

# Craniosynostosis

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## Abstract

Craniosynostosis is a group of conditions characterised by the premature fusion of one or more cranial vault sutures. This may lead to abnormal cranial development with severe skull and craniofacial deformities and if the condition is left untreated, other complications such as raised intracranial pressure and cranial growth restriction may be implicated.

Craniosynostosis can arise as part of a genetic syndrome, or nonsyndromically where the pathophysiology remains less clear. Occurring in 1 in 2,000 to 2,500 live births, diagnosis is carried out shortly after birth and treatment of craniosynostosis mostly involves surgery varying from less invasive procedures in those patients diagnosed early to single or repeated open calvarial reconstruction in the more complex cases.

This article reviews the different types of craniosynostosis with their variable presentations, underlying genetic mutations, associated complications and neuro-psychological outcomes before discussing its management with distinct emphasis on surgical treatment options within a multidisciplinary team.

## Introduction

Craniosynostosis is a group of conditions characterised by premature fusion of one or more of the cranial vault sutures. This can lead to abnormal cranial development and give rise to severe skull and craniofacial deformities. Craniosynostosis can arise as part of syndromes, with specific gene mutations resulting in other non-cranial manifestations in addition to synostosis, or nonsyndromically where the pathophysiology remains less clear. Both types of craniosynostosis can be familial or sporadic. Occurring in 1 in 2,000 to 2,500 live births,<sup>1,3</sup> infants are diagnosed at birth or within a few months thereafter<sup>4</sup> and should preferably have treatment within their first year of life.<sup>5</sup> If the condition is left untreated, craniosynostosis can lead to further deformity and other complications such as raised intracranial pressure<sup>6-7</sup> and cranial growth restriction. The treatment mostly involves surgery varying from less invasive procedures in those patients diagnosed early<sup>8-10</sup> to single or repeated open calvarial reconstruction in the more complex cases.<sup>11,12</sup> There are a number of clinicians involved in the care of children with this condition, highlighting the importance of a multidisciplinary team. This article will review the different types of craniosynostoses with their variable presentations, the underlying genetic mutations, complications and neuro-psychological outcomes before discussing its management with distinct emphasis on surgical treatment options within a multidisciplinary team.

## Embryology

The human cranium is divided into the neurocranium housing the brain, and the viscerocranium, comprising the face. The neurocranium forms from embryonic mesenchyme of neural crest (frontal bone) and paraxial mesoderm (parietal bone) origin,<sup>13</sup> which surrounds the brain and forms primary ossification centres termed bone spicules. Each island of mineralised tissue migrates and undergoes intramembranous ossification to form the plates of the neurocranium. These plates remain separated in early infancy, allowing for passage during labour and continued growth of the brain after birth. The metopic suture fuses between 3 to 9 months whilst the sagittal, coronal and lambdoid sutures do not stop growing until the second decade and eventually fuse within the third decade.<sup>14-16</sup> Each plate approaches one another but remains separated by the formation of a suture: the two halves of the frontal bone by the metopic suture; the frontal and parietal bones by the sagittal suture; the two halves of the parietal bone by the coronal suture; and the parietal and occipital bones by the lambdoid suture. Fontanelles, namely membrane-covered "soft spots", are located at the intersection of sutures: the larger anterior fontanelle at the intersection of the metopic, coronal and sagittal sutures and the smaller posterior fontanelle at the intersection of the sagittal and the lambdoid sutures. These fontanelles usually fuse by the age of 18 months and 3 to 6 months respectively.<sup>14</sup>

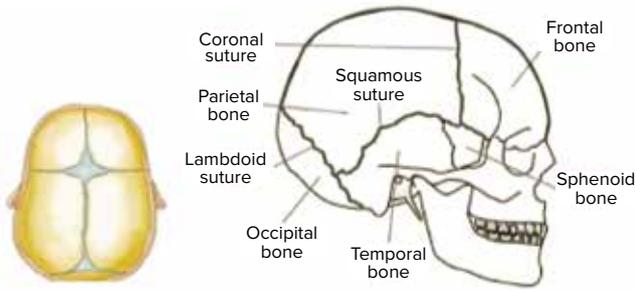
## Types

Premature fusion of the sutures implicates that the normal growth of the neurocranium is arrested at one or more sites. In order to accommodate the growing brain, compensatory growth occurs at other sites leading to abnormal cranial development and deformity. This was described in 1851 through Virchow's law that states that if a suture prematurely fuses, growth is arrested perpendicular to the suture and is increased parallel to it.<sup>17,18</sup> Thus, it explains the characteristic and predictable patterns of cranial growth that occur as a result of the premature fusion of distinctive sutures (see Figure 1, adapted from Senarath-Yapa et al., 2012<sup>19</sup>).

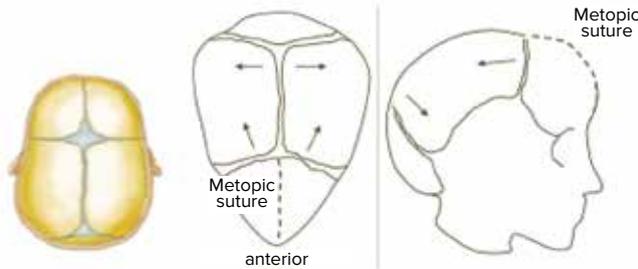
Sagittal synostosis is the most common type, accounting for 40-55% of nonsyndromic craniosynostosis.<sup>17,20</sup> Caused by premature fusion of the sagittal suture, growth is arrested in the transverse direction and increased in the anteroposterior direction, resulting in an anteroposterior elongation with frontal bossing and occipital prominence. This characteristic "long boat" shape skull is termed scaphocephaly (derived from *skaphos*: Greek term for skiff).

Coronal synostosis has been superseded

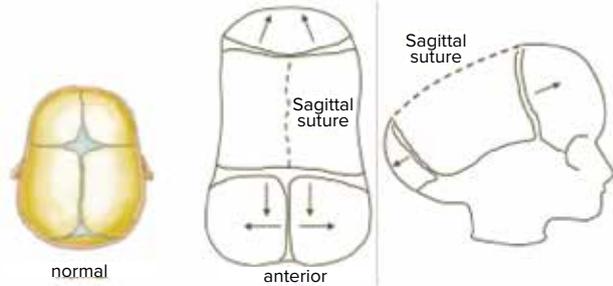
**A Normal skull**



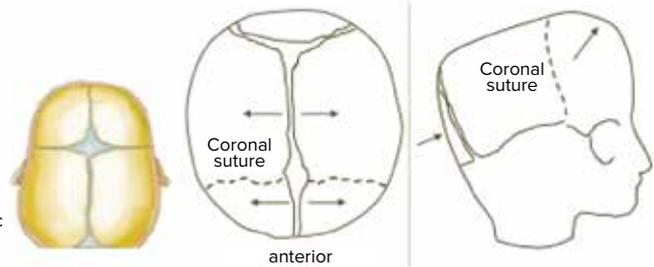
**B Metopic synostosis with trigonocephaly**



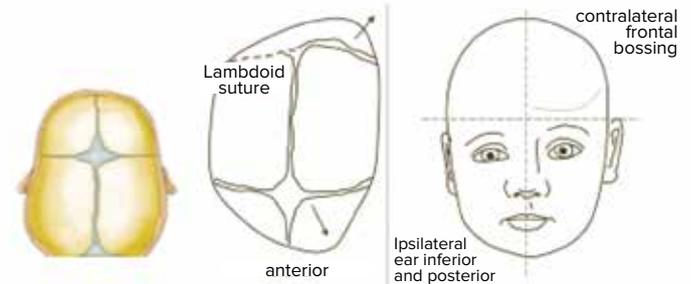
**C Sagittal synostosis with scaphocephaly**



**D Uniconal synostosis with nasal deviation (left) / Biconal synostosis with brachiocephaly (middle/right)**



**E Unilateral lambdoid synostosis with posterior plagiocephaly**



**Figure 1. Cranial sutures and deformity of single suture craniosynostosis. With permission from Senarath-Yapa.**

by metopic as the second most common nonsyndromic synostosis as several studies have shown over the past decade.<sup>3,21,22</sup> It occurs in 20-24% of nonsyndromic cases<sup>23,24</sup> and can be either unilateral or bilateral.

Premature fusion of the coronal suture bilaterally produces the opposite pattern of abnormal growth to sagittal synostosis, arresting growth in the anteroposterior direction and increased growth in the transverse direction, producing a short wide head called brachycephaly (from the Greek term *brachkus* for short). Unilateral coronal synostosis causes flattening of the ipsilateral forehead and displacement of the ipsilateral lesser wing of the sphenoid bone superolaterally called the "harlequin eye deformity" since radiographically it has the appearance of a masquerade mask. Other features include ipsilateral nasal deviation and contralateral displacement of the anterior fontanelle. This skull pattern produced by unilateral coronal synostosis is termed anterior plagiocephaly (*plagos*: Greek for slant).

Metopic synostosis is found in 20-29% of non-syndromic cases but studies have shown increasing prevalence.<sup>24,25</sup> Premature fusion of the metopic suture causes arrested growth of the cranium in the transverse direction anteriorly and increased anteroposterior growth.

This narrowing of the frontal bone produces a pointed triangular forehead with orbital hypotelorism and a ridge along the fused metopic suture and there may be compensatory posterior growth causing widening of the parietal regions. This is called trigonocephaly (*trigonos*: Greek term for triangle). However, it is important to note that ridging not infrequently occurs with normal fusion during the first few months of life and does not require surgery.<sup>26</sup>

Lambdoid synostosis is rare, occurring in 0-5% of non-syndromic cases<sup>17,20</sup> and is usually unilateral. Due to premature fusion of one of the lambda sutures there is arrested growth of the ipsilateral occipital region causing ipsilateral occipital flattening, posteroinferior displacement of the ipsilateral ear and tilting of the skull base towards the affected suture. Compensatory growth occurs at the contralateral occipital and frontal regions resulting in contralateral forehead and occipital protuberances as well as inferior mastoid elongation. This posterior slanting shape is called posterior plagiocephaly. Bilateral lambdoid synostosis is very rare and causes symmetrical flattening of the occiput with compensatory heightening of the skull. This is called posterior brachycephaly and in combination with posterior sagittal synostosis also known as the

"Mercedes Benz" sign due to the changes on the X-rays.<sup>27</sup> Bilateral lambdoid synostosis is associated with a Chiari I abnormality (with protrusion of cerebellar tonsils through the Foramen magnum) and can appear similar to brachycephaly due to coronal synostosis.

A similar presentation, and by far the most common one, can occur in positional plagiocephaly ("moulding"), a prevalent acquired cranial asymmetry that emerges at 6 weeks of age and can largely be attributed to the supine sleeping position recommended for infant safety (in the UK generally referred to as the "Back to Sleep" campaign for the prevention of Sudden Infant Death Syndrome).<sup>28-30</sup>

The two can be difficult to distinguish (see Figure 2), but the ipsilateral ear is anteriorly displaced in positional plagiocephaly and skull base tilt is absent. Positional plagiocephaly is asserted to be benign and may resolve spontaneously in some cases<sup>32,33</sup> or with simple measures such as position changes, "tummy time" and physical therapy for any torticollis that may be present.<sup>30,31</sup>

Although orthotic ("moulding") helmets are frequently used (particularly in Europe and the USA),<sup>33,34</sup> Wijk et al. demonstrated in HEADS (HElmet therapy Assessment in Deformed Skulls), a single blinded, randomised controlled trial, that there is no benefit

**Unilateral plagiocephaly**

- Unilateral occipital flattening
- Anterior displacement of the ipsilateral ear
- Ipsilateral frontal bossing (bossing opposite occiput)
- Contralateral forehead flattening
- Parallelogram shape

**Lambdoidal synostosis**

- Ipsilateral flattening of the occipitoparietal region
- Posterior displacement of the ipsilateral ear
- Contralateral parietal/frontal bossing
- Tilted cranial base with mastoid deformity
- 'Windswept' deformity

**Bilateral plagiocephaly**

- Bilateral occipital flattening
- Central posterior flattening
- Posterior skull widening
- Bitemporal bossing

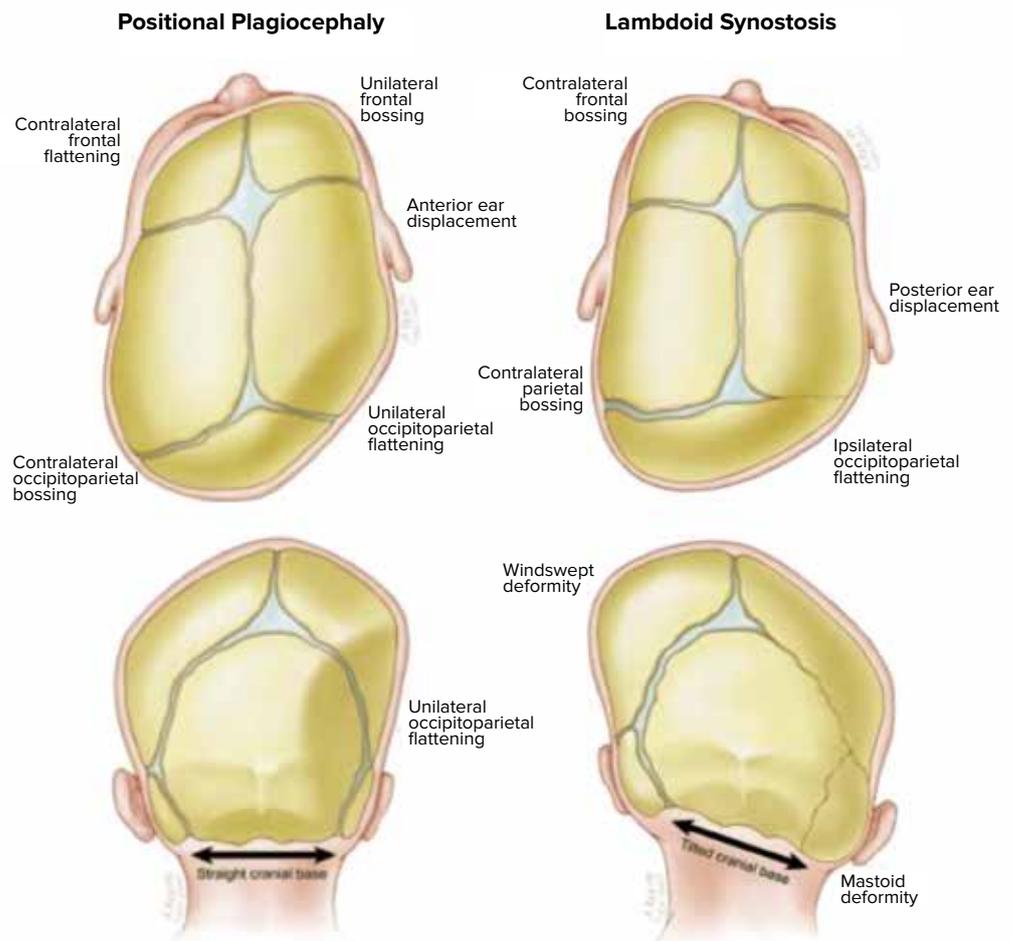


Figure 2. Positional Plagiocephaly. Adapted from International Society of Paediatric Neurosurgery (ISPN) website.<sup>31</sup>

from the administration of a moulding helmet and discouraged its use due to the association with large costs and prevalent side effects.<sup>35</sup> The overall consensus in the UK is to not recommend it.

Synostoses occur in multiple sutures in 5-15% of non-syndromic cases,<sup>17,20</sup> presenting with more complex deformities. Synostosis of three or more sutures is referred to as pansynostosis<sup>36,37</sup> and can present either with microcephaly or as a "Kleeblattschädel" (cloverleaf skull), named due to the bulging of the frontal and temporal bones giving rise to a tri-lobular shaped skull.

**Genetics**

Nonsyndromic craniosynostosis accounts for approximately 85% of cases<sup>3</sup> and although positive family histories have been reported,<sup>38,39</sup> the aetiology remains unknown. However, one cohort study genetic analysis found single gene mutations in *FGFR2*, *FGFR3*, *TWIST1* and *EFNB1* in 11 out of 204 (5.4%) of non-syndromic cases, 9/11 of which were unilateral or bilateral coronal.<sup>40</sup>

Other factors, including increased thyroid hormone level during pregnancy, and environmental stimuli such as head compression *in utero*, maternal smoking and teratogenic medications have also been implicated.<sup>41</sup> Of

particular note is the association between maternal use of sodium valproate and metopic craniosynostosis.<sup>42</sup> On the other hand, most types of syndromic craniosynostoses are inherited in an autosomal dominant fashion<sup>43,44</sup> and genetic analysis studies have provided strong links to a number of genes.<sup>43</sup>

One such group of genes implicated is the fibroblast growth factor receptor family, of which mutations in genes encoding *FGFR1*, *FGFR2* and *FGFR3* have been found in syndromic craniosynostoses. These are receptor tyrosine kinases that undergo auto-phosphorylation upon fibroblast growth factor binding and are involved in a vast range of cell functions and developmental processes.<sup>45,46</sup> Indeed, targeted mutagenesis of individual *FGFR* isoforms has been shown to lead to both lethal or viable defects in embryological development such as gastrulation,<sup>45</sup> placenta and limb bud formation,<sup>47,48</sup> organogenesis<sup>49</sup> and bone ossification.<sup>50</sup>

*FGFR* mutation results in gain of function causing abundant activation of the *FGF/FGFR* signalling pathway, which is then leading to expression of runt-related transcription-factor 2 (*RUNX2*). The result is early onset differentiation of mesenchyme cells into osteoblasts that deposit bone and eventually lead to premature suture closure.<sup>51,52</sup> *FGFR1* muta-

tions have been identified in Pfeiffer and Jackson Weiss syndromes; *FGFR2* mutations in Crouzon, Jackson Weiss, Apert, Pfeiffer and Beare Stevenson syndrome; and *FGFR3* mutations in Crouzon syndrome with Acanthosis, Muenke syndrome and Thanatophoric dysplasia (see Table 1 and Figure 3). The mechanism resulting in significantly differing phenotypes arising from the same mutation is yet to be fully understood.

*TWIST1* (twist-related protein 1) is another gene linked to craniosynostosis syndromes and mutations have been found in the Saethre-Chotzen syndrome. *TWIST1* is a basic loop-helix-loop transcription factor and thought to be involved in determining the lineage of osteoblasts. Cells over-expressing *TWIST1* showed decreased response to *FGF* and remained undifferentiated while cells under-expressing *TWIST1* differentiated into a mature osteoblast-like state.<sup>53</sup>

Therefore, it has been hypothesised that *TWIST1* is involved with delaying suture fusion, upstream of *FGF*. Indeed, the majority of *TWIST1* mutations found in Saethre-Chotzen syndrome confer a loss of function through haplo-insufficiency.<sup>54</sup> Furthermore, *FGFR2* and *FGFR3* mutations have also been found in Saethre-Chotzen syndrome<sup>55</sup> further supporting a common molecular pathway.

**Table 1. Genetic mutations and their craniofacial phenotype.**

Adapted from Senarath-Yapa et al., 2012 and Flaherty et al., 2016. The phenotypic features described may not be present in all individuals diagnosed with the condition. According to Wilkie et al., 2010, Muenke syndrome is clinically not diagnostic as phenotypic appearances vary from no characteristics to overlapping with other craniosynostosis syndromes.

Gene Chromosome	Syndrome Characteristic phenotype	Hydrocephalus?
FGFR1 8p	<b>Pfeiffer syndrome</b> Premature suture closure, brachycephaly, cutaneous syndactyly, hypertelorism, high forehead, midfacial retrusion, beaked nose, hearing loss, dental problems, brachydactyly, digit webbing, syndactyly, cloverleaf skull deformity, developmental delay, cognitive deficits	Yes (>90%)
	<b>Jackson Weiss syndrome</b>	
FGFR2 10q	<b>Crouzon syndrome</b> Premature suture closure, brachycephaly, flat forehead, midfacial retrusion, eye proptosis, hypertelorism, mandibular prognathism, beaked nose, mild limb abnormalities, variable cognitive function	Yes (>90%) Chiari I
	<b>Jackson Weiss syndrome</b>	
	<b>Apert syndrome</b> Premature suture closure, brachycephaly, eye proptosis, midfacial retrusion, exorbitism, hypertelorism, heterotropia, high arched palate, cleft palate, structural brain anomalies, cognitive impairment, complex syndactyly	Yes (~70%)
	<b>Pfeiffer syndrome</b>	Yes
	<b>Beare Stevenson syndrome</b>	
FGFR3 4p	<b>Crouzon syndrome</b> with Acanthosis Premature suture closure, brachycephaly, midfacial retrusion, acanthosis nigricans	
	<b>Muenke syndrome</b> Premature suture closure brachycephaly, orbital hypertelorism, midfacial retrusion, high arched palate, hearing loss, mild anomalies of the hands and feet, developmental delay	Yes (Seldom)
	<b>Thantophoric Dysplasia</b>	
EFNB1 Xq	<b>Craniofrontonasal syndrome</b>	Seldom
TWIST1 7p	<b>Saethre-Chotzen syndrome</b> Premature suture fusion, brachycephaly, high forehead, low frontal hairline, ptosis, hypertelorism, broad nasal bridge	Yes (30-50%)

More recently, Zhao et al., 2015 discovered that *Gli1+* cells in the suture mesenchyme form the osteogenic front, periosteum, dura and all craniofacial bones, and are involved in injury repair.<sup>56</sup> Ablation of *Gli1+* cells in mice was found to cause pansynostosis, arresting of skull growth and reduced injury repair. Moreover, the *Gli1+* population was reduced in *Twist1*<sup>-/-</sup> mice, a widely used model of craniosynostosis mimicking the *TWIST1* mutation in Saethre-Chotzen syndrome, and causing increased mesenchyme apoptosis and reduced proliferation. Therefore, the authors showed that *Gli1+* cells in the suture mesenchyme form the osteogenic stem cells of the craniofacial sutures and that pathogenesis of craniosynostosis may be due to reduced numbers of *Gli1+* cells.

### Associated complications

Each type of craniosynostosis can vary in its severity of phenotypic features. In particular, sagittal and metopic suture synostosis may show a very mild clinical presentation in which only one bone ridge at the afflicted suture is visible and/or palpable. Therefore, parents are often confronted with health care professionals who do not recognise the craniosynostosis in a timely manner shortly after childbirth. This may not only cause distress for the parents but also lead to delayed diagnosis and treatment.<sup>64</sup> In syndromic and complex nonsyndromic craniosynostoses the patients may suffer from cognitive impairment and raised intracranial pressure (ICP). Several syndromic craniosynostoses are associated with skeletal hypoplasia of the midface resulting in a narrowed airway. In approximately 50% of cases this leads to OSAS (obstructive sleep apnoea syndrome). Other risks and complications include cornea injury due to exorbitism, malocclusion and

### Figure 3. Most common craniosynostosis syndromes.

**Crouzon syndrome**,<sup>57</sup> first described by Octave Crouzon in 1935, is the most common of the craniosynostosis syndromes, occurring in 1 in 25,000 live births. Like the majority of the syndromes including Apert, Pfeiffer and Saethre-Chotzen, it follows an autosomal dominant inheritance pattern<sup>7</sup> and mutations have been found in *FGFR2* and *FGFR3*. Most commonly affected are the bilateral coronal sutures causing brachycephaly. Also seen is hypertelorism, shallow orbits resulting in exophthalmos, maxillary hypoplasia causing mandibular prognathism, high arched palate and low set ears associated with hearing impairment. Crouzon syndrome is also thought to convey an increased risk of raised intracranial pressure<sup>58</sup> and this has been proposed to be due to the early closure of the sagittal and lambdoid sutures.<sup>59</sup> As a result cognitive function in individuals with Crouzon syndrome is variable. Additionally, this syndrome may well be progressive in the first 2-3 years of life and even within

the same family can have quite marked differences in phenotype.

**Apert syndrome** is the second most common, found in 1 in 100,000 newborns, the majority of which are sporadic mutations in *FGFR2*. It also affects the coronal sutures bilaterally causing a brachycephaly<sup>60</sup> with hypertelorism, shallow orbits, exophthalmos and high arched palate. However, maxillary hypoplasia is more severe than observed in Crouzon syndrome and can lead to life-threatening airway compromise. Also seen is an anterior open bite, downslanting palpebral fissures, a "parrot beak" nose and syndactyly of the second, third and fourth digits.

**Pfeiffer syndrome** also occurs in 1 in 100,000 live births, most commonly due to *FGFR2* mutations, but *FGFR1* mutations have been found in 5% of cases, causing a less severe presentation.<sup>61</sup> The coronal, lambdoid and sagittal sutures are all affected, but heterogeneity of the syndrome has led to a classification into three clinical types. Type I

is the classic, most common and least severe type associated with turribrachycephaly, hypertelorism, strabismus, maxillary hypoplasia causing mandibular prognathism and characteristic broad thumbs. Type II is more severe, with a cloverleaf skull, severe exophthalmos, hydrocephalus and poor prognosis. Type III is very similar to type II but lacks the cloverleaf skull.<sup>62</sup>

**Saethre-Chotzen** is found in 1 in 25,000 to 50,000 newborns and caused by mutations in *TWIST1*. The phenotype is heterogenous and synostosis can be bicoronal, unicoronal, sagittal, metopic or multisutural<sup>63</sup> leading to a great variety of head shapes. Other features include a low hairline, ptosis, facial asymmetry and ear deformities. Additionally, syndactyly of the second and third digits may be present. Overall, Saethre-Chotzen syndrome perhaps displays the widest phenotype of the common syndromic conditions and family members may remain undiagnosed due to portraying mild phenotypic features (e.g. subtle ptosis).

aesthetic/psychosocial problems. Associated intracranial abnormalities in syndromic craniosynostoses are increased ICP, Chiari I malformation, ventriculomegaly and hydrocephalus. Hearing loss is described for all types of syndromic craniosynostoses. Visual pathologies such as astigmatism and strabismus are very frequent in syndromic craniosynostoses. In nonsyndromic craniosynostosis, specifically unicoronal craniosynostosis, children are at risk of developing astigmatism in the eye opposed to the coronal suture synostosis.<sup>65</sup> Limb deformities are largely restricted to syndromic craniosynostoses, and notably associated to the Apert syndrome. Both types of craniosynostosis, nonsyndromic and syndromic, may co-occur with cognitive and behavioural impairments. These are either intrinsic due to the congenital defect or secondary to intracranial hypertension or physical deformities. Interestingly, there is continued debate on decreased intracranial volumes, hydrocephalus and raised ICP in patients with single-suture craniosynostosis.<sup>27</sup> So far, there is little to no difference in intracranial volumes among various types of craniosynostoses to be found.<sup>66,67</sup> Similarly, there was no correlation between hydrocephalus and nonsyndromic craniosynostosis established,<sup>68</sup> unless there is bilateral involvement of the lambdoid suture.

However, several studies have shown that children with nonsyndromic craniosynostosis are at high risk of developing intracranial hypertension.<sup>58</sup> In fact, elevated intracranial pressure was found in 24-30% of nonsyndromic craniosynostoses.<sup>6,69</sup> Yet in 1982, Renier et al.<sup>6</sup> reported abnormal ICP recordings (meaning  $\geq 15$  mmHg during Slow-Wave sleep) in 14% of cases where only one suture is involved and in 47% of cases with multiple sutures intricated. However, in most nonsyndromic cases indication for surgery remains cosmetic. Invasive ICP monitoring is reserved for children with visual and/or developmental deficits, in cases where surgery has been refused and the head circumference is falling off or they have a "Copper beaten skull" on X-ray - although this is a weak clinical sign.

Apart from its association with intracranial hypertension, premature fusion of cranial sutures is also known to affect the underlying brain morphology. In a series of studies, conducted by Aldridge et al. from 2002 to 2005, the authors demonstrated that both cortical and subcortical structures of the central nervous system are dysmorphic in craniosynostosis. Specifically, studies of brain morphology in cases of sagittal and unicoronal synostosis have demonstrated that changes in the brain's structure are found in adjacent as well as distant and in subcortical regions away from the fused suture.<sup>70-72</sup>

The highest percentage of associated intra- and extracranial midline problems can be found in children with metopic synostosis. These patients also most commonly present with an IQ deficit. Birth weight, parental age and sodium valproate use during pregnancy

have been identified as potential risk factors for the development of metopic craniosynostosis.<sup>42,73</sup>

Hydrocephalus and tonsillar descent (Chiari I malformation) merit a specific discussion. Chiari I (for the purpose of this article refers to tonsillar descent and crowding of the foramen magnum) has a clear association with the syndromic craniosynostoses shown in Figure 3. An association between non-syndromic lambdoid synostosis (and not other sutures) and Chiari I has also been noted.<sup>74</sup> Chiari I and craniosynostosis co-existing have a significant association with syringomyelia,<sup>74</sup> which needs to be taken into account when evaluating and imaging these children. One of the hypotheses for the aetiology of Chiari malformation is the "box being too small for the contents" due to occipital hypoplasia. Craniosynostosis, whilst obviously not due to occipital hypoplasia, results in the net same outcome of the skull being disproportionately too small for the brain. This provides a plausible mechanism for the association between Chiari and craniosynostosis as well as potentially giving greater insights into the pathogenesis of Chiari malformation itself.

Hydrocephalus associated with craniosynostosis is common. There is variation in the reported figures for hydrocephalus across the literature, but overall syndromic craniosynostosis is associated with hydrocephalus in up to 30-70% of cases,<sup>68,75</sup> as opposed to nonsyndromic craniosynostoses where it occurs in less than 2%. Furthermore, there is no evidence to suggest any causality between the two in most cases of nonsyndromic synostosis.<sup>76</sup>

The first and key point is to establish whether one is dealing with genuine hydrocephalus or static ventriculomegaly with no increased pressure. This is not always a straightforward task as the synostosis itself may cause raised ICP and the clinical picture is complex, head circumference is not possible to use and radiological signs may be atypical.

The mechanism of hydrocephalus in craniosynostosis is believed to be a mixture of obstructive and absorptive<sup>77</sup> arising from venous hypertension.<sup>78</sup> Brain atrophy may contribute to static ventriculomegaly, producing a "hydrocephalus ex vacuo" picture.<sup>76</sup> Although not the focus of this article, the existence of acquired craniosynostosis secondary to shunt over drainage in the presence of non-fused sutures should be mentioned as well.

- Cranial growth restriction/ physical deformity
- Raised ICP
- Cognitive impairment

#### Multidisciplinary team

With regard to the number of complications that can arise intra- and post-operatively from open cranial vault procedures the multidisciplinary team concept has developed and is widely used. It is largely based around

protocols for workup, delivery of anaesthesia, streamlined surgical procedures and complex post-operative care and assessment.<sup>79</sup>

The involved specialties usually include Plastic Surgery, Neurosurgery, Otolaryngology, Dentistry, Audiology, Ophthalmology, Speech & Language therapy, Developmental Paediatrics, Neuropsychology, Medical Genetics, Social Work and Nursing Care. Other specialists, such as cardiologists and gastroenterologists, may be consulted for management of associated defects and clearance for surgery. Often parents can easily be overwhelmed by all the information discussed when meeting all the different specialists. Moreover, congenital defects involving a child's face and skull seem to evoke particularly strong emotional responses from the parents, who must contend with a host of potentially stressful events and circumstances, including the infant's unusual physical appearance, the perspective of potentially life-threatening surgeries ahead, and the possibility of future neuropsychological and educational problems.<sup>4</sup>

#### Diagnosis

In order to achieve optimal treatment and satisfactory surgical outcome,<sup>80</sup> early diagnosis is essential in children with craniosynostosis. However, patients are not infrequently referred late or not referred at all due to late recognition of the head shape deformity.<sup>64</sup>

Usually the abnormal skull shape is recognised shortly after birth by either the parents themselves, the treating obstetrician or paediatrician, midwife or general practitioner. The main diagnostic screening tools are physical examination of the skull shape<sup>80,81</sup> in combination with taking the history.<sup>82,83</sup> The anamnestic flowchart of Bredero may serve as a guideline to distinguish craniosynostosis from positional skull deformities.<sup>84</sup> When craniosynostosis is suspected, the paediatrician should refer the child to a craniofacial centre for further diagnostic investigations. X-rays of the skull (A-P, lateral, Towne's view) are still often performed in cases of suspected craniosynostosis. If the result remains uncertain, the X-ray may be repeated after 1 to 2 months. Alternatively, an experienced investigator can perform ultrasound scanning of the cranial sutures.

CT-scan with 3D-reconstruction is performed as an alternative in some centres.<sup>64</sup> Whilst the imaging will also give some detail relating to the brain (hydrocephalus, etc.) it is associated with significantly more radiation and not necessarily of added value in many/most cases of "simple" craniosynostosis.<sup>85</sup> Image findings may include bony ridging along the suture, heaping up of bone at the suture, sutural narrowing, and indistinctness of the suture as primary signs of craniosynostosis.<sup>86</sup> Secondary signs include an altered calvarial shape, the general changes in shape and timing of closure of fontanels, and other facial anomalies. The lack of growth across a suture commonly results in effacement of the

underlying subarachnoid spaces. Patients with craniosynostosis may also have an enlarged subarachnoid space beneath regions of compensatory skull growth.<sup>87</sup>

In summary, the diagnosis of craniosynostosis is based on the calvarial shape with relation to a calvarial suture. Nonsyndromic craniosynostosis is diagnosed mainly clinically with help of X-rays and CT scans performed in some centres. In contrast to that, syndromic craniosynostosis is diagnosed mainly clinically with help of X-rays and CT scans performed in some centres. In contrast to that, syndromic craniosynostosis is often more complex and often requires both CT and MRI imaging to look at the structures within the posterior fossa and venous drainage. For both syndromic and non-syndromic craniosynostosis other investigations should include: regular measurement of the head circumference (and the Cranial Index - width/length), ophthalmology, ENT, neurocognitive, Speech & Language assessments, and where appropriate dental review, measurement of overnight Oxygen saturations (to exclude sleep apnoeas associated with airway problems) and Plastic Surgery opinion for hand and feet abnormalities.

Genetic testing and counselling can assist in making or confirming a specific diagnosis and this may have prognostic implications both for the individual patient but also for future planned pregnancies.<sup>64</sup>

- Physical examination and history taking
- Diagnostic imaging: X-skull/ ultrasound, 3D-CT scan of the head
- Genetic testing

**Neuropsychological outcomes**

In syndromic cases surgery is often indicated for morphological (aesthetic) and functional (cognitive, airway, ophthalmic, etc.) reasons. However, in non-syndromic cases, the indication for surgery is still generally considered to be cosmetic. Although, recent evidence suggests that corrective surgery may also positively impact developmental outcomes assessed during long term follow up in non-syndromic synostoses.<sup>88</sup>

Many of the older studies looking at cognitive outcomes poorly defined mental retardation, lacked control subjects, adequate follow-up periods and valid, standardised psychometric tests. On the other hand, more recent, high quality studies applying the above mentioned principles including formal assessments, such as the Bayley Scales of Infant Development and Wechsler Intelligence Scales for Children, have raised the possibility of mild cognitive impairment even in non-syndromic cases. A systematic review by Knight et al., 2014<sup>89</sup> of 33 articles with particular emphasis on methodological quality found 10 studies showing developmental delays in motor functioning and cognition, including language, both before and after surgery. Five studies of school-age children with single suture craniosynostosis found Intellectual Quotient to be within the normal range, but three studies found increased learning, behavioural and language deficits documented

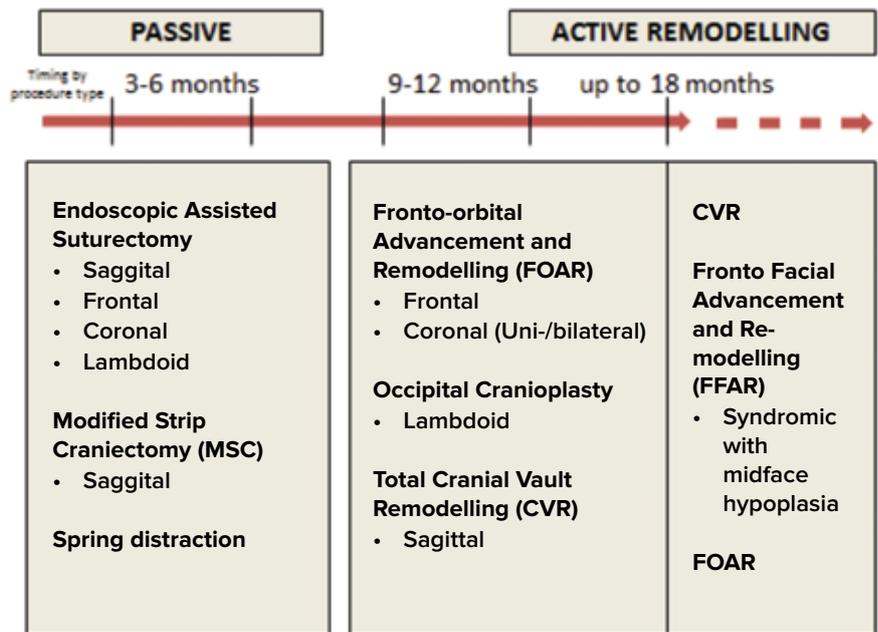


Figure 4. Overview on operative techniques for simple craniosynostosis. Early surgery allows for brain growth to passively reshape skull. Later surgery aims to actively remodel skull shape. The time bar reflects procedure type in broad terms.

on medical records or reported by parents, and five studies showed greater speech and language impairment by more formal testing. A few studies uncovered impairment in visual spatial skills, memory and attention, and school performance. Knight at al., 2014 also investigated the literature on correlations between neurodevelopmental outcome and a variety of factors: no articles to date have significantly correlated neurodevelopmental outcomes and brain imaging, severity of deformity, sutures affected, genetics or gender. Interestingly, there is mixed evidence for the association between early surgery and the reduction of neurodevelopmental impairments, with some studies reporting better outcomes with surgery within one year of age and worse outcomes with delayed surgery after four years;<sup>90</sup> other studies have reported no such difference.<sup>91-93</sup>

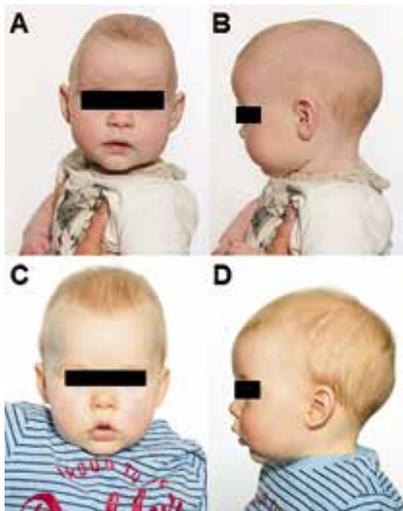
In addition to cognitive difficulties, psychosocial aspects of craniosynostosis have been investigated. Clearly during early years of infancy, the major psychosocial burden lies with the parents and this is reflected in the need for parental support. Particularly, parents of a child with syndromic craniosynostosis may have to cope with negative reactions from others, a possible discrepancy between deviating physical appearance and cognition, and be confronted with problems of school choice.<sup>64</sup> Once the child grows older and attends school, they may be themselves presented with psychosocial challenges and management of these should in turn focus on the child. A variety of outcomes such as post-traumatic stress, successful completion of treatment and the child's resilience and coping strategies have been linked to parental factors such as support as well as the parents' own coping ability.<sup>94</sup>

Post-traumatic stress disorder (PTSD) is an

important issue in all children heavily engaged in the healthcare system and relates to iatrogenic factors such as handling by multiple different clinicians, experiencing pain, separation from parents and undergoing procedures (e.g. phlebotomy, imaging) against the infant's will, with severe developmental and psychosocial implications later in life. Indeed, 10% of children admitted to an intensive care unit were found to develop PTSD, with parental stress reactions as the strongest correlated predictor,<sup>95</sup> highlighting again the importance of addressing psychosocial issues within the whole family. Unsurprisingly, psychosocial outcomes relating to self-image and resilience are also influenced by parental response and resilience.<sup>94</sup>

Evidence on behavioural problems has been mixed: using the Child Behaviour Checklist, Becker at al., 2005 reported significant differences between children with craniosynostosis and the general population,<sup>96</sup> whereas Van der Vlugt et al., 2009 found no difference to the general population when accounting for IQ.<sup>97</sup> At school age, Kelleher et al., 2006 found that in children with nonsyndromic trigonocephaly, 33% required assessment by a school psychologist; 47% required remedial or resource hours; 20% required a special needs classroom due to behaviour issues; and 37% were reported to have behavioural issues such as attention deficit disorder, autism and hyperactivity by their parents.<sup>98</sup>

In later school life and adolescence, issues pertain to stigma and bullying, with a third of craniosynostosis patients experiencing this.<sup>64</sup> Most cope sufficiently but continued support is important, with social skills interventions proving beneficial.<sup>99</sup> Another issue arising in adolescent patients is autonomy to make decisions relating to treatment as they reach the age required for consent: it is of vital import-



**Figure 5:** Sagittal craniosynostosis  
A and B: pre-operative photograph of a child with sagittal craniosynostosis (A frontal view, B lateral view) resulting in a "long-boat" shaped skull; C and D: post-operative photographs (C frontal view, D lateral view) after treatment with spring distractors.



**Figure 6:** Metopic craniosynostosis  
A and B: pre-operative photograph of a child with metopic craniosynostosis (A frontal view, B top view) resulting in a triangular headshape; C: pre-operative CT 3D Reconstruction demonstrating premature fusion of the metopic suture; D and E: post-operative photograph after treatment (D frontal view, E top view); F: post-operative CT 3D Reconstruction.



**Figure 7:** Unilateral unicoronal craniosynostosis  
A and B: pre-operative photographs (A frontal view, B top view) of a child with right unicoronal craniosynostosis resulting in flattening of the ipsilateral forehead and displacement of the ipsilateral lesser wing of the sphenoid bone superolaterally; C and D: post-operative photographs after treatment (C frontal view, D top view).

ance for them to be involved in the decision-making process in order to optimise their cooperation and satisfaction.<sup>100</sup> Furthermore, it is critical that adolescents have realistic expectations of treatment.

Although there have been no studies following up nonsyndromic craniosynostosis patients for psychosocial problems in adulthood, some have identified psychosocial problems in adults with syndromic craniosynostosis. Relative to controls, adults with Apert and Crouzon syndromes had a lower level of education, were less often married, experienced less sexual relationships and more commonly had periods of depressive mood, but were as likely to report a positive attitude to life as controls.<sup>101,102</sup> Some adults with non-surgically treated craniosynostosis reported such pronounced psychological problems that they were willing to undergo correction in adulthood, a fundamentally more complicated operation than in infants.<sup>103</sup>

### Treatment

The surgical treatment of patients with syndromic craniosynostosis was developed in Paris in the early 1970s by Tessier<sup>104</sup> and then later by Marchac and Renier.<sup>105</sup> Surgery had a 2-fold aim: to achieve an enlargement of the cranial volume so as to prevent sequelae of ICP (e.g. developmental delay, visual impairment, etc.), and the correction of morphologic abnormalities of the cranium, the orbits, and the upper jaw.

Since the first surgical intervention for craniosynostosis, a great many surgical techniques for the various types of craniosynostosis have been described and it must be emphasized that there is no consensus on the optimal surgical techniques for skull reconstruction in any form of craniosynostosis.<sup>26</sup>

However, a broad distinction can be made

between "passive" techniques and "active" remodelling procedures (see Figure 4). Passive methods involve resection of bone, thereby allowing the developing and expanding brain to modify the skull shape (with or without assistance of a moulding helmet). As can be seen from a standard head circumference chart the first few months of life are associated with the greatest rate of skull growth (due to rapid brain growth) – most skull growth occurring in the first 2 years of life. More recently, these passive techniques have been further refined by minimally invasive techniques which are associated with smaller skin incisions and the need for less blood transfusions.<sup>9</sup> Such techniques include endoscopic strip craniectomy (+/- moulding helmet) as pioneered by Jimenez<sup>106,107</sup> or the use of spring distraction.<sup>108-115</sup>

The active remodelling techniques, on the other hand, do not rely on the self-correcting capability, but attempt to obtain the desired skull shape by direct reconstruction (often utilising rigid fixation using absorbable plates and screw).<sup>64</sup> This type of surgery can also be broadly divided into that used to correct sagittal synostosis<sup>116</sup> (Figure 5) and that used to treat metopic (Figure 6) and coronal synostosis (Figure 7) – which usually involves a fronto-orbital advancement and remodelling (FOAR). This latter procedure requires the orbital bar to also be removed as well as the abnormal area of the front of the skull.

It has to be considered that in contrast to open craniosynostosis correction surgeries, which are generally performed between the ages of 6 to 18 months, minimally invasive procedures are performed much earlier within the first 3-6 months of age requiring early diagnosis and referral.<sup>117,118</sup>

However, the best surgical treatment has to be evaluated by the surgeon for each individual. Furthermore, especially in more

complex syndromic craniosynostosis more than one surgery may be required.

- a. Early intervention: Endoscopic or open strip craniectomy or spring distraction +/- post-operative orthotic helmet vs.
- b. Later intervention: Open calvarial reconstruction

### Conclusions

The identification of the underlying genetic mutations and molecular mechanisms in craniosynostoses has led to a breakthrough in our understanding of these pathologies. A variety of procedures may be used to correct the deformity but over recent decades there has been increasing interest in early minimally invasive interventions where possible. Therefore, early diagnosis of craniosynostosis is imperative.

A multidisciplinary team approach in children with craniosynostosis and offering support to the entire family, including the parents, remains a vital factor in management of children with these pathologies. Long-term follow-up is particularly important as these children may encounter various problems throughout different stages in their development, including school age, adolescence and even further into early adulthood. Also, arising cognitive difficulties in non-syndromic craniosynostoses may be very subtle.<sup>119</sup> Consequently, children will benefit from continuous assessments throughout childhood and early adulthood and in this way neuropsychological issues can be discussed and addressed accordingly.

**References:** A full list of references can be found online at [www.acnr.co.uk](http://www.acnr.co.uk)