and cleft palate in Apert syndrome. Among 70 unrelated patients with Apert syndrome, 45 had the S252 W mutation and 25 had the P253R mutation. The syndactyly in both the hands and the feet was more severe in patients with the P253R mutation. In contrast, cleft palate was significantly more common in patients with the S252 W mutation. No convincing differences were found in the prevalence of other malformations associated with Apert syndrome. Mutations in FGFR2 produce an increase in the number of precursor cells that

take part in osteogenesis (preosteoblastic cells) and lead to an increase in subperiosteal osseous matrix formation, precocious ossification, and premature closure of the cranial vault during the fetal development.

Early cranial decompression with occipital expansion or fronto-orbital advancement is the treatment of choice, although some authors have advocated avoiding routine vault expansion in the first year of life. Instead, careful clinical, ophthalmologic, and respiratory monitoring would allow raised ICP to be treated in the most appropriate manner only when it occurs (Marucci et al. 2008). Midface hypoplasia accounts for the exorbitism, strabismus, and respiratory difficulties seen in this condition. In the absence of any clinical sequelae from this hypoplasia, midface advancement is usually postponed until an age of 4 to 6 years. When needed, it may be necessary to intervene earlier with different techniques, such as monobloc advancement, maxillotomies, and/or mandible distraction. Facial hypoplasia and ogival palate abnormalities are responsible for phonetic disorders, abnormal dental eruption, and malocclusion.

Varying degrees of mental deficiency have been associated with Apert syndrome; however, individuals with normal intelligence have also been reported. Individuals who have craniectomy early in life may have improved intelligence. Some authors have shown that less than 50% of patients with Apert syndrome have a normal or near-normal intelligence quotient (IQ), with the rest being moderately to severely retarded. Patton et al. (1988) did a long-term follow-up on 29 patients of whom 14 (48%) had a normal or borderline IQ, 9 had mild mental retardation (IQ, 50–70), 4 were moderately retarded (IQ, 35–49), and 2 (7%) were severely retarded (IQ less than 35). Early craniectomy did not appear to improve intellectual outcome in this series. Six of seven school drop-outs with normal or borderline intelligence were in full-time employment or vocational training. In a series of 30 patients with Apert syndrome with malformations of the corpus callosum, the limbic structures, or both, Cohen and Kreiborg concluded that many patients are mentally retarded, suggesting that these malformations may be responsible for mental retardation (Cohen and Kreiborg 1990).

Early treatment of the craniosynostosis has been related to better outcomes in other series. Renier et al. (1996) found an IQ greater than 70 in 50% of Apert syndrome patients when they were treated by cranial expansion in the first year of life but only in 7.1% of those who were treated later.

Pfeiffer Syndrome

Pfeiffer syndrome is an autosomal dominant craniosynostosis syndrome with characteristic anomalies of the hands and feet. Initially described by Pfeiffer in 1964 (Glaser et al. 2000; Cohen 1993), this syndrome is characterized by turribrachycephaly, maxillary hypoplasia, and antimongoloid slant of the orbits. There is hypertelorism and a marked degree of proptosis due to the bicoronal synostosis and subsequent recession of supraorbital rim and short anterior fossa. Extremities are notable for broad short thumbs and large toes. There may be a variable degree and number of soft tissue syndactyly (most commonly between the second and the third digits), in comparison to Apert syndrome, where bony syndactyly is the hallmark. There may also be symphalangism (phalangeal fusion), ankylosis of the elbow joints, and cervical vertebral fusions (all of them also possible in Apert syndrome).

Pfeiffer syndrome can be caused by heterozygous mutations in the FGFR1 gene on chromosome 8 or in the FGFR2 gene on chromosome 10 (Robin et al. 1994; Schell et al. 1995).

Three clinical subtypes, which have important diagnostic and prognostic implications, have been identified (Cohen 1993). Type 1, the classic syndrome, is compatible with life and consists of craniosynostosis (usually mild bicoronal synostosis), midface deficiency, broad thumbs, broad great toes, brachydactyly, and variable syndactyly. It is usually associated with normal or near-normal intelligence. Children with this type of Pfeiffer syndrome can develop normally, but there is often increased ICP if the synostoses is left uncorrected (Fearon and Rhodes 2009). Type

2 consists of cloverleaf skull with Pfeiffer hands and feet, together with ankylosis of the elbows. Type 3 is similar to type 2 but without cloverleaf skull. Ocular proptosis is severe, and the anterior cranial base is markedly short. Various visceral malformations have been found in association with type 3. Early demise is characteristic of types 2 and 3.

Cloverleaf Skull (Kleeblattschädel)

Kleeblattschädel syndrome is characterized by a trilobar skull caused by frontal and bitemporal bossing. The first description of a trilobar cranial malformation in a newborn was made by Vrolik in 1849 (Gosain et al. 1997), but the term "kleeblattschädel syndrome" was not introduced until 1960 by Holtermuller and Wiederman (Gosain et al. 1997; Thompson et al. 1995a). These authors reported a series of children with a trilobar or "cloverleaf" cranium associated with multiple craniosynostoses. In 1965, Commings et al. published the first case in the United States and translated the term kleeblattschädel syndrome into cloverleaf skull (Thompson et al. 1995a). This malformation has been described in children with Crouzon, Apert, Carpenter, Beare-Stevenson, and in type II Pfeiffer syndrome, where it is most frequently associated (up to 20% in some series) (Cohen 1993; Thompson et al. 1995a).

Kleeblattschädel syndrome results from the fusion of the coronal, posterior sagittal, and lambdoid sutures and a wide diastasis of the squamosal sutures. This results in a characteristic trilobar skull which appears when the growing brain, unable to expand in its usual conformation, bulges through the diastased squamosal sutures. Methopic and anterior sagittal suture may or may not be fused early.

The etiology of this syndrome is multiple and related to different genetic figures. It has been attributed to abnormalities of both the calvarium and the skull base, probably due to the presence of a combination of prematurely fused cranial sutures and hydrocephalus.

The surgical management of cloverleaf skull remains one of the most formidable challenges for the craniofacial surgeon (Fig. 4). The natural history of this deformity without surgery was well described in the 1960s and 1970s. Just a few of these children survived beyond infancy, and those who did developed severe neurologic deficits. The first attempt at surgical correction was reported by Angle in 1967 (Gosain et al. 1997; Angle et al. 1997). Since then, a number of surgical series have been reported, without a clear conclusion on prognosis and outcome. Review of the literature reveals a lack of consistent surgical strategies (Renier et al. 1996; Cohen 1993; Gosain et al. 1997; Thompson et al. 1995a; Blount et al. 2007; Muller and Hoffman 1975). Postoperative data are scarce, and reoperation is the rule in these patients, with a consequent increased morbidity. In addition to the significant cosmetic deformity, the constant coexistence of intracranial hypertension, hydrocephalus, hindbrain herniation, severe skull base dysplasia, and anomaly in venous drainage (Fig. 4c) imposes important neurosurgical considerations throughout treatment.

Intracranial Pressure in Complex Craniosynostoses

Increased intracranial pressure has been documented in 47–67% of children with complex craniosynostoses (Blount et al. 2007; Cinalli et al. 1998b; Hayward 2005; Tamburrini et al. 2005, 2012; Pollack et al. 1996b). Although elevated intracranial pressure is a well-known occurrence in multiple synostosis, detection and definition of its limits are often difficult. The classic signs of elevated intracranial pressure, such as papilledema on funduscopic examination, increased optic nerve sheath diameters or skull markings on plain skull films ("copper beaten"), lack sensitivity and specificity for the diagnosis of increased ICP in children with craniosynostoses (Tamburrini et al. 2012; Taylor et al. 2001). Papilledema has a specificity of 87% as an indicator of elevated ICP, while sensitivity is only 30%. This is even less reliable in younger patients

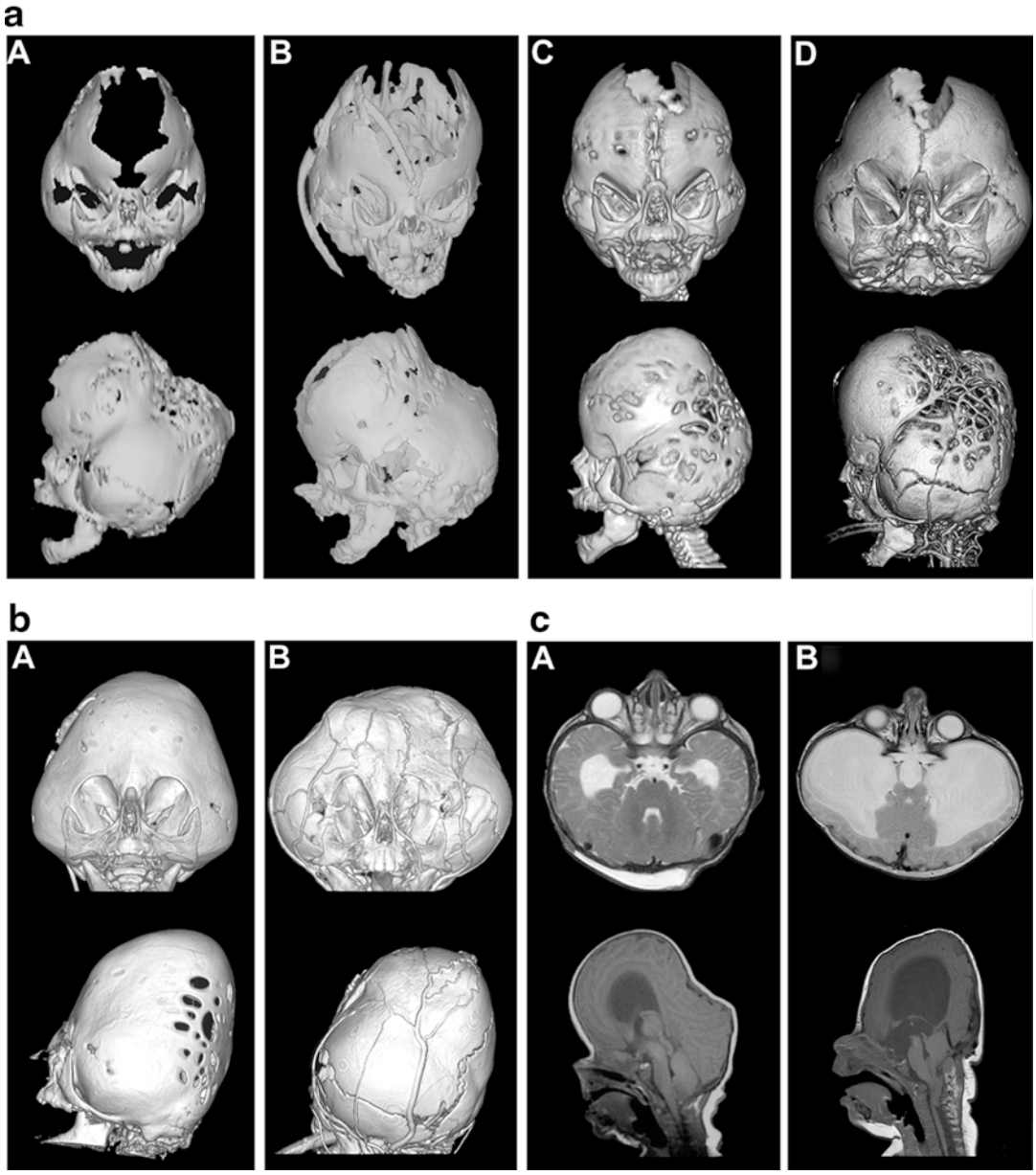

Fig. 4 (**a**) Cloverleaf skull in cases with patent sagittal suture; (**b**) a case of cloverleaf skull with closed sagittal suture; (**c**) observe the bitemporal expansion of the skull as compared with (**a**)

(Tuite et al. 1996). Although optic nerve sheath measurement has improved detection rate, this method still has a poor positive and negative predictive value (Driessen et al. 2011).

Direct measurement with invasive methods is still the only reliable way to ascertain increased ICP. However, this is not always easy and more importantly, there is a lack of universally accepted scales of normal and abnormal ICP values in children (Tamburrini et al. 2005; Wiegand and Richards 2007; Thompson et al. 1995b). Several authors have proposed to consider children with

craniosynostoses as comparable to children above 1 year/with closed sutures (Tamburrini et al. 2005; Pople et al. 1995; Siddiqi et al. 1995) and to evaluate the ICP in them according to adult parameters (normal range, below 10 mmHg; borderline, 10–15 mmHg; abnormal, above 15 mmHg). However, for some other authors this approach is not reliable due to the reduced cerebral compliance and chronic alteration of the intracranial pressure in these children (Gambardella et al. 1993; Pople et al. 1995). Together with different authors, the presence of Lundberg A waves (rises in ICP above 50 mmHg lasting 5 min) and/or Lundberg B waves (rises in ICP up to 50 mmHg of 0.5–2-min duration) has been considered as definitive for the diagnosis of increased ICP (Tamburrini et al. 2005, 2012; Wiegand and Richards 2007).

The relationship between complex craniosynostoses and increased intracranial pressure (ICP) is multifactorial and includes multiple pathological pathways apart from changes in intracranial volume. Small cranial volume due to fusion of multiple sutures is not the only mechanism of increased ICP in syndromic craniosynostosis. In fact, intracranial volume is normal or even enlarged in most children with complex craniosynostoses. In a study by De Jong no statistically significant difference was found in the intracranial volumes between a group of complex craniosynostoses children when compared with normal values in age-matched normal children (de Jong et al. 2012). On the contrary, the total CSF volume was significantly higher in children with craniosynostoses, suggesting that this might be the main driving force for the compensatory skull growth (Tamburrini et al. 2012; de Jong et al. 2012).

Other possible mechanisms to explain increased ICP are associated hydrocephalus and obliteration of venous return caused by impaired venous outflow from hypoplastic cranial foramina. Venous hypertension is associated with lambdoid synostosis, encasement of dural sinuses by sinostosed sutures or impinging spiculae in cloverleaf skull cases (Hayward 2005; Taylor et al. 2001). Small posterior fossa results also from lambdoid synostosis and might have some effect on the development of hydrocephalus by disturbing the movement of the cerebrospinal fluid in severely deformed posterior cranial fossa.

Chronic tonsillar herniation caused by overcrowding in the small posterior fossa might also induce an increase in the ICP by obliteration of the CSF circulation in the posterior fossa and between the intracranial and the spinal subarachnoid space (Cinalli et al. 1995, 2005; Thompson et al. 1997). Finally, impaired breathing due to associated midface hypoplasia and airway compromise results in abnormally high PaCO2 which also raises the ICP interacting with all previous factors.

Among these lesions, small and deformed cranial vault, hydrocephalus (Cinalli et al. 1998b; Collman et al. 2005), upper airway obstruction, and chronic tonsillar herniation (Cinalli et al. 1998a) must be surgically treated to control and decrease raised ICP.

Chiari Malformation in Craniosynostosis

The association between Chiari malformation (CM) and faciocraniosynostosis was first noted by Saldino et al. (1972) in 1972 in one patient with Pfeiffer syndrome. Since then numerous authors have reported the incidence of chronic tonsillar herniation in multiple suture craniosynostosis (Cinalli et al. 1995; Francis et al. 1992; Sainte-Rose et al. 1984; Frim et al. 1990; Mulliken et al. 1999), and it is a frequent finding in syndromic and multiple sutures craniosynostosis, characterized by early fusion of lambdoid sutures and cranial base synchondroses. The incidence of CM has been reported as high as 70% in Crouzon's syndrome (Mulliken et al. 1999; Sainte-Rose et al. 1995; Esparza and Hinojosa 2008; Renier et al. 1997), 75% in nonsyndromic oxycephaly (Renier et al. 1997), 50% in Pfeiffer's syndrome, and 100% in Kleeblattschädel deformity (Cinalli et al. 1998a). CM was also found in other types of syndromic craniosynostosis, some cases of nonsyndromic complex craniosynostosis involving the lambdoid suture and in some rare cases of scaphocephaly.

Downward herniation of neural tissue through the foramen magnum is usually an acquired

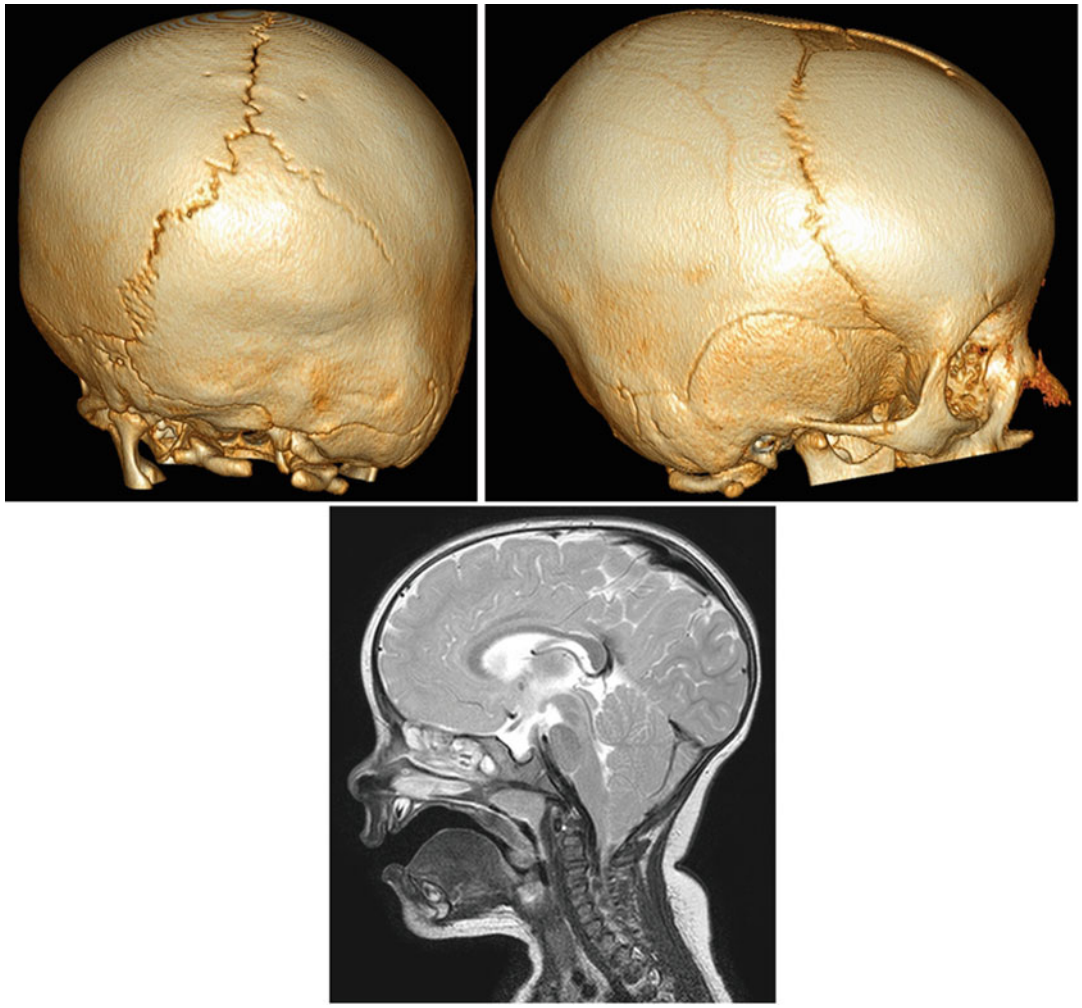

Fig. 5 Lambdoid synostosis. Acquired Chiari malformation related to decreased volume in the posterior fossa

malformation in craniosynostosis and may be secondary to a disproportion between the posterior fossa and the growing hindbrain structures (Cinalli et al. 2005; Tamburrini et al. 2012; Nishikawa et al. 1997). In most cases of craniosynostosis hindbrain herniation is not present at birth. It develops in response to the changes in the skull base and posterior fossa secondary to premature closure of the lambdoid and cranial base sutures (usually between 3 and 6 months of age) supporting the pathogenetic hypothesis of overcrowding of the posterior fossa secondary to premature sutural fusion (Cinalli et al. 2005; Sainte-Rose et al. 1995) (Fig. 5). The excellent review from Cinalli et al. gives an exhaustive overview on the pathogenic mechanisms involved in the developing of the hindbrain herniation in craniosynostosis (Cinalli et al. 2005). The progressive fusion of the lambdoid suture produces alteration in the skull base and stenosis of the jugular foramina (if the petro-occipital synchondroses are primarily involved). The first result would be 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. The second result would be venous hypertension, induced both by jugular foramen stenosis and crowding of the posterior fossa with

consequent compression of the sigmoid sinus. These factors can alter the CSF circulation at the level of the posterior fossa with an obstructive mechanism and impairing CSF reabsorption at the level of the pacchionian granulations, with the overall final result of an increased CSF outflow resistance (Tamburrini et al. 2012). The severe crowding in the foramen magnum may result not only in hindbrain herniation but also in brain stem compression and deformation of the fourth ventricle. Thus, hindbrain herniation can be considered to be a condition creating or aggravating a hydrocephalic state, not the consequence of hydrocephalus. This explains the cases of CM without hydrocephalus frequently observed in craniosynostosis without primary involvement of the skull base synchondrosis (e.g., oxycephaly) or in the first stages of Crouzon's, where CM is a frequent finding without hydrocephalus.

Under normal conditions, the posterior cranial fossa grows in length in early childhood in the intra-occipital, petro-occipital, and spheno-occipital synchondroses. Growth in the intra-occipital ceases in early childhood, while growth in the spheno-occipital continues after puberty (Fujisawa et al. 2002). In syndromic and complex multisutural craniosynostosis, unlike monosutural craniosynostosis, the facial skeleton and the cartilaginous cranial base are primarily involved (Fujisawa et al. 2002; Goodrich 2005). In Crouzon's and Apert's syndrome, the degree of involvement of the skull base synchondrosis and the timing of fusion are different. Earlier closure of the lambdoid suture is considered as the main contributor for the higher rate of CM in patients with Crouzon and Pfeiffer syndromes if compared with those with Apert syndrome. It has also been observed that lambdoid suture synostosis occurs significantly earlier in the cases of Crouzon syndrome associated with CM compared with Crouzon's patients without CM (Cinalli et al. 1998a, 2005). In the Apert's syndrome the spheno-occipital, petro-occipital, and occipital synchondrosis are fused later (beginning after 12 to 48 months of life and ending at the age of 4 years) than in Crouzon's syndrome where they can be completely fused in the first year of life. All this could be conditioned by a different genetic pattern. In syndromic craniosynostosis the genetic mutations responsible for the disease are located mainly in FGFR1 (Pfeiffer's syndrome), FGF2 (Crouzon's, Apert's, and Pfeiffer's), and FGFR3 (Crouzon's and acantosis nigricans). Some authors have suggested a correlation between the mutation observed and the presence of CM. In Crouzon's syndrome, the patients affected by CM and syringomyelia would present a variety of mutation that spreads over exons IIIa and IIIc of the FGFR2 gene (Mulliken et al. 1999; Fujisawa et al. 2002). This could explain the significant differences found in the final anatomy of the skull base and the posterior cranial fossa. The Apert basiocciput is larger than normal while in Crouzon's syndrome is smaller (Kreiborg 1986). According to Cinalli et al., Crouzon preferentially expands along a supero-inferior axis whereas little or no growth is allowed along an antero-posterior axis (Cinalli et al. 2005; Tamburrini et al. 2012); the foramen and the basion–opisthion area present only small changes, whereas the more significant alterations occur in the cranial base posterior to the foramen (Kreiborg 1986). Previous conditions would result in altered dimensions of the posterior cranial fossa: normal or larger than normal in the Apert syndrome (Kreiborg 1986), smaller, shortened in the antero-posterior axis and elongated in the supero-inferior and lateral axis in Crouzon's syndrome.

If the petro-occipital synchondroses are involved, their premature closure may lead to stenosis or atresia of the jugular foramen. Venous hypertension induced by jugular foramen stenosis (Rollins et al. 2000) increases the sagittal sinus pressure and results in a higher CSF pressure request to maintain CSF balance. In patients with closed sutures, intracranial pressure may rise to very high levels, overcoming the high sagittal sinus pressure and permitting absorption of CSF, with normal-sized or small ventricles, as seen in some cases of pseudotumor cerebri (Cinalli et al. 1998b; Sainte-Rose et al. 1995). In contrast, in infants and children with open sutures (or following surgical cranial suture release), increased CSF pressure induces progressive head enlargement and dilatation of the ventricles and subarachnoid spaces (Cinalli et al. 1998b; Sainte-Rose et al. 1995). This is usually followed by the

development of collateral venous drainage, through the foramen magnum and/or through emissary and scalp veins. This venous pattern has to be beared in mind as in some cases the main venous drainage occurs through emissary veins rather than through the usual jugular pathway and the distortion of the previous could lead to a fatal outcome after surgery (Richtsmeier 1987). Venography should form part of the routine MR imaging protocol for diagnostic assessment of children with complex and syndromic craniosynostosis (Rollins et al. 2000). Quantification of venous hemodynamics may also have a role, allowing more accurate, noninvasive monitoring of change at follow-up studies (Rich et al. 2003).

The remaining sutures on the vault (lambdoid, sagittal, coronal, and metopic) could play also a role in the development of CM. In case of in utero closure of sagittal and coronal sutures, a cephalocranial disproportion in the supratentorial compartment occurs early, forcing the neural growth to be directed posteriorly and inferiorly, pushing down the tentorium. This could induce a lower attachment of the tentorium, near the foramen magnum, reducing the size of the posterior fossa, and increasing the risk of CM, especially if premature lambdoid synostosis is also involved. The precocity of coronal and sagittal suture synostosis does not seem to play a role in the pathophysiology of CM in Apert's (where sagittal suture is widely open) and Crouzon's syndrome. The premature closure of the lambdoid suture reflects the primary closure of the sphenooccipital synchondrosis and could be a reliable radiological indicator of the synostosis of the posterior cranial base sutures. As we have seen, in Crouzon's syndrome the sagittal and lambdoid sutures close very early (median 6 and 21 months respectively) and significantly earlier in the cases of Crouzon's syndrome associated with CM compared with Crouzon's patients without CM (Sainte-Rose et al. 1995). On the contrary, in the Apert syndrome, where the CM occurs in only approximately 2–5% of the cases, the cranial vault synostosis occurs very early for the coronal suture (median 5 months) and significantly later (51 and 60 months respectively) for the sagittal and lambdoid sutures.

More than one third of patients with hindbrain herniation become symptomatic for chronic tonsillar herniation (CTH) or develop syringomyelic cavities. Usually, the onset of symptoms occurs late in life but they may be dramatic especially in very young children, with respiratory problems such as central apnea, bilateral vocal cord paralysis, bulbar palsy, ventilatory control abnormalities, persistent cyanosis, and breath-holding spells (Cinalli et al. 2005). Careful radiologic and clinical follow-up are needed in patients with syndromic or complex craniosynostosis to assess the presence and the evolution of CTH. MRI with venous angiography is the gold standard for the evaluation of these patients (Esparza and Hinojosa 2008; Rollins et al. 2000).

Management of Chiari Malformation in Craniosynostosis

The management of the Chiari I malformation in children with complex craniosynostoses depends on the clinical and radiological condition as well as on the age of the patient at the time of diagnosis.

In cases where an active ventricular dilation is present, hydrocephalus should be managed as first step. Extrathecal shunt will be usually the first choice, but there is increasing evidence that ETV could be considered as a valid alternative to VP shunt implantation in cases where a functional stenosis of the Sylvius aqueduct or a chronic tonsillar herniation causing an obstructive hydrocephalus can be established (Di Rocco et al. 2010). Children in the first years of life, with controlled hydrocephalus or without a symptomatic ventricular dilation, should undergo primarily a cranial vault expansion (McCarthy et al. 1995; Pollack et al. 1996a; Hoffman and Hendrick 1979; Posnick and Ruiz 2000). Surgical treatment centered only in the foramen magnum is prone to failure as it does not deal with any of the factors that contribute to the development of the Chiari malformation (craniocerebral disproportion, venous hypertension, and hydrocephalus) and because of the usual rapid regrowth of the removed foramen magnum bone that would lead to an early failure of the temporary craniocervical

junction decompression (Cinalli et al. 1995; Tamburrini et al. 2012).

The most frequent condition is the early involvement of the lambdoid sutures associated with CTH. In these cases, occipital cranial vault remodeling and expansion should be considered as the preferred first surgical procedure. This allows to enlarge the posterior compartment primarily, protecting posterior fossa intracranial structures and to decompress the main dural venous sinuses (Tamburrini et al. 2012). Different techniques have been proposed for posterior cranial vault expansion. Free bone flaps are considered in the most severe cases in the first months of life. It is an easy technique that relies on the possibility of progressively enlarging the intracranial space through the brain pulsation (Sgouros et al. 1996). It is useful in the reduction of the blood losses. However, it fails to predict the amount of cranial space enlargement and lacks the possibility of cosmetic remodeling. In cases like the cloverleaf malformation, parietal craniectomy can be performed only in a piecemeal fashion and extreme care has to be adopted when dissecting free the thin external layer of the superior sagittal sinus, which is often imbibed or pinched by bone spikes that enter the sinus (Gosain et al. 1997; Thompson et al. 1995a; Esparza and Hinojosa 2008).

Posterior distraction advancement has been proposed as an alternative approach. These techniques also avoid the split of the bone from the dural sinuses and reduce both operative times and blood losses (Sgouros et al. 1996) (Fig. 3). The main limitation of this technique is the incidence of bone fractures during distraction in the very young children and an up to 30% rate of complications related to dislodgement or breakage of the implants (Tamburrini et al. 2012; Esparza and Hinojosa 2008). The use of resorbable distractors has recently overcome the need for a second surgery required to remove the distractors (White et al. 2009). Usually, for patients with severe syndromes and marked flattening of the posterior vault and overcrowding of the posterior fossa, an occipital expansion with or without suboccipital craniectomy may be indicated (Cinalli et al. 1998a).

In cases of multiple suture synostosis, mainly in patients with a Crouzon's syndrome or kleeblattschädel deformity, where cranial vault (bicoronal and both lambdoid) and skull base sutures are affected, the correction of a Chiari malformation may need to be treated by a complete calvarial reconstruction. This may be performed as a one-step procedure as described by Pollack et al. (1996a). The child is set in the "modified prone position" allowing exposure from the orbital ridge to the foramen magnum. This approach, however, requires marked hyperextension of the neck and it is contraindicated for patients who present with anomalies of the craniovertebral junction, because hyperextending the neck for several hours may lead to prolonged severe compression on the spinal cord and medulla (Pollack et al. 1996a). We have used the same approach (holocranial dismantling; technique X) but in two steps: first fronto-orbital advancement with the child supine and then, after closure of the skin incisions, an occipital expansion with the patient prone in the same surgical session without a relevant increase in morbidity (Esparza and Hinojosa 2008).

It is possible to perform occipital craniectomy and remodeling through a bicoronal incision. Dissection proceeds in the subperiosteal plane elevating the occipital muscles over the inion and exposing all the suboccipital bone that can be removed then reaching the posterior and lateral margins of the foramen magnum. A midline suboccipital craniectomy should be added, widely opening the lateral margins of the foramen magnum, in order to avoid failures related to bone regrowth (Sgouros et al. 1996). The infratentorial compartment is left uncovered and the occipitoparietal region is conformed repositioning the bone. Opening of the dura is not advised, unless the patient presents clinical signs of severe compression of the brain stem; severe bleeding from the dural edges has been described due to the significant collateral venous circulation at the level of the foramen magnum (Cinalli et al. 1995; Strahle et al. 2011). In these cases often it is not possible to perform an intradural approach but even if some degree of tonsillar herniation still remains after suboccipital craniectomy, crowding

of the foramen magnum is reduced and more CSF can be observed around the medulla on postoperative MRI.

Dura opening and cervical laminectomy may be indicated in cases of severe compression of the medulla but carries the risk of severe bleeding from the dural lays, because of the abnormal anatomy of dural venous sinuses which usually includes prominent occipital longitudinal sinus over the suboccipital bone and dominant marginal occipital sinus around the foramen magnum and frequently a significant collateral circulation in the muscular plane. AngioCT and/or angio-MRI are mandatory studies in these patients to avoid catastrophic intraoperative bleeding (Esparza and Hinojosa 2008; Rollins et al. 2000).

In older children with asymptomatic Chiari malformation, observation alone may be adopted. If clinical symptoms appear at any stage, opening of the foramen magnum with or without duroplasty can be considered as an elective therapeutic approach. Craniocerebral disproportion and venous sinuses compression are usually less severe than in younger children and the risk of bone regrowth is significantly lower (Cinalli et al. 1995).

Posterior cranial vault expansion has proved to deal adequately with the problems related to craniocerebral disproportion early in life. For this reason, fronto-orbital advancement is usually differed unless severe respiratory conditions or oculoscleral exposition coexist (McCarthy et al. 1995; Pollack et al. 1996a; Posnick and Ruiz 2000).

Hydrocephalus and Alteration of CSF Dynamics

Ventriculomegaly and ventricular asymmetry may be found even in children with single-suture craniosynostosis, but they require treatment only in selected cases. Abnormal dilatation of the subarachnoid spaces is a common finding in this patients and may be related to some disturbance in CSF absorption (Gosain et al. 1997). In sagittal synostosis, for example, the frequent encasing of the superior sagittal sinus in the groove of the fused suture may account for some impairment of CSF absorption. This may lead to mild ventricular dilatation and enlarged CSF subarachnoid spaces over the cerebral hemispheres. True hydrocephalus has seldom been reported in single-suture craniosynostosis and is always related to coincidental disorders such as ventricular hemorrhage, meningitis, aqueductal stenosis, or neural tube defects.

On the contrary, ventricular dilatation is a common feature in patients with complex craniosynostosis. This dilatation may vary from nonprogressive ventriculomegaly (including some cases of patients with syndromic craniosynostosis where simple ventricular distortion should be considered a normal anatomic pattern) to true progressive hydrocephalus. Ventricular dilatation has been reported in 30% to 70% of patients with Crouzon and Pfeiffer syndromes and in 40% to 90% of Apert syndrome patients (Gosain et al. 1997; Thompson et al. 1995a; Taylor et al. 2001). In Apert syndrome, most cases of enlarged ventricles remain stable without a shunt, but in Crouzon's and severe forms of Pfeiffer syndrome, shunting is frequently necessary at some stage of treatment. In these patients, the indication for shunting is mainly based on progressive ventricular dilatation or evidence of persistent intracranial hypertension, which may need to be ascertained by direct pressure monitoring. After cranial surgery, the artificially created spaces are quite often accommodated by some enlargement of the intra- and extracerebral CSF spaces, and the possibility of a compensated or even slowly progressive hydrocephalic state should be taken into account (Collman et al. 2005).

If we consider only the active forms of hydrocephalus, a rate of 12.1–15% has been reported (Collman et al. 2005). Several pathogenetic mechanisms are involved in its development. In Crouzon's syndrome, the premature fusion of the synchondroses in the cranial base leads to a stenosis of the jugular foramina (Rich et al. 2003; Hayward 2005; Taylor et al. 2001). Abnormal venous drainage through the jugular veins resulting in venous hypertension leads to increased CSF hydrostatic pressure. This situation is frequently worsened by a concomitant

premature fusion of other cranial vault sutures like the lambdoid sutures, which lead to a crowded posterior fossa, compression of the sigmoid sinuses and secondary hindbrain herniation (Cinalli et al. 1995; Hayward 2005; Francis et al. 1992).

Some patients develop rapidly evolving hydrocephalus before any surgical intervention, as in kleeblattschädel or severe conditions of Pfeiffer syndrome. In most of the remaining patients, ventricular dilatation only develops following decompressive surgery for craniosynostosis. For instance, two different forms of Crouzon syndrome have been described by Cinalli et al. in relation to CSF dynamics alterations. The first group, when simultaneous closure of sagittal and coronal sutures occur. They usually present with a pseudo-tumor-like state, having normal or small size ventricles but clinical signs of increased intracranial pressure. Closure of sagittal and coronal sutures results in an oxycephaly, which prevents ventricles from dilatation due to a complete closure of the cranial vault. In this group, ventricle size will increase only after cranial vault remodeling, requiring often a surgical shunting of the progressive hydrocephalus. The second group of Crouzon patients were those with sequential closure of the sagittal and coronal sutures; in these patients, a variable degree of ventricular dilation was present at diagnosis depending from the residual skull vault compliance (Cinalli et al. 1998b). Apert syndrome significantly differs from other syndromic forms in terms of alteration of the CSF dynamics. Although coronal sutures close very early in the first phases of the disease, both lambdoid sutures and cranial base synchondrosis close usually late, resulting in a less severe jugular foramina stenosis and venous hypertension. For this reason ventriculomegaly is a common finding in children with Apert syndrome, while active hydrocephalus occurs very seldom or late in the evolution (Cinalli et al. 1998b; Hayward 2005).

Two combined pathogenic factors have been offered as an explanation for the frequent association of hydrocephalus and complex craniosynostosis: a mechanical increase of the CSF outflow resistance due to constricted growth of the posterior fossa (Cinalli et al. 1995; Tamburrini et al. 2012) and an impaired CSF absorption resulting from venous outflow obstruction (Cinalli et al. 1995, 1998b; Francis et al. 1992). Crowding of the posterior fossa appears to be an acquired disorder secondary to deficient occipital cranial expansion (Collman et al. 2005; Thompson et al. 1997). It has been related to the timing of fusion of the lambdoid suture, which in Crouzon and Pfeiffer syndromes is completed at an earlier age than in Apert syndrome. This would explain the delayed appearance of hydrocephalus in patients with Apert syndrome. The mechanical restriction to CSF outflow would worsen after the development of tonsillar herniation in a small posterior fossa. This theory alone fails to explain the incidence of hydrocephalus, because hindbrain herniation is missing in a number of cases of progressive hydrocephalus (Cinalli et al. 1998a, b). And while it is present in many other cases not affected by hydrocephalus, posterior fossa decompression has often failed to sufficiently restore normal CSF circulation (Tamburrini et al. 2012; Antón-Pacheco et al. 2012). Therefore, constriction of the posterior fossa may not be a single causative mechanism for hydrocephalus in craniosynostosis (Cinalli et al. 1995, 2005).

Together with the mechanical obstruction to the CSF outflow due to posterior fossa crowding a major role of venous pathways obstruction has been proposed by different authors (Hoffman and Hendrick 1979). In the most severe forms of complex craniosynostosis, venous outflow impairment, due to the jugular foramina stenosis, hindbrain caudal displacement, and constriction of the posterior fossa structures within a hypoplastic posterior cranial fossa all would contribute to obstruct the major CSF pathways (Cinalli et al. 2005; Hayward 2005; Hayward and Gonsalez 2005). In a cloverleaf skull deformity (like in many children with Pfeiffer syndrome), the perinatal fusion of multiple sutures – both of the skull base and cranial vault – exacerbate all potential factors responsible for a disturbance in the CSF circulation.

We can currently accept a coexistence of the two mechanisms assuming that venous

hypertension causes a CSF absorption deficit as well as brain swelling leading to the tonsillar herniation (Francis et al. 1992). Further progression would be favored by the progressive closure of the cranial vault and skull base sutures. It has been suggested that an abnormal venous anatomy could be a primary rather than a secondary event and would result from the same dysplastic processes that affect the cranial vault sutures, the basicranium, and the facial skeleton. The expression of FGFR gene products in the infant synostotic sutures has been described; these products have been also localized by immunohistochemistry in the vascular endothelia of patients with syndromic craniosynostosis (Cinalli et al. 1998b; Collman et al. 2005; Sainte-Rose et al. 1984). Therefore, premature endothelial proliferation and subsequent differentiation in the sigmoid and jugular sinuses may result in the narrowed lumen (Cinalli et al. 1998b). Most patients with progressive hydrocephalus simultaneously exhibit signs of venous outflow obstruction and crowded posterior fossa, favoring a combined action of both mechanisms by assuming that venous hypertension causes a CSF absorption déficit (Gosain et al. 1997), as well as brain swelling resulting in tonsillar herniation (Cinalli et al. 1995), or that it aggravates the preexistent cephalocranial disproportion by venous engorgement (Cinalli et al. 1995, 1998a; Collman et al. 2005) (Fig. 6).

Finally, the contribution of upper airway obstruction to raised ICP has long been recognized; in particular, an increase in ICP during episodes of respiratory obstruction has been documented, and improvements in the ophthalmologic signs of increased ICP can be demonstrated after nasal airway dilation, nocturnal positive airway pressure, or maxillofacial advancement procedures. Possible underlying mechanisms include carbon dioxide retention during obstructive episodes in nocturnal apneas and cerebral flow changes during active sleep, particularly if they occur in the presence of reduced cerebral compliance (Cinalli et al. 1998a, b; Goodrich 2005). All these factors would lead in the end to a venous hypertension that would ultimately interfere with the CSF absorption.

Clinical Implications of Abnormal Venous Circulation

Premature closure of the cranial base synchondrosis can contribute to increased ICP in syndromic craniosynostoses, independently from their role in chronic tonsillar herniation (CTH) or in alterations in the CSF dynamics (Tamburrini et al. 2012; Taylor et al. 2001). It is well known the fact that patients with complex craniosynostosis may develop increased ICP in the absence of associated hydrocephalus. In a study by Taylor et al. (2001), the venous drainage angiographic pattern of 23 patients with syndromic or multiple suture craniosynostosis showed a significant degree of stenosis (51–99% reduction in normal diameter or the complete absence of flow) at the level of the complex represented by the sigmoid sinus, intraosseous portion of the jugular sinus, and the jugular bulb. In those cases with more severe narrowing of the sigmoid/jugular complex, a rich venous collateral circulation developed in the region of the mastoid emissary veins and coexisted with transosseous venous drainages in all cases (Taylor et al. 2001). Another study by Rollins et al. documented a venous outflow obstruction by MR venography in the majority of children with complex craniosynostosis. Some of these patients did not have hydrocephalus in spite of clinical signs of increased ICP; again, the main venous outflow collaterals in this series was through the posterior condylar veins (Rollins et al. 2000). A study with reformatted helical CT scans by Rich et al. compared the size of the jugular foramina in 12 children with complex or syndromic craniosynostosis and raised ICP with two control groups of children with respectively nonsyndromic (10 cases) and syndromic (9 cases) craniosynostosis, but normal ICP. Children with raised ICP had significantly narrower jugular foramina than did the age-matched control subjects showing the relevance of sigmoid/jugular bulb stenosis in the pathogenesis of increased ICP (Rich et al. 2003).

The main reason for venous obstructions in children with syndromic craniosynostosis would be the skull base anomalies due to premature closure of petrous bone and occipital

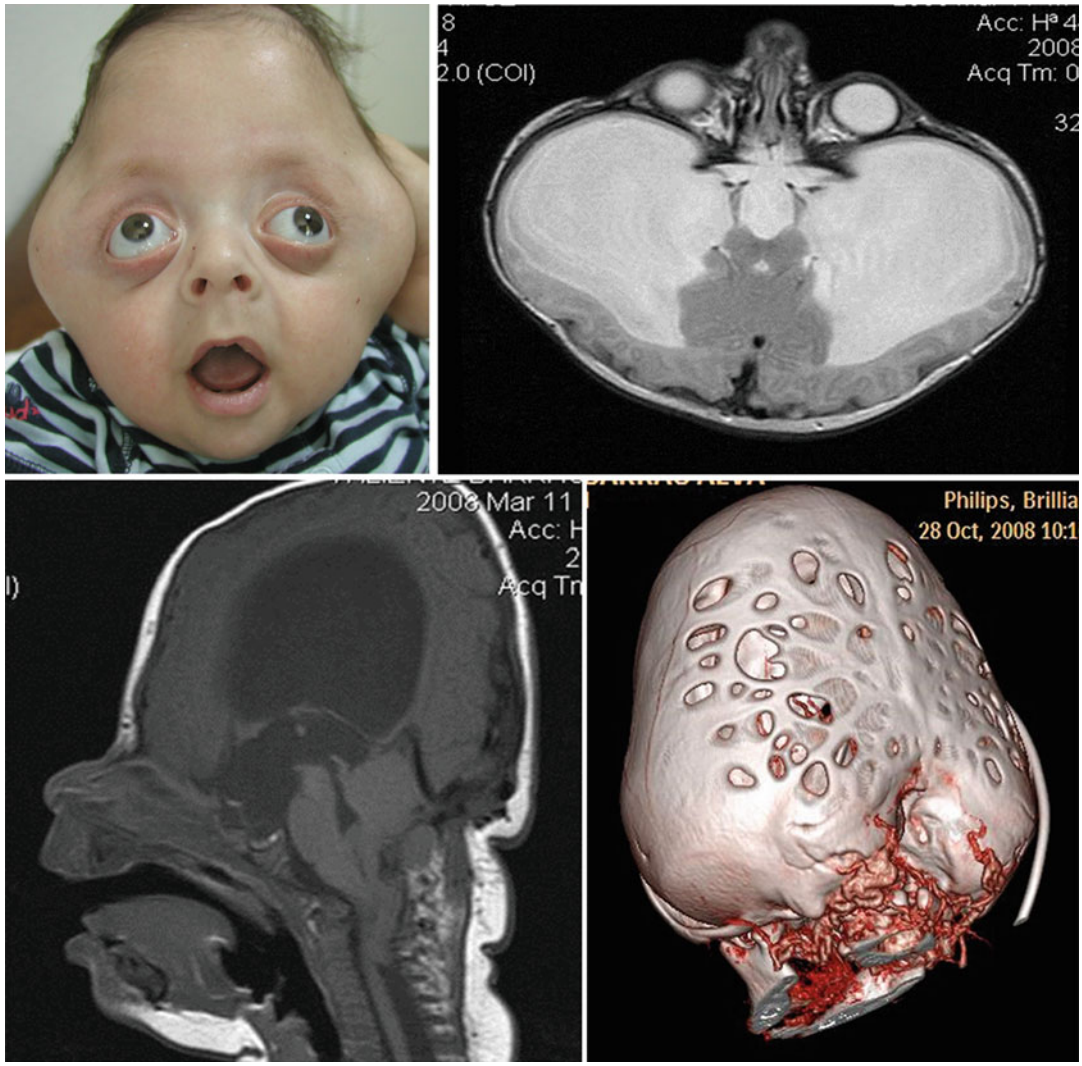

Fig. 6 AngioCT study in a patient with a cloverleaf skull malformation. Chiari malformation is a condition developed after a combination of issues; petrous-occipital synchondrosis and lambdoid synostosis, hydrocephalus, and venous hypertension

synchondrosis, constricting the normal venous pathways, with involvement of the jugular foramen. Another mechanism involved in the stenosis of the sigmoid sinus and jugular complex could be the overexpression of fibroblast growth factors (FGFR1–3) at the level of the vascular endothelia that could determine endothelial proliferation and differentiation and consequent narrowing of their lumen (Naski et al. 1996).

Considering the etiology of venous outflow obstruction, venous decompression at the level of their exit from the skull base would appear to represent the treatment of choice. However, direct osseus decompression is not without risk and may be insufficient. Also, it would not treat the stenosis at the sigmoid sinus and the outflow from the sigmoid sinus to the jugular bulb (Rich et al. 2003). Different approaches like a bypass between the transverse sinus and the jugular vein (Sainte-Rose et al. 1984) or interventional radiological stenting have been proposed, but they are not without risk, or as in the case of stenting, may be not

accounted because of the bone/vascular walls hyperplasia (Rich et al. 2003; Hayward 2005).

For this reason, cranial vault expansion directed at the posterior parietal and occipital region remains as the treatment of choice. Clinical data and ICP monitoring confirm the efficacy of this procedure (Tamburrini et al. 2012). However, the stenosis of the jugular foramina is not eliminated by this procedure, and patients with this anomaly remain at high risk of a persisting increased ICP and under the possibility of developing a secondary hydrocephalus (Hayward 2005).

Management of Hydrocephalus in Complex Craniosynostosis

CSF dynamics disorders in children with complex craniosynostoses have a complex and often multifactorial etiology, and many factors are to be beared in mind when approaching the treatment of these disorders. There is little evidence that dilated ventricles per se have an adverse effect on intelligence (Wheaton 1894; Gosain et al. 1997) except that severe congenital hydrocephalus, as observed in the most complex craniofacial syndromes, carries an increased risk of a lower performance level. As in other hydrocephalic states, the prognosis mainly depends on coincidental cerebral abnormalities and on the detrimental effect of long-standing elevated CSF pressure (Gosain et al. 1997).

Clinical evaluation is aimed at identifying progressive active hydrocephalus, diagnosis is sometimes difficult, and ventricular dilatation often becomes evident only after decompressive cranial surgery has been performed. Classical symptoms of intracranial hypertension like headaches, nausea, or vomiting will be absent in younger patients. Papilledema, a rather common sign in other pathologies, is often the only sign of increased ICP but also frequently missing in these patient. Mild ventriculomegaly may also exist with or without (like in Apert syndrome) intracranial hypertension;

Therefore, a strict protocol to rule out intracranial hypertension in complex craniosynostosis must include close monitoring of these patients with frequent neuroimaging, ophthalmologic survey (funduscopic examination, optic nerve sheath diameters measurements at ecography, and visual evoked potentials), polysomnography to detect sleep apnea, and invasive monitoring of ICP and cerebral blood flow when necessary to rule out a chronic increase in ICP. A prolonged intracranial pressure monitoring is also advised whenever clinical or radiological signs of altered CSF and venous circulation are suggested by MR/angio MR examinations (Tamburrini et al. 2005, 2012).

Improvement of ventricular dilatation has been anecdotally reported following removal of constricting bony ridges or decompressive craniectomies alone (Cinalli et al. 1998b; Hayward 2005). However, many syndromic patients will develop active hydrocephalus in spite of (and frequently after) surgery for a cranial vault expansion. The role of posterior fossa decompression, aimed to address the posterior fossa volume constriction and the main venous outflow compression, has been also questioned (Cinalli et al. 1995, 1998b, 2005; Hayward 2005).

Therefore, ventriculoperitoneal shunting is widely accepted as the most effective treatment for patients who develop a progressive hydrocephalus. However, there are several concerns related to the use of extrathecal shunts in these patients. Shunt morbidity seems to be higher in this subset of patients as compared with other pathologies (Tamburrini et al. 2012). Risk of hemorrhage (dilated veins and venous engorgement; abnormal position of dural sinuses), infection (coexisting factors such as tracheostomy and/or gastrostomy), or proximal dysfunction due to malpositioning of catheters in distorted ventricular anatomies could be some of the factors related to this.

At the same time, extrathecal shunting does not address the venous hypertension, with the possibility of continuing intracranial hypertension in spite of an apparently working shunt (Tamburrini et al. 2012). After shunting of the CSF, the growing brain will fill the drained spaces, the pulse wave will be diminished, and the skull will be withdrawn of an important growing stimulus (Tamburrini et al. 2012); consequently, the tendency of the cranial vault and base sutures to close will be even favored (Cinalli et al. 1998b; Hayward 2005; Collman et al. 2005).

Overdrainage must be then avoided when selecting a shunting system, because it may induce a pseudo-tumor-like state of venous origin, worsening the preexisting venous problems (Cinalli et al. 1998b). When shunting is needed soon after cranial reconstruction, the stability of synostosis surgery may be endangered if the dural envelope does not rapidly expand because of artificial depletion of CSF spaces (Cinalli et al. 1998b) and failure of cranial contents to support the bone plates. Whenever possible, any procedure of cranial reconstruction should be planned at least 2 month later from the shunting procedure, to avoid the possible bone retrusion due to the reduction in intracranial pressure induced by the shunt (Tamburrini et al. 2012; Collman et al. 2005).

Endoscopic third ventriculostomy has been proposed as an alternative for the management of the hydrocephalus in selected children with complex craniosynostosis. This technique could be taken into consideration in case of distortion of the Sylvian aqueduct due to periaqueductal compression or when a caudal herniation of the cerebellar tonsils associated to constriction of posterior fossa intracranial structures is documented (Di Rocco et al. 2010). Di Rocco et al. have recently published their experience with ETV in a series of 11 children with complex craniosynostosis (Kubler et al. 2004). ETV was performed after cranial expansion in four cases and as first-line treatment in seven cases. At a mean follow-up of 53 months, a stable control of the hydrocephalus was documented in 6 of the 10 available patients. Other authors have reported similar experiences (Cinalli, Genitori personal communications) pointing that, in spite of the low number of cases, ETV might be a valid option for the management of an obstructive hydrocephalus in complex craniostenosis.

In the presence of hindbrain herniation, there is certainly no place for lumbar peritoneal shunts.

Upper Airway Obstruction

Upper airway obstruction is related to hypoplasia and distortion of mid and low third of the maxillary and mandibular bones, which can compromise both nasopharyngeal and oropharyngeal spaces.

The causes of upper airways obstruction include reduction of the naso- and oropharyngeal spaces, thick velum and redundant soft palate, short and distorted hard palate, marked reduction of the posterior cranial base, choanal stenosis or atresia (frequent and severe in Pfeiffer), midnasal stenosis, tracheal cartilaginous sleeve, maxillary hypoplasia, and mandible retrusion (Antón-Pacheco et al. 2012; Cohen and Kreiborg 1992; Mixter et al. 1990; Noorily et al. 1999). Many of these features are already present at birth and worsen during craniofacial growth (Peterson-Falzone et al. 1981) as maxillary bone remains hypoplastic while the oxygen consumption significantly increases with body growth (Sakamoto et al. 2016).

All this results in sleep-related breathing disorders, namely, obstructive sleep apnea (OSA), central sleep apnea (CSA), periodic breathing, and hypoventilation (Al-Saleh et al. 2011). Obstructive sleep apnea is a disorder of breathing during sleep characterized by prolonged partial upper airway obstruction (obstructive hypopnea) and/or intermittent complete obstruction (obstructive apnea) that disrupts normal ventilation during sleep and normal sleep patterns (Tamburrini et al. 2012; Cohen and Kreiborg 1992). It occurs in as much as 40–85% of the cases of craniofacial syndromes (Noorily et al. 1999; Al-Saleh et al. 2011; Ahmed et al. 2008; Pijpers et al. 2004; Pang and Terris 2006). Polysomnography is the ideal diagnostic tool and necessary to approach therapeutic decisions, but parental questionnaires have proved to be quite reliable for the screening of OSA when applied to children with complex craniosynostosis (Bannink et al. 2010a, b). A complete polysomnography examination should include electroencephalogram, electrooculogram, submental electromyogram (EMG), and bilateral anterior tibialis EMG. Respiratory measurements include chest wall and abdominal movement using chest wall and abdominal belts; nasal airflow measurements using nasal air pressure transducer and/or oronasal thermal sensor, oxygen saturation (SaO2), transcutaneous carbon dioxide, and end-tidal carbon dioxide (Tamburrini et al. 2012; Pang and Terris 2006).

Severe airway obstruction and abnormal anatomy (thick pharyngeal velum, retruded mandible, macroglossia, or retroposition of the tongue) may also interfere with swallowing and sucking, resulting in insufficient weight gain due to poor nutrition. In most complex patients, an alternative way of feeding such as tube feeding should be considered.

Treatment options for OSA in children with syndromic craniosynostoses include choanal dilatation, continuous positive airway pressure (CPAP), nasopharyngeal airways, palatal surgery, adenotonsillectomy, midface advancement surgeries, or tracheostomy.

Adenoidectomy and tonsillectomy are only effective in cases where the main cause for OSA is the hypertrophy of the soft tissue components of upper airways. Removal of the adenoid and tonsils is clearly ineffective when OSA is determined by a midface hypoplasia and a reduction of respiratory spaces, as it adds only a modest increase in the upper airway space (Tamburrini et al. 2012; Fleisher and Krieger 2007). CPAP has also a limited value. It is aimed to maintain a constant pressure along the upper airways during inspiration and expiration but frequently fails to improve OSA as it does not address the main cause for obstructive apnea in this children (Bannink et al. 2010b; Fleisher and Krieger 2007). It has also indirect effects including a paradoxical increase in ICP, but the main problem with CPAP is the low tolerance and difficulty to use it in the pediatric population (Fleisher and Krieger 2007).

Midface advancements are the best option to improve breathing-related disorders but are technically difficult below the age of 7 (Tamburrini et al. 2012; Sakamoto et al. 2016; Arnaud et al. 2001). Mandibular distraction (Fig. 7), Lefort III osteotomies (Witherow et al. 2008; Flores et al. 2009), and monobloc distraction (Cohen et al. 1999; Arnaud et al. 2001; Flores et al. 2009; Arnaud et al. 2007; Lauritzen et al. 1998; Kubler et al. 2004) have been applied to these cases with variable success. When performed before the end

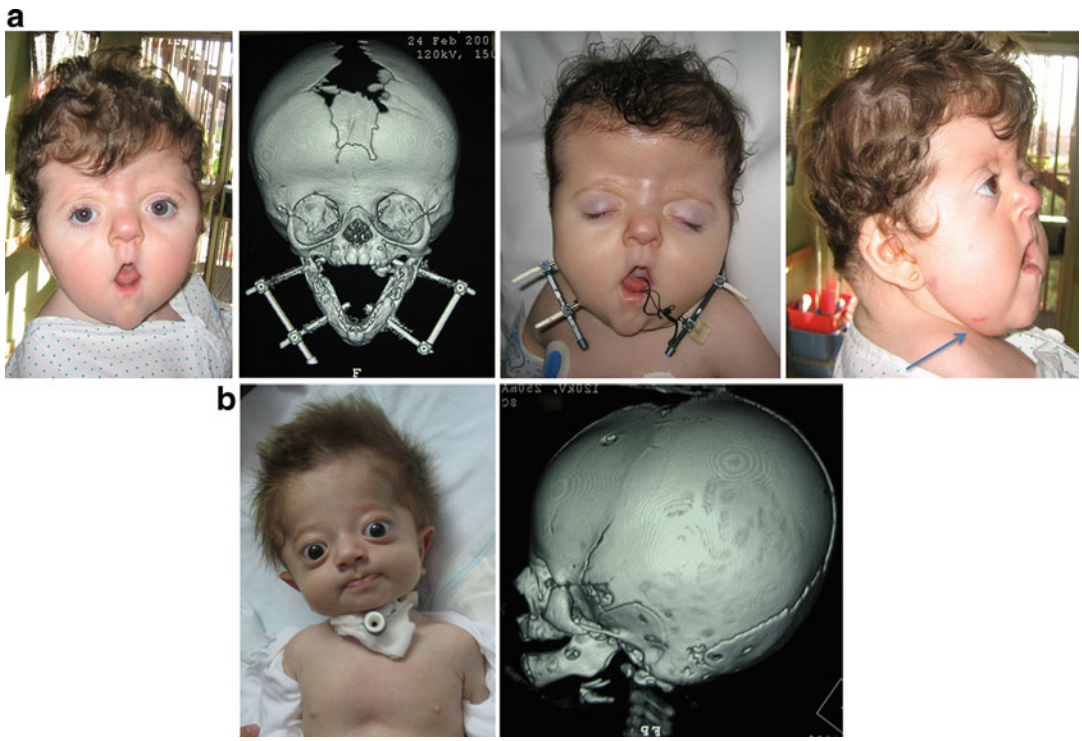

Fig. 7 Two similar cases of Pfeiffer syndrome with severe OSA (obstructive sleep apnea). In case 1, tracheostomy was avoided after mandibular distraction. (**a**) Case 1. Observe scar from distracting device; (**b**) Case 2

of maxillofacial bone structure growth (seventh year of life), these techniques yield a high incidence of early recurrences (Tamburrini et al. 2012), mostly if static techniques are used. To overcome this problem, a number of osteogenic distraction devices have been developed (Arnaud et al. 2001, 2007; Lauritzen et al. 1998; Pelo et al. 2007).

A technical limit of the distraction devices is that they cannot be used in very young population as cranial bones of infants are very thin, inconsistent, and fragile, and the risk of complications (intracranial injuries or skull/maxillary bone fractures) is relatively high. For the same reason, there is a high percentage of failures because of breakage or displacement of the devices both at the time of the system implantation and during the period of osteodistraction (Arnaud et al. 2001, 2007). Trying to overcome these problems, some authors have proposed the use of midface distracting systems through transfacial pins (Pellerin et al. 2001; Arnaud et al. 2001).

Tracheostomy is required in up to 33% of syndromic craniosynostosis patients before 1 year of age (Fujimoto et al. 2011), when all these options are not effective. Tracheostomy should be considered mostly in infants showing sever stridor, apnea due to upper airway obstruction, or SOa2 below 90% in spite of all the above techniques. It is not to neglect that tracheostomy in very young population is difficult to perform, and even more complex to maintain, and meticulous care and intensive support from patient's family are needed in every patient.

Treatment

The surgical management of children with syndromic craniosynostosis seeks to improve cerebral, ocular, and occlusal function and to simultaneously obtain an optimal craniofacial appearance outcome. The challenges inherent in the treatment for these children are enormous. The type and timing of surgery are controversial, but aim mainly the control of airway and breathing, ocular protection to avoid corneal exposure and raised intracranial pressure (Marchac 1987). Apart from this, one must try to correct severe cranial and facial deformities soon and in as few procedures as possible (McCarthy et al. 1995; Sun and Persing 2001; Swanson et al. 2016). Proponents of early intervention favor the need to achieve corneal protection and cranial expansion for the constricted brain (Hashim et al. 2014). Conversely, if later surgery is performed, results tend to be more stable, with less need for subsequent revisions (Fearon 2014; Fearon and Podner 2013). Because of all the previous concerns, treatment of syndromic craniosynostosis vary widely across craniofacial centers, and therapeutic decisions must be taken in a case to case basis. Besides, syndromic craniosynostoses are inherently rare, and the severity of different features is not only heterogeneous between the major syndromes (e.g., Apert, Crouzon, Pfeiffer) but also within them.

According to other craniofacial units, we have settled an algorithm for the treatment of these patients, taking into account the function and life-threatening issues, and confronting different treatments according to the need of every patient. Based on the acronym AOHCR (where A stands for *Airway*, O for *Ocular protection*, H for *Hydrocephalus*, C for symptomatic *Chiari malformation*, and R for *multifactorial Raised ICP*) a staged approach for every problem is selected on a case to case based decision as discussed earlier (Fig. 8). Only after the previous pathologies have been treated and secured, a cranial vault expansion is scheduled. Cosmetic issues are postponed usually until complete cranial and facial growth has finished at the age of puberty.

Posterior Vault Distraction

Cranial vault expansion is one of the major elements in the management of raised ICP in both syndromic and nonsyndromic patients (Blount et al. 2007; White et al. 2009). Calvarial remodeling with fronto-orbital or posterior vault advancement is an established surgical technique to achieve skull vault expansion (Renier et al. 2000).

It has been reported that posterior calvarial advancement techniques offer a greater

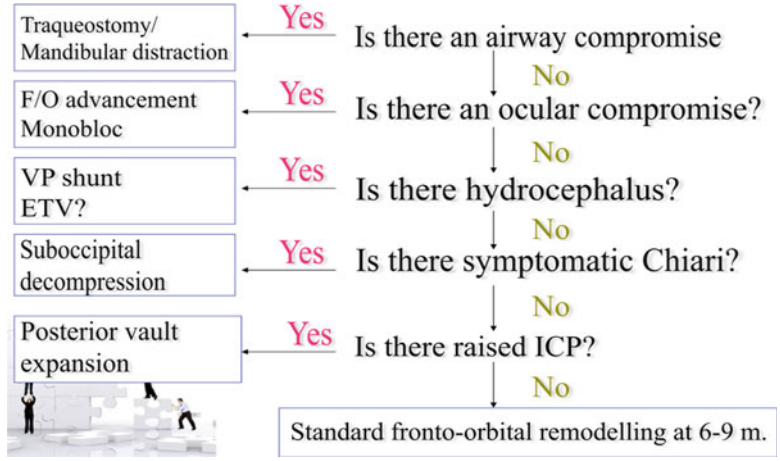

Fig. 8 Algorithm followed in our institution for the treatment of complex and syndromic craniosynostosis

volumetric increase when compared to traditional fronto-orbital advancement (Sgouros et al. 1996). The large area of the bone encompassed by the calvarial osteotomies allows a large increase in cranial volume, and the distractors avoid relapse secondary to supine positioning of the child (White et al. 2009; Nowinski et al. 2012). At the same time, posterior distraction directly targets the region of the brain that needs expansion in the presence of Chiari malformation (White et al. 2009; Derderian et al. 2015; Nowinski et al. 2012; Utria et al. 2015). White et al. interestingly noted that posterior distraction also had an anterior affect with significant anterior fossa expansion observed during distraction (White et al. 2009). They suggested that the calvarial plasticity in babies below 2 years of age as well as the horizontal direction of the distraction vectors could be the reason for this amelioration in the anterior aspect of their patients.

Different techniques have been used to achieve a posterior vault distraction, including free-floating parieto-occipital cranial vault release, distractors (Rich et al. 2003; White et al. 2009; Nowinski et al. 2012), and springs (White et al. 2009; Nowinski et al. 2012; Lauritzen et al. 1996, 1998, 2008).

Posterior cranial vault reconstruction without distraction has been used in several craniofacial units (Utria et al. 2015; Nadal et al. 2000). The main concern with this approach is that expansion is limited to at most 6–8 mm of advancement (Swanson et al. 2016) and that the rate of relapse is very high (McCarthy et al. 1995; Derderian et al. 2015; Nowinski et al. 2012). Some authors have also reported new-onset craniosynostosis following posterior vault distraction, the clinical significance of which is unclear (Swanson et al. 2016).

Springs are widely utilized for distraction in the treatment of craniosynostosis (Lauritzen et al. 2008; Arnaud et al. 2012; Mundinger et al. 2016). The spring consists of a metallic wire bent and placed across an osteotomy or an open calvarial suture (Nowinski et al. 2012; Arnaud et al. 2012) and anchored through holes made in the calvarium or at the edges of the osteotomy or suture (Nowinski et al. 2012). Bone fragments separate gradually on each side as the metallic wire straightens out. The separation stops once the force of the spring reaches equilibrium with counteracting tissue forces (Nowinski et al. 2012; Davis et al. 2010; Davis and Lauritzen 2010). The correction of cranial shape is based thereby on forces applied to the calvarium rather than on rearrangement of bone fragments. Potential advantages of spring-mediated distraction are reduced bleeding, surgical time, and overall surgical trauma as it obviates the need for multiple osteotomies (Nowinski et al. 2012; Lauritzen et al. 2008; Arnaud et al. 2012; Mundinger et al. 2016; de Jong et al. 2013).

The main drawbacks in the springs technique are the lack of control over vectors, forces and

degree of bone fragments separation, and the possible spring-related complications (such as spring-dislodgement, skin penetration, or pressure sores) (Nowinski et al. 2012). Springs as well as distractors require removal in a second separate procedure (Lauritzen et al. 2008; Mundinger et al. 2016; de Jong et al. 2013).

Distraction osteosynthesis is another widely extended technique for posterior cranial vault expansion. It is based on gradual, controlled separation of bone fragments, at a rate that allows for progressive bone formation in the distraction gap, created by an osteotomy (Nowinski et al. 2012). These techniques have the potential to generate bone in areas of skeletal hypoplasia, such as the cranial vault, the mandible, and the middle face (Fig. 7). Following the standard distraction protocol, originally introduced by Ilizarov for the extension of long bones, we have settled a latency phase of 3–5 days, and a 1-mm/day average distraction rate. Depending on the patient and the area of advancement, consolidation period goes from one to several months (Ilizarov 1990). Distraction osteogenesis have demonstrated to achieve larger bone advancements when compared to conventional techniques based on one-stage, immediate advancement and osteosynthesis and they have clearly a reduced rate of relapse (White et al. 2009; Nowinski et al. 2012).

Several distraction devices and techniques for this goal have been reported including single vector, multiple vector, and spring-assisted vault expansion (Bradley et al. 2006; Hirabayashi et al. 1998, 2002; Lauritzen et al. 1998). Distraction osteogenesis for anterior and combined anterior/midface (monobloc) expansion has been widely reported for the management of various craniosynostoses (Hirabayashi et al. 2002; Polley et al. 1995) (Fig. 9).

The use of early posterior vault distraction osteogenesis delays surgical treatment of the anterior cranium. This likely preserves frontal growth, facilitating improved frontal morphologic changes (Swanson et al. 2016), and increasing the likelihood of optimal frontal contour over the long term, with subsequent fronto-orbital advancement. At the same time, early posterior vault distraction osteogenesis decreases the number of fronto-orbital advancements and is likely to decrease the number of major craniofacial procedures in the in the patient during the first years of life (Swanson et al. 2016). For this reason, treatment patterns are syndrome-specific and should be tailored to specific functional needs and aesthetic differences of each patient.

Advantages of posterior vault distraction osteogenesis are superior cranial volume expansion compared with fronto-orbital advancement (Derderian et al. 2015), reliability of use at a younger age (McCarthy 2012), and a lesser degree of perioperative morbidity profile (McCarthy 2012). Osteogenic distraction does not devascularize the osteotomized bone, minimizing infectious risk but also maximizing, potentially, subsequent cranial growth. It provides soft-tissue expansion, this minimizing relapse, and eliminating the need for osteosynthesis hardware and bone grafting. Its major limitation is the need for a second minor procedure for distractor removal (Pelo et al. 2007; Nowinski et al. 2012; McCarthy 2012).

Prognosis

Prognosis in craniofacial surgery depends mainly on the underlying condition. In the majority of cases with single suture craniosynostosis, there is not a cognitive delay and surgical treatment in proper schedule and conditions will render very good results in terms of cosmetic and functional outcome. Although it has been stressed that the occurrence of raised ICP in single suture synostosis is low (Persing et al. 1990; Sgouros et al. 1996; Roddi et al. 1995), up to 15–20% of patients with single suture craniosynostosis have a documented increase in intracranial pressure (ICP) (Noorily et al. 1999) and special attention must be paid to these children.

The possibility of elevated ICP is higher as the number of affected sutures increases and the risk is very high in untreated patients with a craniofacial syndrome where craniosynostosis is an

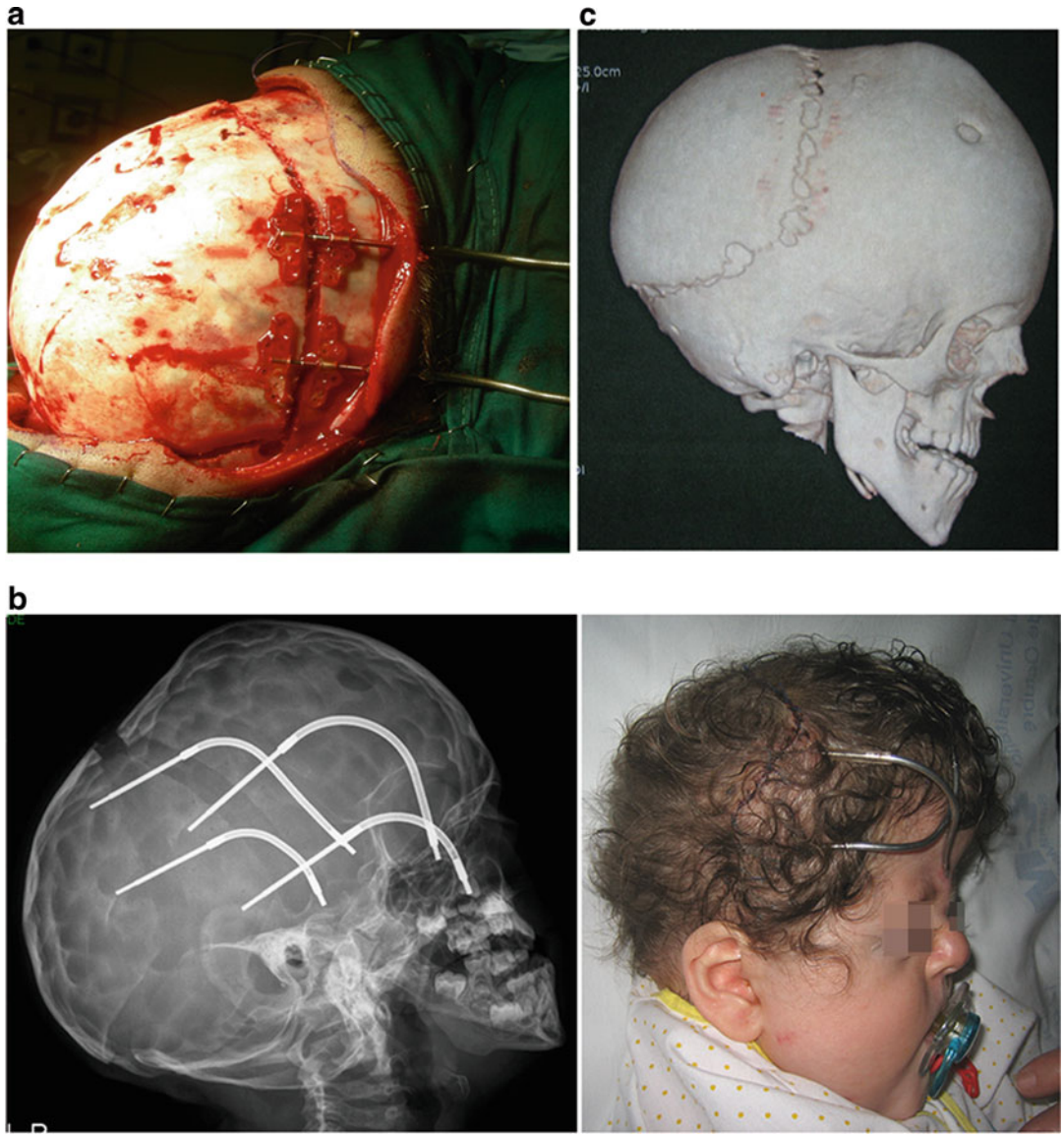

Fig. 9 Occipital vault expansion with resorbable distractors. (**a**) Intraoperative view; (**b**) distracting period; (**c**) postoperative CT

evolving condition which worsens during the first year(s) of life and leads frequently to intracranial hypertension (Derderian and Seaward 2012). Restricted skull volume is not the only factor contributing to this. Venous hypertension (sometimes with anomalous venous drainage), hydrocephalus, and/or upper airway obstruction are often associated in these patients and are together responsible for this raised ICP.

Early detection of intracranial hypertension is important in order to reduce the risks for cognitive delay and visual function. Clinical manifestations of abnormally increased ICP, however, are difficult to detect in children with craniosynostosis.

Most of these patients may have neither warning signs nor symptoms for a long period of time (Tamburrini et al. 2005) and all these children need a clinical prolonged survey.

Conclusion

The treatment of complex craniosynostosis and craniofacial syndromes requires the participation and coordination of a multidisciplinary team, with a deep knowledge of the underlying physiopathology, the use of multiple diagnostic tools, different surgical techniques, staged approach, and management of all the issues that affect these patients. The concourse of neurosurgeons, sindromologists, pediatricians, plastic and maxillofacial surgeons, ENTs, psychologists, and occupational therapists in a multidisciplinary team is the only way to approach effectively this pathology. The support given by specific associations of parents and patients is also a great help for many of these families.

References

Ahmed J, Marucci D, Cochrane L, Heywood RL, Wyatt ME, Leighton SE (2008) The role of the nasopharyngeal airway for obstructive sleep apnoea in syndromic craniosynostosis. J Craniofac Surg 19:659–663

Al-Saleh S, Riekstins A, Forrest CR, Philips JH, Gibbons J, Narang I (2011) Sleep-related disordered breathing in children with syndromic craniosynostosis. J Craniomaxillofac Surg 39:153–157

Angle CR, McIntire MS, Moore RC (1997) Cloverleaf skull: Kleeblattschädel-deformity syndrome. Am J Dis Child 114:198–202

Antón-Pacheco J, Luna C, Martínez A, García G, Martín R, Romance AI (2012) The role of bronchoscopy in the management of patients with severe craniofacial syndromes. J Pediatr Surg 47:1512–1515

Apert ME (1906) De acrocephalosyndactyly. Bull Mem Soc Med Hop Paris 23:1310–1330

Arnaud E, Marchac D, Renier D (2001) Distraction osteogenesis with double internal devices combined with early frontal facial advancement for the correction of facial craniosynostosis: report of clinical cases. Ann Chir Plast Esthet 46:268–276

Arnaud E, Marchac D, Renier D (2007) Reduction of morbidity of the frontofacial monobloc advancement in children by the use of internal distraction. Plast Reconstr Surg 120:1009–1026

Arnaud E, Marchac A, Jeblaoui Y, Renier D, Di Rocco F (2012) Spring assisted posterior skull expansion without osteotomies. Childs Nerv Syst 28:1545–1549

Bannink N, Mathijssen IM, Joosten KF (2010a) Can parents predict obstructive sleep apnea in children with syndromic or complex craniosynostosis? Int J Oral Maxillofac Surg 39:421–423

Bannink N, Nout E, Wolvius EB, Hoeve HL, Joosten KF, Mathijssen IM (2010b) Obstructive sleep apnea in children with syndromic craniosynostosis long-term respiratory outcome of midface advancement. Int J Oral Maxillofac Surg 39:115–121

Blount JP, Louis RG Jr, Tubbs RS, Grant JH (2007) Pansynostosis: a review. Childs Nerv Syst 23:1103–1109

Bradley JP, Gabbay JS, Taub PJ, Heller JB, O'Hara CM, Benhaim P, Kawamoto HK Jr (2006) Monobloc advancement by distraction osteogenesis decreases morbidity and relapse. Plast Reconsr Surg 118(7):1585–1597

Cinalli G, Renier D, Sebag G, Sainte-Rose C, Arnaud E, Pierre-Kahn A (1995) Chronic tonsillar herniation in Crouzon's and Apert's syndromes: the role of premature synostosis of the lambdoid suture. J Neurosurg 83:575–582

Cinalli G, Chumas P, Arnaud E, Sainte- Rose C, Renier D (1998a) Occipital remodelling and suboccipital decompression in severe craniosynostosis associated with tonsillar herniation. Neurosurgery 42:66–73

Cinalli G, Sainte-Rose C, Kollar EM, Zerah M, Brunelle F, Chumas P, Arnaud E, Marchac D, Pierre-Kahn A, Renier D (1998b) Hydrocephalus and craniosynostosis. J Neurosurg 88:209–214

Cinalli G, Spennato P, Sainte-Rose C, Arnaud E, Aliberti F, Brunelle F, Cianciulli E, Renier D (2005) Chiari malformation in craniosynostosis. Childs Nerv Syst 21:889–901

Cohen M (1993) Pfeiffer syndrome: update, clinical subtype and guidelines for differential diagnosis. Am J Gen 45:300–307

Cohen MM (2000) Epidemiology of craniosynostosis. In: Michael Cohen M Jr, MacLean RE (eds) Craniosynostosis: diagnosis, evaluation and management. Oxford University Press, New York

Cohen MM Jr, Kreiborg S (1990) The central nervous system in the Apert syndrome. Am J Med Genet 35:36–45

Cohen MM Jr, Kreiborg S (1992) Upper and lower airway compromise in the Apert syndrome. Am J Med Genet 44:90–93

Cohen SR, Boydston W, Hudgins R, Burstein FD (1999) Monobloc and facial bipartition distraction with internal devices. J Craniofac Surg 10:244–251

Collman H, Sörensen N, Krauß J (2005) Hydrocephalus in craniosynostosis: a review. Childs Nerv Syst 21: 902–912

Crouzon O (1912) Dysostose cranio-faciale hereditaire. Bull Mem Soc Med Hop Paris 33:545–555

Cunningham ML, Seto ML, Ratisoontorn C, Heike CL, Hing AV (2007) Syndromic craniosynostosis: from

history to hydrogen bonds. Orthod Craniofac Res 10:67–81
Davis C, Lauritzen CG (2010) The biomechanical characteristics of cranial sutures are altered by spring cranioplasty forces. Plast Reconstr Surg 125: 1111–1118
Davis C, Windh P, Lauritzen CG (2010) Spring expansion is influenced by cranial biomechanics. J Craniofac Surg 21:843–846
de Jong T, Rijken BF, Lequin MH, van Veelen ML, Mathijssen IM (2012) Brain and ventricular volume in patients with syndromic and complex craniosynostosis. Childs Nerv Syst 28(1):137–140
de Jong T, van Veelen ML, Mathijssen IM (2013) Spring-assisted posterior vault expansion in multiple suture craniosynostosis. Childs Nerv Syst 29:815–820
Derderian C, Seaward J (2012) Syndromic craniosynostosis. Semin Plast Surg 26:64–75
Derderian CA, Wink JD, McGrath JL, Collinsworth A, Bartlett SP, Taylor JA (2015) Volumetric changes in cranial vault expansion: comparison of fronto-orbital advancement and posterior cranial vault distraction osteogenesis. Plast Reconstr Surg 135:1665–1672
Di Rocco F, Jucà CE, Arnaud E, Renier D, Sainte-Rose C (2010) The role of endoscopic third ventriculostomy in the treatment of hydrocephalus associated with faciocraniosynostosis. J Neurosurg Pediat 6:17–22
Driessen C, Bannink N, Lequin M, van Veelen ML, Naus NC, Joosten KF, Mathijssen IM (2011) Are ultrasonography measurements of optic nerve sheath diameter an alternative to funduscopy in children with syndromic craniosynostosis? J Neurosurg Pediatr 8(3):329–334
Esparza J, Hinojosa J (2008) Complications in the surgical treatment of craniosynostosis and craniofacial syndromes: a propos of 306 transcranial procedures. Childs Nerv Syst 24:1421–1430
Fearon JA (2014) Evidence-based medicine: craniosynostosis. Plast Reconstr Surg 133:1261–1275
Fearon JA, Podner C (2013) Apert syndrome: evaluation of a treatment algorithm. Plast Reconstr Surg 131:132–142
Fearon JA, Rhodes J (2009) Pfeiffer syndrome: a treatment evaluation. Plast Reconstr Surg 23:1560–1569
Fleisher KE, Krieger AC (2007) Current trends in the treatment of obstructive sleep apnea. J Oral Maxillofac Surg 65:2056–2068
Flores RL, Shetye PR, Zeitler D et al (2009) Airway changes following Le Fort III distraction osteogenesis for syndromic craniosynostosis: a clinical and cephalometric study. Plast Reconstr Surg 124:590–601
Francis PM, Beals S, Rekate HL, Pittmann HW, Manwaring K, Reiff J (1992) Chronic tonsillar herniation and Crouzon's syndrome. Pediatr Neurosurg 18:202–206
Frim DM, Jones D, Goumnerova L (1990) Development of symptomatic Chiari malformation in a child with craniofacial dysmorphism. Pediatr Neurosurg 16:228–231
Fujimoto T, Imai K, Matsumoto H, Sakamoto H, Nakano T (2011) Tracheobronchial anomalies in syndromic craniosynostosis with 3-dimensional CT image and bronchoscopy. J Craniofac Surg 22:1579–1583
Fujisawa H, Hasegawa M, Kida S, Yamashita J (2002) A novel fibroblast growth factor. receptor 2 mutation in Crouzon syndrome associated with Chiari type I malformation and syringomyelia. J Neurosurg 97:396–400
Gambardella G, Zaccone C, Cardia E, Tomasello F (1993) Intracranial pressure monitoring in children: comparison of external ventricular device with the fiberoptic system. Childs Nerv Syst 9:470–473
Glaser RL, Jiang W, Boyadjiev SA, Tran AK, Zachary AA, Van Maldergem L, Johnson D, Walsh S, Oldridge M, Wall SA, Wilkie AOM, Jabs EW (2000) Paternal origin of FGFR2 mutations in sporadic cases of Crouzon syndrome and Pfeiffer syndrome. Am J Hum Genet 66:768–777
Goodrich JT (2005) Skull base growth in craniosynostosis. Child's Nervs Syst 21:871–879
Gosain AK, Moore FO, Hemmy DC (1997) The Kleeblattschädel anomaly in Apert syndrome: intracranial anatomy, surgical correction, and subsequent cranial vault development. J Plast Reconstr Surg 100:1796–1802
Hashim PW, Patel A, Yang JF et al (2014) The effects of whole-vault cranioplasty versus strip craniectomy on long-term neuro-psychological outcomes in sagittal craniosynostosis. Plast Reconstr Surg 134:491–501
Hayward R (2005) Venous hypertension and craniosynostosis. Childs Nerv Syst 21(10):880–888
Hayward R, Gonsalez S (2005) How low can you go? Intracranial pressure, cerebral perfusion pressure, and respiratory obstruction in children with complex craniosynostosis. J Neurosurg 102(1 Suppl):16–22
Hirabayashi S, Sugawara Y, Sakurai A et al (1998) Fronto-orbital advancement by gradual distraction. J Neurosurg 89:1058–1061
Hirabayashi S, Sugawara Y, Sakurai A, Tachi M, Harii K, Sato S (2002) Fronto-orbital advancement by distraction: the latest modification. Ann Plast Surg 49:447–451
Hoffman HJ, Hendrick EB (1979) Early neurosurgical repair in craniofacial dysmorphism. J Neurosurg 51:796–803
Ilizarov GA (1990) Clinical application of the tension-stress effect for limb lengthening. Clin Orthop Relat Res 250:8–26
Kreiborg S (1986) Postnatal growth and development of the craniofacial complex in premature craniosynostosis. In: Cohen MM Jr (ed) Craniosynostosis: diagnosis, evaluation, and management. Raven, New York, pp 157–189
Kubler AC, Speder B, Zoller JE (2004) Fronto-orbital advancement with simultaneous LeFort III-distraction. J Craniomaxillofac Surg 32:291–295
Lauritzen C, Friede H, Elander A, Olsson R, Jensen P (1996) Dynamic cranioplasty for brachycephaly. Plast Reconstr Surg 98:7–14., discussion 15–16
Lauritzen C, Sugawara Y, Kocabalkan O, Olsson R (1998) Spring mediated dynamic craniofacial reshaping. Case report. Scand J Plast Reconstr Surg Hand Surg 32: 331–338
Lauritzen CG, Davis C, Ivarsson A, Sanger C, Hewitt TD (2008) The evolving role of springs in craniofacial

surgery: the first 100 clinical cases. Plast Reconstr Surg 121:545–554
Leonard CO, Daikoku NH, Winn K (1982) Prenatal fetoscopic diagnosis of the Apert syndrome. Am J Med Genet 11:5–9
Marchac D (1987) Craniosynostosis: an analysis of the timing treatment and complications in 164 consecutive patients [discussion]. Plast Recontr Surg 20:207–212
Marchac D, Renier D, Broumand S (1994) Timing of treatment for craniosynostosis and faciocraniosynostosis: a 20 years experience. Br J Plast Surg 47:211–222
Marucci DD, Dunaway DJ, Jones BM, Hayward RD (2008) Raised intracranial pressure in apert syndrome. Plast Reconst Surg 122:1162–1168
McCarthy JG (2012) Distraction of the craniofacial skeleton. Springer, New York
McCarthy JG, Glasberg SB, Cutting CB, Epstein FJ, Gravson BH, Ruff G, Thorne CH, Wisoff J, Zide BM (1995) Twenty-year experience with early surgery for craniosynostosis: II. The craniofacial synostosis syndromes and pansynostosis – results and unsolved problems. Plast Reconstr Surg 96(2):284–295
Meling AC, Due-Tonnessen BJ, Hogevold HE, Skelbred P, Arctander K (2004) Monobloc distraction osteogenesis in pediatric patients with severe syndromal craniosynostosis. J Craniofac Surg 15(6):990–1000
Meyers GA, Orlow SJ, Munro IR, Przylepa KA, Jabs EW (1995) Fibroblast growth factor receptor 3 (FGFR3) transmembrane mutation in Crouzon syndrome with acanthosis nigricans. Nat Genet 11:462–464
Mixter RC, David DJ, Perloff WH, Green CG, Pauli RM, Popic PM (1990) Obstructive sleep apnoea in Apert's and Pfeiffer's syndromes: more than a craniofacial abnormality. Plast Reconstr Surg 86:457–463
Moss ML (1959) The pathogenesis of premature cranial synostosis in man. Acta Anat 37:351–370
Muller PJ, Hoffman HJ (1975) Cloverleaf skull syndrome. Case report. J Neurosurg 43:86–91
Mulliken JB, Steinberger D, Kunze S et al (1999) Molecular diagnosis of bilateral bicoronal synostosis. Plast Reconstr Surg 104:1603–1615
Mundinger GS, Rehim SA, Johnson O, Zhou J, Tong A, Wallner C, Dorafshar AH (2016) Distraction osteogenesis for surgical treatment of craniosynostosis: a systematic review. Plast Reconstr Surg 138:657–669
Nadal E, Doghliotti PL, Rodríguez JC, Zuccaro G (2000) Craniofacial distraction osteogenesis en bloc. J Craniofac Surg 11:246–251
Naski MC, Wang Q, Xu J, Ornitz DM (1996) Graded activation of fibroblast growth factor. receptor 3 by mutations causing achondroplasia and thanatophoric dysplasia. Nat Genet 13:233–237
Nishikawa M, Sakamoto H, Hakuba A, Nakanishi N, Inoue Y (1997) Pathogenesis of Chiari malformation: a morphometric study of the posterior cranial fossa. J Neurosurg 86:40–47
Noorily MR, Farmer DL, Belenky WM, Philippart AI (1999) Congenital tracheal anomalies in the craniosynostosis syndromes. J Pediatr Surg 34:1036–1039
Nowinski D, Di Rocco F, Renier D, Sainte-Rose C, Leikola J, Arnaud E (2012) Posterior cranial vault expansion in the treatment of craniosynostosis. Comparison of current techniques. Childs Nerv Syst 28:1537–1544
Otto AW (1830) Lehrbuch der pathologischen Anatomie des Menschen und der Thiere. Rücker, Berlin
Pang KP, Terris DJ (2006) Screening for obstructive sleep apnea: an evidence-based analysis. Am J Otolaryngol 27(2):112–118
Patton MA, Goodship J, Hayward R, Lansdown R (1988) Intellectual development in Apert's syndrome: a long term follow up of 29 patients. J Med Genet 25: 164–167
Pellerin P, Capon-Desgardin N, Martinot-Duquennoy V et al (2001) Mid-facial distraction without osteotomy with a transfacial pin: report of 4 clinical cases. Ann Chir Plast Esthet 46:277–284
Pelo S, Gasparini G, Di Petrillo A, Tamburini G, Di Rocco C (2007) Distraction osteogenesis in the surgical treatment of craniostenosis: a comparison of internal and external craniofacial distractor devices. Childs Nerv Syst 23:1447–1453
Persing JA, Jane JA, Delashaw JB (1990) Treatment of bilateral coronal synostosis in infancy: a holistic approach. J Neurosurg 72:171–175
Peterson-Falzone SJ, Pruzansky S, Parris PJ, Laffer JL (1981) Nasopharyngeal dysmorphology in the syndromes of Apert and Crouzon. Cleft Palate J 18:237–250
Pijpers M, Poels PJ, Vaandrager JM, de Hoog M, van den Berg S, Hoeve HJ (2004) Undiagnosed obstructive sleep apnoea syndrome in children with syndromal craniofacial synostosis. J Craniofac Surg 15:670–674
Pollack IF, Losken HW, Hurwitz DJ (1996a) A combined frontoorbital and occipital advancement technique for use in total calvarial reconstruction. J Neurosurg 84:424–429
Pollack IF, Losken HW, Biglan AW (1996b) Incidence of increased intracranial pressure after early surgical treatment of syndromic craniosynostosis. Pediatr Neurosurg 24:202–209
Polley JW, Figueroa AA, Charbel FT, Berkowitz R, Reisberg D, Cohen M (1995) Monobloc craniomaxillofacial distraction osteogenesis in a newborn with severe craniofacial synostosis: a preliminary report. J Craniofac Surg 6:421–423
Pople IK, Muhlbauer MS, Sanford RA, Kirk E (1995) Results and complications of intracranial pressure monitoring in 303 children. Pediatr Neurosurg 23:64–67
Posnick JC, Ruiz RL (2000) The craniofacial dysostosis syndromes: current surgical thinking and future directions. Cleft Palate Craniofac J 434:1–24
Reardon W, Winter RM, Rutland P, Pulleyn LJ, Jones BM, Malcolm S (1994) Mutations in the fibroblast growth factor receptor 2 gene cause Crouzon syndrome. Nat Genet 8:98–103
Renier D, Arnaud E, Cinalli G, Sebag G, Zerah M, Marchac D (1996) Prognosis for mental function in Apert's syndrome. J Neurosurg 85:66–72

Renier D, Cinalli G, Lajeunie E, Arnoud E, Marchac D (1997) L'oxycéphalie, une craniosténose sévère. A propos d'une série de 129 cas. Arch Pediatr 4:722–729

Renier D, Lajeunie E, Arnaud E, Marchac D (2000) Management of craniosynostoses. Childs Nerv Syst 16:645–658

Rich PM, Cox TC, Hayward RD (2003) The jugular foramen in complex and syndromic craniosynostosis and its relationship to raised intracranial pressure. AJNR Am J Neuroradiol 24:45–51

Richtsmeier JT (1987) Comparative study of normal, Crouzon and Apert craniofacial morphology using finite element scaling analysis. Am J Phys Anthropol 74:473–493

Roberts KB, Hall JG (1971) Apert's acrocephalosyndactyly in mother and daughter: cleft palate in the mother. Birth Defects Orig Art Ser VII(7):262–264

Robin NH, Feldman GJ, Mitchell HF, Lorenz P, Wilroy RS, Zackai EH, Allanson JE, Reich EW, Pfeiffer RA, Clarke LA, Warman ML, Mulliken JB, Brueton LA, Winter RM, Price RA, Gasser DL, Muenke M (1994) Linkage of Pfeiffer syndrome to chromosome 8 centromere and evidence for genetic heterogeneity. Hum Molec Genet 3:2153–2158

Roddi R, Jansen MA, Vaandrager JM, Van der Meulen JCH (1995) Plagiocephaly – new classification and clinical study of a series of 100 patients. J Craniomaxillofac Surg 23:347–354

Rollins N, Booth T, Shapiro K (2000) MR venography in children with complex craniosynostosis. Pediatr Neurosurg 32:308–315

Sainte-Rose C, LaCombe J, Pierre-Kahn A, Renier D, Hirsch JF (1984) Intracranial venous sinus hypertension: cause or conse- quence of hydrocephalus in infants? J Neurosurg 60:727–736

Sainte-Rose C, Arnaud E, Pierre-Kahn A (1995) Chronic tonsillar herniation in Crouzon and Apert syndrome: the role of the premature synostosis of the lambdoid suture. J Neurosurg 83:575–582

Sakamoto H, Matsusaka Y, Kunihiro N, Imai K (2016) Physiological changes and clinical implications of syndromic craniosynostosis. J Korean Neurosurg Soc 59:204–213

Saldino RM, Steinbach HL, Epstein CJ (1972) Familial acrocephalosyndactyly (Pfeiffer syndrome). AJR 116:609–622

Schell U, Hehr A, Feldman GJ, Robin NH, Zackai EH, de Die-Smulders C, Viskochil DH, Stewart JM, Wolff G, Ohashi H, Price RA, Cohen MM Jr, Muenke M (1995) Mutations in FGFR1 and FGFR2 cause familial and sporadic Pfeiffer syndrome. Hum Mol Genet 4:323–328

Sgouros S, Goldin JH, Hockley AD, Wake MJC (1996) Posterior skull surgery in craniosynostosis. Childs Nerv Syst 12:727–733

Shiller JG (1959) Craniofacial dysostosis of Crouzon: a case report and pedigree with emphasis on heredity. Pediatrics 23:107–112

Siddiqi SN, Posnick JC, Buncic R, Humphreys RP, Hoffman HJ, Drake JM, Rutka JT (1995) The detection and management of intracranial hypertension after initial suture release and decompression for craniofacial dysostosis syndromes. Neurosurgery 36:703–708., discussion 708–709

Slaney SF, Oldridge M, Hurst JA, Morriss-Kay GM, Hall CM, Poole MD, Wilkie AOM (1996) Differential effects of FGFR2 mutations on syndactyly and cleft palate in Apert syndrome. Am J Hum Genet 58: 923–932

Sömmering ST (1800) Vom Baue des Menschlichen Körpers, 1st edn. Voss, Leipzig

Strahle J, Muraszko KM, Buchman SR, Kapurch J, Garton HJ, Maher CO (2011) Chiari malformation associated with craniosynostosis. Neurosurg Focus 31(3):E2

Sun PP, Persing JA (2001) Craniosynostosis. In: Albright AL, Pollack IF, Adelson PD (eds) Operative techniques in pediatric neurosurgery. Thieme, New York, pp 51–64

Swanson J, Samra F, Bauder A, Mitchel B, Taylor J, Bartlett S (2016) An algorithm for managing syndromic craniosynostosis using posterior vault distraction osteogenesis. Plast Reconstr Surg 137:829–841

Tamburrini G, Caldarelli M, Massimi L, Santini P, Di Rocco C (2005) Intracranial pressure monitoring in children with single suture and complex craniosynostosis: a review. Childs Nerv Syst 21(10):913–921

Tamburrini G, Caldarelli M, Gasparini G, Pelo S, Di Rocco C (2012) Complex craniosynostoses: a review of the prominent clinical features and the related management strategies. Childs Nerv Syst 28:1511–1523

Taylor WJ, Hayward RD, Lasjaunias P, Britto JA, Thompson DN, Jones BM et al (2001) Enigma of raised intracranial pressure in patients with complex craniosynostosis : the role of abnormal intracranial venous drainage. J Neurosurg 94:377–385

Thompson DN, Hayward RD, Harkness WJ, Bingham RM, Jones BM (1995a) Lessons from a case of kleeblattschädel. Case report. J Neurosurg 82: 1071–1074

Thompson DN, Harkness W, Jones B et al (1995b) Subdural intracranial pressure monitoring in craniosynostosis: its role in surgical management. Childs Nerv Syst 11:269–275

Thompson DN, Harkness W, Jones BM, Hayward RD (1997) Aetiology of herniation of the hindbrain in craniosynostosis. Pediatr Neurosurg 26:288–295

Tuite GF, Chong WK, Evanson J, Narita A, Taylor D, Harkness WF, Jones BM, Hayward RD (1996) The effectiveness of papilledema as an indicator of raised intracranial pressure in children with craniosynostosis. Neurosurgery 38(2):272–278

Utria AF, Mundinger GS, Bellamy JL, Zhou J, Ghasemzadeh A, Yang R, Jallo GI, Ahn ES, Dorafshar AH (2015) The importance of timing in optimizing cranial vault remodeling in syndromic craniosynostosis. Plast Reconstr Surg 135:1077–1084

Van der Meulen J, Arnaud E, Hinojosa J et al (2009) The increase of metopic synostosis, a pan-european observation. J Craniofac Surg 20(2):283–286

Virchow R (1851) Uber den Cretinismus, namentlich in Franken. Und ueber pathologische Schädelformen. Verh Phys Med Gesamte Wurzburg 2:230–270

Wheaton SW (1894) Two specimens of congenital cranial deformity in infants associated with fusion of the fingers and toes. Trans Path Soc Lon 45:238–241

Whitaker LA, Bartlett SP, Shut L, Bruce D (1987) Craniosynostosis: an analysis of the timing, treatment and complications in 164 consecutive patients. Plast Reconstr Surg 80:195–206

White N, Evans M, Dover MS, Noons P, Solanki G, Nishikawa H (2009) Posterior calvarial vault expansion using distraction osteogenesis. Childs Nerv Syst 25:231–236

Wiegand C, Richards P (2007) Measurement of intracranial pressure in children: a critical review of current methods. Dev Med Child Neurol 49:935–941

Witherow H, Dunaway D, Evans R, Nischal KK, Shipster C, Pereira V, Hearst D, White M, Jones BM, Hayward R (2008) Functional outcomes in monobloc advancement by distraction using the rigid external distractor device. Plast Reconstr Surg 121:1311–1132