Pediatric Neurology 53 (2015) 394–401

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Topical Review

Craniosynostosis

Lance S. Governale MD [a,b,*]

[a] *Division of Pediatric Neurosurgery, Nationwide Children's Hospital, Columbus, Ohio*
[b] *Department of Neurosurgery, Ohio State University, Columbus, Ohio*

ABSTRACT

Craniosynostosis is the premature fusion of one or more of the cranial sutures. About 8% of the patients have familial or syndromic forms of synostosis, and in the remainder it occurs as a spontaneous isolated defect. Familial craniosynostosis syndromes are typically transmitted as an autosomal dominant trait resulting in disruption of the fibroblast growth factor receptor pathway. Familiarity with the characteristic head shapes resulting from craniosynostosis allows bedside diagnosis and differentiation from positional plagiocephaly. Because of the risks associated with untreated craniosynostosis, surgical treatment is usually undertaken soon after diagnosis. Current surgical methods include open calvarial reconstruction, minimally invasive strip craniectomy with use of postoperative molding helmet, minimally invasive strip craniectomy with spring implantation, and cranial distraction. Early referral to a pediatric craniofacial center allows all treatment options to be explored.

Keywords: craniosynostosis, minimally invasive, neurosurgery, pediatric, craniofacial, plagiocephaly

Pediatr Neurol 2015; 53: 394-401

Craniosynostosis is the premature fusion of one or more of the cranial sutures. Its incidence is estimated to be 1 in 2000-2500 live births.[1] It may be spontaneous, syndromic, or familial and can involve one or multiple cranial sutures. Familiarity with associated head shapes can allow bedside diagnosis and differentiation from positional plagiocephaly. Multiple surgical options for craniosynostosis currently exist, but early referral to a pediatric craniofacial center is needed to allow all options to be explored. This review seeks to familiarize pediatric neurologists with the nuances of craniosynostosis.

Only about 8% of patients are syndromic or familial.[2] Multiple syndromes have been described, each with their own associated facial features, systemic features, and relationship to hydrocephalus. The Table provides a review of some of the more common syndromes. The fibroblast growth factor receptor pathway is most frequently involved. This tyrosine kinase receptor pathway is active in osteoblast differentiation and maturation with mutations usually gain of function.[3] Craniosynostosis syndromes usually have an autosomal dominant inheritance pattern; however, penetrance is incomplete and expressivity is variable.[2] Bilateral coronal sutures are most affected, and there is often associated syndactyly and/or midface hypoplasia.

Most craniosynostosis cases are not syndromic or familial. Most frequently affected is the sagittal suture, and the cause is usually not known. Spontaneous mutation of a syndromic gene is possible.[2] Other risk factors may include: fetal constraint (nulliparity, plurality, macrosomia), low birth weight, preterm delivery, maternal valproate use, and shunted hydrocephalus.[4-6]

Classification

The cranial sutures are characterized as "major" or "minor." Major sutures are the sagittal, metopic, coronals, and lambdoids (Fig 1). Minor sutures include the squamosals, mendosals, intraoccipitals, and others. Premature closure of a major suture can result in cranial deformity and, potentially, overall cranial growth restriction with resultant increased intracranial pressure. When a suture closes early, the skull cannot grow perpendicular to the suture and

Article History:
Received March 19, 2015; Accepted in final form July 17, 2015

* Communications should be addressed to: Dr. Governale; Pediatric Neurosurgery; Nationwide Children's Hospital; 555 South 18th Street, Columbus, OH 43205, USA.
E-mail address: lance.governale@nationwidechildrens.org

0887-8994/$ – see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2015.07.006

TABLE.
Summary of Craniosynostosis Syndromes

Syndrome	Gene	Inheritance	Sutures Affected	Craniofacial Features	Systemic Features	Hydrocephalus Reported?
Apert	*FGFR2*	Autosomal dominant	Coronal	Midface hypoplasia, hypertelorism	Syndactyly of hands/feet, cervical vertebral fusion, hearing loss	Yes
Crouzon	*FGFR2*, *FGFR3*	Autosomal dominant	Coronal, sagittal, and/or lambdoid	Midface hypoplasia, exophthalmos, hypertelorism	Cervical vertebral fusion, hearing loss	Yes
Pfeiffer	*FGFR1*, F*GFR2*	Autosomal dominant	Coronal and/or sagittal, possible cloverleaf	Midface hypoplasia, hypertelorism	Broad thumbs/great toes, brachydactyly, syndactyly, cervical vertebral fusion, hearing loss	Yes
Muenke	*FGFR3*	Autosomal dominant	Coronal (unilateral or bilateral)	Midface hypoplasia, Hypertelorism, macrocephaly	Hearing loss	Yes
Saethre-Chotzen	*TWIST1*, *FGFR2*	Autosomal dominant	Coronal, lambdoid, and/or metopic	Parietal foramina	Syndactyly, heart defects	Yes
Antley-Bixler	*FGFR2*	Autosomal recessive	Coronal and/or lambdoid	Midface hypoplasia, choanal atresia	Joint contractures, radiohumeral synostosis	Yes

Sources: Jezela-Stanek A, Krajewska-Walasek M. Genetic causes of syndromic craniosynostoses. *Eur J Paediatr Neurol.* 2013; 17:221-224; and Online Mendelian Inheritance in Man. Available at: http://omim.org. Accessed May 29, 2015.

instead grows parallel to it. This is known as Virchow's law and predicts the shape of the cranial deformity. Although specific terminology for different head shapes exist (and can be confusing), it is more important to recognize the shape on examination than to know the term for it.

Sagittal craniosynostosis causes a long (anteroposterior) and narrow (transverse) head (Fig 2). There is frequently "bossing" or prominence of the forehead and occiput. The occipital prominence is sometimes termed a "bullet" because of associated narrowing. The anterior fontanel may be open or closed. This head shape is called scaphocephaly or dolichocephaly.

Bilateral coronal craniosynostosis causes a short (anteroposterior) and wide (transverse) head (Fig 3). The anterior fontanel may be open or closed. The discovery of this type of craniosynostosis should prompt a search for a syndromic diagnosis. This head shape is called brachycephaly.

Unilateral coronal craniosynostosis causes ipsilateral forehead flattening and elevation of the ipsilateral sphenoid wing and orbital roof (Fig 4). This elevation is termed a Harlequin eye deformity because, when viewed on a frontal x-ray, it resembles the shape of the similarly named masquerade mask. The nasal root is deviated toward the side of the closed suture. The anterior fontanel, which can

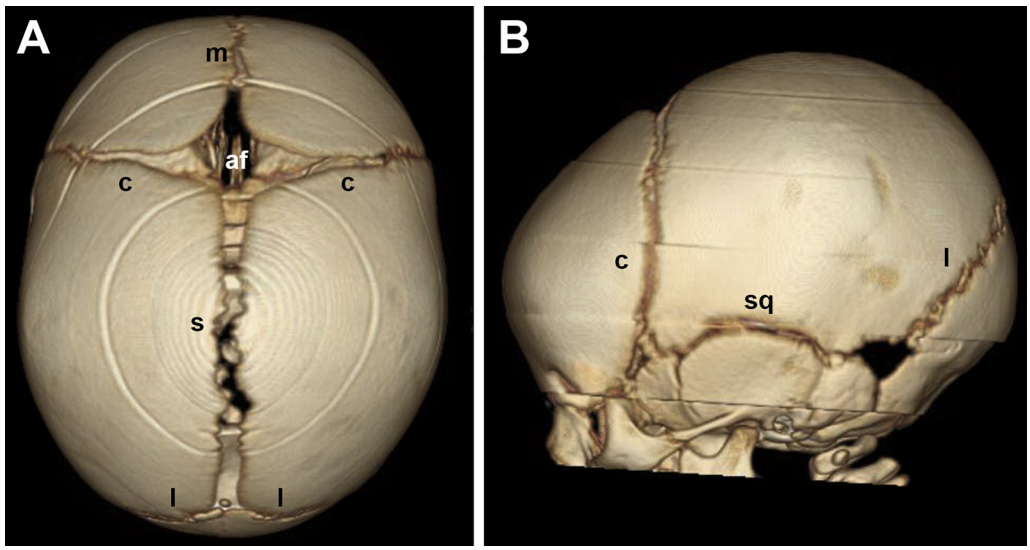

FIGURE 1.
Normal cranial sutures and skull shape. Top (A) and side (B) views of a three-dimensional computed tomography scan shows metopic (m), coronal (c), sagittal (s), lambdoid (l), and squamosal (sq) sutures as well as the anterior fontanel (af). (The color version of this figure is available in the online edition.)

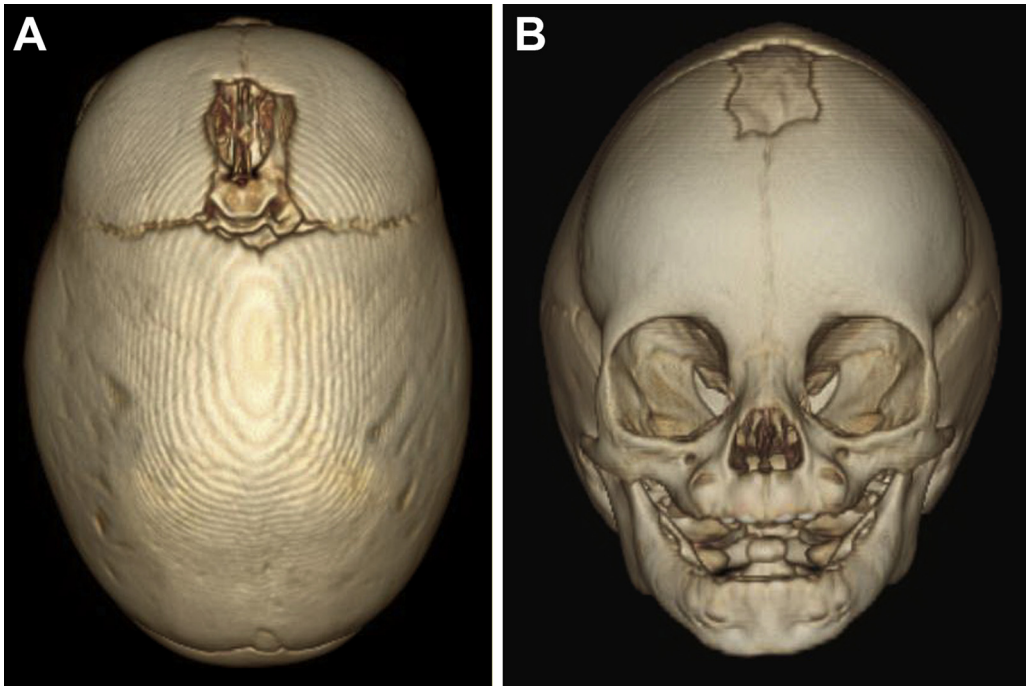

FIGURE 2.
Sagittal craniosynostosis. Top (A) and front (B) views of a three-dimensional computed tomography scan showing a skull long on the anteroposterior axis and narrow on the transverse axis. The sagittal suture is closed; the anterior fontanel is open in this case. (The color version of this figure is available in the online edition.)

be open or closed, may be displaced contralaterally. This head shape is called anterior plagiocephaly.

Metopic craniosynostosis causes a pointed and narrow forehead with a triangular shape when viewed from above (Fig 5). This head shape is called trigonocephaly. Hypotelorism may be present. Metopic craniosynostosis needs to be differentiated on examination from metopic ridging. The metopic suture normally closes within the first months of life. Age-appropriate closure may be associated with ridging over the suture line that does not require surgical correction. The key is that age-appropriate closure should not cause trigonocephaly.

Unilateral lambdoid craniosynostosis causes ipsilateral occipital flattening (Fig 6). The ipsilateral ear (and possibly

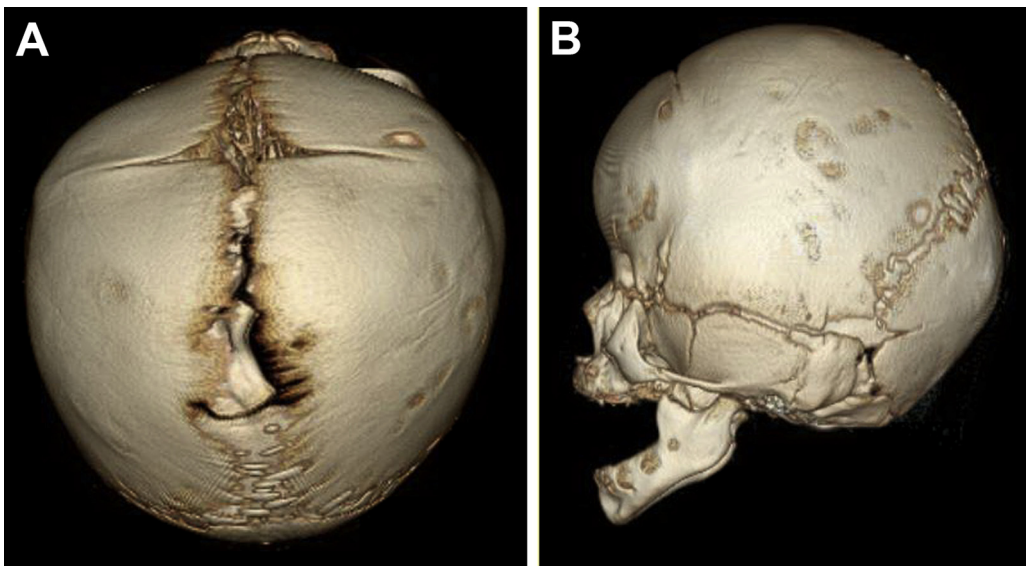

FIGURE 3.
Bilateral coronal craniosynostosis. Top (A) and side (B) views of a three-dimensional computed tomography scan showing a skull short on the anteroposterior axis and wide on the transverse axis. Both coronal sutures are closed; the anterior fontanel is open in this case. (The color version of this figure is available in the online edition.)

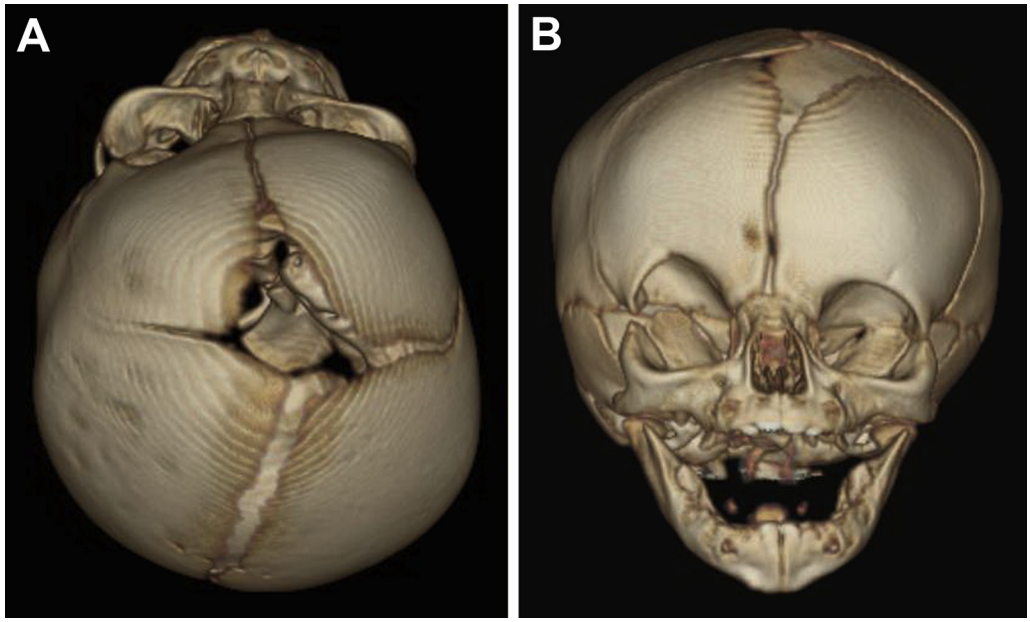

FIGURE 4.
Unilateral coronal craniosynostosis. Top (A) and front (B) views of a three-dimensional computed tomography scan showing closure of one coronal suture. The ipsilateral forehead is flattened, the anterior fontanel is displaced contralaterally, the ipsilateral orbital roof and sphenoid wing are displaced superiorly, and the nasal root is deviated toward the side of the closed suture. The superior displacement of the ipsilateral orbital roof and sphenoid wing is termed a Harlequin eye deformity because, when viewed on a frontal x-ray, it resembles the shape of the similarly named masquerade mask. (The color version of this figure is available in the online edition.)

forehead) is displaced posteriorly resulting in a trapezoidal head shape. The ipsilateral mastoid elongates drawing the ipsilateral ear inferiorly. Early closure of this suture is very rare, and the head shape is called posterior plagiocephaly.

The most common cranial deformity is positional plagiocephaly. It is important on examination to differentiate this entity from craniosynostosis because they have vastly different implications. Unlike craniosynostosis, positional

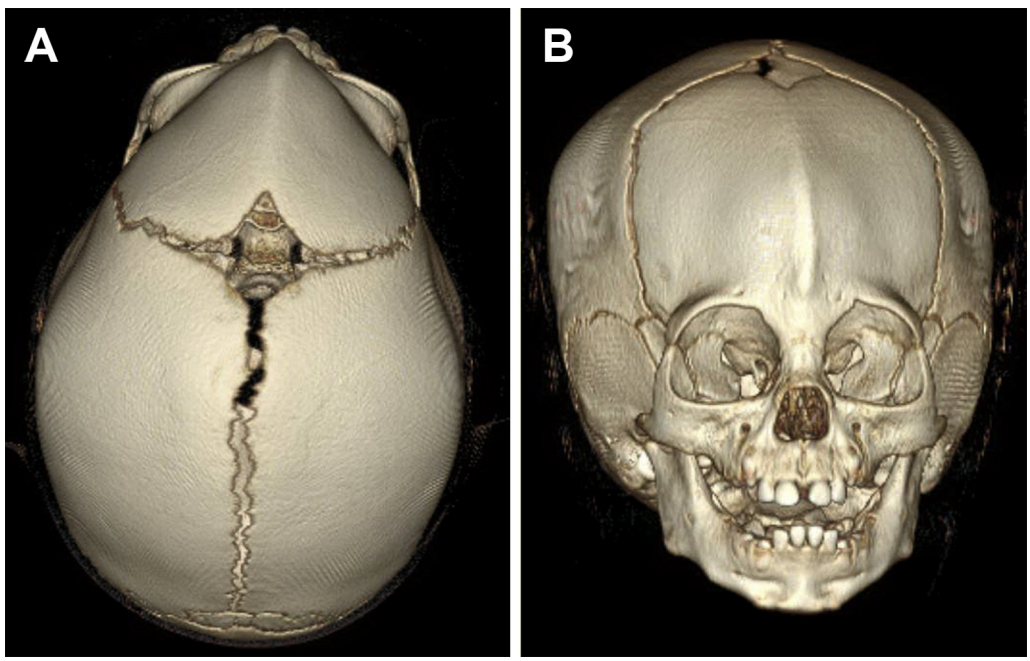

FIGURE 5.
Metopic craniosynostosis. Top (A) and front (B) views of a three-dimensional computed tomography scan showing a narrow, pointed forehead with a triangular shape when viewed from above. Hypotelorism is present. The metopic suture is closed; the anterior fontanel is open in this case. (The color version of this figure is available in the online edition.)

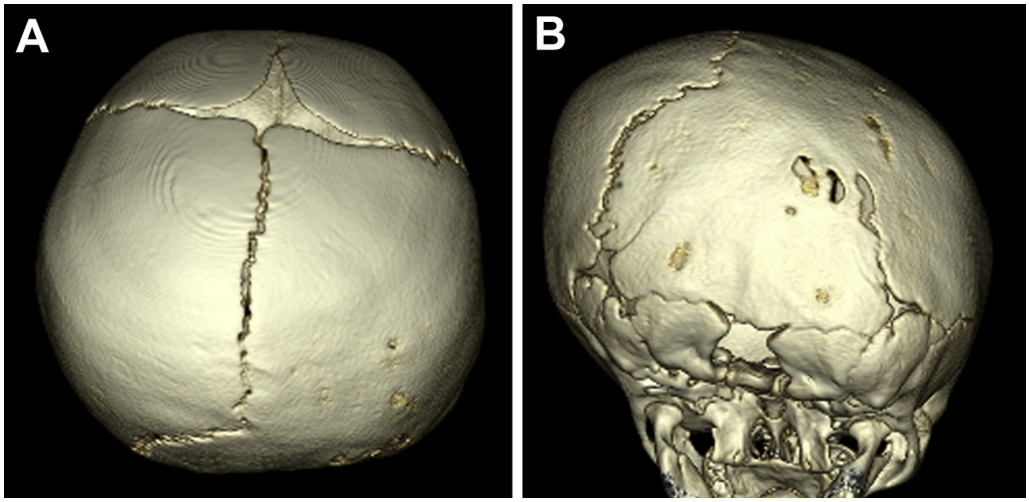

FIGURE 6.
Lambdoid craniosynostosis. Top (A) and back (B) views of a three-dimensional computed tomography scan showing closure of the right lambdoid suture. The skull has a trapezoidal shape with right posterior flattening and posterior displacement of the right forehead. If it were visible, the ear ipsilateral to the posterior flattening would be posteriorly displaced. Also seen is inferior elongation of the ipsilateral mastoid that would also displace the ipsilateral ear inferiorly. (The color version of this figure is available in the online edition.)

plagiocephaly is not associated with a risk of head growth restriction or increased intracranial pressure. As such, treatment is nonsurgical, usually with position changes, "tummy time," and physical therapy for any torticollis that may be present. The flattening is likely to diminish as the child obtains gross motor milestones and lies on the area less. The use of molding helmets is controversial.

The cranial deformity associated with positional plagiocephaly is predictable (Fig 7). When an infant lays his or her head in a particular spot repeatedly, that area of the head tends to flatten. Because the recommendation to decrease sudden infant death syndrome is for supine sleep, the flattened area is occipital. The flattened area is typically unilateral, where it must be distinguished from unilateral lambdoid craniosynostosis (a rare condition). In positional plagiocephaly, the ear (and possibly forehead) ipsilateral to the flattening is displaced anteriorly compared with the contralateral ear, resulting in a parallelogram shape. In unilateral lambdoid craniosynostosis, the ear (and possibly forehead) ipsilateral to the flattening is displaced posteriorly compared with the contralateral ear, resulting in a trapezoid shape. The ipsilateral mastoid elongation and inferior displacement of

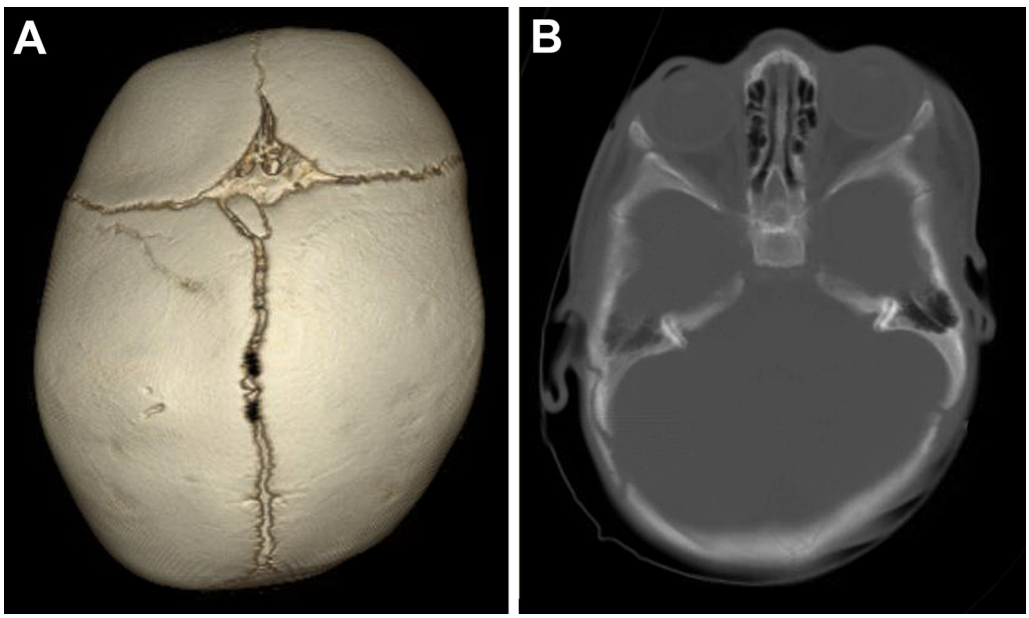

FIGURE 7.
Positional plagiocephaly. Top view (A) of a three-dimensional computed tomography scan (done for other reasons) showing a skull with a parallelogram shape. There is right posterior flattening and anterior displacement of the right forehead. Axial computed tomography scan (B) showing anterior displacement of the ear ipsilateral to the posterior flattening. The sutures are open. (The color version of this figure is available in the online edition.)

the ipsilateral ear seen in unilateral lambdoid craniosynostosis is not seen in positional plagiocephaly. Symmetric bilateral flattening can mimic bilateral coronal craniosynostosis and may require imaging to make a distinction.

The diagnosis of craniosynostosis can often be made with a clinical examination of the head shape. In cases of diagnostic uncertainty or for confirmation, radiographic imaging can be acquired. A simple initial method is a skull x-ray series consisting of an anteroposterior, Townes, and two lateral views. If skull x-rays are not definitive, a noncontrast head computed tomography scan with three-dimensional reconstructions of the bone windows should be obtained.

Natural history

Left untreated, craniosynostosis can result in worsened cranial deformity and, potentially, overall cranial growth restriction with resultant increased intracranial pressure (ICP). The deformity may lead to psychosocial issues as the child interacts with peers during development. In addition to cranial growth restriction, increased ICP may develop in the syndromic patients because of venous outflow stenosis at the jugular foramina, elevated central venous pressures from obstructive sleep apnea, and hydrocephalus from aqueductal stenosis or fourth ventricular outflow obstruction.[7] These comorbidities result in a higher risk of elevated ICP in syndromic cases and are themselves treated when possible with continuous positive airway pressure and endoscopic third ventriculostomy. Cerebrospinal fluid shunts are avoided whenever possible because of the risk of slit ventricle syndrome and hemorrhage in this patient population.

Although the risk of elevated ICP is more controversial in the nonsyndromic cases, there are studies demonstrating it. Several studies reported in the 1990s showed an estimated incidence of between 4.5% and 24%.[8] A 2014 study from Oxford found a 44% incidence of increased ICP as measured by invasive ICP monitoring among 39 patients with isolated nonsyndromic sagittal craniosynostosis.[8] A 2012 study by the same group found high or borderline ICP in five of seven patients with isolated nonsyndromic unilateral coronal craniosynostosis.[9]

Intracranial pressure is usually monitored by noninvasive means. These may include surveillance for classical symptoms of elevated ICP (e.g., headache, nausea, emesis, upgaze palsy), measurement of the orbitofrontal circumference, palpation of the fontanel (if present), funduscopy to assess for papilledema, and/or optical coherence tomography to measure the thickness of the retinal nerve fiber layer. Cranial imaging may show effacement of the cisterns or the convexity sulci, a secondary Chiari malformation, and/or a "copper-beaten" appearance to the skull (resulting from pressure-related gyral imprinting on the inner table of the skull). Lumbar puncture and/or use of a cranial pressure monitor can be considered in cases of diagnostic uncertainty.

Treatment

Because of the risks associated with untreated craniosynostosis, it is usually treated surgically soon after diagnosis to unlock and reshape the bones. There are currently four surgical methods: open calvarial reconstruction, minimally invasive strip craniectomy with use of postoperative molding helmet, minimally invasive strip craniectomy with spring implantation, and cranial distraction. One group has advocated the use of a molding helmet without surgery for sagittal craniosynostosis,[10] but this is highly controversial and not recommended.[11]

The traditional open calvarial reconstruction involves removal, reshaping, and replacement of the deformed portions of the bony convexity, including the fused suture. For sagittal and lambdoid craniosynostosis, the posterior half of the convexity is reshaped, usually from the coronal sutures

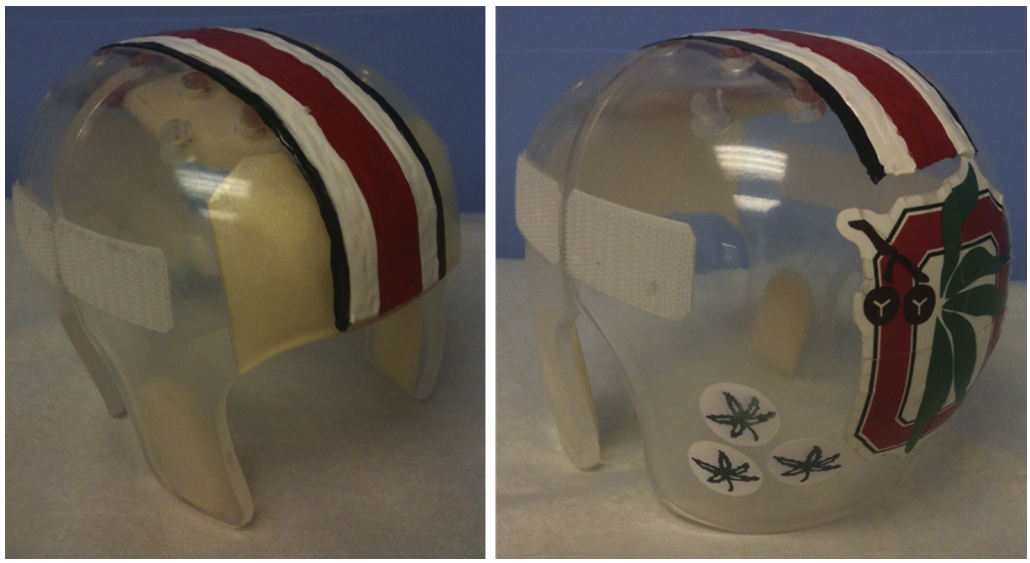

FIGURE 8.
Craniosynostosis molding helmet. The orthosis consists of a rigid outer shell and customizable inner foam padding. The foam contacts skull regions where less growth is desired. Open areas are positioned over skull regions where more growth is desired. In this way, overall skull growth is strategically directed. The helmet may be decorated in an attempt to reduce social stigma associated with medical orthoses. This helmet has been well-adorned by the child's parents. (The color version of this figure is available in the online edition.)

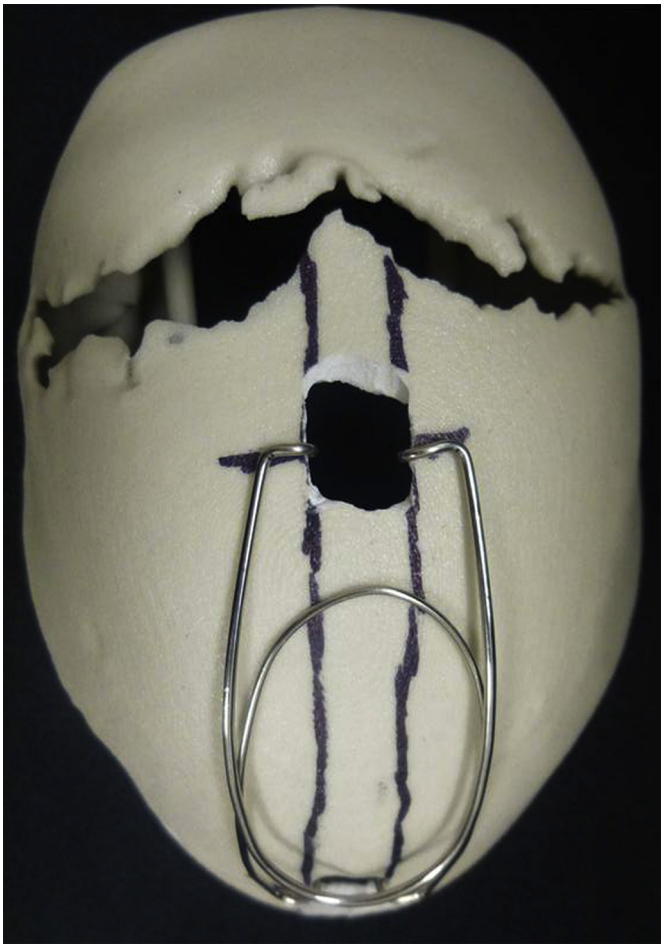

FIGURE 9.
Cranial expander spring. The stainless steel springs are implanted after the fused suture is resected and then removed 3 months later. The amount of distraction force selected is based on the patient's age, bone thickness, and deformity severity. (The color version of this figure is available in the online edition.)

to the inion. For coronal and metopic craniosynostosis, the anterior half of the convexity is reshaped, usually from the coronal sutures to and including the orbital rim (fronto-orbital advancement). The lateral extent on both sides is typically the skull base. A bicoronal incision from ear to ear provides access. The surgery lasts approximately 4 hours and often a blood transfusion is required. Postoperatively, the child is typically observed in the intensive care unit overnight then spends approximately 3 days on the regular neurosurgical ward. Periorbital edema usually causes the eyes to swell closed and should reopen before discharge. To decrease surgical risk, the operation is generally performed after the child reaches 6 months of age. Patients are unlikely to experience intracranial pressure sequelae of craniosynostosis before then. Open calvarial reconstruction is frequently performed in conjunction with a craniofacial plastic surgeon. Because reshaping occurs at the time of surgery, no further adjuncts are required.

The two minimally invasive options involve excision of only the fused suture to unlock the bones. Reshaping then occurs postoperatively with the assistance of either a cranial molding helmet[12,13] or implanted custom springs.[14,15] The helmet (Fig 8) consists of a rigid outer shell and customizable inner foam padding. The foam contacts skull regions where less growth is desired. Open areas are positioned over skull regions where more growth is desired. In this way, overall skull growth is strategically directed. Stainless steel cranial expander springs (Fig 9) are implanted after the fused suture is resected and then removed 3 months later. The amount of distraction force selected is based on the patient's age, bone thickness, and deformity severity. The bony excision is endoscope-assisted and done via one or two small incisions depending on the involved suture. The surgery lasts approximately 1 hour; a blood transfusion is only rarely required. Postoperatively, the child typically is observed overnight on the regular neurosurgical ward then is ready for discharge. Usually, there is no periorbital edema. The postoperative reshaping

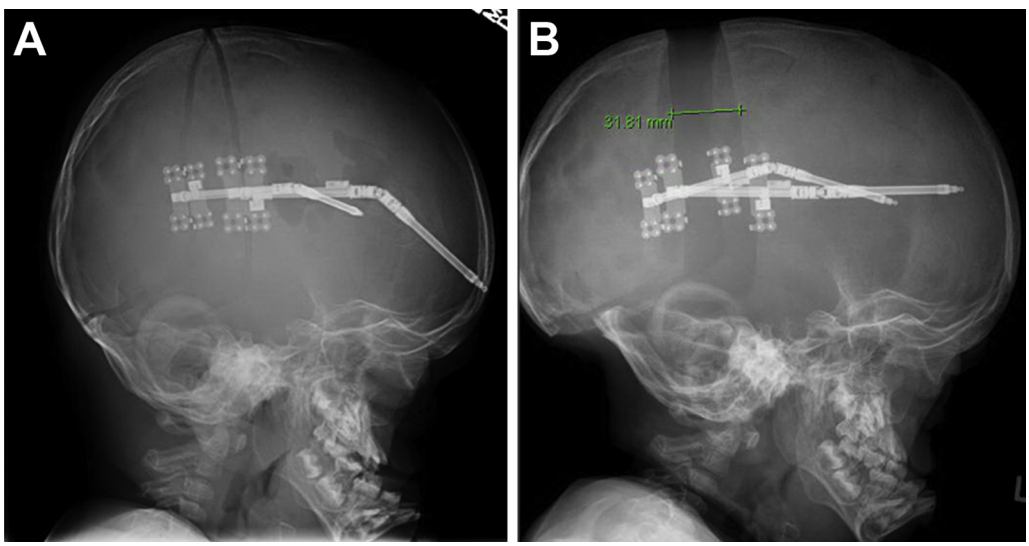

FIGURE 10.
Cranial distractors. In the case of pansynostosis with delayed skull growth but normal shape, the surgical goal is creation of intracranial volume. A biparieto-occipital craniotomy is performed and distractors implanted spanning the bone cut (A). Each side of the distractor is fixed to the bone. At the rate of 1 mm per day, the sides are separated by turning the screw that connects them using the posts that project through the skin. After 30 days, distraction osteogenesis results in 3 cm of new bone (B). The posts are then removed and the skin closed in the office. Three months later, the distractors are removed.

adjuncts, however, do have some drawbacks. The helmet must be worn 23 hours per day often until the child's first birthday and requires frequent visits to an orthotist. The springs require a second surgery 3 months later for removal.

The fourth surgical option is cranial distraction. In the case of pansynostosis with delayed skull growth but normal shape, the surgical goal is creation of intracranial volume. A biparieto-occipital craniotomy is performed and distractors implanted that span the bone cut (Fig 10). Each side of the distractor is fixed to the bone. At the rate of 1 mm per day, the sides are separated by turning the screw that connects them using the posts that project through the skin. After 30 days, distraction osteogenesis results in 3 cm of new bone. The posts are then removed and the skin closed in the office. Three months later, the distractors are removed. Distraction may also be used anteriorly to advance the anterior skull base and midface as a unit in a procedure called monobloc.

The decision of which procedure to perform is the result of a discussion between the surgeon and the family, because each has its positive and negative attributes. Key to being able to offer all options, however, is early diagnosis and referral. The age window to perform the helmet endoscopic option is ideally 2.5-3.5 months of age, although some will attempt the procedure slightly later. The age window for the spring endoscopic option is ideally 3-6 months of age.

Syndromic and multiple suture cases are most frequently treated with open calvarial reconstruction, but application of the minimally invasive options to this patient population is being investigated.[16,17]

Conclusions

Craniosynostosis may present in many different forms, but familiarity with associated head shapes can allow bedside diagnosis and differentiation from positional plagiocephaly. Multiple surgical options for craniosynostosis currently exist, but early referral to a pediatric craniofacial center is needed to allow all options to be offered.

The author would like to thank Greg Pearson, MD, for the cranial expander spring image and Mark Proctor, MD, for the lambdoid craniosynostosis images.

References

1. Di Rocco F, Arnaud E, Renier D. Evolution in the frequency of nonsyndromic craniosynostosis. *J Neurosurg Pediatr*. 2009;4:21-25.
2. Lajeunie E, Crimmins DW, Arnaud E, Renier D. Genetic considerations in nonsyndromic midline craniosynostoses: a study of twins and their families. *J Neurosurg*. 2005;103:353-356.
3. Su N, Jin M, Chen L. Role of FGF/FGFR signaling in skeletal development and homeostasis: learning from mouse models. *Bone Research*. 2014;2:1-24.
4. Lajeunie E, Barcik U, Thorne JA, El Ghouzzi V, Bourgeois M, Renier D. Craniosynostosis and fetal exposure to sodium valproate. *J Neurosurg*. 2001;95:778-782.
5. Sanchez-Lara PA, Carmichael SL, Graham Jr JM, et al. Fetal constraint as a potential risk factor for craniosynostosis. *Am J Med Genet A*. 2010;152A:394-400.
6. Singh RP, Dhariwal D, Bhujel N, et al. Role of parental risk factors in the aetiology of isolated non-syndromic metopic craniosynostosis. *Br J Oral Maxillofac Surg*. 2010;48:438-442.
7. Spruijt B, Joosten KF, Driessen C, et al. Algorithm for the management of intracranial hypertension in children with syndromic craniosynostosis. *Plast Reconstr Surg*. 2015;136:331-340.
8. Wall SA, Thomas GP, Johnson D, et al. The preoperative incidence of raised intracranial pressure in nonsyndromic sagittal craniosynostosis is underestimated in the literature. *J Neurosurg Pediatr*. 2014;14:674-681.
9. Eley KA, Johnson D, Wilkie AO, Jayamohan J, Richards P, Wall SA. Raised intracranial pressure is frequent in untreated nonsyndromic unicoronal synostosis and does not correlate with severity of phenotypic features. *Plast Reconstr Surg*. 2012;130:690e-697e.
10. Sood S, Rozzelle A, Shaqiri B, Sood N, Ham SD. Effect of molding helmet on head shape in nonsurgically treated sagittal craniosynostosis. *J Neurosurg Pediatr*. 2011;7:627-632.
11. Proctor MR, Rogers GF. Helmets and synostosis. *J Neurosurg Pediatr*. 2012;9:680-681. author reply 681-682.
12. Jimenez DF, Barone CM. Endoscopic techniques for craniosynostosis. *Atlas Oral Maxillofac Surg Clin North Am*. 2010;18:93-107.
13. Berry-Candelario J, Ridgway EB, Grondin RT, Rogers GF, Proctor MR. Endoscope-assisted strip craniectomy and postoperative helmet therapy for treatment of craniosynostosis. *Neurosurg Focus*. 2011;31:E5.
14. Lauritzen CG, Davis C, Ivarsson A, Sanger C, Hewitt TD. The evolving role of springs in craniofacial surgery: the first 100 clinical cases. *Plast Reconstr Surg*. 2008;121:545-554.
15. van Veelen ML, Mathijssen IM. Spring-assisted correction of sagittal suture synostosis. *Childs Nerv Syst*. 2012;28:1347-1351.
16. Jimenez DF, Barone CM. Multiple-suture nonsyndromic craniosynostosis: early and effective management using endoscopic techniques. *J Neurosurg Pediatr*. 2010;5:223-231.
17. Jimenez DF, Barone CM. Bilateral endoscopic craniectomies in the treatment of an infant with Apert syndrome. *J Neurosurg Pediatr*. 2012;10:310-314.