Craniosynostosis/ Paediatric Craniovertebral Anomalies

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INTRODUCTION

Craniosynostosis is defined here as the premature closure of one or more of the skull vault sutures. While advances in molecular genetics have revolutionised our understanding of the various syndromes that may include craniosynostosis, and improved imaging techniques have provided new information about not only the calvarial sutures but also changes affecting the skull base and facial skeletons, the initial diagnosis (or more accurately the initial suspicion) of craniosynostosis still depends primarily on the patient’s – usually a child’s – appearance.

The aim of this chapter is to provide for the paediatric neurologist a broad overview of this complex subject. For convenience craniosynostosis affecting a single vault suture (sometimes referred to as ‘simple’ synostosis) will be dealt with separately from the various complex/syndromic forms in which premature closure of several – sometimes all – of the skull sutures is usual although overlap between the two groups is not uncommon. Johnson and Wilkie have provided a useful overview from a craniofacial surgeon and geneticist’s perspective (Johnson and Wilkie 2011).

AETIOLOGY OF CRANIOSYNOSTOSIS

The various causes of craniosynostosis (or conditions with which it may be associated) can be broadly classified as shown in Table 6.1.

Table 6.1

<table>
<thead>
<tr>
<th>Category</th>
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<tr>
<td>Primary</td>
<td>Idiopathic</td>
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<tr>
<td>Genetic cause known or suspected</td>
<td>Gene mutation(^b)</td>
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<tr>
<td>Secondary</td>
<td>Metabolic:</td>
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<td>Disorders of bone metabolism</td>
<td>Vitamin D deficient rickets, Hyperthyroidism</td>
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<tr>
<td>Storage disorders</td>
<td>Cranio-meta/diaphyseal dysplasia, Osteopetrosis</td>
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<td>Drug induced:</td>
<td>Metopic synostosis, as part of the fetal valproate syndrome</td>
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<tr>
<td>Physical distortion:</td>
<td>Post-CSF shunting positional scaphocephaly</td>
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\(^{a}\)The majority of single suture synostosis fall into this category – in particular those affecting the sagittal and metopic sutures.

\(^{b}\)This includes not only the syndromes once described eponymously (Crouzon, Apert etc.) but also many previously labelled as non-syndromic that have now had their underlying gene mutation mapped.

\(^{c}\)The metopic suture appears to be the most vulnerable when craniosynostosis forms part of a chromosomal abnormality – a deletion of part of the short arm of 7, for example.

While the majority of cases of single suture synostosis arise as isolated events the possible genetic implications of the diagnosis should not be overlooked particularly for uniconoral synostosis (Moloney et al. 1997) (see Uniconoral [and Fronto-Sphenoidal] Synostosis). Whereas no common candidate genes are presently known for isolated sagittal and metopic synostosis, it is essential that all children with uniconoral synostosis are referred for evaluation by a geneticist (Johnson and Wilkie 2011).
**Pathogenesis**

The first ‘modern’ explanation for the head shape that results from single suture synostosis is attributed to Virchow (quoted by Alden et al. 1999) who described restricted growth at 90° to the affected suture and exaggerated growth parallel to it. Add a palpable and sometimes visible ridge along the suture itself and, though this analysis can be considered simplistic in the light of more contemporary studies of suture biology, it still serves as a convenient model for discussions with parents.

Modern interest (Coussens et al. 2007) in the biology of premature suture closure was initiated by Moss who introduced the concept of the ‘Functional matrix’ in which both morphogenetic and functional forces combine to produce the final anatomical result (Moss 1975). Since then there has been great progress in the actions of various genes (TCF12 (Sharma et al. 2013) and ERF (Tigg et al. 2013), for example) on the biology of osteogenesis in general and suture formation in particular (see The Molecular Genetics of Syndromic Craniosynostosis).

**Diagnosis**

The diagnosis of single suture craniosynostosis is primarily one of pattern recognition. The various types produce head shapes so characteristic that confirmation by some form of imaging is rarely required by those with craniofacial experience. For those without this advantage the following imaging modalities can be useful.

1. **Plain X-rays** can be diagnostic for sagittal, unicoronal and lambdoid synostosis. The metopic suture closes so early in life (during the first year) that its absence on an X-ray is no proof that it might have closed early. The hypotelorism and vertical medial orbital walls associated with metopic synostosis are however recognisable on an antero-posterior skull X-ray.

2. **Computerised Tomographic (CT) scans** can be diagnostic by revealing not only the skull shape (visible anyway on clinical examination) but by demonstrating the absent suture – particularly on three-dimensional reconstructions. They will also reveal any associated cerebral abnormalities.

3. **Magnetic resonance imaging (MRI)** does not show bone with sufficient resolution to have a role in the routine diagnosis of craniosynostosis. It is only indicated when neurological/developmental concerns suggest a possible brain abnormality.

**Natural History**

The natural history of most forms of single suture synostosis is that the abnormality of head shape for which they are responsible commences well before birth – as shown by their occasional presence in the preterm infant. The change in head shape may become more obvious over the first year of life but major changes are unusual. The parents of an affected child can therefore be told that without intervention their child’s head shape is likely to remain much as it is when first seen.

**Implications**

Parents need to be warned that single suture synostosis does carry implications for the affected child’s neuro-developmental progress (Starr et al. 2012). Although the majority are likely to be unaffected a significant proportion will manifest a degree of delay. This is most frequent when there is an associated chromosomal abnormality (seen most in children with metopic synostosis) or gene mutation (unicoronal synostosis due to Muenke or FGFR3-associated synostosis, for example). The fetal valproate syndrome also combines developmental delay/learning difficulties with metopic synostosis (Lajeunie et al. 2001).

The cause of such cognitive impairment in most cases however remains unknown. Although it has sometimes been attributed to occult raised intracranial pressure (ICP) the evidence remains weak (see Functional Complications of Syndromic Craniosynostosis for a discussion of raised of ICP in children with complex/syndromic forms of craniosynostosis).

Reviewing single suture synostosis in general, Kapp-Simon et al. (2007) stated that, ‘Surgical intervention on morphologic [appearance] grounds remains the only absolute indication.’ And single ‘Suture fusion may serve as an indicator of neureodevelopmental concern’. In other words, the relationship between single suture premature fusion (such as the metopic) and neurocognitive problems may not be causal. Finally, Hankinson et al. (2010) concluded that, ‘Taken as a whole, the current literature suggests that cognitive impairment in children with SSC [single suture craniosynostosis] occurs despite early surgical intervention.’

Nevertheless, there remains a body of opinion amongst those involved in the management of children with single suture synostosis that a certain percentage will, if left untreated, develop otherwise avoidable cognitive/developmental problems (Eley et al. 2012).

In brief, however, although raised ICP as confirmed by the discovery of papilloedema can occasionally occur in children with single suture synostosis (particularly in older children with sagittal synostosis regardless of whether or not they have had surgery), the premature closure of a single skull vault suture remains a primarily cosmetic issue when the benefits and risks of intervention are discussed with parents.

**Management**

Decisions concerning treatment for a primarily cosmetic condition in a child usually too young to have an input to the decision-making process involves a delicate discussion between parents and specialist in which they (the parents) have to weigh the severity with which they view the abnormality of their child’s appearance (and its possible consequences – teasing at school, for example) against the benefits (in terms of appearance change) and the risks (to the brain from some unexpected complication of surgery such as haemorrhage or
infection, for example) never absent from what is never a minor cranial operation.

The various surgical interventions (and their timing) currently employed in the management of each single suture synostosis are here briefly described. For a more detailed summary, see the review by Garza and Khosla (2012).

**Sagittal Synostosis**

Premature closure of the sagittal suture is the most frequent form of craniosynostosis and leads to a characteristic scaphocephalic (boat-shaped) deformity of the skull. A prevalence of approximately 1 in 5000 children has been estimated and the condition is more frequently seen in boys. Six per cent of cases are familial with transmission following an autosomal dominant pattern with a penetrance of 38% (Lajeunie et al. 1996).

The affected skull has an increased antero-posterior diameter, its bi-parietal diameter is reduced (Fig. 6.1) and a bony ridge can often be both seen and felt along the line of the fused suture. Victims of teasing may be called ‘peanut head’. The synostotic process does not always involve the entire suture and even when it does the severity with which the child’s head shape is affected is very variable, with a mild prominence of the forehead at one end of the spectrum to gross elongation (frontal and occipital bossing) plus narrowing (particularly in the pterional regions) at the other.

The variety of surgical treatments presently employed for the correction of sagittal synostosis (for those children whose parents have opted for intervention) suggests either that all are equally effective – or equally non-effective! The operations vary in scale from removal of the fused suture (suturectomy) combined with internal springs (de Jong et al. 2013) or external (helmet/orthosis) manoeuvres (Proctor 2012) designed to induce a more round shape (all of which need to be performed before six months of age to be most effective) to increasingly major forms of skull reconstruction for which there are no age limits.

**Unicoronal (and Fronto-Sphenoidal) Synostosis**

Craniosynostosis of a single coronal suture produces a characteristic asymmetry of the forehead: frontal plagiocephaly. The supra-orbital ridge on the affected side is recessed as is the forehead above while the temporal region is unusually prominent. On the contralateral side the frontal region is often bossed, accentuating the asymmetry and the nose is set at an angle, its root ‘pointing’ towards the side of the affected suture. The net result is to give the face a characteristic ‘scoliosis’ or curve convex to the affected side. The anterior skull base is also curved – but concave to the affected side (Fig. 6.2).

The elevation of the lateral wing of the sphenoid bone on the affected side is responsible for the characteristic ‘harlequin eye’ appearance on an antero-posterior skull X-ray. The deformation of the orbit results in a subtle malposition of the extra-ocular muscle attachments that may in turn cause a complex abnormality of eye movement and a secondary compensatory head tilt (Gosain et al. 1996). All children with unicoronal synostosis should therefore be referred to a paediatric ophthalmologist.

Although the cause of unicoronal synostosis is in many cases unknown it can result from a variety of genetically mediated disorders. Most prominent amongst these is the Muenke (or FGFR3-associated synostosis) (Muenke et al. 1997). Saethre–Chotzen syndrome (Reardon and Winter 1994) and craniofrontonasal dysplasia (Cohen, Jr 1979) may also involve premature closure of a single coronal suture but their other features are usually sufficiently characteristic to suggest the diagnosis.

**Figure 6.1** Three-dimensional CT scans showing the typical scaphocephalic head shape caused by sagittal synostosis.

**Figure 6.2** Three-dimensional CT scan showing the typical deformity caused by unicoronal synostosis.
It is unusual for children with isolated non-genetically mediated unicoronal synostosis to have impaired neurocognitive development. Such problems are however well described for children with the FGFR3 mutation (Johnson and Wilkie 2011, Wilkie et al. 2010).

Treatment of unicoronal synostosis consists of a fronto-orbital reconstruction (FOR), a procedure that for the most satisfactory result may require attention to both the affected and contralateral sides. Although a gratifying immediate result can usually be obtained with abolition of the previous frontal plagiocephaly, there is over the years that follow a tendency for some element of the previous deformity to reassert itself. This is seen at its greatest extent in those children harbouring the FGFR3 mutation (Wilkie et al. 2010).

A rare cause of unilateral frontal flattening that can be confused with unicoronal synostosis is premature closure of the fronto-sphenoidal suture. It can be recognised clinically by the degree of frontal plagiocephaly being particularly severe and the nose angled in the opposite direction – its root away from the affected side. Its treatment however is the same as for unicoronal synostosis. CT reveals a normal coronal suture with an absent fronto-sphenoidal suture.

**Metopic Synostosis**

The metopic suture is the first of the major calvarial sutures to close, a process often completed by the end of the first year. Mild vertical ridging along the line of the suture is not uncommon and should be considered a normal variation for which investigation in the absence of other issues is not required. Premature closure of the metopic suture however produces a characteristic triangular (when viewed from above) deformity of the anterior skull (trigonocephaly). There is a keel-like prominence running vertically down the centre of the forehead while the supra-orbital ridges and the frontal bones above them are flattened on each side (Fig. 6.3). The anterior cranial vault is narrow with approximation of the orbits – hypotelorism – and prominent epicanthic folds.

In a large study of metopic craniosynostosis, Lajeunie et al. (1998) estimated a prevalence of 1 in 15,000 with 5.6% of cases being familial. As with sagittal synostosis there is a male preponderance of approximately three to one. Maternal exposure to sodium valproate is also a risk factor in the development of metopic craniosynostosis (Lajeunie et al. 2001) but the affected child has (in addition to learning difficulties and other components of the syndrome) hyper- rather than hypo-telorism.

Even in the absence of an associated syndromic or chromosomal abnormality, children with metopic synostosis may grow up with learning difficulties (Bottero et al. 1998). The effect of the orbital deformity upon their ophthalmic function include a higher incidence of both refractive errors and astigmatism than would otherwise be expected – and no relationship to age at surgery (Macintosh et al. 2011).

Treatment involves, as for unicoronal synostosis, a fronto-orbital reconstruction in which the central keel is removed together with the recessed superior orbital margins and the flattened frontal bones. These pieces are reconstructed into a more regular contour and replaced. As with unicoronal synostosis some reversion is not uncommon with a return of a (usually minor) degree of lateral frontal flattening.

**Lambdoid Synostosis – and Posterior Positional Moulding**

Isolated unilambdoid synostosis is rare, accounting for only 2.3% of Shillito and Matson’s series of 519 patients (Shillito, Jr and Matson 1968). Its importance lies in its differentiation from acquired positional posterior flattening (plagiocephaly).

The affected child is born with the posterior parietal/occipital area on one side of the head flattened and restricted in volume while the contralateral frontal area may be more prominent than the ipsilateral (Matushita et al. 2014). As with the other isolated single suture synostoses this deformity shows little spontaneous tendency either to progress or to worsen. Given its posterior (eventually hidden by hair) location and the adjacent major venous sinuses, reconstructive surgery is rarely recommended.

**Lambdoid Synostosis Versus Posterior Positional Moulding**

Posterior flattening of the skull (uni- or bilateral) can also occur as a result of skull moulding, a condition seen with greatly increased frequency since the advent of the ‘Back to sleep’ campaign to reduce the risk of cot death/sudden infant death syndrome (SIDS) (Kane et al. 1996). The risk factors for acquired positional moulding include prematurity, a head with some intra-uterine flattening at birth, a tendency to lie with the head turned preferentially in one direction (torticollis – with or without a sternomastoid ‘tumour’), a firm mattress to sleep on, no pillow and finally a ‘good baby’ – one who
sleeps through the night with little change in position. With these factors at work an infant whose head might have been perfectly round at birth can by the age of six weeks or so have developed marked flattening of one side of the back of the head. Viewed from above it is as if that region has been pushed forward, taking with it the ipsilateral ear (moving it closer to the eye on the affected side – Fig. 6.4) and producing a degree of ipsilateral frontal prominence (Huang et al. 1998). For the next six months or so there a tendency for the deformity to become more pronounced until with the child’s greater independence of movement he or she no longer lies throughout the night in the same position and the skull has acquired sufficient rigidity to resist further pressure-inflicted change. From then on there is a tendency for further skull growth to bring with it a degree of ‘correction’ of the head shape although when marked to begin with this, this is never complete.

Posterior positional moulding can be associated with motor delay but the causal connection is due to the less active child being more liable to develop the flattening – not the other way round. Given the history and the typical head shape (Huang et al. 1998), it is usually possible to differentiate posterior positional moulding from lambdoid synostosis on clinical grounds alone; but when in doubt a skull X-ray will show whether that suture is open or not.

The mainstays of management are awareness and prevention. Once the condition has been recognised for what it is, however, treatment consists of repositioning during sleeping and feeding, physiotherapy as required for torticollis, and moulding mattresses. Head re-shaping orthoses (moulding helmets) may have a role in both limiting the degree of deformity and restoring a more regular growth pattern particularly when instituted below the age of six months (Collett 2014; van Wijk et al. 2014). There is as little if any place for the surgical correction of the posterior deformity that results from positional moulding as there is for that due to lambdoid synostosis.

CRANIOFACIAL SYNDROMES

Introduction

The craniofacial syndromes are a heterogeneous group of rare conditions in which craniosynostosis occurs alongside various manifestations of disordered craniofacial development (Rice 2008) as well as other skeletal abnormalities that can affect, in particular, the hands and feet (Britto et al. 2001a, Panthaki and Armstrong 2003).

The conditions seen most frequently are the eponymous syndromes of Crouzon, Apert, Pfeiffer, Saethre–Chotzen, Muenke (FGFR3-associated synostosis) and crano-frontonasal dysplasia. Less commonly encountered are Carpenter, Antley–Bixler (Antley and Bixler 1975, Bradley et al. 2003), Jackson–Weiss (Jackson et al. 1976) and Boston-type syndromes.

The aim of management is to ensure that affected children realise their full developmental potential. Although a major component of treatment is surgical there is now recognition of the needs of the child as a whole. The centres best placed to achieve this are those that can field the multidisciplinary team that, in addition to its neuro-, plastics and maxilla-facial surgeons, includes specialists in ENT (ORL) and audiology, genetics, paediatrics, neurology, psychology, orthodontics, respiratory medicine, speech therapy, ophthalmology and, of course paediatrics (Hayward and Jones 2004).

Crouzon Syndrome

Crouzon syndrome (Cohen and Kreiborg 1992), like the majority of craniofacial syndromes, is transmitted as an autosomal dominant condition although it occurs with near equal frequency as a new mutation. As in Apert syndrome, its occurrence is associated with increased paternal age (Glaser et al. 2000).

Typical clinical features include a retracted maxilla that leaves the lower teeth projecting anterior to the upper teeth (class III malocclusion), a ‘beaky’ nose, a recessed frontal region (brachycephaly) due to biconoral synostosis and prominent eyes (exorbitism) due to the combined recession of the infra- and supra-orbital regions (Fig. 6.5).

Its expression is highly variable, ranging from severe exorbitism with midface retrusion and airway obstruction at one extreme to a mild prominence of the eyes at the other. A catch for the unwary is that suture fusions need not be present at birth but may develop during the first two years of life (Reddy et al. 1990, Connolly et al. 2004). Extracranial manifestations (Anderson 1997) seen in severe cases include vertebral fusion (most commonly cervical) (Anderson et al. 1997a, Anderson et al. 1998a) and ankylosis affecting particularly the elbows (Anderson et al. 1998a).

A genetically distinct type of Crouzon syndrome is associated with rugated thickened skin and hyperpigmentation that affects particularly the flexure creases – acanthosis nigricans (Wilkes et al. 1996).

Intelligence may be normal in Crouzon syndrome but the more severe the phenotype the more likely the child is to have
developmental and learning difficulties. Marked intellectual compromise was present in 3% of Kreiborg’s series (Kreiborg 1981).

Apert Syndrome

The child with Apert syndrome has a head that is tall and shortened from front to back (turri-brachycephaly), midfacial (maxillary) retrusion, proptosis, a downward cant to the palpebral fissures and hypertelorism (Lajeunie et al. 1999) (Fig. 6.6a). The essential clinical feature however is a complex fusion (syndactyly) of the fingers and toes (Anderson et al. 1997d, Anderson et al. 1999, Cohen and Kreiborg 1995b) that may require multiple surgical procedures before functional effectiveness is achieved (Guero et al. 2004) (Fig. 6.6b). Visceral (Cohen and Kreiborg 1993) and cutaneous (Cohen and Kreiborg 1995a) abnormalities can also occur. Palatal abnormalities (Kreiborg and Cohen 1992) ranging in severity from frank clefts to a bifid uvula are common and occur with a frequency of up to 75% (Peterson and Pruzansky 1974, Slaney et al. 1996). Cervical vertebral fusions that may be progressive occur in over half of affected children although it is unusual for them to become clinically significant (Thompson et al. 1996).

Developmental and learning difficulties are the norm in Apert syndrome although a combination of developmental assessment tools designed for non-Apert children and low societal expectations may overestimate their severity (Shipster et al. 2002). While a small percentage of children may complete secondary education (and usually only with assistance in the classroom), many drop out of mainstream education during their primary school years while a small percentage are too affected for the mainstream education system at anything above kindergarten level (Patton et al. 1988, Renier et al. 1996).

Pfeiffer Syndrome

Although described separately for historical reasons, the genetic overlap between Pfeiffer and Crouzon syndromes is such that they are now often considered together as ‘Crouzon–Pfeiffer syndrome’.

The ‘traditional’ Pfeiffer syndrome is an autosomal dominant condition characterised by suture fusions that range from bicornal synostosis alone to pan-synostosis (with or without the cloverleaf skull deformity – see next section) (Winter 1994). Affected patients also have digital abnormalities (Panthaki and Armstrong 2003) that include curved and shortened thumbs and great toes (Anderson et al. 1998b) and, less commonly, digital fusions (although to a lesser degree than in Apert syndrome [Panthaki and Armstrong 2003]).

Cohen (1993) divided children with Pfeiffer syndrome into three types based on their clinical severity. Type 1, those least affected, may display little more than bicornal synostosis and midface retrusion (in addition to their digital...
abnormalities). Their neurocognitive development may be unaffected, particularly if early complications have been aggressively treated (Kohan et al. 2009) (Fig. 6.7).

In Types 2 and 3 Pfeiffer syndrome, the degree of midface and frontal retrusion is severe enough to obstruct the upper airway and cause eye protrusion sufficient to threaten the corneas. The shortening of the skull base and crowding of the posterior fossa due to the bi-lambdoid component of their pan-synostosis produces an increased risk of hydrocephalus. Ankylosis (bony and soft tissue) of the elbows (Anderson et al. 1998a) and knees is common as are fusions of the cervical vertebrae (Anderson et al. 1996b).

The difference between Types 2 and 3 is that Type 2 has the cloverleaf pattern of skull deformity (see next section).

Neurocognitive development in Types 2 and 3 Pfeiffer syndrome is usually delayed although with active intervention aimed at improving the airway and reducing raised ICP the outlook is not as dire as was once assumed (Robin et al. 1998).

Cloverleaf Skull (Kleebblattschaedel) Deformity

The Kleeblattschaedel anomaly, or cloverleaf skull, is the descriptive term given to a particularly severe form of synostosis-associated cranial deformity (Zuleta and Basauri 1984) – and one that poses a particular challenge for the craniofacial surgeon (Thompson et al. 1995b, Zuccaro et al. 1996). Although it usually occurs as a manifestation of Pfeiffer syndrome (Type 2) it can occasionally complicate Apert and Crouzon syndromes (Fig. 6.8).

Its cause is a particular combination of suture fusions and an ICP that is raised from hydrocephalus. The sagittal and squamo-parietal sutures are open but in addition to bicoronal synostosis, a bony constriction band runs posteriorly from the pterions to the lambdoids. With the addition of hydrocephalus the infant’s skull expands upwards (above) and laterally (below) this constriction band to produce the characteristic trefoil (cloverleaf) shape (Cohen 1972, Cohen 1993, Eaton et al. 1975, Kroczek et al. 1986).

Saethre–Chotzen Syndrome

Saethre in 1931 and Chotzen in 1932 described an autosomal dominant condition that combines with great variability (Reardon and Winter 1994) coronal synostosis (uni- or bilateral) and digital abnormalities that include short digits and partial syndactylies (Anderson et al. 1996a), low frontal hairline, a prominent nose and ptosis, and more rarely fusions of the cervical spine (Anderson et al. 1997b) (Fig. 6.11). Complications such as exorbitism and airway obstruction are uncommon. Raised ICP is rarely of functional significance (de Jong et al. 2010) and the neurocognitive outcome may be only modestly affected if at all (Reardon and Winter 1994).
Muenke Syndrome (FGFR3-Associated Synostosis)

This condition, one of the less severe of the craniosynostosis-associated syndromes, is of interest because rather than being first described on the basis of the appearance of those affected it was ‘discovered’ during the explosion of knowledge about the genetic basis of the craniofacial syndromes that occurred during the 1990s (Muenke et al. 1997).

It has multiple manifestations (Reardon et al. 1997) but the synostosis typically affects one or both coronal sutures (Moloney et al. 1997). It is now appreciated that many patients previously diagnosed as isolated unicoronal craniosynostosis carry the FGFR3 mutation (Lajeunie et al. 1995a). Those with bicornal synostosis typically have a broad and shallow supra-orbital region with a protruding upper forehead forward (Fig. 6.12 a,b). Complications such as raised ICP and airway obstruction are uncommon but although a child’s development may be unaffected, a degree of learning difficulty is well described (Muenke et al. 1997).

Cranio-Fronto-Nasal Dysplasia

In this X-linked (Pulleyn et al. 1999) syndrome, bicornal synostosis (usually asymmetric in its effect) is associated with hypertelorism, wiry (‘unruly’) hair, a prominent gap between the central incisors, a bifid nose (Cohen 1979, Pruzansky et al. 1982, Saavedra et al. 1996) and sometimes abnormalities of the optic discs (Lees et al. 1998). Development is usually unaffected and treatment is indicated on predominantly cosmetic grounds (Kawamoto et al. 2007).

Carpenter Syndrome

This very rare condition (Carpenter 1909) is mentioned here for completeness because it has an autosomal recessive pattern of inheritance. Also known as acrocephalopolysyndactyly because of the extra digits that form part of the clinical picture, the cranial deformity is due to various combinations of craniosynostosis (Eaton et al. 1974, Gershoni-Baruch 1990).
THE MOLECULAR GENETICS OF SYNDROMIC CRANIOSYNOSTOSIS

It was hoped that when the genetic basis of many of the craniofacial syndromes was discovered in the 1990s it would allow their classification to move from the eponymous nomenclature that had been in use for so many years. Unfortunately, as the genetic ‘overlap’ between Crouzon and Pfeiffer syndromes demonstrates, the situation proved to be more complex – a single mutation capable of causing both Pfeiffer and Crouzon syndrome and mutations on either of two chromosomes responsible for Pfeiffer syndrome (Rutland et al. 1995, Schell et al. 1995, Britto et al. 2001c). It is for this reason that some specialists now prefer the designation ‘Crouzon–Pfeiffer syndrome’ to two separate entities – which, from a clinical management perspective, makes little difference to established practice.

With the exception of Carpenter syndrome (autosomal recessive [Jenkins et al. 2007]) and craniomandibular dysplasia (X-linked [Pulley et al. 1999]) the craniosynostosis-associated syndromes have an autosomal dominant pattern of transmission. (For a summary linking the clinical features of syndromic craniosynostosis to their underlying genetic abnormalities see the review by Rice (2008).

The realisation that many of the craniofacial syndromes were monogenetic (due to a single gene mutation) combined with investigation of families with several affected members led, in the 1990s, to an intense examination of the fibroblast growth factor group of tyrosine kinase receptors (FGFRs I–III) as candidate genes. These receptors are well preserved across a range of species and are involved (amongst many other activities) in cranial and limb development (Britto et al. 2001b, Johnson and Williams 1993, Robin et al. 2011). It is now known that a particular position within each FGFR protein is strongly linked to craniosynostosis as mutations there in FGFR 1, 2 and 3 cause respectively Pfeiffer, Apert and Muenke syndromes (Bellus et al. 1996).

More recent genetic discoveries have further reduced the number of cases of craniosynostosis that were once labelled as ‘non-syndromic’. These include mutations involving the TCF12 and ERF genes.

Mutations of TCF12 have been reported in 32% and 10% of children with ‘non-syndromic’ bi- and unicoronal synostosis respectively in whom Muenke, FGFR2 and Saethre–Chotzen mutations had been excluded. The gene is located on chromosome 15, acts synergistically with TWIST1 through ‘loss of function’ and appears to be necessary for the production of a functioning coronal suture (Sharma et al. 2013).

Mutations of ERF are less common than those of TCF12, found in only 1–2% of 402 cases of craniosynostosis operated on by the Oxford craniofacial unit (Twigg et al. 2013). They also act by loss of function to cause complex multi-suture fusions that when associated with facial abnormalities may resemble Crouzon syndrome (there is a ‘pathway-based phenotypic link with FGFR2’ [Twigg et al. 2013]). The sagittal is the most likely to be involved when only one suture is prematurely fused (Twigg et al. 2013).

Although confirmation of a particular mutation may not affect a child’s immediate management, it does allow a more informed developmental prognosis and the likely need for subsequent operations to be explained to parents. (Wilkie et al. 2010). Knowledge of the responsible mutation also has important implications for genetic counselling. Parents who have already had an affected child may also wish to avail themselves of the opportunity not only for prenatal ultrasound examination of the foetus (Gorincour et al. 2005, Chitty and Lau 2011, Khalil et al. 2011, Shaw et al. 2011) but also for pre-implantation diagnosis when considering further pregnancies (Abou-Sleiman et al. 2002, Harper et al. 2002).

PRINCIPLES OF MANAGEMENT OF SYNDROMIC CRANIOSYNOSTOSIS

The complexity of decision-making for children with syndromic craniosynostosis means that their management should only be undertaken in multidisciplinary units specialising in their care (de Jong et al. 2010, McCarthy et al. 1995). It is therefore essential that these children are referred to such a unit as early as possible so that the correct diagnosis (both genetic and clinical) can be made, the risk of complications assessed and a management plan made that is tailored to each individual child’s needs.

As the majority of craniofacial syndromes result from a particular gene mutation (either of, or connected to, the FGFR series) it should be no surprise that such mutations continue to exert their ill effects for as long as the cranial and facial skeletons are growing. The consequence of this is that the majority of children with Apert syndrome (Carr et al. 1992) and the more severe forms of Pfeiffer, Crouzon (Carr et al. 1992) and cloverleaf (Jarrahy et al. 2009) syndromes may need several procedures during their early years to treat such functional issues as raised ICP, exorbitism, airway obstruction and psychological issues related to their appearance (teasing etc.) (Allam et al. 2011) This is in contrast to more mildly affected children (with Saethre–Chotzen and Muenke syndromes [Ridgway et al. 2011], for example) for whom a single reconstructive procedure may be all that is required.

The problems affecting children with syndromic craniosynostosis can be divided somewhat arbitrarily into those affecting clinical function and those not.

FUNCTIONAL COMPLICATIONS OF SYNDROMIC CRANIOSYNOSTOSIS

Raised Intracranial Pressure

Raised ICP is a well recognised complication of syndromic craniosynostosis (Renier et al. 1982, Thompson et al. 1995a). Its incidence is strongly related to the severity of the phenotype making it unusual in Muenke and Saethre–Chotzen
syndrome and near inevitable in Pfeiffer Type 2 (cloverleaf skull deformity).

Raised ICP can, as a consequence of unrelieved papilloedema, be responsible for a progressive deterioration in vision leading eventually to blindness (Liasis et al. 2011, Stavrou et al. 1997). Whether it can (in the absence of hydrocephalus) affect cognitive development is more assumed than proven. Renier et al. (1996) and others have proposed such a connection but it is difficult to untangle the effects of raised ICP alone from such other manifestations of the affected child’s phenotype as the direct brain effects of the disordered gene or chromosome (Wilkie et al. 2010), hydrocephalus, chronic airway obstruction, feeding difficulties and ‘failure to thrive’, the developmental consequences of impaired vision and/or hearing coupled with low societal and family expectations (including teasing) – not to mention any unintended side effects of earlier cranial surgery (Naumann et al. 2012).

The Diagnosis of Raised Intracranial Pressure

- **Clinical** Bulging of still open fontanelles, stretched sutures and cranietomy defects; and in the older child headache and vomiting although these are of very low sensitivity and specificity.
- **Radiological** A generalised copper-beaten appearance on skull radiographs in the presence of multiple suture fusions (Tuite et al. 1996b), progressive ventriculomegaly and effacement of cortical sulci on magnetic resonance and/or CT scans (Collmann et al. 2005).
- **Ophthalmological** Papilloedema (Tuite et al. 1996a) with or without abnormal electro-diagnostic studies and a fall in visual acuity (Liasis et al. 2003, 2006 Thompson et al. 2006).
- **Invasive ICP monitoring** Transcranial parenchymal pressure monitoring allows ICP to be measured (Renier et al. 1982, Thompson et al. 1995a). However, it is important to recognise that the figures most often used to interpret the results of ICP monitoring in childhood (normal, <10mmHg; borderline, 11–15mmHg! and raised, >15mmHg) are ‘best guesses’ based on a variety of assumptions (parents of healthy children being understandably reluctant to submit them to an invasive procedure for essentially academic interest).

It is important to remember that although ICP may be normal when a child first presents, the dynamic nature of the syndromic craniosynostosis process means that surveillance (which in our unit includes regular ophthalmic assessments) should continue until a child is at least 8 years old; our experience being that it is unusual for it to develop – or recur – after that age.

Causes of Raised Intracranial Pressure in Syndromic Craniosynostosis

The four principle contributors to raised ICP in children with syndromic craniosynostosis are cranio-cerebral disproportion, hydrocephalus, venous hypertension and airway obstruction.

1. Cranio-cerebral disproportion Although it was once thought that a growing brain restrained by a skull restricted in its ability to expand was the principle cause of raised ICP in syndromic synostosis, it is now recognised that this situation is relatively unusual and a reduced intracranial volume (ICV) is an unreliable predictor of raised ICP (Fok et al. 1992, Gault et al. 1992). Indeed in Apert syndrome ICP, although normal at birth, may actually be greater than normal by the time raised ICP declares itself (Gosain et al. 1995, Sgouros et al. 1999). Fortunately the various forms of vault expansion surgery originally designed to increase ICV are equally effective in reducing raised ICP due to a more common cause – venous hypertension (see Raised Venous Pressure).

2. Airway obstruction Impairment of the upper airway is common in the severely affected child with syndromic synostosis and is an important contributor to the vicious cycle that determines ICP in these children (Gonzalez et al. 1997). The peaks of ICP that can reduce cerebral perfusion pressure to a mean of around 30mmHg are invariably associated with episodes of airway obstruction during rapid eye movement (REM) sleep. The practical importance of this is that improvement to the airway (see Airway Obstruction) may be all that is needed to reduce the ICP (Fig. 6.9).

3. Hydrocephalus – and the Chiari 1 deformity of children with syndromic synostosis, 40% may have a degree of ventricular enlargement (Collmann et al. 2005) but in many this is non-progressive. It is important therefore that the craniofacial surgeon does not proceed to treatment – a shunt insertion, for example – unless ventriculomegaly is worsening and other indicators of raised ICP are present. Hydrocephalus occurs particularly when there is constriction of the skull base and early closure of the lambdoid sutures – which is why it occurs more frequently in Crouzon and Pfeiffer (Types 2 and 3) than in Apert syndrome (Cinalli et al. 1995). Constriction of the skull base, hydrocephalus and raised ICP and herniation of the cerebellar tonsils (the Chiari I deformity) are linked in a cycle of cause and effect (Cinalli et al. 1995, Thompson et al. 1997). The Chiari I deformity is seen particularly in children with a constricted skull base and while its progression (with additional buckling of the lower brainstem) is aided by raised ICP it is also a risk factor for the development of hydrocephalus (de Jong et al. 2012). When tonsillar herniation and brainstem compression in a child with syndromic synostosis becomes symptomatic (when respiratory studies suggest a central as well as an obstructive contribution to breathing problems (Gonzalez et al. 1998) or with the development of syringomyelia, for example) a foramen magnum decompression may be indicated.

4. Raised venous pressure Intracranial venous hypertension is a major contributor to raised ICP in children with syndromic synostosis (Hayward 2005). It is caused by...
narrowing or occlusion of venous channel exiting through the skull base (Rich et al. 2003) and aggravated by airway obstruction. In a digital subtraction angiography study of 23 syndromic children with raised ICP, (Taylor et al. 2001) 18 had either complete or more than 50% occlusion of the sigmoid/jugular complex on one or both sides. Extensive collaterals through the retromastoid region and other trans-osseous channels can cause troublesome haemorrhage when reflecting the extensive skin flaps often required for craniofacial surgery (Anderson et al. 1997c, Thompson et al. 1995b) (Fig. 6.10). Although considered separately here, some overlap between these contributors to raised ICP in complex/syndromic craniosynostosis is common. Indeed they often interact in a vicious cycle (Fig. 6.11 in which during active/REM sleep airway obstruction and periods of apnoea cause CO₂ retention and cerebral vasodilatation to produce waves of very high pressure lasting 10–20 minutes superimposed upon a baseline that may be only moderately elevated. During these waves of pressure (most obvious on overnight recordings) mean cerebral perfusion pressures can fall as low as 32mmHg (Hayward and Gonzalez 2005).

Airway Obstruction

Impaired respiratory function, particularly at night when snoring is a frequent complaint, is a common problem for the more severely affected child with syndromic craniosynostosis. It is usually due to airway obstruction from narrowed nares, cramped nasal passages, a hypoplastic maxilla constricted in all planes and tracheal softening but a central component occurs when there is brainstem compression from a Chiari I deformity (Gonsalez et al. 1998). An airway clear at birth may become obstructed later from tonsillar and (in particular) adenoidal hypertrophy in the restricted pharyngeal space available to them.

In addition to contributing to raised ICP, breathing difficulties impair the ability of the infant and young child to feed and are an important contributor to their failure to thrive. In older children disturbed nights lead to sleepiness during the day and can interfere with schooling.

All children in whom breathing difficulties are suspected should undergo an overnight respiratory sleep study. Although the commonest cause is upper airway obstruction, such a study will determine whether there is a central component which if associated with a Chiari I deformity may require a foramen magnum decompression (Gonzalez et al. 1998).

Management involves (in ascending order of magnitude) the insertion of a naso-pharyngeal airway (Ahmed et al. 2008), adeno-tonsillectomy (which may need to be repeated as the child grows) (Liasis et al. 2005), continuous positive airway pressure (CPAP) (Gonzalez et al. 1996, Massa et al. 2002), tracheostomy and, finally, operations that open the airway by advancing the maxilla – the LeFort III advance and the monobloc fronto-facial advance (Witherow et al. 2008) with or without distraction.

Failure to Thrive

Regardless of any contribution from the disordered gene, severe breathing difficulties due to a combination of airway obstruction and any central depression of respiration can so interfere with feeding that the affected child may fail to gain weight – or even lose it. A dyspraxia of oro-pharyngeal movements may also contribute.

Adjuvent feeding of infants via a naso-gastric tube and occasionally a gastrostomy may be required but the most dramatic improvements are seen following procedures aimed at restoring a more effective airway.

Developmental Delay/Learning Difficulties

Developmental delay, learning difficulties and a wide range of cognitive issues can affect the child with craniosynostosis including those with no more than single suture involvement. While many may be related to effects of the disordered gene (and particularly any associated chromosomal abnormality), an important role of the multidisciplinary craniofacial unit is to manage any potentially remedial causes that can also contribute. These include hydrocephalus, chronic airway obstruction, feeding difficulties and ‘failure to thrive’, the developmental consequences of impaired vision and/or hearing and the effects of low societal and family expectations (including teasing). Experienced input is needed to ensure that such problems are recognised early and appropriate therapy instituted at an age when it is most likely to be of benefit.

Epilepsy is rare in craniosynostosis but has a higher than expected incidence in Muenke (Agochukwu et al. 2012) and Apert (Agochukwu et al. 2012) syndromes, in children with the fetal valproate syndrome and those with associat-

Vision

Corneal Exposure

Recession of the maxilla below and the fronto-orbital region above can leave the corneas exposed and in danger of permanent scarring. Temporary measures to protect them include the instillation of lubricating drops (particularly useful when the eyes do not close completely at night) and tarsorrhopies although these can raise intraocular pressure when the exorbitism is severe. Longer term protection requires the advance of the bony orbital rim – either in part (a fronto-orbital advance [FOA]), or complete (an FOA combined with a LeFort III maxillary advance or a fronto-facial monobloc procedure which can in exceptional circumstances be performed in the very young [Britto et al. 1998]).

The vision of children with syndromic craniosynostosis can be affected also by raised ICP, astigmatism and amblyopia. In one assessment of visual acuities in children with syndromic craniosynostosis 40% had function in their better eye below a level (6/12) that would allow them to hold a driving licence in the United Kingdom (Khan et al. 2003) a proportion of which morbidity can be attributed to raised ICP.
ed chromosomal abnormalities. It may also occur as a post-operative complication, a consequence of the frontal lobe retraction required during fronto-facial monobloc and bipartition procedures in children with severe frontal bone recession (Cobb et al. 2013).

**Cosmesis**

The cosmetic disabilities that most trouble patients with syndromic synostosis and their families include a missshapen forehead, eyes that protrude, eyes set too far apart (hypertelorism) and an upper jaw set back while the lower jaw protrudes.

When correcting for cosmesis alone it is important to remember that surgery carried out on a part of the craniofacial skeleton that is still growing may need to be repeated either wholly or in part in order to achieve a result that will prove stable over time. Our own policy, based more on clinical observation than measurement, is to assume that a forehead and supra-orbital region in a satisfactory configuration at around 10 years of age is unlikely to need further correction and essentially cosmetic reconstructions after that age can focus more on the maxilla and mandible where growth will continue until secondary dentition is complete – the mid to late teens.

**CONCLUSION**

Primary craniosynostosis whether it affects one or multiple sutures and is associated or not with a particular syndrome is rare and its management should only be undertaken by a unit with sufficient experience to ensure affected children achieve their developmental potential.

Early assessment by such a unit will enable the correct diagnosis (both genetic and clinical) to be made, the risk of complications assessed and a management plan made that is tailored to each individual child’s needs.

While in non-syndromic unisutural synostosis treatment may require no more than a single reconstructive operation, more complex cases require input from a wide range of specialists including the paediatric neurologist often until the completion of skeletal maturity.

**REFERENCES**


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