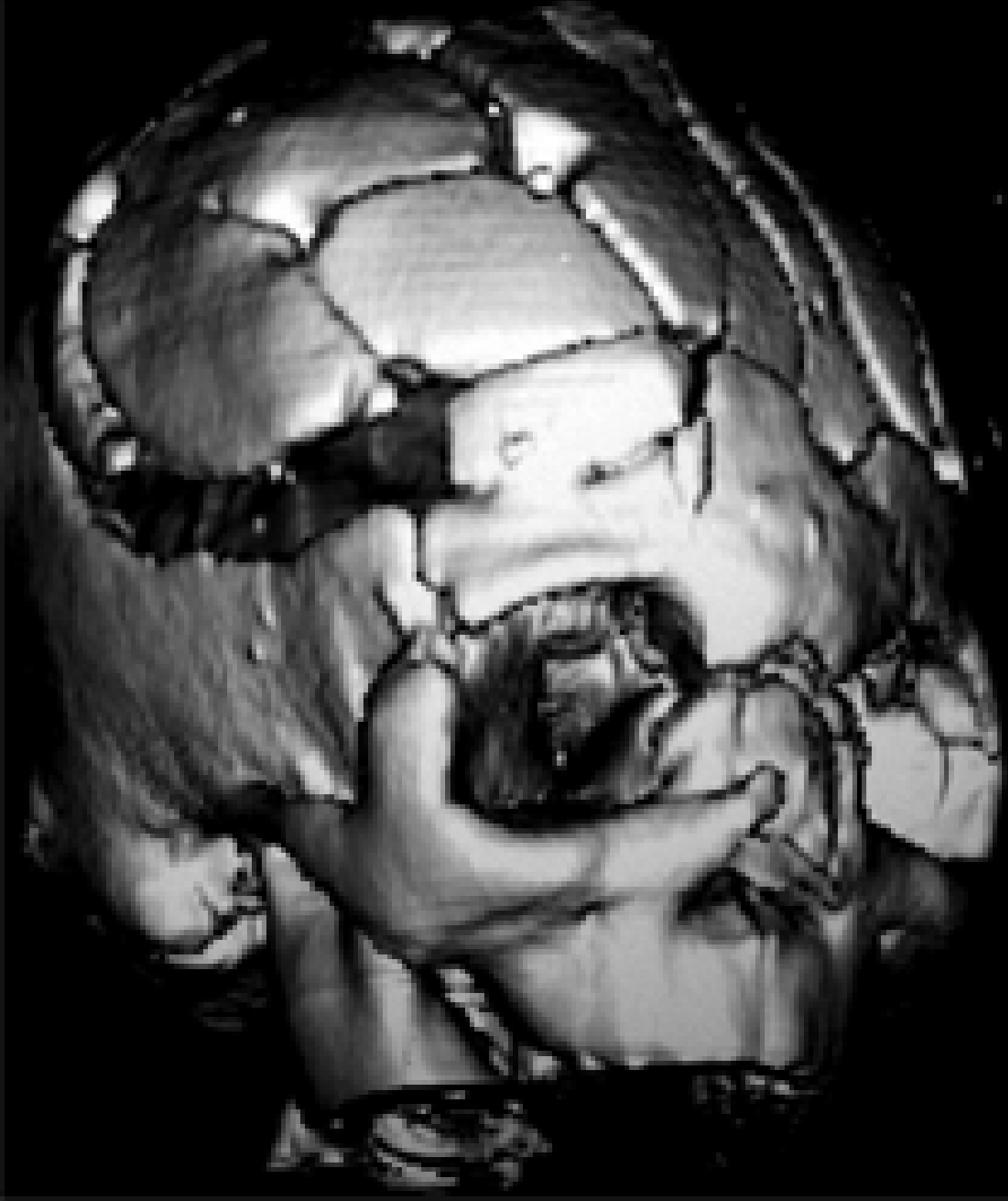

Introduction

Craniofacial deformity

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Interest in abnormal head shape has been recorded since the time before Hippocrates. He, however, is credited for noting fused sutures in malformed skulls. More intense investigation of this subject did not follow until the late 18th and mid-19th centuries with contributions by von Sömmerring[10] and Virchow.[9] Irregularities in skull shape and associated fused sutures were attributable to inflammation of the skull and soft tissues; in particular, malaria and syphilis were thought to play a role in this condition. As time has passed, clearly our understanding of the pathology and the treatment of craniosynostosis has improved greatly. Although the final pathology of this condition still eludes us, more effective treatment strategies have been developed with successive generations.

The first surgical treatment of craniosynostosis was performed in the 1890s by Lane[5] and Lannelongue[6] but the outcomes were unfavorable. In the early 1950s and onward, the techniques used by these men were supplanted as conceptions of how to treat this condition evolved. Strip craniectomies were largely overtaken by procedures that more adequately reshaped the deformed skull bone, repositioning it, as well as removing the fused suture. As the entirety of the skull deformity became more scrutinized, it was clear that not only were there hypoplastic deformities, but compensatory skull abnormalities that had developed as a result of continued growth of the brain. Initially, it was recognized that there is a flattened frontal bone skull deformity associated with conditions like unilateral coronal synostosis. Subsequently, it was apparent that there was also contralateral frontal bossing evident in this condition, and bilateral, oriented operative procedures were developed.[3] In addition, it was recognized that the cranial vault influenced the orbital structures, and procedures that included correction of upper facial deformities (orbital rims) were added to the comprehensive management of the conditions of craniosynostosis, in appropriate situations. Further analysis by colleagues recognized that there were not only bilateral abnormalities, but abnormalities in height, abnormalities in the posterior skull, and abnormalities in the base of the skull in both with nonsyndromic and syndromic craniosynostosis.[2] Strategies needed to be developed to correct these abnormalities completely and reduce residual deformities.

The real problem, of course, all along, has been an inability to control for growth and adequately correct the abnormal basal skull. These problems are still vexing us today. Frustration with these techniques' inability to control such factors resulted in a belief that it is futile to attempt to obtain an absolutely normal-looking skull by surgical means early in infancy. Instead, we should delay surgery until a later period so that bone can be adequately fixed in normal positions and better shaping of the skull can be achieved. This strategy would not have gained much support were it not believed that there were no significant neurological sequelae due to untreated craniosynostosis, except in a minority of patients.

Renier and Marchac[8] are to be credited for their investigative studies that demonstrated that there are neurological consequences of delaying or withholding of treatment of craniosynostosis. However, because many patients in the nonsyndromic cases were reportedly unaffected by this condition neurologically, it was popular to state that the operative procedures for craniosynostosis were basically cosmetic in the vast majority of patients. Delays in surgery were recommended.[4] These recommendations, too, however, had some problems. Although it is true that many children with nonsyndromic craniosynostosis have an IQ that is virtually normal, anecdotally it was found that there are many other children who, despite having a normal IQ, were experiencing great difficulty in learning in school. A subsequent investigation found that many more children, in fact, have learning disabilities that are nearly unrecognized because their IQ scores are normal. The subtle neurological sequelae of craniosynostosis are now appreciated, and the timing of surgery in the treatment of craniosynostosis is again being reevaluated.

It is clear from most standpoints that early surgery yields improved results in terms of overall skull development and, presumably, brain function. Clearly, this discussion represents the new frontier in the management of craniosynostosis. There have been numerous technologi-

cal advances that have aided this concept; in particular, endoscopic strip craniectomy procedures have emphasized earlier treatment of patients, which, we believe, is admirable. The concern with this approach, however, is that endoscopic approaches do not comprehensively correct the irregularities in the skull as rapidly as comprehensive procedures. Despite the earlier surgery, the delay in completely resolving the compression on the brain may contribute to delayed neurological development as much as nontreatment; however, this relationship has yet to be determined. Interesting observations have also been made regarding intracranial volume in patients with craniosynostosis. The usual interpretation is that the pathology of craniosynostosis, including intracranial volume, will be reduced if there is a fused suture due to the constricting bone capsule for brain development, but this has not been found to be the case consistently, at least in sagittal synostosis (other forms of craniosynostosis have not yet been completely analyzed). In fact, in sagittal synostosis, patients begin with a relatively normal intracranial volume,[1] but as the condition is left untreated for months, and perhaps even years,[7] intracranial volume continues to enlarge beyond its normal volume. Quantitative CT scanning has revealed that brain volume actually decreases over time, suggesting that there may be an associated pathology, in addition to the bone abnormality (possibly a form of occult hydrocephalus), that is active in the development of some forms of craniosynostosis.

Clearly, the mandate at this time is to help define the neurological outcomes in patients with craniosynostosis, the optimal timing of surgery, and the optimal surgical management of this condition. Now that we have objective measures to assist in this process, as well as a better understanding of the basic pathology, a more appropriate and effective management strategy can be developed. Potential neurological sequelae should be the focus of attention.

We are indebted to the many investigative and surgical pioneers who have brought forth many advancements in the conceptions and treatment of craniosynostosis over the last 200 years.

We hope you enjoy this issue of *Neurosurgical Focus* on craniofacial deformity, which includes 7 articles that address some of the issues that are of ongoing importance in our field. *(DOI: 10.3171/2011.6.FOCUS11171)*

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Need for standard outcome reporting systems in craniosynostosis

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Craniosynostosis is the premature fusion of one or more cranial sutures. When a cranial suture fuses prematurely, skull growth is altered and the head takes on a characteristic pathological shape determined by the suture(s) that fuses. Numerous treatment options have been proposed, but until recently there were no parameters or guidelines of care. Establishing such parameters was an important step forward in the treatment of patients with craniosynostosis, but results are still assessed using radiographic measurements, complication rates, and ad hoc reporting scales. Therefore, clinical outcome reporting in the treatment of craniosynostosis is inconsistent and lacks methodological rigor.

Today, most reported evidence in the treatment of craniosynostosis is level 5 (expert opinion) or level 4 (case series) data. Challenges in obtaining higher quality level 1 or level 2 data include randomizing patients in a clinical trial as well as selecting the appropriate outcome measure for the trial. Therefore, determining core outcome sets that are important to both patients and health care professionals is an essential step in the evolution of caring for patients with craniosynostosis.

Traditional clinical outcomes will remain important, but patient-reported outcomes, such as satisfaction, body image, functional results, and aesthetic outcomes, must also be incorporated if the selected outcomes are to be valuable to patients and families making decisions about treatment. In this article, the authors review the most commonly used tools to assess craniosynostosis outcomes and propose a list of longitudinal parameters of care that should be considered in the evaluation, diagnosis, and treatment evaluation of a patient with craniosynostosis.
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Key Words • craniosynostosis • cranial suture • patient-reported outcome • standardized parameter

Craniosynostosis is the premature fusion of one or more cranial sutures[29] and affects 1 in 2000 to 2500 live births annually worldwide.[29] Fusion of a cranial suture results in a predictable pattern of cranial dysmorphology. Craniosynostosis can occur in association with more than 130 different syndromes, such as Crouzon, Apert, or Pfeiffer syndromes, but it is nonsyndromic (sporadic) in most patients. Those with craniosynostosis may have not only calvarial dysmorphology, but also midface hypoplasia, hydrocephalus, deafness, blindness, mental retardation, heart and lung abnormalities, and extremity anomalies.[31]

The diagnosis, management, and treatment of craniosynostosis can be complex. While recognizing that adequate care can be provided outside of craniofacial centers, given the complex nature of the disorder, optimal care may best be accomplished by teams of interdisciplinary specialists who are dedicated to the care of patients with craniofacial anomalies and see a sufficient number of affected patients to understand the management complexities. Interdisciplinary team care, such as that found in craniofacial centers, has been practiced for many years in treating children with cleft lip and cleft palate and complex craniofacial anomalies. For the management of craniosynostosis, these interdisciplinary teams may be composed of professionals from various disciplines: from anesthesiology to craniofacial surgery, hand surgery, ophthalmology, or orthodontics, to cite only a few.

Coordinated care is necessary given the complexity of the pertinent medical, surgical, and psychosocial factors. While early management can lead to better outcomes (for example, fewer operations and lower costs), the continuity of care in a team setting is essential because outcomes are measured throughout the child's growth and development. Until recently, there was no consensus on the parameters of care in patients with craniosynostosis. In a recent Centers

Abbreviations used in this paper: HRQOL = health-related quality of life; OSA = obstructive sleep apnea; OMERACT = Outcome Measures in Rheumatology; PRO = patient-reported outcome; QALY = quality-adjusted life year; QOL = quality of life; SF-36 = 36-Item Short Form Health Survey; WISC = Wechsler Intelligence Scale for Children; WPPSI-III = Wechsler Preschool and Primary Scale of Intelligence Test, Third Edition.

for Disease Control and Prevention–sponsored meeting, McCarthy et al. (unpublished data, 2011) defined the parameters of care for patients with craniosynostosis. While this consensus meeting was an important step forward in the treatment of patients with craniosynostosis, it still did not provide core outcome sets, which are important to both patients and health care professionals.

Outcome measures in craniosynostosis must be valid and consistent to allow cross-study comparisons and to facilitate meta-analyses. Members of the OMERACT group were among the first to recognize this need, and they developed core outcome sets for specific conditions to improve the quality and value of clinical trials and longitudinal research.[30] The OMERACT group used a "data driven, iterative alignment process" to select measures that satisfy the criteria of the OMERACT filter—truth, discrimination, and feasibility. While traditional clinical outcomes will remain important in the treatment of patients with craniosyostosis, core outcome sets that include patient-reported data, such as satisfaction, body image, functional results, and aesthetic outcomes, must be developed to collect higher level data that is meaningful to both patients and physicians.

In this article, we address the challenges in evaluating treatment outcomes as well as the lack of standardized instruments to assess the outcomes of treatment in patients with craniosynostosis, especially from the patient's perspective. We also describe a variety of tools, scales, and indices that can be used to create an evaluation algorithm specific to patients with craniosynostosis.

Evaluation Before Treatment

Evaluation and assessment of the degree of craniofacial dysmorphology, associated systemic findings, and psychosocial impact of the disease process on patients and their families are essential before beginning a treatment process. Currently, there are no validated instruments to measure the impact of craniofacial dysmorphology on a patient's psychosocial function. Instead, numerous groups have compiled age- and sex-specific normative anthropometric data sets to evaluate the dimensions of a patient's head and face.[18] By comparing the measurements of an affected patient with the values in a normative database, one can, for example, determine the number of millimeters or degrees of difference in an affected patient's brow position or basicranial angle, respectively. While careful and precise measurement of a patient's craniofacial differences is important and cannot be achieved without these traditional measures, these same tools do not calculate the impact that craniosynostosis and its treatments have on a patient's QOL. Below, we review common instruments currently used to evaluate patients with craniosynostosis.

Radiographic Assessment

Cephalography and CT have revolutionized surgical planning and follow-up. These radiological studies allow us not only to assess bony shape and position, but also to plan surgical treatment and to measure our surgical movements.[17] Two-dimensional and 3D cephalometric landmarks are typically used to assess the success of our operations (Table 1).

Brain MR imaging, PET, and transcranial ultrasonography are performed selectively in patients with craniosynostosis. Some surgeons have speculated that premature cranial suture fusion leads to alterations in cerebral blood flow, which in turn result in cognitive, speech, language, and/or behavioral problems, but this suggestion remains a point of controversy.[4,5,14–16,20,22,24–26,32,33] Others have speculated that reduced intracranial volume and/or elevated intracranial pressure impair brain development.[9] However, Hill et al.[12] recently demonstrated that intracranial volume constraint was not responsible for alterations in brain function. Radiographic assessment of patients with craniosynostosis remains an important step in treatment planning and provides a baseline from which to measure surgical outcomes, but imaging lacks the responsiveness necessary to determine how an anatomical finding impacts a patient's well-being. Furthermore, the millimeters of movement or degrees of rotation that we measure on our postoperative radiographs provide little insight into the enormous impact that our operations have on patients with craniosynostosis.

Otolaryngology Assessment

Children with craniofacial anomalies often exhibit airway obstructions, and a high index of suspicion should be maintained for OSA throughout childhood and adolescence. Patients with OSA usually, but not always, present with suggestive signs and symptoms, such as loud breathing, snoring, poor feeding, hyperactivity, hypersomno-

TABLE 1: Craniometric measurements

Angle	Distance	Index	Vol
posterior fossa deflection angle	temporomandibular joint displacement	cranial index	hypopharynx/oropharynx cavity vol
petrous ridge angle	maxillary & mandibular dimensions	trigonocephaly severity index	nasopharynx/nasal cavity vol
mandibular plane–Frankfort horizontal angle			
mandibular plane–sella nasion angle*			

* See Hwang and Kim, 2010.

lence, behavorial problems, and poor quality of life[2] or failure to thrive.[6,21,23] However, OSA can be insidious and must be ruled out when any patient with craniosynostosis is evaluated. While there are a variety of traditional ways to assess OSA (Table 2), recently Bannink et al.[3] developed the first OSA-specific QOL questionnaire (OSA-18) to address the impact of OSA in patients with syndromic craniosynostosis.

Children with syndromic craniosynostosis should also be assessed for feeding difficulties. Altered orofacial anatomy as well as CNS, cardiovascular, respiratory, and intestinal abnormalities may contribute to feeding disorders. Initial evaluations should focus on the safety of feeding and assess the aspiration risk. The most commonly used tests are listed in Table 2.

An important aspect of caring for patients with craniosynostosis is the diagnosis, treatment, and rehabilitation of auditory impairment. Procedural assessments are listed in Table 2. Interventions range from hearing aids to middle ear reconstruction or vestibular therapy. While attention should be directed at the development of speech and communication skills, we need new instruments to understand how a patient with craniosynostosis and hearing impairment is affected. For example, is the psychological well-being of a girl with deafness more affected than a boy's? Do children develop maladaptive strategies to cope with their hearing impairment? How do our treatments affect a patient's activity, participation, satisfaction, and HRQOL? Does early correction of unilateral hearing impairment lead to more substantial improvements in QALYs?

Ophthalmological Assessment

Ocular and visual health, maintenance, and restoration are important parts of the overall care of a child or adolescent with isolated and syndromic craniosynostosis. Common abnormalities include orbital hypertelorism, telecanthus, abnormal slant of the palpebral fissures due to superior displacement of the medial canthi, ptosis, epiphora, proptosis, and nasolacrimal apparatus abnormality, such as duct obstruction and punctal anomalies. Many of these manifestations are disfiguring and can threaten vision as a result of corneal exposure and globe luxation. Patients with syndromic craniosynostosis often have decreased vision that can be attributed to a variety of causes. Amblyopia is common in patients with syndromic craniosynostosis, occurring in up to 40%, and is less common in those with the nonsyndromic form of the disease.[28] Patients with the syndromic variety also have a much higher prevalence of strabismus than do those with nonsyndromic craniosynostosis.[27]

While early assessment and appropriate correction of vision impairment are essential, it is also important to understand how impaired vision affects a patient's day-to-day activities such as dressing, eating, writing, communications or interactions with others, travel, mood, and social relationships. In 2008 Cochrane et al.[7] first identified the different aspects that needed to be addressed to develop a complete questionnaire to evaluate the impact of vision impairment in children (ages 8–18 years), based on information from vision-impaired children and their support providers. These authors interviewed visually impaired children and their families, teachers, and special instructors to include all perspectives. Interestingly, their study showed that parents and children put more emphasis on communication, social interactions and orientation, and mobility, whereas teachers considered social skills and academic performance to be more important. Further, specialist instructors demonstrated greater concern for academic participation and instruction than for social skills. Cochrane and colleagues[8] further validated their questionnaire in 2011. Although it only concerns children from 8 to 18 years old with different causes of impaired vision (albinism, congenital conditions, or juvenile-onset degenerative conditions) and it does not address treatment options, it does underline the major differences between families and professionnals about a patient's needs and concerns.[7,8] Wen et al.[34] also showed that preschool children with strabismus had a significantly worse QOL than unaffected children, confirming what was long suspected.

Dental and Orthodontics Assessment

Oral health is a critical part of overall health and is especially important for patients with craniosynostosis. The care of individuals with special health care needs, including craniosynostosis, involves specialized knowl-

TABLE 2: Tests used in the assessment of OSA, feeding difficulties, and auditory impairment

OSA	Feeding Difficulties	Auditory Impairment
hypopharynx/oropharynx vols	videofluoroscopy	audiometry
nasopharynx/nasal cavity vols	endoscopic swallow	tympanometry w/ acoustic reflexes
polysomnography	microlaryngoscopy	evoked otoacoustic emission testing
rhinomanometry	esophagoscopy	auditory brainstem testing
nasoendoscopy	esophageal manometry	vestibular testing
flexible endoscopy	pH probe	CT
flexible or rigid bronchoscopy	gastrointestinal endoscopy	MRI
microlaryngoscopy		
sleep fluoroscopy		
sleep endoscopy		
cine MRI		

edge, training, increased awareness, and innovative solutions. Since craniosynostosis can lead to facial growth disturbances, the orthodontist plays an important role in determining the type and timing of orofacial interventions as well as performing the necessary presurgical preparations and providing postsurgical care. From studies performed in children with orofacial clefting, we realize that poor oral health significantly impacts social functioning.[19] Boys with orofacial clefts experience a lower QOL than girls. Moreover, children with cleft lip and palate and those with cleft palate alone experienced a lower QOL than children with cleft lip alone. Surprisingly, even years after successful cleft reconstruction, coping with and mastering a diagnosis of orofacial cleft continued to significantly affect social functioning. Currently, there are few data assessing the impact of craniosynostosis-induced midfacial growth impairment and oral health.

Neurodevelopmental Assessment

Children with craniosynostosis have a higher risk for problems related to cognitive development, learning difficulties, and academic delay. This risk varies by specific diagnosis but is present to some degree in all children born with craniosynostosis. Each of the following described instruments has been validated for children of a given age, sex, geographic region, race/ethnicity, and level of parental education (Table 3). To our knowledge, the listed scales have been validated but are still not widely used for children with craniosynostosis. Their application could shed some light on neurological development before and after surgery in children with craniosynostosis and should be recommended.

Children 0 Months to 7 Years Old

Bayley Scales of Infant Development. The Bayley Scales assess the motor (fine and gross), language (receptive and expressive), and cognitive development of infants and toddlers, ages 0–3 years. The instrument includes a motor scale, mental scale (generating the Mental Development Index and evaluating a variety of abilities), and behavior scale (rating relevant test-taking behaviors; Table 3). Raw scores of successfully completed items are converted to scale scores and composite scores. These scores are used to determine the child's performance compared with norms taken from typically developing children of the same age (in months). The assessment is often used in conjunction with the Social-Emotional Adaptive Behavior Questionnaire. Completed by the parent or caregiver, this questionnaire establishes the range of adaptive behaviors that the child can currently achieve and enables comparison with age norms.

Preschool Language Scale. This test is administered to identify language disorders or delay among children from birth to 6 years, 11 months old. It targets receptive and expressive language skills in the various areas listed in Table 3.

Wechsler Intelligence Scale for Children. The WISC is an intelligence test for children from 3 to 7 years of age and is standardized to include special group samples including children identified as gifted, children with mild or moderate mental retardation, children with learning disorders (reading, reading/writing, math, or reading/writing/math), children with attention deficit hyperactivity disorder, children with expressive and mixed receptive-expressive language disorders, children with autistic disorder, children with Asperger syndrome, children with

TABLE 3: Neurocognitive scales used in children with craniosynostosis

Bayley Scales of Infant Development				
Motor Scale	Mental Scale	Behavior Scale	Preschool Language Scale	Wechsler Intelligence Scale for Children
degree of body control	sensory/perceptual acuities	attention/arousal	attention	vocabulary
large muscle coordination	discriminations	orientation/engagement	play	similarities
finer manipulatory skills of hands & fingers	response	emotional regulation	gesture	comprehension
dynamic movement, dynamic praxis	acquisition of object constancy	motor quality	vocal development	information
postural imitation	memory, learning, problem solving		social communication	word reasoning
stereognosis	vocalization		vocabulary	block design
	habituation		concepts	picture concept
	mental mapping		language structure	matrix
	complex language		integrative language skills	reasoning
	basis of abstract thinking		phonological awareness	picture completion
	beginning of verbal communication			digit span
	mathematical concept formation			letter number sequence
				arithmetic
				coding
				symbol search
				cancellation

open- or closed-head injury, and children with motor impairment. The test is divided into 15 subtests with various weights in the total score (Table 3). Interenstingly, the WISC enables comparisons over a lifespan.

Children Older Than 7 Years

Wechsler Preschool and Primary Scale of Intelligence Test, Third Edition. The WPPSI-III test is similar to the WISC test, but it is administered to older children and young adults (6–16 years old; Table 3). The clinical utility of the WPPSI-III can be improved and a richer picture of general function can be achieved when combined with other assessments. For example, when paired with the Children's Memory Scale, a measure of learning and memory functioning in children, or the Wechsler Individual Achievement Test, Second Edition, a measure of academic achievement, information can be gained on both cognitive ability and academic achievement in young children. A further potentially useful pairing includes the WPPSI-III and the Adaptive Behavior Assessment System; this pairing can result in information on cognitive and adaptive functioning, both of which are required for a proper diagnosis of learning difficulties. It is important to recognize the limitations of using such assessments. Some studies have shown that intelligence tests, such as the WPPSI-III, especially for the prekindergarten level, are unreliable and their results vary widely with such factors as retesting, practice (familiarization), test administrator, time, and place.

Quality of Life Assessment

One of the first and so far the largest of the prospective studies on the impact of craniosynostosis on HRQOL was published in 2010 by Bannink et al.[1] Health-related QOL was measured using international standardized QOL questionnaires (Infant Toddler Quality of Life Questionnaire), the Child Health Questionnaire-Parent Form 50, the Child Health Questionnaire-Child Form 87, and the SF-36, and the results were compared with the Dutch population norms of HRQOL scores. Parents' scores for patients with syndromic or complex craniosynostosis were significantly lower than those for the normal population. Importantly, parent QOL was assessed as well; the parents of children with syndromic craniosynostosis self-reported a reduced HRQOL. Interestingly, patients with Apert syndrome were most profoundly affected, having significantly worse "parental impact: emotional and time," "lower physical functioning," and "family activities" domain scores, underlining the need to include parents in the assessment of treatment results.

Patient-Reported Outcome Instruments. These instruments measure self-reported patient data. Patient-reported outcome data are collected via self-administered questionnaires completed by a patient or his or her proxy. Therefore, patient-reported outcome instruments are different from every other instrument described in this article because they measure patient-reported data rather than the data that a surgeon, ophthalmologist, otolaryngologist, radiologist, speech/language pathologist, and so forth might routinely record in daily practice. Patient-reported-outcome questionnaires can assess a single underlying patient characteristic or multiple characteristics using modular scales that each address a single characteristic.

Patient-reported outcome instruments can be generic (designed to be used in any disease population and to cover a broad aspect of the measured construct; Table 4) or condition-specific (developed specifically to measure those aspects of outcome that are important to patients with a given disease; Table 5) questionnaires. Generic and condition-specific questionnaires can differ in their ability to discriminate and evaluate the patient-reported data for any given condition. For example, a condition-specific questionnaire may be more responsive to changes in the status of a patient treated for coronal craniosynostosis than a generic instrument, such as the SF-36. However, choosing the correct condition-specific instrument is important (Table 5). For example, reviewing the domains contained within common head and neck surgery questionnaires quickly reveals the inadequacies of these instruments in assessing a patient with craniosynostosis. Unfortunately, to date, a condition-specific questionnaire for patients with craniosynostosis does not exist. The development of such instruments should probably include the items listed in Table 6.

Operative Treatment

Cranial and facial operations are an integral component of the overall treatment of a patient with craniosynostosis. There is no single best method for treatment, and depending on the philosophy of the institution and the wishes of the parents, there are a variety of treatment options. Ideal therapies will vary by age, location and number of sutures involved, as well as the skill sets and philosophies of the treating teams. As the child ages, however, treatment options become more limited, and less invasive techniques can no longer be considered optimal. Regardless of the chosen surgical technique, in general most surgeons prefer to operate early on to capitalize on the ameliorating effects of skull growth. The goals of cranial and facial surgery are to provide adequate intracranial volume to allow brain development and to create an aesthetically normal skull shape and facial appearance.

Treatment Evaluation

Treatment outcomes for craniosynostosis can be measured from head to toe. As discussed above, more than 15 different subspecialists can participate in the preoperative

TABLE 4: Generic questionnaires

SF-12
SF-36
EQ-5D*
Quality of Well-Being Scale
Health Utilities Index
Pediatric Quality of Life Inventory
Health and Activities Limitations Index
Visual Functioning Questionnaire

* Previously known as the EuroQol Instrument.

TABLE 5: Head and neck surgery outcome assessment questionnaires*

Parameter	EORTC QLQ-H&N35	FACT-H&N	HNQOLQ	HNCI	UW-QOL	NDII	AQLQ	H&NS	Leeds QOLQ	FSS-SR	LASA of Voice Quality	MDADI	DSHNC	PSS-H&N	VoiSS
facial appearance															
satisfaction w/ appearance	x	x	x	x			x		x	x					
noticeable change in affect/self-esteem				x				x	x						
social contacts/activities					x			x							
type of H&N surgery															
size of disfigurement													x		
affects facial expression													x		
distortion of face or neck													x		
visibility of disfigured area													x		
speech															
voice quality/understandability		x	x	x	x			x	x	x	x			x	
voice strength/vol			x	x				x			x				x
variation in voice throughout day															x
hoarseness	x			x							x				x
communication/talking	x	x	x	x			x				x			x	x
phone communication															x
voice fatigue/loss											x				x
ability to sing/whistle											x				x
satisfaction w/ voice											x				
attracting attention															x
competition against background noise															x
people asking about voice															x
swallowing															
saliva/dry mouth	x	x	x	x	x		x		x	x	x				
bad breath									x						
chewing			x	x	x					x		x			
problem w/ teeth/dentures	x			x											
swallowing	x	x	x	x	x			x	x	x					
trismus		x										x			
normalcy of diet quality	x	x		x			x	x				x		x	
normalcy of diet quantity				x					x						
speed of eating				x											
appetite							x		x						
food enjoyment	x														

(continued)

TABLE 5: Head and neck surgery outcome assessment questionnaires* *(continued)*

Parameter	EORTC QLQ-H&N35	FACT-H&N	HNQOLQ	HNCI	UW-QOL	NDII	AQLQ	H&NS	Leeds QOLQ	FSS-SR	LASA of Voice Quality	MDADI	DSHNC	PSS-H&N	VoiSS
swallowing *(continued)*															
social eating	x						x	x		x		x		x	
taste	x		x		x				x	x					
cough/need to clear throat															x
feeling of something stuck in throat															x
swollen glands															x
blocked nose/throat infections															x
phlegm in throat															x
smell	x														
pain															
pain (H&N)	x	x	x	x	x		x	x	x	x			x		
respiratory symptoms (breathing/cough)	x	x					x			x					
shoulder pain/function			x		x	x	x			x					
hearing loss															
loss of vision															
skin symptoms															
smoking and alcohol use															
shoulder pain/weakness													x		
activity															
change in activity													x		
fatigue													x		
strength													x		
recreation													x		
QOL															
physical/functional/sexual well-being	x	x	x	x	x	x	x		x	x		x			
social well-being	x	x		x		x	x		x			x			
emotional well-being	x	x	x				x		x			x			
overall HRQOL			x	x	x		x			x			x		
overall QOL													x		
satisfaction w/ treatment			x						x						
life satisfaction							x		x						
change in mood													x		
anxiety													x		x
depression													x		x

(continued)

TABLE 5: Head and neck surgery outcome assessment questionnaires* *(continued)*

Parameter	EORTC QLQ-H&N35	FACT-H&N	HNQOLQ	HNCI	UW-QOL	NDII	AQLQ	H&NS	Leeds QOLQ	FSS-SR	LASA of Voice Quality	MDADI	DSHNC	PSS-H&N	VoiSS
QOL *(continued)*															
impact on friends & family															x
loneliness because of problem															x
shame/embarrassment															x
feeling of incompetence															x

* AQLQ = Auckland QOL Questionnaire; DSHNC= Disfigurement Scale for Head and Neck Cancer; EORTC QLQ-H&N35 = European Organisation for Research and Treatment of Cancer QOL Questionnaire–Head and Neck; FACT-H&N = Functional Assessment of Cancer Therapy–Head and Neck Version 4; FSS-SR = Functional Status Scale Self Report; H&N = head and neck; H&NS = Head and Neck Survey; HNCI = Head and Neck Cancer Inventory; HNQOLQ = University of Michigan Head and Neck QOL Questionnaire; LASA = linear analogue self-assessment; Leeds QOLQ = Leeds QOL Questionnaire; MDADI = MD Anderson Dysphagia Inventory; NDII = Neck Dissection Impairment Index; PSS-H&N= Performance Status Scale for Head and Neck Cancer Patients; UW-QOL = University of Washington QOL Questionnaire Version 4; VoiSS = Voice Symptoms Scale.

assessment of a patient with craniosynostosis. Herein, we confine our review to craniofacial and neurodevelopmental assessments. It is important to note that the limitations in each of the conventional assessment tools for craniofacial and neurodevelopmental outcomes are pervasive in each of the subspecialty areas involved in the care of a patient with craniosynostosis.

Objective Evaluation: Craniofacial Morphological and Functional Evaluation

Surgeons have typically assessed operative outcomes by measuring the same angles, distances, indices, and volumes used in the evaluation of patients before surgery (Tables 1–2). These tools have already been discussed and play a major role in the objective evaluation of surgical treatment. Typically, a craniofacial surgeon or neurosurgeon will assess operative outcomes by using global variables such as cephalic index, head circumference, or intracranial volume. For example, Heller et al.[11] reported that cranial vault remodeling normalized intracranial volume in patients older than 30 months and increased the cranial index to normal values (within 1 SD) at 1 year after surgery. Other surgeons will assess the functional impact of an operation. For example, Flores et al.[10] performed a retrospective review of 20 patients with syndromic craniosynostosis who underwent Le Fort III distraction osteogenesis. These authors measured changes in the velar angle and the nasopharyngeal, velopharyngeal, oropharyngeal, and hypopharyngeal spaces cephalometrically. Furthermore, they created 3D airway casts from CT data to ascertain circumferential airspace changes. They found that Le Fort III distraction osteogenesis significantly increases nasopharyngeal and velopharyngeal airspaces in patients with syndromic craniosynostosis and concluded that midface distraction improves but does not resolve all causes of OSA in this patient population.

Subjective Evaluation: Patient Questionnaires

With the evolution of psychometric testing, it has become increasingly recognized that a patient's assessment of the surgical outcome can be measured. While there are currently no questionnaires designed to address the factors important to patients with craniosynostosis, based on a systematic review of the literature, Table 6 contains domain areas that will be important for questionnaire development. It is important to remember that in the pediatric population, the health and well-being of a child are inseparable from his or her parents' well-being and that ideally the parent(s) and child should be considered as a unit. Questionnaire development for patients with craniosynostosis and their care providers will allow us not only to compare the impact of different treatments on the aforementioned unit, but also to target the areas and aspects of care that need improvement. For example, how does the amount of time the parents are taking off from work to care for their child affect the family? Does the stress of missing work negatively impact a parent's feelings toward his or her child? Does a less invasive technique that requires frequent postoperative follow-up visits with a molding helmet company cause more stress for the

TABLE 6: Patient-reported outcomes: topics to investigate in patients with craniosynostosis

appearance	ear, nose, & throat
satisfaction w/ appearance*†	blocked nose/throat infections
associated malformations	OSA
noticeable change in affect/self-esteem*†	cardiovascular abnormalities
social contacts/activities*†	respiratory abnormalities
type of surgery	snoring*
size of disfigurement	apnea*
affects facial expression*	emotional distress/irritation*
distortion of face*	respiratory symptoms (breathing/cough)*
visibility of disfigured area*	hearing loss/deafness*
vision	hypersomnolence*
dry eyes	behavioral problems*
strabismus	extremities anomalies
amblyopia	motor skills*
corneal exposure	pain
pain	hand use*
impact on social interaction*†	appearance
impact on daily activities*†	type of surgery
impact on development*	impact on daily activities*†
impact on learning/education*	impact on development*
oral health	QOL
saliva	physical/functional well-being*
chewing	social well-being*†
problem with teeth/dentures	emotional well-being*†
swallowing	overall HRQOL*†
speech/need for speech therapy	overall QOL*†
language	satisfaction w/ treatment†
diet	life satisfaction†
normalcy of diet quality*	education*
normalcy of diet quantity*	school integration*
speed of eating*	change in mood*†
appetite*	anxiety*†
food enjoyment*	depression*†
social eating*†	impact on friends/family/school*†
intestinal abnormalities	loneliness*
pain	shame/embarrassment*†
activity	feeling of incompetence*†
change in activity*†	cost†
fatigue*†	impact on work/working time loss†
strength*	impact on family/other children's life*†
recreation*	impact on couple's life†
cognitive development*	travel for care†
	stress*†

* Involves parents to answer the questions.
† These topics should also be investigated from the parents' points of view.

family? How long is the family's commute to the hospital, and is it an important factor for the parents? These are questions that need to be answered, and we tried in Table 6 to highlight the main areas that need to be investigated.

Conclusions

While traditional outcome measures continue to be important, they overlook the impact of surgery on a pa-

tient's QOL. Moreover, they do not provide information necessary to perform a cost-effectiveness analysis of the procedure. Finally, traditional outcomes do not indicate how the operative change in the disease burden affects a patient's QALYs. Since craniosynostosis is a complex disease, we need new instruments to measure the effects of our treatments to predict the long-term costs and consequences associated with craniosynostosis and to ensure an adequate allocation of health care dollars.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Warren, Szpalski. Acquisition of data: Szpalski, Sagebin. Analysis and interpretation of data: Warren, Szpalski. Drafting the article: Szpalski. Critically revising the article: Warren, Szpalski, Weichman. Reviewed submitted version of manuscript: Warren, Szpalski, Weichman. Administrative/technical/material support: Warren, Szpalski.

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Combined metopic and sagittal craniosynostosis: is it worse than sagittal synostosis alone?

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Object. Combined metopic and sagittal craniosynostosis is a common variant of the nonsyndromic, multiple-suture synostoses. It is unknown whether this combined form causes reduced intracranial volume (ICV) and potentially more brain dysfunction than sagittal synostosis alone. This study is a volumetric comparison of these 2 forms of craniosynostosis.

Methods. The authors conducted a retrospective chart and CT review of 36 cases of isolated sagittal synostosis or combined metopic and sagittal synostosis, involving patients seen between 1998 and 2006. Values were obtained for the intracranial compartment, brain tissue, CSF space, and ventricular volumes. Patients with craniosynostosis were then compared on these measures to 39 age- and sex-matched controls.

Results. In patients with isolated sagittal synostosis and in those with combined metopic and sagittal synostosis, there was a trend toward smaller ICV than in controls ($p < 0.1$). In female patients older than 4.5 months of age, there was also a trend toward smaller ICV in patients with the combined form than in those with sagittal synostosis alone ($p < 0.1$), and the ICV of patients with the combined form was significantly smaller than the volume in controls in the same age group ($p < 0.05$). Brain tissue volume was significantly smaller in both patient groups than in controls ($p < 0.05$). Ventricular volume was significantly increased (compared with controls) only in the patients with isolated sagittal synostosis who were younger than 4.5 months of age ($p < 0.05$). Overall CSF space, however, was significantly larger in both patient groups in patients younger than 4.5 months of age ($p < 0.05$).

Conclusions. These findings raise concerns about intracranial and brain volume reduction in patients with sagittal and combined metopic and sagittal synostoses and the possibility that this volume reduction may be associated with brain dysfunction. Because the ICV reduction is greater in combined metopic and sagittal synostosis in patients older than 4.5 months of age than in sagittal synostosis in this age group, the potential for brain dysfunction may be particularly true for these younger infants. *(DOI: 10.3171/2011.6.FOCUS11100)*

Key Words • **craniosynostosis** • **metopic** • **sagittal** • **volume**

Sagittal craniosynostosis is the most common of the single-suture synostoses, with an incidence between 1 in 2000 and 1 in 5000 live births. Reported rates of metopic synostosis vary between 1 in 10,000 and 1 in 100,000 live births, and the incidence of this synostosis is on the rise. While premature fusion of the sagittal suture results in scaphocephaly, characterized by biparietal narrowing, frontal bossing, and occipital prominences, isolated metopic synostosis results in the well-recognized frontal bone deformity, trigonocephaly. The combination of these 2 forms of craniosynostosis yields a skull shape that is long and narrow (scaphocephaly), but the deformity may appear less severe due to the metopic synostosis–induced inability to develop compensatory frontal bossing. In truth however, this combined form may be less benign than sagittal synostosis alone due to greater restriction on the growing brain (Fig. 1).

In the normal pediatric skull, ICV, BTV, and CSF volume continually increase through early childhood. Yet, this increase is most rapid during the first 2.5 years of life, allowing the brain to reach more than 80% of its adult size in this period. Untreated craniosynostosis may lead to an inhibition of brain growth and in some cases an increase in intracranial pressure. It has been previously demonstrated that infants with sagittal craniosynostosis have higher intracranial pressure and an increased incidence of learning disabilities.[10,13]

Of note, the surgical technique for correcting these

Abbreviations used in this paper: BTV = brain tissue volume; HSD = Honestly Significant Difference; ICV = intracranial volume; VV = ventricle volume.

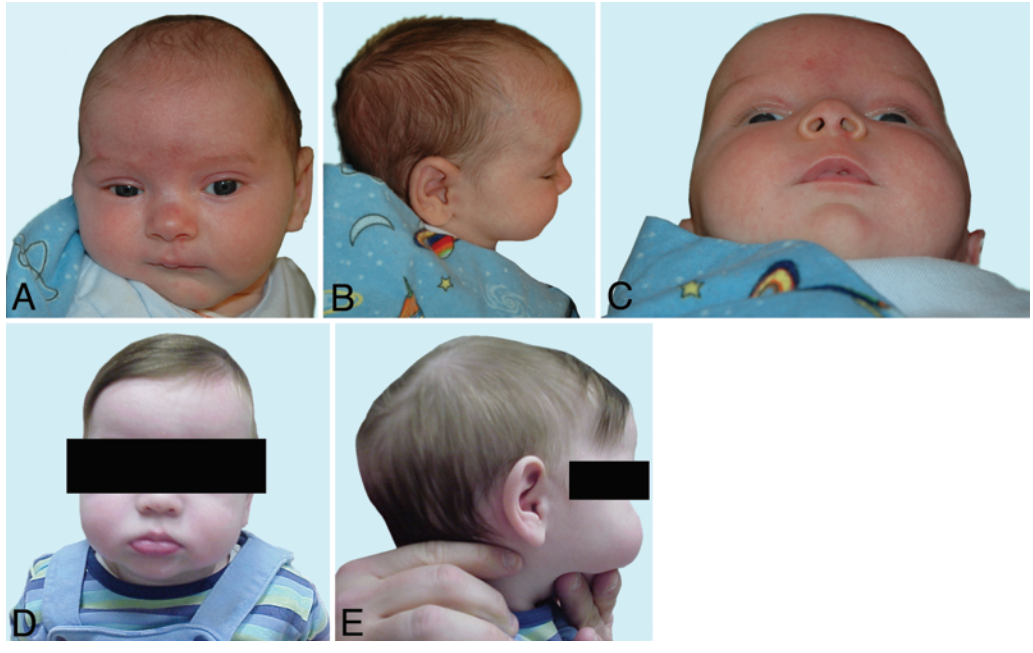

Fig. 1. A–C: Frontal **(A)**, lateral **(B)**, and birds-eye **(C)** views of a patient with isolated sagittal craniosynostosis showing prominent frontal bossing and scaphocephaly with superimposed deformational plagiocephaly. **D and E:** Frontal **(D)** and lateral **(E)** views of a patient with combined sagittal and metopic craniosynostosis showing a deceivingly less severe–appearing deformity.

conditions can vary significantly. In scaphocephaly, a multitude of techniques have been employed. Strip craniectomies are often performed either as open surgical procedures or endoscopically.[8] However, concerns over lack of complete and early correction of the restrictive nature of the deformity have led to more extensive procedures being used. These include the modified pi-plasty and more comprehensive cranioplasty.[3,6] In trigonocephaly, strip craniectomy or bifrontal craniotomy with orbital rim advancement have been used to correct for the lack of lateral frontal orbital projection.

Previous studies by Posnick et al.,[12] Hill et al.,[7] and Lee et al.[9] demonstrated normal or increased preoperative mean ICV (relative to controls) in patients with sagittal synostosis who were older than 6 months of age. The degree of difference appears to be age dependent.[7,9,12] The older the patient, the greater the increase in ICV compared with normal values.

Currently, no data exist regarding ICV in patients with combined metopic and sagittal synostosis. It is also unknown whether timing of surgery, specifically early surgical intervention, or alternatively, a different surgical technique may prove beneficial in these patients. Intracranial volume measurements may aid in this determination and can be calculated noninvasively using CT scans. Such techniques have already been employed to measure ICV in patients with isolated sagittal synostosis. Using these CT-based techniques, we sought to clarify the volumetric changes associated with the combined form of metopic and sagittal craniosynostosis versus isolated sagittal synostosis and compare these to each other as well as to values obtained in specific age- and sex-matched controls, who were evaluated using the same methods at the same institution.

Methods

Patient Population

Between November 1998 and October 2006, 77 consecutive children with previously untreated sagittal synostosis underwent whole-vault cranioplasty at Yale–New Haven Hospital. These children presented with scaphocephaly and a palpable ridge along the sagittal plane. Preoperative CT scans were obtained to confirm the diagnosis of sagittal craniosynostosis and determine the patency of other calvarial sutures. Fifty-three patients (15 female, 38 male) had pre- and postoperative CT scans available for review.

Based on both radiographic data (omega sign present in the metopic area) and direct observation at the time of surgery, a subset of these patients was identified as having concurrent metopic and sagittal synostosis. Because the metopic suture normally closes at approximately 9 months of age, only patients who were 9 months of age or younger were included in this study.

After applying these criteria, 16 patients (7 female, 9 male) with combined metopic and sagittal synostosis (the M/S group), and 19 (5 female, 14 male) with sagittal synostosis alone (the S group), were included in the analysis. Additionally, data from age- and sex-matched controls (39 children) from the same institution, were compared with these groups; the control data had been obtained using the same data acquisition methodology as was used in the synostosis cases. Available data included preoperative ICV, BTV, CSF space, and VV. Data were analyzed using a combination of R (www.R-project.org) and Microsoft Excel software. The research protocol was approved by the Human Investigation Committee at Yale University School of Medicine.

Computed Tomography and Volume Measurement

All patients underwent axial CT scanning on a Lightspeed-16 CT scanner (General Electric) with a 3-mm pitch and slice thickness at Yale–New Haven Hospital. Some patients underwent CT scanning at a higher resolution preoperatively with a 1.25-mm pitch and slice thickness. Volume determination was based on measuring the area in each CT section.

The ImageJ software package, downloaded from the Internet (National Institutes of Health, http://rsb.info.nih.gov/ij/download.html) was used to measure the CT image. The ImageJ software read the CT data and calibrated the images automatically. The threshold was set at the intensity that corresponded to the interface between brain tissue and the signal void caused by the dense bone of the inner table of the cranium. The software outlined the bone inner cortex contour in each slice at the specified soft-tissue–bone threshold automatically. Also, it provided tools for selecting and editing the contours. Manual editing was used to define the intracranial border where the automatic threshold was questionable. The CT slices were processed individually for volume measurement to obtain the area of intersection of the region of interest with each slice. The volume of the intracranial cavity was measured by S.S.L. on a slice-by-slice basis. Results of measurements were copied into Excel (Microsoft Corp.). The ICVs were calculated at the end of each slice by multiplying the cumulative area by the CT scan thickness (for example, 3 or 1.25 mm). The accuracy and reliability of this measurement paradigm have been shown previously by Posnick et al.[12]

To measure the CSF space and VV, we used the tools of ImageJ to convert the CT image into a black/white mode, then adjusted the threshold of the system to allow black color to just fully fill the ventricle space. The threshold number for each different CT series was recorded. The rater used the tools of the ImageJ system to define the appropriate area for measurement. Again, CT slices were processed individually for measuring the area of intersection of the region of interest\ with each slice. The CSF space volumes and VVs were calculated at the end of each slice by multiplying the cumulative area by the CT scan thickness. Finally, these measurement results were put into Excel to record for further analysis of the CSF space or VV. The BTV was calculated by subtracting the CSF space volume from the ICV.

The reliability and accuracy of these measurements were tested. We randomly selected 15 T series to check the interrater error (accuracy). The interrater error between 2 was on average 0.755% ± 0.65% (range 0.1%–2.47%). Seven T series were remeasured 1 week later to check for intrarater error. The intrarater error was on average 0.77% ± 0.46% (range 0.15%–1.45%).

Results

Data were available for analysis from 19 patients with sagittal craniosynostosis (S group: 5 girls and 14 boys), 16 patients with combined metopic and sagittal synostosis (M/S group: 7 girls and 9 boys), and 39 unaffected infants (controls: 16 girls and 23 boys) under the age of 9 months. Data acquired included preoperative ICV, BTV, CSF space, and VV. Data were analyzed using a combination of R, JMP (SAS Institute, Inc.), and Excel software.

Preoperative ICV

A 1-way ANOVA was conducted to compare the preoperative ICV of the patients in the S group with that of the patients in the M/S group. The results of this initial test were significant ($p = 0.029$), and the differences between the 3 groups (S, M/S, and control) were then explored using the Tukey HSD test. This subsequent step showed a trend for both the S and M/S groups to have, on average, smaller preoperative ICV than controls ($p = 0.086$, $p = 0.065$, respectively).

A multiple linear regression model was applied, and sex and age were both found to be important influences on ICV ($p = 0.001$ for sex, $p < 0.0001$ for age). The groups were subdivided to account for both age and sex (Table 1). In this case, a 1-way ANOVA demonstrated a statistically significant difference only for females between 4.5 and 9 months of age ($p = 0.0165$). The Tukey HSD test revealed that the preoperative ICV for the female patients in the M/S group was, on average, smaller than that of controls ($p = 0.022$). The preoperative ICV for the female patients in the M/S group also demonstrated a trend toward being smaller than that of their S group counterparts ($p = 0.065$). No differences were found between the S and control groups in this case (female infants between 4.5 and 9 months of age, $p = 0.682$).

Preoperative BTV

A similar analysis was conducted to compare the preoperative BTV of the S, M/S, and control groups (summarized in Table 2). In this case, the results of a 1-way ANOVA considering all patients, regardless of age or sex, were statistically significant ($p = 0.007$). The Tukey HSD test showed that BTV was significantly smaller in both the M/S and the S groups than in the controls regardless of age or sex ($p = 0.031$ and $p = 0.022$, respectively). However, no significant differences could be determined between the M/S and S groups ($p = 0.997$).

When considering male infants alone in both groups, the results of a 1-way ANOVA remained statistically significant ($p = 0.004$). In male infants, we still observed that the BTV for the S group was, on average, smaller than that of controls ($p = 0.003$). However, in this case, no statistically significant differences between the M/S and control groups ($p = 0.243$), or the M/S and S groups ($p = 0.387$), were observed. When considering female infants alone, the significance was reduced, although a 1-way ANOVA still demonstrated a trend toward significance ($p = 0.088$). In this case, there was a trend for the BTV of females in the M/S group to be smaller than that of controls ($p = 0.073$). No statistically significant differences could be found between the S and control groups ($p = 0.917$) or the M/S and S groups ($p = 0.399$).

In terms of age, when considering patients 4.5 months old or younger, a 1-way ANOVA demonstrated a trend toward significance ($p = 0.058$), and the Tukey HSD test

TABLE 1: Intracranial volume in different age subgroups*

Characteristics	S Group	M/S Group	Controls
≤4.5 mos of age at CT			
male			
ICV (cm^3)	724.7 ± 107.8	687.6 ± 75.2	736.238 ± 96.8
no. of CT scans	12	4	8
female			
ICV (cm^3)	718.9 ± 94.2	591.0 ± 95.5	681.350 ± 81.1
no. of CT scans	4	3	8
total			
ICV (cm^3)	723.2 ± 101.5	646.2 ± 92.4	708.8 ± 90.8
no. of CT scans	16	7	16
4.5–9 mos of age at CT			
male			
ICV (cm^3)	922.2 ± 128.7	899.0 ± 67.4	980.0 ± 112.2
no. of CT scans	2	5	15
female			
ICV (cm^3)	947.3	686.0 ± 51.5	865.652 ± 103.03
no. of CT scans	1	4	8
total			
ICV (cm^3)	930.6 ± 92.1	821.5 ± 140.7	940.2 ± 120.4
no. of CT scans	3	9	23

* Data are presented as mean values (± SD) unless otherwise indicated.

showed a trend for the infants in the M/S group to have a smaller BTV than controls ($p = 0.053$). Differences between the S group and controls and between the M/S and S groups in this age category could not be established ($p = 0.917$ and $p = 0.107$, respectively). When considering patients between 4.5 and 9 months of age, we obtained similar results (ANOVA, $p = 0.084$). The M/S group demonstrated a trend toward a smaller BTV on average than controls ($p = 0.069$), while no statistically significant differences could be found between the S and control groups ($p = 0.953$), or between the M/S and S groups ($p = 0.649$).

The groups were once again further subdivided to account for age and sex. Focusing on female patients older than 4.5 months of age, the results of a 1-way ANOVA comparing the M/S, S, and control groups were statistically significant ($p = 0.042$). The Tukey HSD test revealed a trend for the BTV of female infants in the M/S group to be, on average, smaller than that of controls in this age group (trend toward significance, $p = 0.055$); there were no statistically significant differences between the M/S and S groups.

Ventricular Volume and CSF Space

In terms of VV, when all patients were considered, a 1-way ANOVA yielded no significant results ($p = 0.232$). When only infants 4.5 months of age or younger were considered (regardless of sex), the results of a 1-way ANOVA were significant ($p = 0.032$), and the Tukey HSD test revealed that the VV of patients in the S group was, on average, larger than that of unaffected controls ($p = 0.026$); no statistically significant differences could be found between controls and the M/S group ($p = 0.262$) or between the S and M/S groups ($p = 0.800$). Ventricular volumes for the different age and sex subgroups are summarized in Table 3.

In terms of CSF space overall, when infants 4.5 months of age or younger were considered, once again, the results of a 1-way ANOVA were significant ($p = 0.001$). This time, the Tukey HSD test revealed that the CSF volume of patients with combined metopic and sagittal synostosis in this age group was larger than that of controls ($p = 0.002$), and that the CSF volume of patients with isolated sagittal synostosis was also larger than that of controls on average ($p = 0.015$). No statistically significant differences could be found between the M/S and S groups in this category ($p = 0.320$). Table 4 presents a summary of the CSF space averages for all age and sex subgroups.

Discussion

Van der Meulen et al.[14] reported an increase in prevalence of metopic craniosynostosis between 1997 and 2006; although no clear explanation was provided for these findings, the authors also noted an increasing number of cases of combined metopic and sagittal craniosynostosis. This trend is particularly concerning as multisuture craniosynostosis has been shown to be associated with more negative neurological sequelae than single-suture synostosis (that is, unilateral vs bilateral coronal synostosis).[13] Renier et al.[5] concluded that intracranial pressure was increased in proportion to the number of involved sutures. Additionally, the prevalence of

TABLE 2: Brain tissue volume in different age subgroups

Characteristics	S Group	M/S Group	Controls
≤4.5 mos of age at CT			
male			
BTV (cm^3)	669.8 ± 101.0	616.3 ± 52.9	710.9 ± 89.6
no. of CT scans	12	4	8
female			
BTV (cm^3)	636.5 ± 61.8	529.8 ± 75.1	640.5 ± 75.0
no. of CT scans	3*	3	8
total			
BTV (cm^3)	663.2 ± 93.5	579.2 ± 73.6	675.7 ± 87.7
no. of CT scans	15*	7	16
4.5–9 mos of age at CT			
male			
BTV (cm^3)	819.0	882.1 ± 92.9	930.1 ± 109.6
no. of CT scans	1*	5	14*
female			
BTV (cm^3)	910.2	652.0 ± 52.7	825.9 ± 121.7
no. of CT scans	1	4	8
total			
BTV (cm^3)	864.6 ± 64.5	776.9 ± 139.3	892.2 ± 122.5
no. of CT scans	2*	9	22*

* Data were missing for some patients in this subgroup, and thus the total number of CT scans is smaller than the number presented in Table 1, in which all patients were included.

TABLE 3: Ventricular volume in different age subgroups

Characteristics	S Group	M/S Group	Controls
≤4.5 mos of age at CT			
male			
VV (cm^3)	9.78 ± 5.21	10.7 ± 8.66	4.55 ± 3.11
no. of CT scans	12	4	6*
female			
VV (cm^3)	8.95 ± 2.25	4.90 ± 2.04	4.77 ± 3.03
no. of CT scans	4	3	6*
total			
VV (cm^3)	9.57 ± 4.59	8.21 ± 6.96	4.66 ± 2.93
no. of CT scans	16	7	12*
4.5–9 mos of age at CT			
male			
VV (cm^3)	10.15 ± 5.73	11.1 ± 9.94	9.74 ± 8.51
no. of CT scans	2	5	7*
female			
VV (cm^3)	12.3	6.10 ± 2.16	7.63 ± 4.75
no. of CT scans	1	4	6*
total			
VV (cm^3)	10.87 ± 4.24	8.88 ± 7.62	8.77 ± 6.84
no. of CT scans	3	9	13*

* Data were missing for some patients in this subgroup.

TABLE 4: Cerebrospinal fluid space in different age subgroups

Characteristics	S Group	M/S Group	Controls
≤4.5 mos of age at CT			
male			
CSF (cm^3)	54.88 ± 23.01	71.28 ± 38.64	25.34 ± 15.03
no. of CT scans	12	4	8
female			
CSF (cm^3)	44.35 ± 5.32	61.27 ± 23.41	32.81 ± 23.79
no. of CT scans	4	3	8
total			
CSF (cm^3)	52.24 ± 20.40	66.99 ± 30.95	29.07 ± 19.61
no. of CT scans	16	7	16
4.5–9 mos of age at CT			
male			
CSF (cm^3)	12.20	53.16 ± 39.50	54.27 ± 46.79
no. of CT scans	1*	5	14*
female			
CSF (cm^3)	37.10	33.95 ± 21.12	39.75 ± 35.33
no. of CT scans	1	4	8
total			
CSF (cm^3)	24.65 ± 17.61	44.62 ± 32.40	48.99 ± 42.69
no. of CT scans	2*	9	22*

* Data were missing for some patients in this subgroup.

learning disabilities is noted to be increased in those with metopic or sagittal craniosynostosis compared with the general public (Magge SN, unpublished data, 2002).[10] Subsequently, Becker et al.[2] found that 57% of patients with nonsyndromic metopic craniosynostosis presented with speech, cognitive, or behavioral abnormalities, confirming the findings of earlier studies in which 39% of patients with nonsyndromic sagittal craniosynostosis had similar learning dysfunction.

In this study, we evaluated only infants ranging in age from newborn to 9 months, as this is the time of normal physiological metopic fusion. We were especially interested in those measures of ICV, BTV, VV, and CSF space. A previous study by Lee et al.[9] showed that there is expanded skull and brain volume in patients with sagittal synostosis preoperatively, and increased or normal ICV in younger patients (7–12 months of age). As the patients grew (to > 30 months of age), their ICV increased but BTV decreased compared with normal controls.

In terms of ICV, this study shows a trend toward an initial smaller ICV in patients with isolated sagittal synostosis (the S group) as well as in those with combined metopic and sagittal synostosis (the M/S group) compared with nonaffected controls. This pattern was statistically significant in female infants older than 4.5 months of age with combined metopic and sagittal synostosis. Of note, we found a trend toward smaller ICV in patients with combined metopic and sagittal synostosis than in those with isolated sagittal synostosis in the group between 4.5 and 9 months of age. This is important, as this trend does not exist in the younger age group, perhaps indicating that as these infants develop, their ICV becomes further reduced. This differs from previous work done by Lee et al.:[9] even when the S and M/S groups were combined into one, we found that the combined group had a smaller ICV than controls ($p = 0.05$). This contrast is due to the difference between the 2 studies in the subdivision of age groups: Lee et al. noted increased ICV in patients 7–12 months of age. Because we were interested in looking at the S and M/S groups independently, we only included infants up to 9 months of age in our analysis. Our grouping of patients between 4.5 and 9 months of age resulted in a subgroup of patients in which ICV tends to be smaller than that of controls. It is likely that the results found by Lee et al. are most applicable to the older infants in their 7- to 12-month-old group. It is also important to consider the notion of global volume versus regional compression. Although in some age groups, the overall ICV is increased, with craniosynostosis, there is concern over regional compression because the fused suture restricts growth perpendicular to it.

We also considered VV and CSF space. Here, we found that patients in the S group initially had significantly larger VVs than controls. Also, the CSF space was larger in both subject groups compared with controls, especially in the younger age group.

When considering the constellation of findings here—decreased BTV and ICV with increased VV and CSF space—a pattern similar to hydrocephalus is noted. External hydrocephalus has a relatively subtle clinical course characterized by an isolated increase in subarachnoid space and intracranial pressure often associated with

macrocephaly.[1] Although we did not record intracranial pressure, it is important to note the similarities here, indicating that there may be some impact of craniosynostosis on CSF absorption.

Additionally, we considered BTV in the S and M/S groups compared with nonaffected controls. We found that in both synostosis groups, the BTV was significantly smaller than in the control group. As above, it is important to consider that brain mass is reduced in both synostosis groups, a finding that is apparent even in the younger infants, perhaps indicating an important component of cognitive maldevelopment in children with sagittal synostosis.

The relationship between decreased ICV and smaller brain mass in those infants with isolated sagittal synostosis or combined metopic and sagittal synostosis is especially concerning in light of the documented effects on neurodevelopment. A more comprehensive surgical approach also may be more prudent as it has the capability of immediately correcting the skull constraint on brain growth. This is especially true for patients with combined metopic and sagittal synostosis, as a trend was noted for an even smaller ICV than in patients with isolated synostosis counterparts. A number of reports have presented the utility of early surgery, whether in reference to skull shape and growth or neurodevelopment.[11] That reduced ICV is more apparent in the older age group (4.5–9 months of age) may be more evidence that surgery at a younger age may prevent later negative neurocognitive sequelae. Our study suggests that 4.5 months of age is a particularly important cut-off point, after which we begin to see some differences between affected infants and controls. Though it is tempting to recommend surgery specifically prior to 4.5 months of age, follow-up studies with larger samples should be undertaken before such a specific recommendation is given. In summary, there is mounting evidence that craniosynostosis has important effects not only on skull growth, but also on brain growth and development. These trends were noted in all parameters examined, including ICV, BTV, VV, and CSF space. Although in several parameters the combined form of craniosynostosis did not differ significantly from the isolated sagittal form, the trend toward a difference in ICV, and importantly BTV, may indicate an important process at play, which is worth examining further. One important note is that the analysis in this study is not a functional test, but rather a volumetric one. As effects on neurodevelopment are subtle learning disabilities, it is not surprising that marked changes in brain volume are not seen in this study. The marginal difficulties are not likely to be associated with major visible structural brain damage. Further research considering neurocognitive assessment and comparison of patients with isolated sagittal synostosis and those with combined metopic and sagittal synostosis would be beneficial.

Conclusions

This study shows a trend toward smaller ICV in patients with isolated sagittal synostosis as well as those with combined metopic and sagittal synostosis compared with nonaffected controls, a pattern which is significant in female patients with combined metopic and sagittal synostosis who are older than 4.5 months of age. Also, there was a trend toward a smaller ICV in the M/S group as compared with the S group. Furthermore, the BTV of both groups was significantly smaller than that of controls. Additionally, in patients younger than 4.5 months of age, the VV (for patients in the S group) and CSF space (for patients in the S group and those in the M/S group) were noted to be larger than in controls. That not all measures show significance, but rather trends, is consistent with findings that these patients do not have gross developmental delay. We emphasize that the effects on brain growth and development are subtle, and thus more subtle learning disabilities will reflect this fact.

Is the combination of metopic and sagittal synostosis worse than the presence of sagittal craniosynostosis alone? A recent study by Domeshek et al.[4] found that, although there were morphological differences between isolated sagittal synostosis and combined metopic and sagittal synostosis, these differences were not statistically significant. Despite this and our small sample size, we did find some trends indicating that combined metopic and sagittal synostosis may indeed be worse than sagittal synostosis alone, at least for some subgroups. It is important to note that the major influence, it seems, continues to be the sagittal suture. This observation is compatible with findings of previous work, given that the metopic suture fusion is not expected to have as much an influence on volume, as it has an earlier closure, and there is potential for accommodation elsewhere. Still, in the present study, patients in both the S and M/S groups had smaller volumes than unaffected controls, and this restriction may be enough to affect brain growth.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Persing, Terner, Travieso, Lee. Acquisition of data: Lee. Analysis and interpretation of data: Persing, Terner, Travieso, Forte, Patel. Drafting the article: Persing, Terner, Travieso, Forte, Patel. Critically revising the article: Persing, Terner, Travieso, Forte, Patel. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Persing. Statistical analysis: Terner, Travieso. Study supervision: Persing.

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Cranial vault remodeling for sagittal craniosynostosis in older children

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Object. Sagittal craniosynostosis is the most common form of craniosynostosis and is commonly treated within the first year of life. Optimal treatment of patients older than 1 year of age is not well characterized. The authors reviewed cases of sagittal craniosynostosis involving patients who were treated surgically at their institution when they were older than 1 year in order to determine the rate of intracranial hypertension (ICH), potential to develop nonhealing cranial defects, and the need for various surgical procedures to treat the more mature phenotype.

Methods. A retrospective chart review was conducted of all cases in the Children's Hospital of Pittsburgh Neurosurgery Database involving patients who underwent cranial vault remodeling for scaphocephaly after 1 year of age between October 2000 and December 2010.

Results. Ten patients were identified who met the inclusion criteria. Five patients underwent anterior two-thirds cranial vault remodeling procedures, 3 patients underwent posterior vault remodeling, and 2 patients underwent 2-staged total vault remodeling. All patients had improved head shapes, and mean cephalic indices improved from 65.4 to 69.1 ($p = 0.05$). Six patients exhibited signs of ICH. No patients with more than 3 months of follow-up exhibited palpable calvarial defects.

Conclusions. Patients with sagittal synostosis treated after 1 year of age demonstrate increased rates of ICH, warranting diligent evaluations and surveillance to detect it; rarely develop clinically significant cranial defects if appropriate bone grafting is performed at the time of surgery; and achieve acceptable improvements in head shape.
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Key Words • **craniosynostosis** • **sagittal craniosynostosis** • **scaphocephaly** • **dolicocephaly** • **cranioplasty** • **craniofacial deformity**

Craniosynostosis is the early fusion of one or more of the cranial sutures, which results in restricted skull growth perpendicular to the involved suture and compensatory growth parallel to it. The ultimate result of this is a pathological head shape and potentially elevated intracranial pressure, which occurs in 14% of cases of single-suture fusion.[14] Sagittal craniosynostosis is the most common form craniosynostosis. It occurs in 1 in 5000 children and affects boys more frequently than girls.[9] Sagittal suture fusion results in an elongated, or scaphocephalic, head shape.

Both minimally invasive strip craniectomy and more extensive cranial remodeling procedures for sagittal synostosis within the 1st year of life have been described. Debate exists regarding the relative benefits of each.[4–8,11,13,15,18] Regardless of the technique employed, most surgeons advocate for operative intervention within the 1st year of life. As scaphocephaly is usually apparent at birth, this is often accomplished. Less commonly, children will present after 1 year of age or require delayed interventions due to associated comorbidities. These older patients with scaphocephaly are a poorly characterized population with unique considerations regarding their risk of intracranial hypertension (ICH), potential to develop nonhealing cranial bone defects, and need for more extensive operations to achieve an aesthetic head shape. We report our experience with scaphocephalic children who underwent cranial vault remodeling for scaphocephaly after 1 year of life, highlighting these issues.

Abbreviations used in this paper: AP = anterior-posterior; CI = cephalic index; eu-eu = eurion-eurion measurement; g-op = glabella-opisthocranion measurement; ICH = intracranial hypertension; ICU = intensive care unit.

Methods

The neurosurgery patient database of the Children's Hospital of Pittsburgh of UPMC was queried for all patients with the diagnosis of nonsyndromic sagittal craniosynostosis who underwent cranial vault remodeling procedures at an age greater than 1 year between October 2000 and December 2010. Patients with multisuture synostosis were excluded if the remodeling procedure performed was intended to address abnormal head shape resulting from the other fused sutures and did not address the finding of scaphocephaly. A retrospective review was performed of the medical records of all patients. Factors studied included: 1) patient demographic characteristics, 2) intraoperative blood loss and transfusion rates, 3) ICU and hospital length of stay, 4) type of calvarial remodeling performed, 5) signs and symptoms of ICH, 6) postoperative complications, 7) the incidence of residual cranial bone defects, and 8) changes in head shape as measured by the cephalic index (CI).

The CI was calculated from anthropomorphic measurements obtained in the clinic and measurements taken from available CT scans. This value is defined as the widest dimension of the cranium (eurion-eurion [eu-eu]) divided by the maximal length of the cranium (glabella-opisthocranion [g-op]) multiplied by 100. The CT measurements were made using 3D reconstructions when available. When they were not, 2D CT scans were analyzed. In these cases, lateral scout views or sagittal reconstructions of 2D CT scans were used to measure the g-op dimension, while axial cuts were used to measure the eu-eu dimension. Preoperative and postoperative CI values were compared using a paired t-test. The assumption of normality was confirmed using the Shapiro-Wilk test. Comparisons were only made between pre- and postoperative measurements derived from the same imaging modality to maintain internal consistency for each individual. Single measurements without a corresponding pre- or postoperative value attained with the same modality were not analyzed. In instances in which multiple measurement modalities were available, anthropomorphic measurements (actual measurements of the patient's head) were prioritized. Any 3D CT reconstructions were prioritized next as they limited possible distortions caused by rendering a 3D structure in 2 dimensions. Finally, 2D CT scans were analyzed if 3D reconstructions were not available.

Surgical Approach

A defect-targeted strategy was employed in designing each patient's reconstruction. Patients were assessed to determine their degree of scaphocephaly, the severity of their occipital constriction and bulleting, frontal bossing, temporal narrowing, and hypotelorism. A procedure was designed to adequately address all significant pathology. All procedures were carried out through a zig-zag–shaped bicoronal incision.

For patients with pathology that was predominantly anterior with frontal bossing and temporal narrowing, an anterior two-thirds cranial remodeling procedure was performed, including bifrontal and biparietal craniotomies with reshaping and interpositional bone grafting to widen the frontal bone, trimming of the parietal bones to decrease the anterior-posterior (AP) diameter, and barrel staving with out-fracture of the temporal bones to widen the skull base (Fig. 1). If hypotelorism and/or superior orbital rim retrusion was present, a supraorbital expansion and/or advancement was completed by removing the supraorbital bandeau, cutting it in the midline, and placing an interpositional bone graft at the radix. Those patients with more pronounced occipital restriction and bulleting were treated with posterior cranial remodeling with occipital craniotomies, flattening of the occipital bone through barrel staving, parietal craniotomies and trimming to decrease the AP diameter, and barrel staving with out-fracture of the parietal and temporal bones to release constriction. Patients with severely altered anterior and posterior head shapes were treated with a staged procedure addressing each region sequentially (Fig. 2).

Our bone-grafting technique of choice was previously described and was employed in the last 8 patients in this series to fill residual bone defects after remodeling.[3] Briefly, demineralized bone matrix, particulate bone material, and blood were mixed and protected in a sandwich between 2 layers of resorbable mesh to achieve protected bone regeneration.

Results

Thirteen patients were initially identified from the database who had sagittal craniosynostosis and had un-

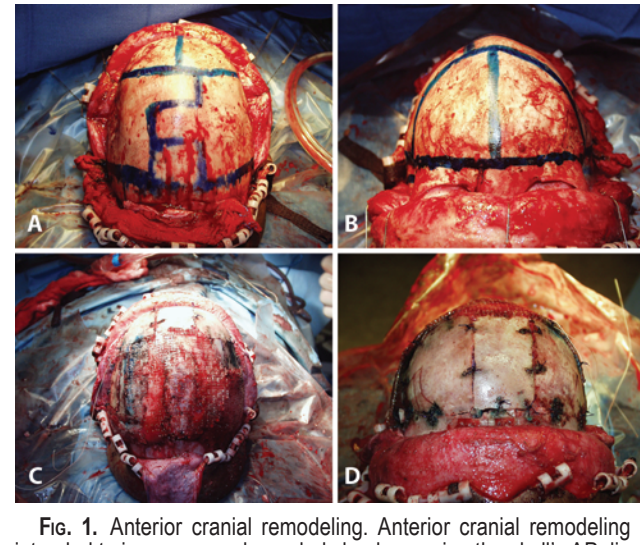

Fig. 1. Anterior cranial remodeling. Anterior cranial remodeling is intended to improve scaphocephaly by decreasing the skull's AP diameter, reduce frontal bossing by remodeling the frontal bone and placing an interpositional bone graft to widen it, and decrease bitemporal narrowing with out-fracture intended to widen the cranial base. **A:** Vertex view of planned osteotomies intended for out-fracture of the temporal/parietal bones and narrowing of the AP diameter. **B:** Frontal view of the exposed frontal bone with planned osteotomies for rearrangement of the frontal segments and placement of interpositional bone graft. **C:** Completed out-fracture with placement of demineralized bone matrix between a "sandwich" of absorbable plates, which offer rigidity and protect the regenerating bone from the destructive forces of dural pulsation. **D:** Frontal view with frontal bone rearrangement and widening with bone graft. Segments are fixed in place with PDS suture (Ethicon).

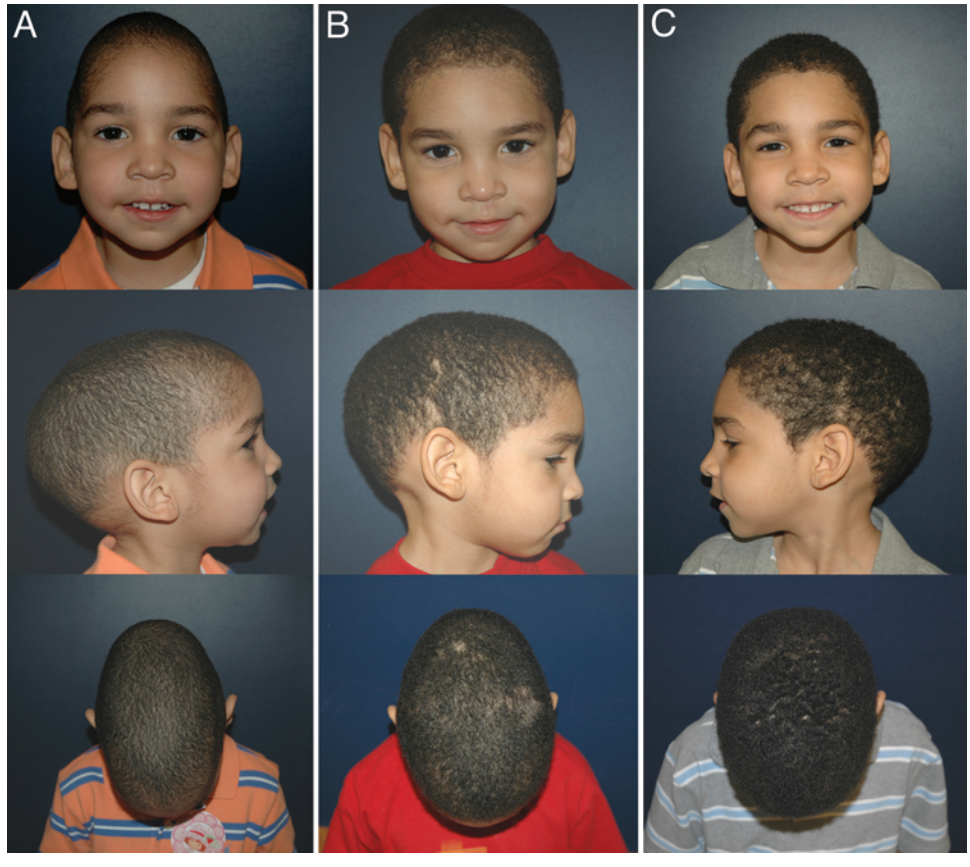

Fig. 2. Staged total cranial remodeling. Anterior and posterior approaches to cranial remodeling may be employed to target the regions of the head with the greatest pathology. In individuals with significant anterior and posterior pathology, we favor a staged approach for total cranial remodeling. **A:** Preoperative images showing significant anterior and posterior pathology with frontal bossing, bitemporal narrowing, and occipital constriction with bulleting. **B:** Seven-month postoperative images following anterior cranial remodeling showing improvement in frontal bossing, bitemporal narrowing and scaphocephaly, but persistent occipital bulleting. **C:** Thirteen-month postoperative images following a second-stage posterior cranial remodeling showing improvement of the occipital bulleting with further improvement of scaphocephaly.

dergone a cranial vault remodeling procedure at an age greater than 1 year. Two patients had inadequate records available and were excluded. One additional patient who underwent cranial vault expansion at 4.86 years of age for multisuture craniosynostosis was also excluded.

The remaining 10 patients presented at an average age of 1.75 years (range 0.93–3.14 years). Nine patients were boys. Eight patients underwent single-stage cranial vault procedures (5 anterior and 3 posterior). Three of the patients treated with anterior approaches underwent a frontal orbital expansion as part of this procedure. Two of the patients undergoing posterior approaches had Chiari malformation Type 1 and underwent concurrent decompression procedures. Two patients were treated with a 2-staged anterior and posterior approach (Fig. 2). The patients' average age at the time of cranial vault remodeling was 2.64 years (range 1.01–5.26 years). The second procedure was delayed 10.8 and 6.3 months for the patients undergoing staged reconstructions (Table 1). The average follow-up period was 2.24 years (range 0.2–9.3 years). All neurosurgical procedures were performed by a single surgeon (I.F.P.). Eight of the 10 patients were operated on by a single craniofacial surgeon (J.E.L.).

The average hospital length of stay for 12 operations completed in 10 patients was 4.1 days, with an average ICU stay of 1.3 days. Procedures were completed with an average surgical time of 5.4 hours. The average estimated blood loss volume was 544 ml. Intraoperative cell salvage was used for 7 patients in 9 cases, and an average volume of 187 ml of autologous blood was returned to the patients. Seven patients received packed red blood cell transfusions intraoperatively during 8 procedures. The average transfusion volume was 423 ml. Two of these patients and 1 additional patient received postoperative transfusions.

Intracranial Hypertension

Six patients exhibited clinical evidence of ICH during their preoperative evaluation (Table 1). In 4 patients, dilated fundoscopic examinations revealed papilledema. Four patients complained of headaches that were attributed to ICH. Of the 6 patients with clinical evidence of ICH, 2 had preoperative lumbar punctures performed under general anesthesia to confirm the presence of ICH; in both cases the pressure was greater than 30 mm Hg.

Despite the high incidence of ICH in our cohort, it was not commonly apparent at initial presentation. Often, diligent screening or longitudinal follow-up was needed to make the diagnosis. Three patients presented with a

TABLE 1: Summary of clinical characteristics in 10 patients who underwent cranial vault remodeling after the age of 1*

Case No.	Op	Age at Op (yrs)	Preop CI	Postop CI	Evidence of ICH	Significant Cranial Defects
1	ant approach w/ FOE	1.2			none	no
2	ant approach	3.0	73.7	72.1	papilledema, headaches, confirmed w/ LP	no
3	ant approach w/ FOE	4.9	63.3	68.3	copper beaten skull, headaches, confirmed w/ LP	no
4	staged ant/pst approach	3.4; 4.3	63.9	71.0	none	no
5	staged ant/pst approach	1.2; 1.8			none	no
6	pst approach w/ CM decompression	5.3	66.2	68.1	papilledema, headaches	no
7	pst approach	2.7	65.3	69.2	papilledema	no
8	ant approach w/ FOE	1.0	60.3	68.0	papilledema	no
9	ant approach	1.6	63.0	68.0	none	present at 3-mo FU
10	pst approach w/ CM decompression	2.2	67.4	68.1	headaches	present at 3-mo FU

* ant = anterior; CM = Chiari malformation; FOE = frontal orbital expansion; FU = follow-up; LP = lumbar puncture; pst = posterior.

chief complaint of scaphocephalic head shape and were subsequently found to have either papilledema or a Chiari malformation associated with occipital headaches, which motivated the decision to operate. The families of 2 patients initially declined surgery to correct the patients' head shape, but the patients later required surgery due to changing clinical conditions and development of ICH symptoms. One of these families was motivated toward operative management by development of posterior headaches associated with a known Chiari malformation. The other family declined surgery for sagittal synostosis when the patient was 9 months old, but the patient returned at 4 years of age with subsequent fusion of the coronal sutures and development of "copper beaten skull" radiographic findings, headaches, listless behavior, and intracranial pressure greater than 30 mm Hg on lumbar puncture. Finally, one patient underwent an extended strip craniectomy at 2 1/2 months of age and during follow-up presented with severe headaches at 3 years old. He was noted to have papilledema on ophthalmological examination; ICH was confirmed by lumbar puncture.

Intracranial hypertension was successfully treated by the described procedures in 5 of 6 patients. The patient previously treated with an extended strip craniectomy underwent an anterior two-thirds vault remodeling procedure at 3 years of age with temporary symptom alleviation and improvement of his papilledema. Unfortunately, his headaches and papilledema recurred and he underwent shunt insertion.

Three Type 1 Chiari malformations were identified in these patients. One patient had papilledema and occipital headaches that motivated surgical intervention and another had occipital headaches alone. Both patients were treated with concurrent posterior cranial vault remodeling and Chiari decompression. The third patient had papilledema but a more significant anterior cranial vault deformity. This patient underwent anterior two-thirds remodeling without Chiari decompression and papilledema resolved postoperatively.

Head Shape

Preoperative and postoperative CI measurements were obtained from the medical records in 8 cases. In 1 case, pre- and postoperative anthropomorphic measurements were available; in 3 cases, pre- and postoperative 3D CT scans were available for measurements; and in 4 cases only 2D axial CT scans were available. Surgical intervention significantly improved the CI from a preoperative mean of 65.4 to 69.1 postoperatively ($p = 0.013$, $t = 3.284$, the assumption of normality was met) (CI ranges: mesocranic 76–80.9, dolichocranic 70–74.9, hyperdolichocranic < 70).[16] The CI measurements increased by 5.7%. Seven of 8 patients showed CI improvement (Table 1). The individual without improvement had developed ICH following extended strip craniectomy in infancy. His head was not significantly scaphocephalic preoperatively (CI 73.7), and the surgical priority was vault expansion for ICH treatment.

Nine of 10 showed complete correction of their most significant cranial pathology (Fig. 2). One patient who underwent an anterior correction maintained significant occipital constriction and bulleting. This patient's most recent clinic visit was only 3 months after surgery. The possibility of staged posterior remodeling was discussed with the family, but the patient did not have ICH as of this writing and the family was not interested in additional interventions.

Cranial Defects

Two of 10 patients had palpable cranial bone defects on physical examination at their last follow-up appointment (Table 1). In both cases, the follow-up appointment was only 3 months after surgery and long-term follow-up findings were not yet available. In 4 additional patients, skull defects were visualized on CT scans, but the defects were small. Since these defects are not palpable, their clinical significance and likelihood of requiring correction are small. No revision bone-grafting procedures have been performed.

Complications

No death, postoperative bleeding, CSF leak, or sagittal sinus injury were documented. In 3 cases, small dural tears were discovered and treated intraoperatively with primary closure. One patient received a narcotic overdose while under observation in the ICU but suffered no long-term sequelae. Two patients were readmitted to the hospital because of fever, but in both cases viral illness was diagnosed when imaging and culture findings were negative. Two minor wound infections were treated successfully with oral antibiotics without operative intervention. Finally, 1 patient developed a small partial-thickness scalp injury that healed with hypertrophic scarring of this region.

Discussion

Surgical corrections performed for sagittal synostosis management are highly variable, and the optimal approach is controversial.[4–8,11,13,15,18] There are proponents of early interventions with open or endoscopically assisted strip craniectomies. These procedures are performed in isolation or with molding of the skull with postoperative helmeting or placement of springs to actively distract the suture site.[8,18] Others have advocated open remodeling of the cranial vault either through an anterior or posterior approach, while still others have advocated total calvarial remodeling either in a single or multiple staged procedures.[4–7,11,13,15,17] Although many case series have been reported in the literature, optimal treatment has yet to be fully defined.

Strip craniectomy techniques are performed in the early postnatal period to take advantage of the higher growth velocity to correct residual skull deformities, whereas advocates of more extensive remodeling procedures wait longer to improve the safety profile relative to blood loss and to decrease the potential for deformity relapse due to abnormal growth.[5,8,18] Regardless, all of these procedures are typically performed before patients reach 1 year of age for presumed improved aesthetic and functional outcomes. First, although the controversy regarding mental outcomes related to craniosynostosis surgery is far from settled, the knowledge that patients presenting after 1 year of age have more ICH and inferior developmental outcomes has motivated surgeons to operate before this age.[2] Second, large calvarial defects can heal spontaneously in infants, but this ability begins to diminish late in the 1st year of life, raising the risk of persistent skull defects.[12]

Because sagittal synostosis can be detected at birth, it is commonly diagnosed prior to 1 year of age. Surgical treatment of this condition at older ages can be successful, although patients who present later may be at higher risk of ICH, are less likely to experience healing of ungrafted cranial defects, and often require more extensive cranial remodeling procedures.[2,12,15,17]

With regard to the risk of ICH, our findings support those previously seen by Arnaud and associates.[2] Patients who present later with scaphocephaly are at a higher risk for ICH (60% in our small series). This may be due to a selection bias inherent in the population prone to present and undergo surgery at an older age, or it may represent the ultimate outcome of restricted suture growth. It does highlight the need for a greater degree of suspicion in approaching these patients, especially since 50% of our patients with ICH did not present with this complaint initially, and only diligent evaluation uncovered it. It also underscores the need for longitudinal care of all patients with craniosynostosis until they have completed their cranial growth, regardless if operative management is undertaken. One of our patients presented at 9 months of age and the family declined operative intervention until ICH developed later in childhood and fusion of the coronal sutures was noted on repeat imaging. Another patient underwent an extended strip craniectomy at 2 1/2 months of age and subsequently developed ICH that did not respond to cranial remodeling and required shunt placement. Development of ICH after strip craniectomy is rare, occurring in 1.5% of cases in one series,[1] but it underscores the importance of ongoing follow-up in patient management. Families must be educated regarding the symptoms of ICH and patients must be seen annually for a dilated fundoscopic examination to rule out papilledema. When present, papilledema and other symptoms must be followed regularly postoperatively to document their resolution.

When operating on older patients with sagittal craniosynostosis, the potential for development of nonhealing calvarial bone defects is higher than when operating on those less than a year old.[12] In our series, no patients with significant follow-up were found to have clinically significant or palpable defects in their cranium. We achieved this result through the aggressive use of bone-grafting techniques. All bone chips and bone dust resulting from the remodeling procedures should be kept and used in the grafting procedure. These were mixed with allogeneic demineralized bone matrix when defect size demanded. Additional technical improvement can be achieved in large calvarial defects by protecting the healing bone graft from the dural pulsations that can fracture and destroy immature regenerating bone. This is achieved by creating a "sandwich" of absorbable mesh above and below the bone-grafting material; the mesh will ultimately be resorbed after calvarial healing is complete.[3]

Our results indicate that a tailored operative approach adequately and reliably addressed each patient's pathology and improved both their CI and cranial shape. Our results demonstrated a significant improvement in CI with operative intervention. While the 5.7% increase was less impressive than that reported in other series, this may be partially explained by the high incidence of ICH in our cohort.[10] While the goal of calvarial remodeling should always be to normalize head shape, one must be cognizant of the need to expand the cranial volume. With a 60% incidence of ICH in our cohort, we may have tempered how vigorously we decreased the cranial AP diameter in these cases. Surgeons should aggressively decrease the AP diameter to improve CI when remodeling the scaphocephalic cranium, but must do so without compromising the goal of resolving ICH. Regardless of this, all but one of our patients showed marked improvement in CI, and all families were uniformly pleased with the outcomes. Additionally, "normal CI" is somewhat of a misnomer. The CI is widely variable between ethnic groups, and with an ethnically heterogeneous population, particularly one as small as ours, the idea of normalizing the CI is erroneous. The surgeon's goal should

be to decrease the AP dimension and widen the head to make the patient's skull more closely approximate a normal appearance in light of his or her ethnicity and other features.

While the most easily standardized, CI should only be one outcome measurement of scaphocephaly correction. Other abnormalities such as temporal narrowing, frontal bossing, and occipital constriction can be more noticeable and problematic than an abnormal CI. Addressing these deformities can be the most important component of management. Our strategy followed an algorithm previously described to target interventions to the area of greatest pathology.[17] The pathological findings in children with craniosynostosis may be widely variable, and not all patients require the same operation. Significant frontal bossing, temporal narrowing, and hypotelorism may be addressed through an anterior approach, while occipital findings of constriction and bulleting may be addressed through a posterior approach. Both interventions afford the opportunity to narrow the AP dimension and out-fracture the skull to improve the CI. If a patient presents with significant anterior and posterior pathology, a total calvarial remodeling may be indicated. We elected to perform this procedure in a staged manner in the cases described here, after discussion with the families about the pros and cons of single versus 2-staged interventions. When taking this approach, one must involve the family in the consent process to identify their understanding of the deformity and to discern which components of it are most troubling to them. As one of our cases demonstrates, for a deformity that may warrant consideration of both anterior and posterior remodeling, the family may opt for and be satisfied with a less-extensive procedure, provided the most significant areas of pathology are addressed.

Conclusions

Surgical treatment of patients with sagittal craniosynostosis after the age of 1 is uncommon and carries with it special considerations. Whether due to selection bias or the evolution of progressive growth restriction, these patients are at increased risk for ICH. Following patients longitudinally until cranial growth is complete to document absence of ICH is essential. Individuals older than 1 year of age are at increased risk for developing nonhealing cranial defects, but the use of protected bone regeneration techniques can prevent this. Significant improvement in head shape can be achieved in this population, and these patients may benefit from having less postoperative growth to complete, which may lead to less recurrence of the phenotype. When using a defect-targeted approach to the anterior, posterior, or total calvaria, involvement of the patient's family in planning is essential to assess their willingness to consider a multi-staged treatment plan and to identify the pathological findings most concerning to them.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Pollack, Kim, Kumar. Acquisition of data: Rottgers. Analysis and interpretation of data: Rottgers, Cray. Drafting the article: Rottgers. Critically revising the article: Pollack, Kim, Kumar, Cray, Losee. Statistical analysis: Cray. Administrative/technical/material support: Losee. Study supervision: Pollack, Losee.

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Reconstruction of unicoronal plagiocephaly with a hypercorrection surgical technique

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Object. Successful surgical repair of unicoronal plagiocephaly remains a challenge for craniofacial surgeons. Many of the surgical techniques directed at correcting the stigmata associated with this craniofacial deformity (for example, ipsilateral supraorbital rim elevation [vertical dystopia], ipsilateral temporal constriction, C-shaped deformity of the face, and so on) are not long lasting and often result in deficient correction and the need for secondary revision surgery. The authors posit that the cause of this relapse was intrinsic deficiencies of the current surgical techniques. The aim of this study was to determine if correction of unilateral coronal plagiocephaly with a novel hypercorrection surgical technique could prevent the relapse of the characteristics associated with unicoronal plagiocephaly.

Methods. The authors performed a retrospective analysis of 40 consecutive patients who underwent surgical repair of unicoronal plagiocephaly at their institution between 1999 and 2009. In all cases, the senior author (S.R.B.) used a hypercorrection technique for surgical reconstruction. Hypercorrection consisted of significant overcorrection of the affected ipsilateral frontal and anterior temporal areas in the sagittal and coronal planes. Demographic, perioperative, and follow-up data were collected for comparison. The postsurgical appearance of the forehead was documented clinically and photographically and then evaluated and scored by 2 independent graders using the expanded Whitaker scoring system. A relapse was defined as a recurrence of preoperative features that required secondary surgical correction.

Results. The mean age of the patients at the time of the operation was 13 months (range 8–28 months). The mean follow-up duration was 57 months (range 3 months to 9.8 years). The postsurgical hypercorrection appearance persisted on average 6–8 months but gradually dissipated and normalized. No patients exhibited a relapse of unicoronal plagiocephalic characteristics that required surgical correction. In all cases the aesthetic results were excellent. Only 3 patients required reoperation for the management of persistent calvarial bone defects (2 cases) and removal of a symptomatic granuloma (1 case).

Conclusions. Our study demonstrates that patients who undergo unicoronal plagiocephaly repair with a hypercorrection surgical technique avoid long-term relapse. Our results suggest that the surgical technique used in the correction of unilateral coronal synostosis is strongly associated with the prevention of postsurgical relapse and that the use of this novel method decreases the need for surgical revision. *(DOI: 10.3171/2011.6.FOCUS1193)*

Key Words • **craniosynostosis** • **unicoronal plagiocephaly** • **frontal plagiocephaly** • **temporal constriction** • **surgical relapse**

Successful repair of all abnormal characteristics of unicoronal plagiocephaly remains a challenge for craniofacial surgeons. Although the phenotypical characteristics of unicoronal plagiocephaly have been clearly described (ipsilateral supraorbital rim elevation [vertical dystopia] and retrusion, ipsilateral frontal bone retrusion, ipsilateral temporal constriction, contralateral frontal boss, contralateral temporal boss, and C-shaped deformity of the face), current surgical techniques often do not successfully achieve long-term correction of all of the associated deformities by a single surgical procedure.[13,22,31] Multiple published reports have demonstrated a sizeable subset of patients with unicoronal plagiocephaly who undergo surgical correction and also require a secondary surgical procedure to correct postsurgical residual deformities, increasing the morbidity rate.[23]

Some resurgence of interest in endoscopic strip craniectomy repair of unilateral coronal synostosis has been shown since the advent of adjuvant helmet therapy, but this technique is limited by the age limitations required for successful outcomes (< 3–5 months of age) and the variable degree of patient compliance with the mandatory postsurgical helmet protocols. The unreliable outcomes have driven craniofacial surgeons to seek different surgical procedures.[17,18] Currently, open approaches are considered the "standard of care" to correct unicoronal plagiocephaly.

Multiple open surgical techniques to correct unicoro-

nal plagiocephaly have been described. Hoffman and Mohr[13] have described the lateral canthal advancement technique for expanding the affected ipsilateral anterior cranial fossa by releasing the frontoethmoidal and frontosphenoidal sutures that were also believed to contribute the characteristics of unicoronal plagiocephaly. Long-term follow-up of this technique has shown that 7 (17.9%) of 39 patients experienced relapse of the original deformity warranting surgical reoperation.[22]

One of the most common postsurgical deformities after unicoronal repair is ipsilateral temporal constriction.[28,31] Hilling et al.[12] published an article on a series of 53 patients who underwent unilateral coronal synostosis repair in which a bandeau advancement technique was used. Patients in whom this technique was used, however, commonly presented with residual postoperative temporal constriction. Oh et al.[27] showed that placement of calvaria bone graft along the osteotomized coronal suture could prevent temporal constriction. However, they did not adequately substantiate their claims as they had an insufficient number of patients to statistically support the reliability of the technique. Strikingly, Steinbacher and colleagues[31] demonstrated that all patients who underwent unicoronal plagiocephaly repair in which a unilateral frontoorbital advancement bandeau technique was used presented with residual postsurgical temporal hollowing. Eppley et al.[9] acknowledged that a significant number of patients who underwent craniosynostosis repair required hydroxyapatite-based cranioplasty to correct postsurgical deformities (relapse). These reports affirm that a current single surgical procedure is unable to successfully and predictably correct all the characteristics of coronal plagiocephaly.

Surgical repair of unicoronal plagiocephaly requires the correction of both the underlying bony deformity associated with the synostotic suture as well as the management of the overlying soft-tissue envelope. In line with the tenets of the law of Wolff as well as the functional matrix theory, we believe that surgical techniques that repair unicoronal plagiocephaly without addressing the postsurgical recoil of the soft-tissue envelope may be associated with a surgical relapse.[25,26,34] We hypothesize that correction of unicoronal plagiocephaly with a hypercorrection technique (one that overstretches the soft-tissue envelope to counteract recoiling forces) is associated with a lower incidence of postsurgical relapse.

Methods

Study Criteria

This study was a retrospective analysis of patient charts in cases in which unilateral coronal synostosis repair was conducted at the University of Michigan Craniofacial Anomalies Program between 1999 and 2009. The study was performed in concordance with the institutional review board.

Demographic data were recorded and included patient age at the time of surgery and at the last follow-up, surgical technique, estimated blood loss, and perioperative transfusion volume. Exclusion criteria included incomplete medical record, absence of follow-up clinical images, multisuture synostosis, syndromic disease, and major concomitant medical conditions.

Surgical Technique

All surgical procedures were performed by the senior author (S.R.B.). A wavy bicoronal scalp incision was used. The anterior scalp flap was dissected in a subgaleal plane and reflected anteriorly. Dissection transitioned to the subpericranial plane 2 cm above the supraorbital rims to avoid damaging the supraorbital neurovascular bundles. Dissection was extended to expose the nasofrontal junction, the anterior orbital aspect of the bilateral supraorbital rim, and the bilateral frontozygomatic sutures. Bilateral temporalis muscles were exposed by dissecting superficially to the deep temporal fascia. A frontal craniotomy was performed by the neurosurgeon in a standard fashion.[5] The supraorbital bar was harvested in a standard fashion without bandeau extensions.[5] Bilateral temporalis muscles flaps were dissected off the temporal fossa subperiosteally to a level inferior to the zygomatic arch. The supraorbital bar was contoured with Tessier bone benders to achieve a smooth flattened contour. The inferolateral edge of the ipsilateral supraorbital rim was contoured with rongeurs to achieve a widened and arched shape that resembled the appearance of the contralateral unaffected side. Barrel stave osteotomies were performed in the ipsilateral temporal bone to widen the cranial vault and cross-strut stabilization was used to hold the correction out against the recoiling forces of the scalp.[20]

The recontoured supraorbital bar is repositioned in a hypercorrected position both in the coronal and sagittal planes. To achieve this hypercorrected position, the supraorbital bar was placed in a declined position (higher on the unaffected side and lower on the affected side) in the coronal plane, with the unaffected side pivoting upon its frontozygomatic suture (Fig. 1 *white arrow*) and the affected side positioned in a relatively inferior position upon the corresponding frontozygomatic suture (vertical hypercorrection) (Fig. 1 *right arrow*). The supraorbital bar is also asymmetrically displaced anteriorly in the sagittal plane so that the unaffected side keeps pivoting at its corresponding frontozygomatic suture and the affected side is positioned significantly anterior to its corresponding frontozygomatic suture (horizontal advancement hypercorrection) (Fig. 1 *yellow arrow*). The hypercorrected frontoorbital bar is held in place at the level of the unaffected frontozygomatic suture side with Vicryl sutures. The frontal bar crosses the frontonasal junction, which helps to support the advanced bone and is also held with Vicryl sutures. Finally, a resorbable plate is used to support the significant advancement of the affected side to achieve hypercorrection. The desired hypercorrection is checked prior to welding the resorbable plate to its bony attachments by reflecting the anterior bicoronal flap and inspecting the degree of displacement. An interpositional bone graft obtained from the endocortical side of the frontal bones is then attached to the resorbable plate to reinforce and add durability to the hypercorrection (Fig. 1). The more malleable frontal bones are then reshaped to correct the ipsilateral flattening and contralateral frontal bossing. Finally, the frontal bone is reattached to the

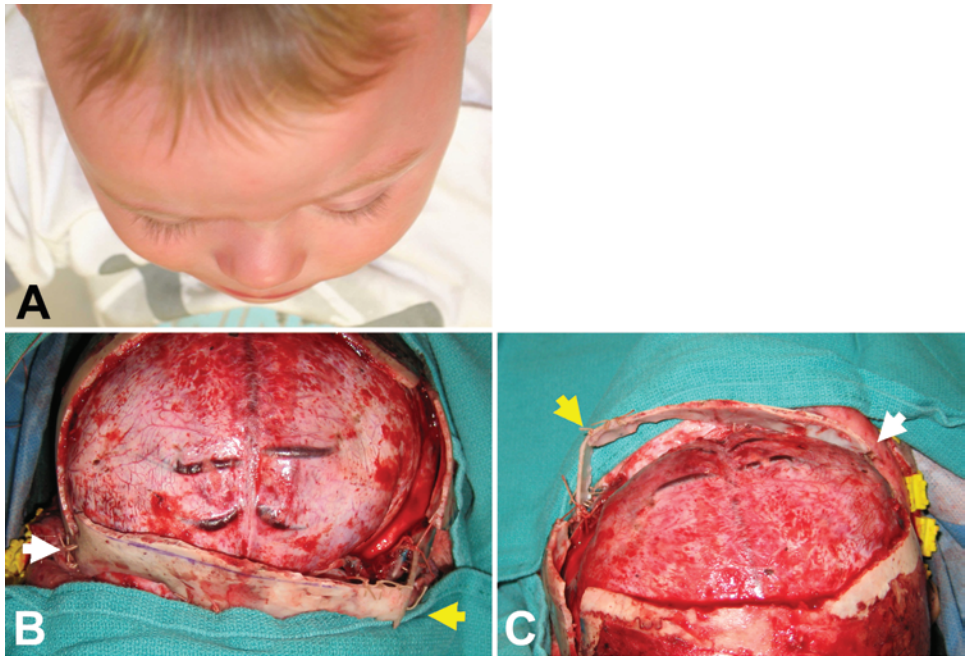

Fig. 1. Surgical hypercorrection of unicoronal synostosis. **A:** Preoperative appearance of the forehead. **B**: Hypercorrection of the supraorbital bar in the coronal plane. **C**: Hypercorrection of the supraorbital bar in the sagittal plane. The *yellow arrows* show hypercorrection of the supraorbital bar on the ipsilateral affected side, and the *white arrows* indicate the pivoting point of the unaffected frontoorbital bar side.

supraorbital bar with either resorbable plates or Vicryl sutures.

The temporalis muscle flap of the affected side is rotated anteriorly over the advanced lateral orbital rim to fill and recontour the anterior aspect of the reconstructed temporal fossa. The temporalis muscle is held in the desired place with Vicryl sutures often anchored to adjoining bone through tactically placed drill holes. The bicoronal flap is once again flipped back to check the contour of the anterior temporal fossa (Fig. 1). If there is clinical evidence of residual temporal undercorrection, the temporalis muscle can be reshaped and "sculpted" by applying Vicryl sutures within the muscle itself. Judicious use of bone grafts can also be used to achieve the desired contour. The temporalis muscle of the unaffected side was minimally repositioned to gain temporal fossa symmetry with the opposite side and secured in the same fashion using Vicryl sutures. The bicoronal incision is closed in layers, leaving the most distal 1–1.5 cm ends of the incision behind the ear open for fluid drainage in both sides. No drains are placed. The incision is covered with topical antibiotic ointment. The head is covered with a sterile head wrap dressing.

Study Data

Clinical progress notes were evaluated to determine complications, causes of reoperation, and postoperative assessment of the patient's cranial vault and face. Preoperative and postoperative photographs were evaluated and scored by 2 independent graders (a senior plastic surgery resident and postgraduate student from the institution not related with the study) using the expanded Whitaker scoring system.[3,32] The elements of the craniofacial evaluation included the position of the ipsilateral supraorbital rim (vertical dystopia), the shape of the ipsilateral and the contralateral forehead, the presence of ipsilateral temporal constriction, and the degree of residual C-shaped deformity. Data were analyzed using standard statistical tests.

Results

A total of 40 patients (16 boys and 24 girls) were included in the study. Thirty-five patients were nonsyndromic and 5 were syndromic. Left coronal synostosis (23 cases) was more common than right coronal synostosis (17 cases) in our cohort. The mean age at the time of surgery was 13 months (range 8–28 months). The average perioperative estimated blood loss was 164 ml (range 25–600 ml). In 18 patients (44%) perioperative blood transfusion was performed. The mean hospital length of stay was 5 days (range 4–6 days). The mean follow-up duration was 57 months (range 3 months to 9.8 years). Patients were routinely seen at the following postoperative intervals: 2 weeks, 2 months, and then every 1 to 2 years until reaching 10 years of age. In accordance with our hospital policy, patients did not undergo routine postoperative radiography or CT scanning.

Our results indicated an immediate intraoperative hypercorrection of the unicoronal plagiocephaly resulting in a lowered and anteriorly projected ipsilateral supraorbital rim and ipsilateral forehead and significant lateral projection of the anterior temporal area compared with the contralateral side and preoperative appearance (Fig. 1).

A hypercorrected appearance was present in all treated patients for an average of 6–8 months, but the hypercorrection gradually dissipated and normalized (Fig. 2). There

were no acute perioperative complications such as infection, surgical wound dehiscence, or collapse of the hypercorrection. There were no deaths.

Review of the charts demonstrated that no patient required reoperation for correction of a surgical relapse (based on either the surgical team physical examination and/or patient's parents' assessment). Only 3 patients required reoperation for reasons not associated with relapse: 2 patients underwent bone grafting of persistent calvarial defects, and 1 patient required removal of a symptomatic scalp granuloma, thought to be secondary to a foreign body reaction of the underlying resorbable plate.

Clinical evaluation of the patients' pre- and postoperative photographs using the expanded Whitaker scoring scale demonstrated that the majority of cases were Category I (no imperfections noted) for the following characteristics analyzed: supraorbital rim elevation (vertical dystopia) 80% (32 cases); shape of ipsilateral forehead (vertical dystopia) 82.5% (33 cases); shape of contralateral forehead 97.5% (39 cases); and ipsilateral temporal constriction 82.5% (33 cases) (Table 1). In the remainder of cases the appearance was Category IIA (minor imperfections noted, but no surgical revision performed or planned) for the same categories: supraorbital rim elevation (vertical dystopia) 20% (8 cases); shape of ipsilateral forehead (vertical dystopia) 17.5% (7 cases); shape of contralateral forehead 2.5% (1 cases); and ipsilateral temporal constriction 17.5% (7 cases) (Table 1). No patient had phenotypic characteristics classified as Category IIB (minor imperfections that required minor soft-tissue or bone contouring revisions), Category III (major bony or soft-tissue imperfections that required major alternative osteotomies for bone grafting), or Category IV (severe relapse that required repetition of the original surgery) (Table 1).

Clinical evaluation of the patients' postoperative photographs for the appearance of the C-shaped deformity showed that this deformity improved in 57.5% (23 cases), remained unchanged in 5% (2 cases), and corrected in 37.5% (15 cases). No patient had worsening of a C-shaped deformity. These differences were statistically significant (Table 2).

Although our patients did not undergo routine postoperative radiography or CT evaluation due to our institution's pediatric patient radiation exposure policy, one of the patients underwent head CT scanning for an unrelated medical condition. The 3D CT scans demonstrated that the affected left supraorbital rim, left forehead region, and left anterior temporal area resembled the appearance of the contralateral normal side (Fig. 3). Close evaluation of axial bone-window CT scans showed a slight difference in the anterior projection of the affected left supraorbital rim compared with the contralateral side but the configuration overlying soft-tissue envelope resembled the radiological contour of the contralateral normal side (Fig. 4). Clinical evaluation of postoperative images showed no evidence of ipsilateral supraorbital rim or forehead retrusion compared with contralateral side (Fig. 4).

Discussion

Relapse after unilateral coronal synostosis repair is a common finding associated with multiple surgical techniques.[22,23,31] Although surgical procedures to correct unicoronal plagiocephaly have evolved significantly, postsurgical deformities (relapse) that warrant secondary corrective surgical revisions are still common.[10,28] Our proposed hypercorrection technique for unicoronal synostosis was not associated with a surgical relapse (Category IIB or above on the expanded Whitaker scale) that warranted a subsequent corrective reoperation (Fig. 2–4, Table 1).

Hoffman and Mohr[13] introduced the lateral canthal advancement of the supraorbital margin as an alternative to strip craniectomies for the correction of unicoronal synostosis. Long-term follow-up of this technique in a se-

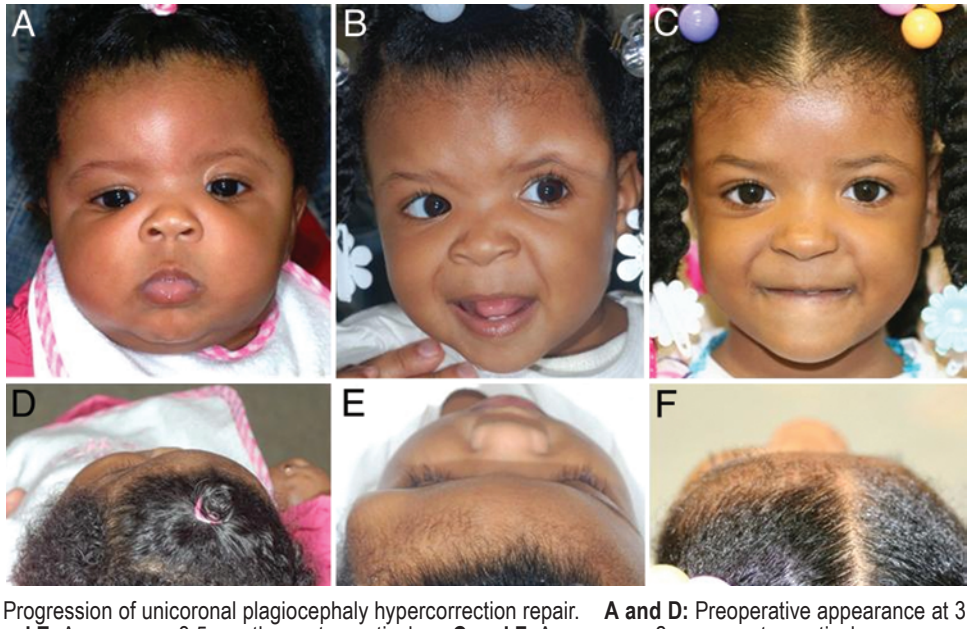

Fig. 2. Progression of unicoronal plagiocephaly hypercorrection repair. **A and D:** Preoperative appearance at 3 months of age. **B and E:** Appearance 3.5 months postoperatively. **C and F:** Appearance 2 years postoperatively.

TABLE 1: Clinical evaluation of photographic appearances after unicoronal plagiocephaly repair with the hypercorrection surgical technique

Extended Whitaker Category	No. of Patients (%)			
	Supraorbital Rim Elevation (vertical dystopia)	Ipsilateral Forehead	Contralateral Forehead	Ipsilateral Temporal Constriction
I	32 (80.0)	33 (82.5)	39 (97.5)	33 (82.5)
IIA	8 (20.0)	7 (17.5)	1 (2.5)	7 (17.5)
IIB	0	0	0	0
III	0	0	0	0
IV	0	0	0	0

ries of 39 patients showed that even though the majority of the patients had good results after surgery (24 [65%] of 37 available for follow-up), a significant number of patients (7 [18.9%]) had postsurgical deformities that required reoperation.[22] The characteristics of the relapse that warranted major reoperation were not described, making it difficult to assess the potential cause of such relapse.

McCarthy et al.,[23] in a report on their 23-year experience in the management of craniosynostosis, indicated that 6 (18.8%) of 32 patients who underwent unicoronal plagiocephaly in which the authors used the tongue-in-groove frontoorbital advancement technique had unchanged vertical dystopia. Bartlett and colleagues[3] compared the surgical outcomes of the uni- and bilateral tongue-in-grove frontoorbital advancement technique in the management of patients with unicoronal plagiocephaly. Approximately 20% of the patients who underwent repair with either the uni- or bilateral technique had a Category IIB appearance according to the extended Whitaker scale. The most common postsurgical deformity was constriction of the lateral temporal area and/or surface irregularities that involved the lateral forehead anterior to the temporal region.

Hilling et al.[12] evaluated the aesthetic results of a frontoorbital advancement technique for the management of unicoronal synostosis. In their large series of 137 patients, the authors noticed that the worst persistent postoperative deformity was temporal constriction and that the problem worsened with time. Interestingly, they noted that the age at which the patient underwent surgery did not influence the postoperative aesthetic result. These results contrast the findings reported by Jane and associates[15] that suggest that a different surgical technique (frontal bone overlaying, modified lateral canthal advancement, and tongue-in-groove technique) should be used depending on the age of the patient at the time of surgery.

Our study demonstrates that patients who underwent unicoronal plagiocephaly repair in which the hypercorrection technique was used did not undergo reoperation for correction of surgical relapse. The majority of the postoperative photographs (> 80%) reflected a Category I result based on the extended Whitaker scale (Table 1). The remainder of the patients (approximately 20%) had minor imperfections (ipsilateral supraorbital rim [8 patients], ipsilateral forehead [7], contralateral forehead [1], and ipsilateral temporal constriction [7]) that did not warrant surgical intervention (Category IIA). Among these minor imperfections, ipsilateral temporal constriction was not the most common finding, contrasting with previous published data (Table 1).[12,31]

TABLE 2: Effects of the unicoronal plagiocephaly hypercorrection surgical technique on C-shaped deformity

Condition of C-shaped Deformity Postop	Incidence (no. of cases)
worse	0.0% (0)
unchanged	5.0% (2)
improved	57.5% (23)
corrected	37.5% (15)

Temporal hollowing is a common finding after unicoronal plagiocephaly repair.[3,28,31] The cause of the temporal hollowing remains a matter of debate. Multiple reports have suggested the role of temporal muscle atrophy,[31] temporal fat atrophy,[30] and type of surgical technique[12,15] in the causation of postsurgical temporal hollowing. Persing et al.[28] described the temporalis musculo-osseous flap surgical technique as a method to prevent temporal hollowing after frontoorbital advancement in a patient with unicoronal plagiocephaly. However, because this report was based on a single case, it is difficult to assess the reliability of the technique. Steinbacher and colleagues[31] found that all the patients who underwent unicoronal plagiocephaly repair with a unilateral bandeau frontoorbital advancement presented with bitemporal constriction due to both the relapse of the bony bandeau and constriction of the temporalis muscle, but not to atrophy of the temporalis fat. Our study showed that the majority of the patients (82.5% [33 patients]) treated with the hypercorrection surgical technique resisted the development of bitemporal constriction (extended Whitaker Category I) (Fig. 3). In contradistinction to the findings of Steinbacher and colleagues all the temporal abnormalities found in our series were classified as extended Whitaker Category IIA, and none of our patients were classified as Category IIB. It is possible that the lateral hypercorrection of the temporal area on the affected side, in addition to the anterior hypercorrection of the ipsilateral frontal area, prevented the occurrence of the temporal constriction relapse commonly seen with other surgical techniques.[31] These data suggest that the type of surgical technique has a strong influence on the aesthetic outcomes of unicoronal plagiocephaly repair, especially in regard to postsurgical temporal constriction.

Hansen et al.[11] compared the outcomes achieved with 3 different surgical techniques in the management of

Fig. 3. Clinical appearance of patients with unilateral coronal plagiocephaly preoperative **(left column)** and after correction with the hypercorrection surgical technique **(right column)**.

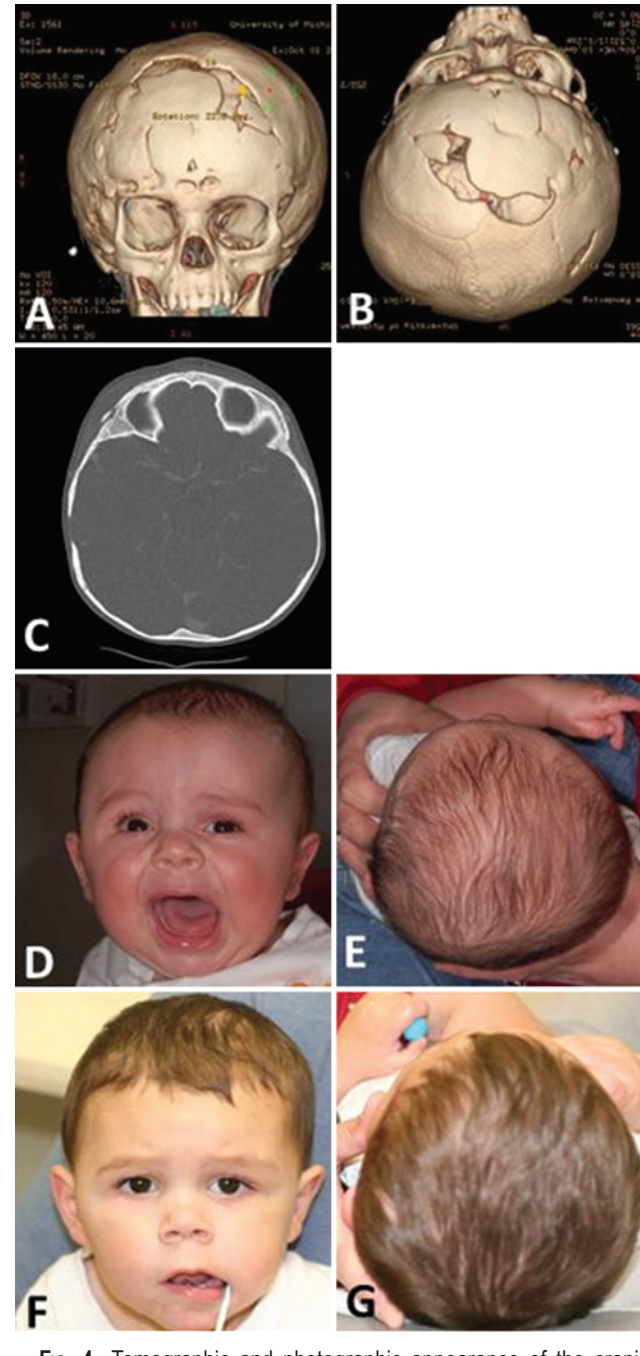

Fig. 4. Tomographic and photographic appearance of the cranial vault and face after unicoronal synostosis repair with the hypercorrection technique. **A and B:** Three-dimensional CT scans. **C:** Axial CT scan. **D and E:** The patient's preoperative clinical appearance. **F and G:** The patient's postoperative appearance.

unicoronal plagiocephaly repair. Their report suggested that only surgical techniques that included the osteotomy of the nasal root significantly improved the nasal canthal associated with the C-shaped deformity of the face. Our hypercorrection surgical technique did not osteotomize the root of the nose. The reason behind not performing nasal osteotomies was to avoid instability of the hypercorrected frontoorbital bar at the nasofrontal junction (pseudobuttress). We did, however, see improvement in our patients. Clinical evaluation of the progression of the C-shaped deformity postoperatively showed that the 15 patients, or 37.5%, had a corrected deformity, 23 (57.5%) had an improved deformity, and 2 (5%) had an unchanged

deformity. Our results with regard to the nasal root deviation and C-shaped deformity are in concordance with reports of surgical techniques that also do not osteotomize the root of the nose.[23]

Split calvarial bone grafts are not routinely used for primary correction of unilateral coronal plagiocephaly.[12,22,23,31] Hoffman and Mohr[13] used calvarial bone graft to maintain the lateral canthal advancement, but their technique was not associated with hypercorrection. Our technique used bone grafts to primarily reinforce a dissolvable plate that maintains the hypercorrection of the frontoorbital bar in the synostotic side (preventing collapse of the construct as the resorbable plate resorbs/weakens with time). Additionally, split calvarial bone grafts are used when appropriate to correct minor imperfection of the hypercorrection that are seen once the anterior bicoronal flap is repositioned over the hypercorrected framework. Because the ultimate goal of the technique is to achieve asymmetrical hypercorrection of the frontoorbital advancement with the soft-tissue envelope in place, any superficial contour irregularities (depressions, edges, and so on) are corrected by placing split calvarial bone grafts underneath the area of concern ("touch up").

The mean age of patients at the time of surgery in our series was 13 months (range 8–28 months). Although our institution's policy is to perform correction of unilateral coronal plagiocephaly when the patient is between 6 and 12 months of age, the timing of surgery was affected by the age of the patient at the time of referral, cancellations due to patient sickness (upper airway respiratory infections, for example), and/or scheduling issues. Performing surgery at ages less than 6 months is associated with very soft calvarial bone that may not be strong enough to withstand the desired hypercorrection. Cranial vault remodeling, performed at ages older than 16 months, could be associated with the persistence of calvarial bone defects due to decreased osteogenic potential of the dura. Additionally, advance age at the time of the operation may be associated with development of elevated intracranial pressure and subsequent developmental delays.[29,33] Although 2 of our patients required reoperation for management of persistent calvarial bone defects, both patients underwent surgery at 12 months of age. Review of patient charts showed that no patient in our series developed clinical signs of elevated intracranial pressure pre- or postoperatively per clinical assessment and ophthalmological funduscopic assessment. Neurological development after correction of unilateral coronal synostosis with the hypercorrection surgical technique was not assessed in this study.

Traditional 2D clinical pre- and postoperative photographs were assessed to evaluate the position of the ipsilateral supraorbital rim (vertical dystopia), shape of the ipsilateral and contralateral forehead, presence of ipsilateral temporal constriction, and degree of residual C-shaped deformity in our study. Two-dimensional photographs were evaluated using the expanded Whitaker scoring system.[3] Two-dimensional photography has been widely used and validated to evaluate the characteristics of craniofacial malformations and to assess the effect of therapeutic surgical procedures in the correction of such conditions.[1,3,10,11,22,32] Three-dimensional photography is a novel technology that allows us to capture a patient's superficial craniofacial anatomy in 3 dimensions.[14,19] This revolutionary imaging technology has the potential of quantifying volumetric changes of the facial soft tissues[6,16,19] as well as cranial vault volume.[24] Three-dimensional photography appears to be the ideal tool to assess and quantify the effect of surgical techniques in the correction of craniofacial malformations such as unilateral coronal plagiocephaly. Analysis and quantification of the effects of the hypercorrection surgical technique in the management of unilateral coronal synostosis, particularly in the forehead, could not be performed in our series because this technology was not readily available for clinical use at the time the majority of the patients underwent preoperative photographic documentation.

Our study did not include routine postoperative radiographic evaluation (radiography or CT scanning) of patients who underwent unicoronal plagiocephaly repair. Our Children's Hospital policy strongly encourages the avoidance of radiation exposure in pediatric patients, especially during the phase of rapid brain growth (from birth up to 3 years of age).[4,7,8,21] This policy is welcomed and practiced by our neurosurgery colleagues. Although valuable information could be obtained from postoperative CT scans to establish the potential structural causes of unicoronal plagiocephaly surgical relapse,[31] the uncommon and minor postsurgical deficiencies observed with our hypercorrection surgical technique did not warrant routine evaluation of postoperative CT scans.

Multiple studies have suggested that the possible cause of surgical relapse associated with surgical techniques was the lack of overcorrection.[11,12,22] We posit that the low incidence of relapse associated with our unicoronal plagiocephaly hypercorrection technique is due to the increased support of the hypercorrected bony framework design, which functions to counter and resist the soft-tissue recoil in patients with unicoronal plagiocephaly (functional matrix theory).[2,25,34]

Conclusions

Our results suggest that the type of surgical technique used in the correction of unilateral coronal synostosis has a strong effect on the occurrence of postoperative relapse. Our report demonstrates that patients who undergo unicoronal plagiocephaly repair with a hypercorrection surgical technique resisted long-term relapse and did not require secondary surgical correction.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Buchman, Mesa. Acquisition of data: Mesa, Fang. Analysis and interpretation of data: Buchman, Mesa, Fang. Drafting the article: Mesa. Critically revising the article: all authors. Statistical analysis: Mesa. Administrative/technical/material support: Buchman, Mesa, Muraszko. Study supervision: Buchman, Mesa.

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Endoscope-assisted strip craniectomy and postoperative helmet therapy for treatment of craniosynostosis

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Object. The primary goals of treatment in the infant with craniosynostosis are to correct the deformity and allow for adequate brain growth in as safe and effective a manner as possible. Herein, the authors present the results of treating craniosynostosis using an endoscope-assisted strip craniectomy and postoperative helmet therapy (EASC + PHT) in the hopes of providing further evidence of its role in the treatment of multiple different forms of craniosynostosis. This is a retrospective review of the patients treated with this technique at Children's Hospital Boston.

Methods. The electronic medical records of all children with craniosynostosis treated using this technique were reviewed retrospectively. A priori, data were collected for deformity type, patient age at surgery, number of transfusions, operative time, length of hospital stay, and anthropometric measurements.

Results. One hundred seventy-three patients (61 females and 112 males) were treated at our institution between July 2004 and March 2011 with EASC + PHT. The mean operative time was 46.30 minutes. Eight (4.6%) of the 173 patients received blood transfusions. The average length of hospital stay was 1.35 days, with the majority of patients being discharged the day after surgery. All complications and any patient who required additional craniofacial reconstructions are discussed. In addition, a subgroup analysis was done for patients who had undergone surgery and had longer than 1 year of follow-up.

Conclusions. The authors' growing database of patients supports the experiences described by others that early treatment of craniosynostosis with an EASC + PHT is a safe and efficacious technique. In addition, cost reduction due to decreased hospital stay and limitation of blood transfusions are demonstrable benefits associated with the use of this technique. *(DOI: 10.3171/2011.6.FOCUS1198)*

Key Words • **craniosynostosis** • **endoscopic surgery** • **helmet therapy** • **strip craniectomy**

The premature fusion of calvarial sutures, better known as craniosynostosis, is a well-known cause of deformational changes to the skull. It has an estimated frequency of 0.4 of 1000 live births, with the majority consisting of isolated single suture defects.[6] The etiology of most cases is sporadic and not well established, although there is a strong genetic component and more than 70 identified syndromes. Early scientific inquiry into this disease entity revealed several theories as to its pathogenesis. Virchow[22] first described the fundamental aberrant growth patterns, noting the "compensatory growth" of the calvaria. Moss[13] espoused the "fundamental matrix theory," which stated that the active growth of the underlying brain dictated the passive cranial growth along the suture lines. These theories, with the presumption that prenatal abnormalities at the fused suture and/or skull base are the cause of the deformity, represents the foundation for early and minimally invasive approaches using endoscope-assisted surgery with postoperative helmet therapies.

The advent of suturectomy began in the late 1800s at a time when craniosynostosis had been recently recognized as an entity that could lead to neurological dysfunction and cognitive comorbidities. Many of the surgeries were likely performed for nonsynostotic microcephaly, and there was an alarmingly high mortality rate associated with the surgery, which resulted in it falling out of favor.[8] This consequence marked the end of surgery for craniosynostosis for more than 30 years. Variations of these suturectomy techniques gradually resurfaced in

Abbreviations used in this paper: EASC + PHT = endoscope-assisted strip craniectomy and postoperative helmet therapy; FOA = frontoorbital advancement; HCP = head circumference percentile.

the mid-1900s and became the standard treatment for craniosynostosis for the next half century. The biggest limitation of these methods was that they relied exclusively on the brain growth to effect changes in cranial shape and size. Consequently, outcomes were variable and often limited by early refusion at the craniectomy sites. Attempts to line the craniectomy defect with a foreign material (for example, polyethylene film, Gore-Tex, and other substances) to prevent refusion also failed to succeed.[7]

In the 1970s, Tessier[20,21] introduced pioneering techniques for treatment of craniosynostosis in which large segments of the cranium were removed, remodeled, and stabilized as the situation required. The limitations of suturectomy for advanced disease fueled these developments, along with the discovery by Delashaw and colleagues[4] that the major cause of the cranial deformity was compensatory overgrowth at adjacent sutures. Thus, the desired changes in shape and volume were established intraoperatively, and the bony segments were fixed to maintain the correction. Because the postoperative cranial result was not dependent on postoperative brain expansion, the outcomes of these operations were more predictable than simple or extended craniectomy procedures, and cranial remodeling became the preferred operation for craniosynostosis. However, these techniques are associated with significant blood loss, lengthy surgical times (3–8 hours) and hospital stays (4–7 days), and often the need for postoperative intensive care unit monitoring.[18] Surgery is often delayed until the infant is older (6–12 months) to limit operative morbidity, but this allows the deformities to become more severe. The reported complications of the cranial vault remodeling procedures include inadequate calvarial shape correction, improper skull reossification, palpable and visible deformities and asymmetries, loosening of hardware, migration of screws into the brain parenchyma through the dura, extensive blood losses, and problems associated with blood transfusion reactions.[7,18] Moreover, many specialists in the field have noted both anecdotally and in published works that even with large repairs, the growth patterns were not normal over time, and there was reversion toward the original dysmorphology.[5] Therefore, the cosmetic results of larger procedures are certainly not perfect.

In 1999, Barone and Jimenez[2] published the endoscopic approach for suturectomy followed by orthotic therapy. In the first 10 cases, they noted a significant difference in blood loss and the need for transfusions, shorter operative times and hospital stays, and decreased hospital costs with the endoscopic approach than with conventional cranial vault remodeling. They expanded their indications to include coronal, metopic, and lambdoid synostoses.[9,10] Other authors have supported the conclusions of Barone and Jimenez.[14] For those who believe that the era of suturectomy has already been tried and failed, it is important to note the use of newer technologies in achieving the result. The effectiveness of the surgery is not simply in the release operation, but in the subsequent redirection of skull growth through the use of external orthoses, springs, or distractor devices. Technologies have changed, and dismissing the operation because it had a high failure rate in the past is problematic.

This report describes the experience of a single surgeon (M.R.P.) using EASC + PHT to treat many forms of craniosynostosis. In addition to demonstrating the effect of this operation on cranial shape and volume, we catalog the complications and limitations of this technique.

Methods

Patient Selection, Preoperative Imaging, and Anesthesia

Infants diagnosed with craniosynostosis who were younger than 6 months of age were considered for the endoscopic approach. Extended discussions on the risks and benefits of open and endoscopic approaches were undertaken with the family. The minimally invasive approach was considered appropriate for all infants younger than 3 months with single suture synostosis and older infants only if they had mild deformity. At our institution, approximately 50% of patients are young enough to be offered endoscopic techniques (this percentage has been increasing over time), and most families have elected to undergo this surgery. The remaining patients undergo open surgery at 8–10 months. We would generally not recommend the endoscopic approach if the child had a significant deformity and was older than 3 months of age. Although there are no absolute guidelines on this, for sagittal synostosis the threshold for endoscopic surgery in a child older than 3 months would generally be a cranial index greater than 0.66–0.68, also subjectively accounting for the more subtle manifestations. For example, the typical saddle deformity responds very well to endoscopic surgery even at older ages, whereas severe frontal bossing and marked bathrocephaly does not. For other synostoses, where objective criteria are less available, the criteria are more difficult to distinguish on an age-related basis. Very profound trigonocephaly in older children and profound turricephaly in children with bilateral coronal synostosis will likely not respond to endoscopic techniques at older ages. Similarly, profound asymmetry in unilateral coronal synostosis is likely best treated when the patient is younger than 3 months. In addition, some patients with multiple suture synostoses were considered for endoscopic release, either as primary treatment or to prevent significant progressive compensatory deformity, with the expectation that another surgery might still be required in the future (that is, to prevent the development of severe turribrachycephaly in children with bilateral coronal synostosis). All infants had routine laboratory samples drawn, and blood was crossmatched and available in the operating room at the start of the case. Computed tomography scans were not routinely obtained for single suture synostosis, but they were acquired when it was thought necessary to establish the diagnosis or guide surgical decisions. For example, we would not perform endoscopic surgery in a child with multisuture synostosis and multiple bony erosions or irregularities on the endocortical surface, as separating the dura from the bone becomes far more complex. In general, endoscopic techniques are feasible because the dura easily separates from the bone at a fused suture, and if preoperative data would indicate that separation is not likely, one should probably not perform the case in a minimally invasive fashion.

General endotracheal anesthesia was used, and 2

intravenous catheter lines were inserted after induction. Early in the series arterial lines were common, but as the technique evolved, they were rarely used. No central lines were used. Precordial Doppler ultrasonography was used in all cases to assess for air embolism.

Positioning and Skin Preparation

For sagittal synostosis, the patients were placed prone using a specialized head holder (DORO cranial stabilization, Promed Instruments; Fig. 1) that kept the head extended, with the torso on chest rolls. For metopic or coronal sutures, the patients were supine, and the head was placed on a horseshoe headholder. For lambdoid synostosis, the patient was kept prone with the head supported on a horseshoe headholder. The scalp was prepared with povidone-iodine solution, and the area of intended incision was infused with Marcaine 0.25% and epinephrine 1/200,000.

Incision and Subgaleal Dissection

The incisions were generally 1.5–2.5 cm in length and all oriented perpendicular to the involved suture but varied in number and location by suture type as follows: sagittal, 2 incisions in the midline, one just posterior to the coronal sutures and the other at the junction of the lambdoids; metopic, 1 midline incision just posterior to the hairline; unilateral and bilateral coronal, 1 incision at the midsuture(s); and lambdoid, 2 incisions, one at the region of lambda and the other at the inferior end of the suture.

Initial Craniectomy and Dural Dissection

After exposure of the suture, a bur hole was placed directly over the affected suture. A Kerrison rongeur was used to increase the diameter of the bur hole to 1 cm. The periosteum was elevated off the overlying skull along the direction of the suture. Finally, the endoscope was inserted through the bur hole and the dura was dissected from the overlying skull under direct visualization. The endoscope was used in all cases. In some instances, it did not provide better visualization than direct inspection with loupes, but it afforded excellent light and allowed the surgeon to transilluminate and see how far the dissection had proceeded when performed in an operating room with the ambient lights turned off. Since the dura is generally not adherent at a fused suture, dissection was usually done in a blunt fashion with the endoscope and suction. Emissary veins were coagulated with bipolar cautery and divided. Heavy scissors were then used to cut a 1- to 2-cm-wide strip of bone centered on the affected suture, and the bone was removed. (Early in the series, wider craniectomies were performed, as well as barrel staving, but this was believed to be unnecessary to achieve good results, and bone removal has been minimized. Using a cadre of objective and subjective measures, we did not find that a wider craniectomy improved results. In addition, a few patients who received barrel staves developed bone callus at the regions that were cut; therefore, this technique was discontinued.) The callus regions remodeled over about 2 years. The wounds were irrigated, and Gelfoam (Pfizer, Inc.) was placed over the craniectomy site. Bone edges were not coagulated. The galea and skin were closed in layers with absorbable sutures. A pressure dressing along the craniectomy was applied for 12 hours.

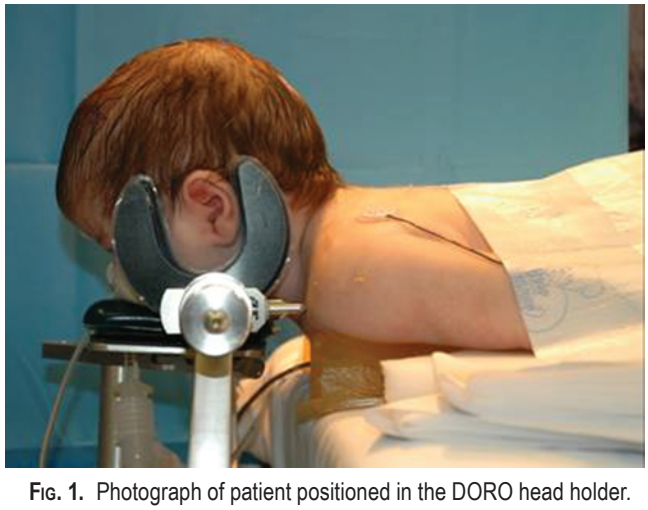

Fig. 1. Photograph of patient positioned in the DORO head holder.

Cranial Remolding Helmets

Within 1 week of the procedure, a cranial molding helmet was fitted for the child. In our opinion, the design and subsequent modifications of the helmet were critical to the success of this procedure. One significant advantage of the helmet, compared with other technologies such as springs and distractors, is the ability to modify the skull growth in 3 dimensions and to be adjustable over time in all dimensions in reaction to actual skull growth. Thus, there was close follow-up by an experienced certified orthotist and the craniofacial team. In general, each helmet was designed and contoured to contact all areas of the infant's cranium except where growth was desirable. Good orthotic fitting requires conceptualization of how cranial growth in specified areas will correct the deformity over time, and there can be a steep learning curve. Since the shape changes are most pronounced early in treatment, careful assessment and thoughtful adjustments were necessary during the first 3–4 months. The helmet was discontinued once the desired phenotype was obtained or when the infant reached 1 year of age. The cost of the orthosis was, on average, $2200/helmet, including design and all subsequent adjustments. Children needed either 1 or 2 helmets during the treatment period. In a separate detailed analysis of costs, even adjusting for cost of helmets and time lost from work for the families, we have seen a substantial cost reduction using the minimally invasive techniques. Comparing 10 patients treated with minimally invasive techniques and 10 patients treated with open reconstruction, the total costs for endoscopic techniques averaged 42% of the costs for open techniques.[1]

Follow-Up

As a rule, all of our patients are monitored until 6 years of age, when brain growth is essentially complete. This is true for patients treated endoscopically and by open techniques. In the results, we list separately the overall group and those patients who have had more than 1 year

of follow-up since completion of treatment (surgery and helmeting).

Results

Between July 2004 and March 2011, 173 patients were treated with endoscopic strip craniectomy by the senior author (M.R.P.). There were 61 girls and 112 boys. The frequency of involved suture(s) in descending order was as follows: sagittal, 55.5% (96 patients); unilateral coronal, 15.0% (26 patients); metopic, 13.9% (24 patients); bilateral coronal, 6.9% (12 patients); multisuture other than bicoronal, 6.4% (11 patients); and lambdoid, 2.3% (4 patients) (Table 1). The average age at operation was 2.9 months (range 0.79–7.75 months), with a median age at operation of 2.89 months. The mean operative time was 46.30 minutes (range 25.0–93.0 minutes). The mean length of hospital stay was 1.35 days (range 1–3 days, with 1 outlier at 23 days; this patient had multisuture synostosis and significant cardiac abnormalities and remained in the hospital for comorbidities). Three patients with comorbid conditions required an overnight stay in the intensive care unit. Eight patients (4.6%) required perioperative blood transfusions. No absolute hematocrit or hemoglobin nadir threshold dictated blood transfusion; however, in the setting of hemodynamic instability and decreasing hemoglobin and/or visible blood loss, a blood transfusion was provided. The nadir was a hematocrit of 20%. There were no deaths. The mean follow-up from the operative date was 3.99 years (Table 2).

In addition, we completed an in-depth analysis of the series of the 111 patients who underwent at least 1 year of follow-up, having thereby completing the treatment protocol. This group of 111 is the subset that was closely analyzed below. Among this subset, the PHT was typically completed in a mean of 7.78 ± 2.55 months (range 2.37–21.55 months).

Patient Outcomes Varied by Fusion Type

Sagittal Synostosis. A total of 61 patients in this group completed helmet therapy and have at least 1 year of follow-up, and all 96 patients are monitored with regular follow-up. The mean duration of helmet therapy was 7.47 months. Patients experienced a 36.85% increase in HCP. Cranial index, as measured by a single observer in all cases (senior author [M.R.P.]), increased from a mean of 0.69 ± 0.04 preoperatively to 0.77 ± 0.04 at the 1-year follow-up and regressed to and stabilized at 0.76 ± 0.03 for patients observed longer than 2 years (Fig. 2). Multivariate regression analysis demonstrated that age at surgery ($p = 0.0005$) was an independent variable for change in cranial index and increase in HCP. Overall, there was uniformly excellent cosmetic correction (Table 3). Complications included 1 incisional abscess requiring admission for incision and drainage but no long-term antibiotics and 1 sagittal suture refusion and 2 cases of additional suture fusion, all 3 of which required open cranial vault remodeling. Among those patients still undergoing helmet therapy, there were no complications, and surveillance of follow-up data indicates similar improvements in cranial index and HCP as those patients who have completed therapy.

TABLE 1: Distribution data in patients who underwent treatment of craniosynostosis

Type of Synostosis	No. of Patients (%)
sagittal	96 (55.5)
metopic	24 (13.9)
unilat coronal	26 (15.0)
bicoronal	12 (6.9)
lambdoid	4 (2.3)
multisuture	11 (6.4)
total	173 (100)

TABLE 2: Hospital course data in 173 patients*

Parameter	Value
mean op duration in mins (range)	46.30 (25.0–93.0)
no. of transfusions (%)	8 (4.6)
mean LOS in days (range)	1.35 (1.0–3.0)†
mean FU length from time of op in yrs (range)	3.99 (1.76–6.66)

* FU = follow-up; LOS = length of stay.
† The value was calculated without the one outlier in the multisuture group with cardiac anomalies.

Unilateral Coronal Synostosis. Twenty patients completed helmet therapy and have longer than 1 year of follow-up, and all 26 patients are monitored with regular follow-up. Eleven of the patients had a left-sided fusion. Helmet therapy lasted an average of 9.19 months. Patients experienced a 12.14% mean increase in HCP. Cranial asymmetry decreased from a mean of 8 mm (range 6–10 mm) to 3.7 mm (range 1–6 mm) (Fig. 3). There was excellent correction of nasal root deviation, facial asymmetry, and orbital dystopia with a trend toward reduced associated ophthalmological findings (for example, astigmatism and ocular torticollis)[5] and good to excellent improve-

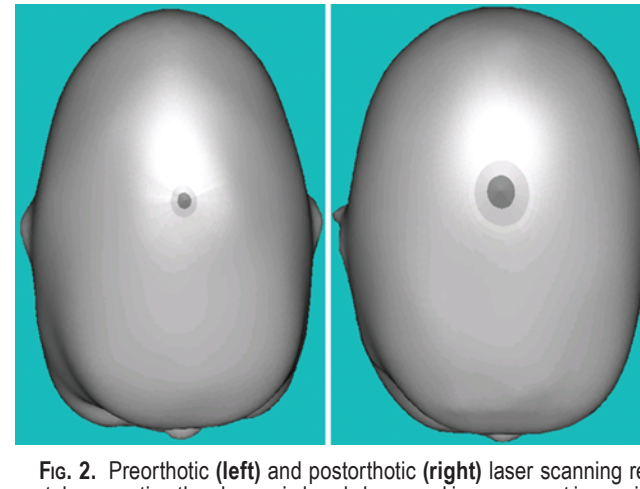

Fig. 2. Preorthotic **(left)** and postorthotic **(right)** laser scanning report documenting the change in head shape and improvement in cranial index in an infant with sagittal synostosis.

TABLE 3: Postoperative clinic outcomes following completion of surgical and helmet therapy*

	Mean ± SD				
Type of Synostosis	Length of FU (yrs)	Length of Helmet Therapy (mos)	Preop HCP	Postop HCP	Change in HCP (%)
bilat coronal (9 patients)	2.21 ± 0.79	8.63 ± 1.58	11.31 ± 1.14	22.84 ± 23.27	11.06 ± 24.58
lambdoid (3 patients)	1.86 ± 1.61	5.43 ± 1.68	23.33 ± 20.0	53.17 ± 46.30	29.83 ± 27.51
metopic (11 patients)	1.01 ± 0.69	7.20 ± 2.52	46.45 ± 25.33	74.21 ± 25.37	27.75 ± 19.08
unilat coronal (20 patients)	2.09 ± 1.48	9.19 ± 4.05	31.14 ± 27.11	50.56 ± 28.84	12.14 ± 17.64
sagittal (61 patients)	2.34 ± 0.94	7.47 ± 1.93	57.10 ± 32.16	93.60 ± 22.06	36.85 ± 33.23
total (104 patients)					

* Includes 111 patients who have 1 year of follow-up since completion of treatment. Seven multisuture patients who have completed therapy are not shown.

ment of forehead symmetry. Although the forehead symmetry was slightly inferior to traditional FOA at 1 year, it continued to improve at each consecutive annual visit. We have analyzed the findings in unilateral coronal synostosis using 3D photogrammetry. Comparing children who had undergone endoscopic versus open techniques, we found statistically significant improvement in facial symmetry in the minimally invasive group and nonsignificant differences in forehead symmetry at a mean age of 2.8 years (unpublished data, 2009). Two patients had persistent deformity for which FOA was recommended. Another patient experienced a small dural tear requiring a larger than average craniectomy at the time of surgery and had a persistent skull defect, which required cranioplasty repaired through the original 1.5-cm incision. Three patients (12%) were diagnosed with Saethre-Chotzen syndrome. One of these patients is currently undergoing helmet therapy. The second patient experienced fusion of the sagittal suture at approximately 2 years of age. He has not developed elevated intracranial pressure and is being observed at this time. The third patient has not had any complications since completing helmet therapy (Table 3).

Bilateral Coronal Synostosis. Nine patients completed helmet therapy, and all 12 patients are monitored with regular follow-up. One patient has been diagnosed with Pfeiffer syndrome (*FGFR1* mutation), and another has been diagnosed with Apert syndrome. For those who have completed treatment, helmet therapy lasted an average of 8.63 months. These patients experienced a mean change in HCP of 11.06% and a mean maximum decrease in cranial index of –0.08 (mean preoperative cranial index 0.94 [range 0.84–1.0] and mean postoperative cranial index 0.86 [range 0.81–0.91]) (Fig. 4). Turribrachycephaly was well corrected and forehead projection improved, although the improvement appeared to be less dramatic than with traditional FOA. These are subjective assessments, and we have not correlated them to objective data. Two patients experienced refusion of the coronal sutures, as well as additional sutures, with the sagittal suture in one patient and sagittal and metopic sutures in the other. Both cases were heralded by a falloff in head circumference, and required open cranial vault remodeling. On genetic evaluation, one of the patients was later diagnosed with Saethre-Chotzen syndrome. The genetic workup of the second patient with refusion was negative for TWIST, and FGFR1, 2, and 3. All other patient genetic evaluations were negative (Table 3).

Metopic Synostosis. Eleven patients completed helmet therapy, and all 24 patients are monitored with regular follow-up. For those who had completed helmet therapy, the average duration of helmet therapy was 7.20 months. Patients experienced a mean increase of 27.75% in head circumference profile. The midline ridge was very effectively treated and paramidline ridges, although slow to

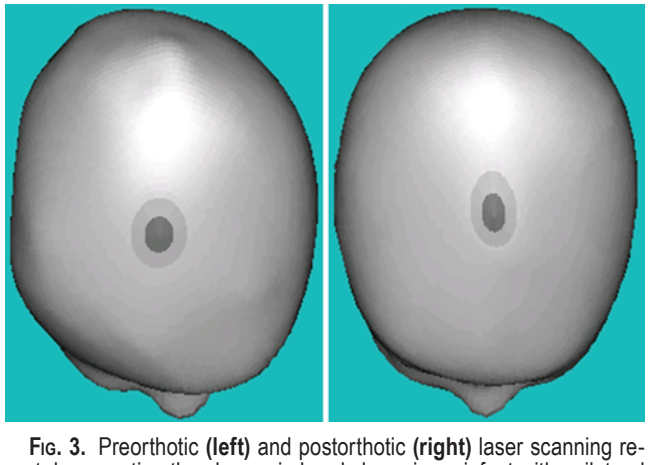

Fig. 3. Preorthotic **(left)** and postorthotic **(right)** laser scanning report documenting the change in head shape in an infant with unilateral coronal synostosis.

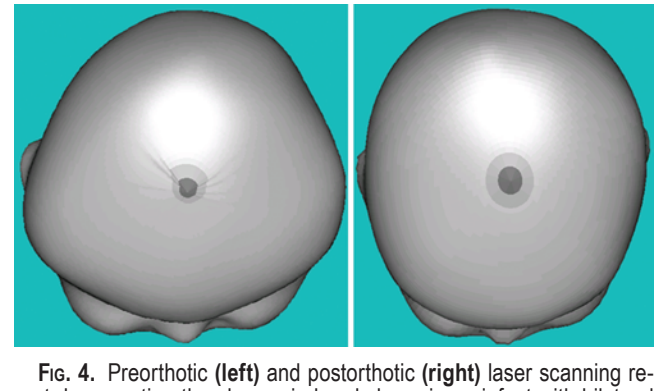

Fig. 4. Preorthotic **(left)** and postorthotic **(right)** laser scanning report documenting the change in head shape in an infant with bilateral coronal synostosis.

resolve, did improve with time (Fig. 5). The correction of superolateral orbital rim retrusion was not consistent in our assessment, and subjectively we believed that FOA offers a superior lateral brow projection. There was no adequate way to document these discrepancies, as we did not routinely obtain images in the child. Interestingly, families tended to be very happy with the results and no revisions were performed or are pending (Table 3). All genetic evaluations were negative. One of the patients developed a postoperative wound infection and was treated with surgical debridement but no long-term antibiotics.

Lambdoid Synostosis. Three patients received helmet therapy that lasted an average of 5.43 months, and all 4 patients are monitored with regular follow-up. Patients experienced a mean increase of 29.83% in HCP. Cranial asymmetry decreased from a mean of 6.5 mm (range 6–7 mm) to a mean of 2 mm (range 1–2 mm). There was an excellent reduction of the windswept appearance and occipital asymmetry. In our subjective opinion, the results appeared better than those achieved with open posterior calvarial vault remodeling, which often seems inadequate in correcting this windswept appearance. There were no good objective measures to assess the outcomes, but we believed that they more than rivaled the larger operations (Table 3). No revisions were performed or are pending. No Chiari malformations were present.

Multisuture Synostosis. Eleven patients had more than 1 fused suture. Three were unable to complete primary helmet therapy due to refusion of the treated suture (1 patient) and/or fusion of additional sutures (2 patients). In these cases, the reclosure was heralded by a falloff in the HCP. One of these patients was later diagnosed with Crouzon syndrome. Genetic anomalies but no syndromes have been found for the remaining patients who experienced refusion. These 3 patients underwent formal cranial vault expansion/remodeling. In addition, 1 patient with sagittal and unilateral coronal synostosis had persistent deformity despite no refusion or additional fusion; FOA was recommended. Seven patients had good results and no complications. An eighth patient is currently undergoing helmet therapy and is being monitored with regular follow-up.

Discussion

This report confirms prior reports that EASC + PHT allows safe, early treatment of craniosynostosis and results in improvement in cranial shape and head circumference in most patients.[2,9,10] Based on available anthropometric measurements and the subjective assessment of our craniofacial team, the shape correction was excellent in patients with sagittal and lambdoid synostosis, good in those with unilateral and bilateral coronal synostosis, and more variable for metopic synostosis. All patients also had a significant increase in HCP after release.

Our data also support the findings of other authors that the most important determinants of success after EASC + PHT is the age at which the suturectomy is done and the compliance with the PHT. We observed that in the subgroup of patients with sagittal synostosis, improvement in shape and HCP was inversely correlated

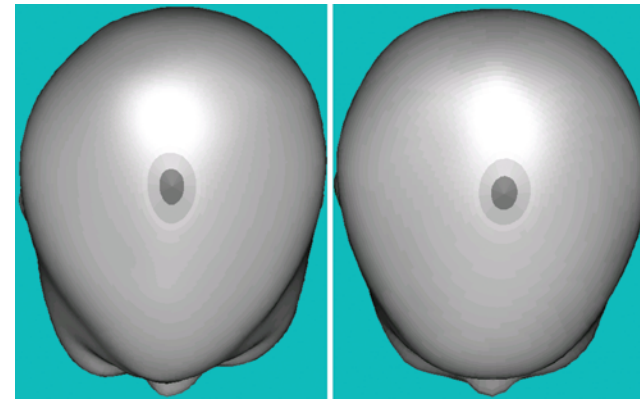

Fig. 5. Preorthotic **(left)** and postorthotic **(right)** laser scanning report documents the change in head shape in an infant with metopic synostosis.

with the age at which the procedure was done. This result is not unexpected given the mechanism by which EASC + PHT works. Because correction is achieved by carefully directed 3D brain expansion, the process is more efficient in younger infants who have the fastest rate and greatest potential for cerebral expansion. Ingraham and colleagues[7] noted that age at the time of suturectomy played a significant role in the long-term outcome. They attributed poor outcomes to either a delay in surgery or surgical procedures that did not adequately free the involved bones or maintain their separation for an adequate length of time.[7,17] Ingraham et al.[7] and Shillito and Matson[18] recommended that treatment for synostosis occur at 4–6 weeks of age to allow for maximum growth to occur. Similarly, Jimenez and colleagues[9,10] reported that their best results were obtained when patients were referred very early in life. Their conclusions were that the best time to perform this procedure is at or before 3 months of age. It is our recommendation that suturectomy be performed as early as possible, balancing factors such as general infant health and weight, but ideally at or slightly before 3 months.

In our view, surgery alone is not adequate, and the other critical component to the success of EASC + PHT is compliant use of a well-designed orthosis. This is philosophically how the procedure is different from the strip craniectomy procedures of years past, and it appears to be a primary determinant of outcome. Although the utility of the helmet after this procedure has been questioned, in our experience, failure to guide the cranial expansion with an external orthotic is a principal reason for poor or under-correction. For the most part, we saw reversion of the deformity if the helmet was discontinued too early and inadequate results in the few children with poor helmet design or compliance. Conversely, a well-designed helmet really allowed for excellent correction in multiple planes of growth. By controlling growth in most areas, the orthotic acts by focusing most or all of the cranial growth in the areas where it is needed. Thus, the brain becomes a very effective internal distractor. Without a guiding orthotic device, expansion occurs in all directions and the correction is less complete. Jimenez and colleagues[9,10] advocated continuing helmet-molding therapy

until 1 year of age to prevent reversion. They reported that given cranial growth dynamics, once the patients have obtained normocephaly at 12 months, the shape will be maintained thereafter.[9] It has been our practice to maintain helmet-molding therapy until 1 year of age or until normocephaly has been achieved and maintained on serial examination. Our data do demonstrate a small regression from maximal cranial index in patients with sagittal synostosis, most noticeably in the 2nd year of life. Consequently, we now maintain the helmet until the cranial index is greater than 0.8, or until 1 year of age. Relapse has also been observed in patients with sagittal synostosis patients treated with open cranial vault remodeling. Fearon and colleagues[5] observed 132 patients for 3–11 years postoperatively (mean follow-up time 4.7 years) and documented initial overcorrection of cephalic index followed by an overall regression of cranial index. They also reported a diminished capacity for head circumference growth; patients had head circumferences significantly above normal preoperatively that decreased to less than 1 standard deviation over the mean. They concluded that there is an overall deficiency in skull growth either as a result of the operative intervention or from inherent osseous undergrowth related to the craniosynostosis. The very slight relapse we observed in our patients suggests that the former explanation is more accurate.

One advantage of early treatment with suturectomy is that it prevents secondary deformity. Numerous investigators have demonstrated that many of the characteristic features associated with craniosynostosis occur because the growth of distant patent sutures is affected by the cranial fusion.[16,17,19] For example, patients with bilateral coronal synostosis often develop secondary turribrachycephaly in early infancy in response to limited anterior cranial expansion. Once established, this can be very difficult to treat surgically. Some groups now recommend performing an early posterior release in children with bilateral coronal synostosis simply to avoid the development of turribrachycephaly (unpublished data, 2009). In our experience, early suturectomy in patients with bilateral coronal synostosis prevents the development of significant turribrachycephaly as the brain can expand anteriorly.

In addition to preventing progressive secondary deformity, we have also noted that early release can also allow normalization of facial and orbital asymmetry in patients with unilateral coronal synostosis. Whereas frontoorbital advancement improves forehead and anterior orbital asymmetry, this procedure does little to improve facial asymmetry or ocular abnormalities inherent in this condition. Oh and coworkers[15] used 3D photogrammetry to document persistent facial asymmetry in older patients (mean age 14 years) with unilateral coronal synostosis who had undergone frontoorbital advancement in infancy. Becker and colleagues[3] reported similar findings using serial CT scans. Thus, the correction of frontofacial deformity in patients managed with FOA is inherently incomplete. This realization was in large part responsible for our early willingness to consider EASC + PHT. Impressed by the substantial facial symmetry in patients with unilateral coronal synostosis who were treated with EASC + PHT by Jimenez and colleagues,[2,9,10] we began to offer this technique to patients with unilateral coronal synostosis in 2004. Consistent with our current protocol, families were advised of the possible need for conventional open cranial remodeling procedure in the event that EASC + PHT failed to produce the desired outcome. However, in a retrospective review using objective and subjective measurements, our observations of the original results of Jimenez and colleagues were correct. Using 3D photogrammetry, we recently demonstrated that EASC + PHT and FOA resulted in similar forehead correction, but the former technique yielded markedly better mid- and lower facial symmetry (see *Results*, *Unilateral Coronal Synostosis*). Similarly, we found that children with unilateral coronal synostosis managed with EASC + PHT had significantly less severe V-pattern strabismus and excyclotorsion than age-matched controls who had undergone FOA. Not a single patient in our endoscopic group has required strabismus surgery, whereas almost 60% of children with unilateral coronal synostosis undergoing standard FOA have persistent strabismus for which surgery is recommended. Therefore, even in the unlikely event that early release failed to gain acceptable cosmetic correction and a secondary open procedure was required, the marked reduction in ocular findings and improved facial symmetry argue for considering this technique.[12]

Like any operative or medical treatment, EASC + PHT can fail if the management is poorly executed. This is well illustrated by the case report of Kohan et al.,[11] wherein they described a pair of twins with sagittal synostosis, one managed by reverse pi procedure and the other by endoscopic release with helmet therapy. They found a posttreatment cranial index of 0.77 in the child managed with cranial vault remodeling and a posttreatment cranial index of 0.63 in the child managed by EASC + PHT.[11] Although the authors chose to interpret this isolated example as evidence that the EASC + PHT procedure does not work, our uniformly good results with this procedure in patients with sagittal synostosis, as well as many other reports found in the literature, would suggest that this unfortunate outcome was more likely the result of inadequate surgery, poor compliance with helmet therapy, or inadequate duration of helmet therapy. We ascribe the success of our program to careful and consistent follow-up of the patients and very close collaboration and communication with the orthotist. It is particularly important to ensure that the orthotist understands which areas of the calvaria are to be contained (that is, limit growth) and which areas are to be allowed to grow freely. The location and extent of the release will largely determine the success of the correction. During the first years of our program, we routinely saw patients every 2–3 weeks postoperatively to ensure that the orthotic was fitted and contoured appropriately. As our orthotists became more experienced, the frequency was relaxed. In our opinion, lack of attention to the postoperative orthotic management is the main reason why some surgeons report seeing patients with poor correction following this procedure. Regarding the case report by Kohan et al.,[11] anecdotally, our group has treated siblings with sagittal synostosis, one treated with open surgery and the other treated 3 years later with endoscopic surgery followed by helmet therapy. Although both had an acceptable outcome, the cranial index results were better in the child treated with EASC +

PHT and the family far preferred the minimally invasive treatment. Given the limited conclusions that can be drawn from such an isolated comparison, we elected not to report this.

Limitations of the Study

Similar to essentially all available studies of surgical technique in the craniofacial literature, our study is limited by it being a retrospective review of a technique with no control group. There was no attempt at randomization, especially as we became more convinced of the efficacy and safety of the minimally invasive techniques. Although we can examine historical controls within our group and the literature, we do not have a direct control group, nor does any other study in the literature. Moreover, the literature and the field are hampered by the lack of objective data by which to interpret and compare results. Even the most objective of our data points, head circumference and cranial index, are often considered poor surrogates by others in the field. In fact, many senior craniofacial experts have argued at national and international meetings that the results in craniofacial surgery are subjective and should not be held to objective standards, and clearly the field is limited by this lack of a firm benchmark. Where available, including the 3D photogrammetry study and the formal ocular studies for unilateral coronal synostosis, we have tried to objectify the data in a fairly subjective field.

Conclusions

As technology has evolved, minimally invasive procedures have grown in popularity in all surgical fields. Gall bladders and colons are removed via laparoscopy, cerebral aneurysms are treated via transarterial embolization, and robots are used in fields such as urology. It is therefore no surprise that the field of craniofacial surgery has seen a similar evolution. For any of these technologies to be adopted, the minimally invasive techniques need to show similar safety and efficacy profiles to the standard open procedures. Not surprisingly, there is often reluctance to accept the newer technologies as equivalent or superior. Our experience with EASC + PHT demonstrates the overall safely and efficacy of this treatment. The treatment is inherently different from what many craniofacial experts consider the failed era of strip craniectomy surgery, because newer technologies substantially change the skull growth patterns after surgery, and refusion of the skull before the correction is achieved is extremely unlikely. In our opinion, and based on a series of objective and subjective criteria, for single suture synostosis, the results can rival or exceed those produced by larger open cranial expansion techniques. The need for revision surgery due to refusion of the operated suture or fusion of other adjacent sutures was higher in children with multisuture synostosis. Failure of shape to improve or a sustained decrease in HCP should alert the physician to this possibility and additional CT scanning is advised. Overall, minimally invasive endoscopic suturectomy offers an excellent alternative to traditional open approaches and should be considered an option for children diagnosed prior to 3 months of age.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: Proctor, Berry-Candelario, Ridgway, Rogers. Reviewed submitted version of manuscript: Proctor, Berry-Candelario. Approved the final version of the manuscript on behalf of all authors: Proctor. Statistical analysis: Proctor, Berry-Candelario, Ridgway, Rogers. Administrative/technical/material support: Proctor. Study supervision: Proctor, Berry-Candelario.

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Intracranial hypertension in 2 cases of craniometaphyseal dysplasia: differing surgical options

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Craniometaphyseal dysplasia (CMD) is a very rare bone disorder characterized by abnormally developed metaphyses in long bones and sclerosis of the craniofacial bones. In this paper, the authors report 2 cases of children diagnosed with CMD and chronic intracranial hypertension with deletion in exon 9 of the human *ANK* gene *(ANKH)*. After intracranial monitoring, a different treatment was chosen for each patient. One of the patients was treated using CSF shunting because ventriculomegaly in the absence of a Chiari malformation was also observed on cerebral MR imaging. The other patient underwent cranial expansion and decompressive craniotomy of the posterior fossa, because ventriculomegaly was excluded after cerebral MR imaging and cervical MR imaging showed a Chiari malformation Type I. The origin of intracranial hypertension in CMD is multifactorial. Previous intracranial pressure monitoring and a thorough understanding of neuroimaging studies are essential to achieve an accurate diagnosis and effective treatment. *(DOI: 10.3171/2011.4.FOCUS1126)*

Key Words • **Chiari malformation** • **craniofacial remodeling** • **craniometaphyseal dysplasia** • **hydrocephalus** • **intracranial hypertension**

Craniometaphyseal dysplasia is a rare genetically transmitted bone disorder characterized by abnormal development of the metaphyses in long bones and sclerosis and hyperostosis of the craniofacial bones. Other rare bone disorders with similar clinical and radiological features are metaphyseal dysplasia (Pyle disease), frontometaphyseal dysplasia, and craniodiaphysial dysplasia.[1,4,5]

Diffuse sclerosis of skull bones can lead to cranial nerve compression that may eventually result in severe visual and neurological impairment, such as facial palsy and hearing loss. Signs of intracranial hypertension may be the result of jugular foramen stenosis together with hyperostosis of the cranial vault and compression of the superior sagittal sinus.[2–6] We present 2 rare cases of intracranial hypertension of multifactorial origin treated using different therapies.

Summary of Cases

In this paper we present 2 patients with CMD who were treated at the Department of Pediatric Neurosurgery of Virgen del Rocío Hospital in Seville, Spain. Both patients showed distinctive craniofacial features of CMD: wide nasal bridge, secondary dystopia canthorum, and scaphocephaly. They also reported progressive loss of bilateral vision and hearing due to cranial nerve compression.

Plain radiographs of these patients revealed abnormal development and osteopenia of the metaphyses in the long bones (Fig. 1), as well as multiple diaphyseal and skull base scleroses. Computed tomography scans of the head demonstrated thickening of the diploe and sclerosis of the skull base. A 3D cranial CT scan obtained later also demonstrated dolichocephaly and severe stenosis of the skull base foramina (Fig. 2). However, the evolution of the clinical course and cerebral MR imaging findings necessitated a different treatment for each patient.

Case Reports

Case 1

This patient was a 9-year-old girl and a carrier of a mutation in the *ANKH* gene (position 1192 of the CCT in exon 9). She presented with a cephalic perimeter of 35 cm at birth (< 90th percentile); 7 months later, her cephalic perimeter had increased by 3.5 standard deviations to 45.5 cm.

A cranial 3D CT scan also demonstrated dolichocephaly and severe stenosis of the skull base foramina (Fig. 2 left). Ventriculomegaly in the absence of periventricular lu-

Abbreviation used in this paper: CMD = craniometaphyseal dysplasia.

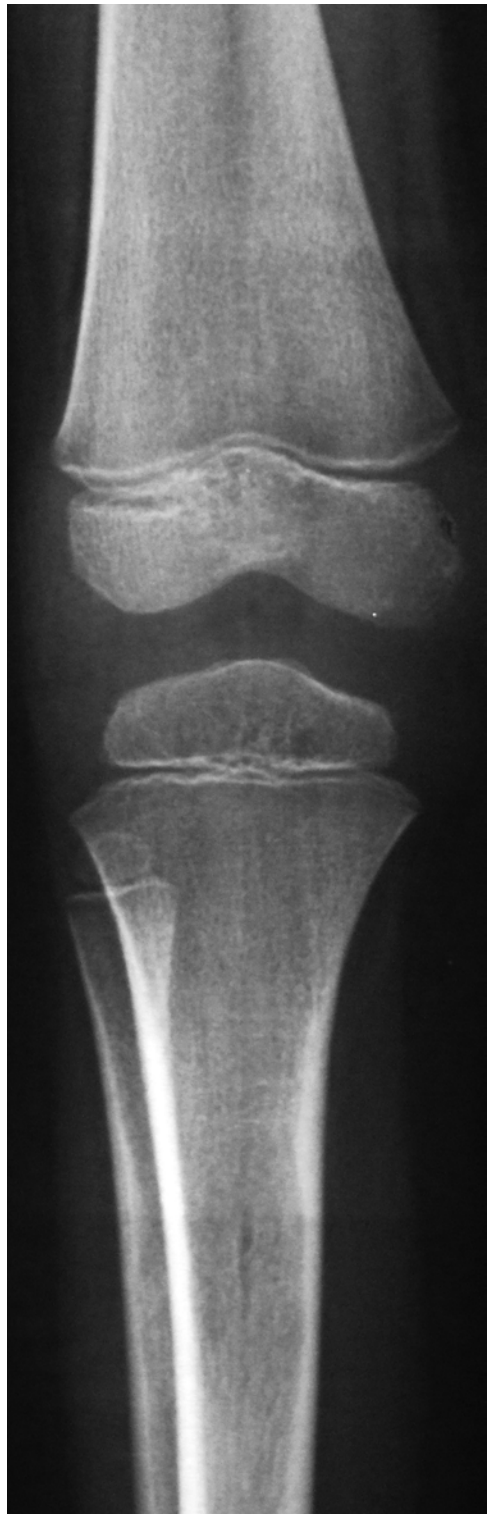

Fig. 1. Case 2. Plain radiograph revealing abnormal development and osteopenia of the metaphyses in the long bones as well as multiple diaphyseal scleroses.

cencies was also observed on cerebral MR imaging without Chiari malformation Type I (Fig. 3A and B). A bilateral auditory prosthesis was required due to progressive loss hearing.

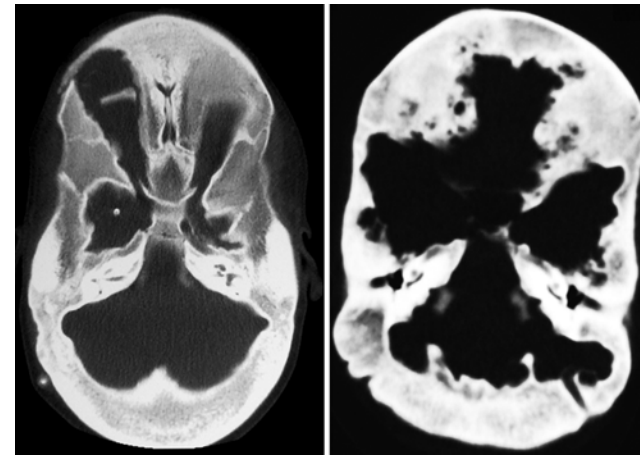

Fig. 2. Case 1 **(left)** and Case 2 **(right)**. Computed tomography scans of the skull showing thickening of the diploe, dolichocephaly, sclerosis of the skull base, and severe stenosis of the skull base foramina in both cases.

Intracranial pressure monitoring was performed by means of external ventricular drainage after the patient experienced referred continuous headache and loss of visual acuity. Intracranial hypertension was then confirmed and controlled using a ventriculoperitoneal shunt when the patient was 4 years old, and the right optic foramina were drilled widely to achieve decompression using a supraciliary approach. Overdrainage complications were documented and successfully corrected when the previously placed valve was replaced by a programmable valve with an extra fluid flow control device. After surgical intervention, visual acuity improved. At present, the patient shows normal neurological and psychomotor development for her age.

Case 2

This 6-year-old boy presented with headache and bilateral loss of visual acuity, which was progressive and became more intense. Intracranial pressure monitoring was performed using an epidural sensor. Continuous sleep recording confirmed a basal intracranial pressure value > 25 cm H_2O and a high incidence of B-waves (> 20%), which led us to perform anterior and middle cranial fossa decompression.

Ventriculomegaly was excluded after reviewing cerebral MR imaging results, which showed bone remodeling and sagittal suture diastasis due to extremely high pressure of the superior sagittal sinus (Fig. 3C). Cerebral MR angiography showed an abnormal venous drainage pattern from the superior sagittal sinus into dilated subcutaneous veins (mimicking sinus pericranii), explained by the increasing pressure and size of the superior sagittal sinus and the jugular venous outflow resistance (Fig. 4). Cervical MR imaging showed a Chiari malformation Type I.

We performed cranial vault expansion using multiple and bilateral osteotomies in the frontal, parietal, and temporal bones, as well as orbital bar advancement and superior sagittal sinus decompression. Optic foramina were drilled widely to achieve optic nerve decompression. Sev-

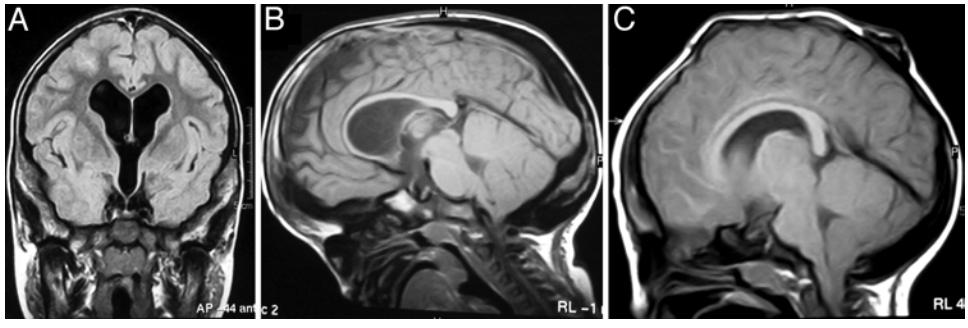

Fig. 3. Magnetic resonance images from the 2 cases. **A:** Axial image showing ventriculomegaly in the absence of periventricular lucencies in Case 1. **B:** Sagittal image demonstrating no Chiari malformation in Case 1. **C:** Sagittal image in Case 2 showing the skull with digitiform projections and the superior sagittal sinus protruding through the sagittal suture, as well as a Chiari malformation.

eral dural tears were observed during the surgical procedure as a result of dural digitiform projections on the bone caused by chronic intracranial hypertension.

After surgery, supratentorial intracranial pressure normalized and ventricle size increased slightly (Fig. 5 left). However, basal cisterns remained collapsed on the follow-up cranial CT scan. Five days after surgery, a CSF leak appeared. In view of these events, we proceeded with surgical decompression of the posterior fossa to solve the foramen magnum obstruction caused by the presence of a Chiari malformation (Fig. 5 right). The patient underwent lumboperitoneal shunt placement in a third surgical intervention. He was finally discharged home when the initial headache resolved, supratentorial intracranial pressure registry returned to normal values, and the CSF leak disappeared.

Discussion

Craniometaphyseal dysplasia, or leontiasis, is a rare bone disorder that affects normal bone synthesis and resorption. A thorough genetic study must be performed to obtain an accurate diagnosis of this disorder, because it may be confused with other pathological entities such as Pyle disease, metaphyseal dysplasia, Gaucher disease, Niemann-Pick disease, or fibrous dysplasia. There are 2 types of CMD that are distinguished by their pattern of inheritance. These 2 types are known as the autosomal dominant and autosomal recessive types. Autosomal recessive CMD is typically more severe than the autosomal dominant form, although in single cases it may be almost impossible to distinguish the real pattern one is facing.[4]

Mutations have been found in the human ankylosis gene *(ANKH)* for autosomal dominant CMD and some simplex cases. The phenotypic severity (expressivity) in autosomal dominant CMD is variable even among affected members of the same family. Penetrance is close to 100% in both sexes. Males and females are equally affected.[3]

Mutations located in cytoplasmic domains close to the C terminus of the *ANKH* gene were identified for the autosomal dominant form of CMD. The *ANK* gene is proposed to act as a pyrophosphate transporter to channel intracellular pyrophosphate into the extracellular matrix. Extracellular pyrophosphate transporter in a physiological concentration acts as a potent inhibitor of mineralization. Low concentrations of extracellular pyrophosphate transporter lead to excess hydroxyapatite deposition, while supersaturation of extracellular pyrophosphate transporter promotes calcium pyrophosphate dehydrate crystal formation. On the other hand, pyrophosphate is a major component and a promoter of hydroxyapatite formation. A tightly controlled balance between extracellular pyrophosphate and extracellular pyrophosphate transporter is required to maintain normal bone mineral content. Homeostasis of pyrophosphate/pyrophosphate transporter is primarily maintained by the concerted activities of *ANK* and other regulators: plasma cell membrane glycoprotein 1, a protein encoded by *Enpp1*, which generates pyrophosphate transporter from extracellular and intracellular nucleoside triphosphate; and TNAP, a protein encoded by Tnap, which hydrolyzes the extracellular pyrophosphate transporter to generate pyrophosphate. Deficiency of any of these 3 proteins can lead to mineral-related pathological conditions in bone.[3]

Progressive sclerosis of the skull base causes stenosis of cranial foramina and cranial nerve compression that may result in hearing loss, loss of visual acuity, or impaired deglutition. In the cases reported in this paper, the initial symptom in both patients was progressive neurosensorial deafness accompanied by severely impaired visual acuity. Optic foramina were decompressed, unilaterally in Case 1 and bilaterally in Case 2.

Sclerosis of the cranial vault may lead to an abnormal increase in the cephalic perimeter or even dolichocephalic morphology. An increase in the cranial vault thickness may result in extremely high pressure of the dural sinuses and thus an increase in intracranial pressure.

In the first case reported in this paper, the patient presented with progressive lateral and third ventricle size increases while the posterior fossa remained unaltered. In view of these findings, we decided to place a ventriculoperitoneal shunt device.[5]

In the second case, the ventricles were normal in size, the skull showed digitiform projections, and the superior sagittal sinus protruded through the sagittal suture with anomalous cutaneous drainage veins, mimicking sinus pericranii; possibly this extracranial venous drainage reduces venous pressure within the longitudinal sinus, and resorption of CSF is not altered; therefore, ventricular

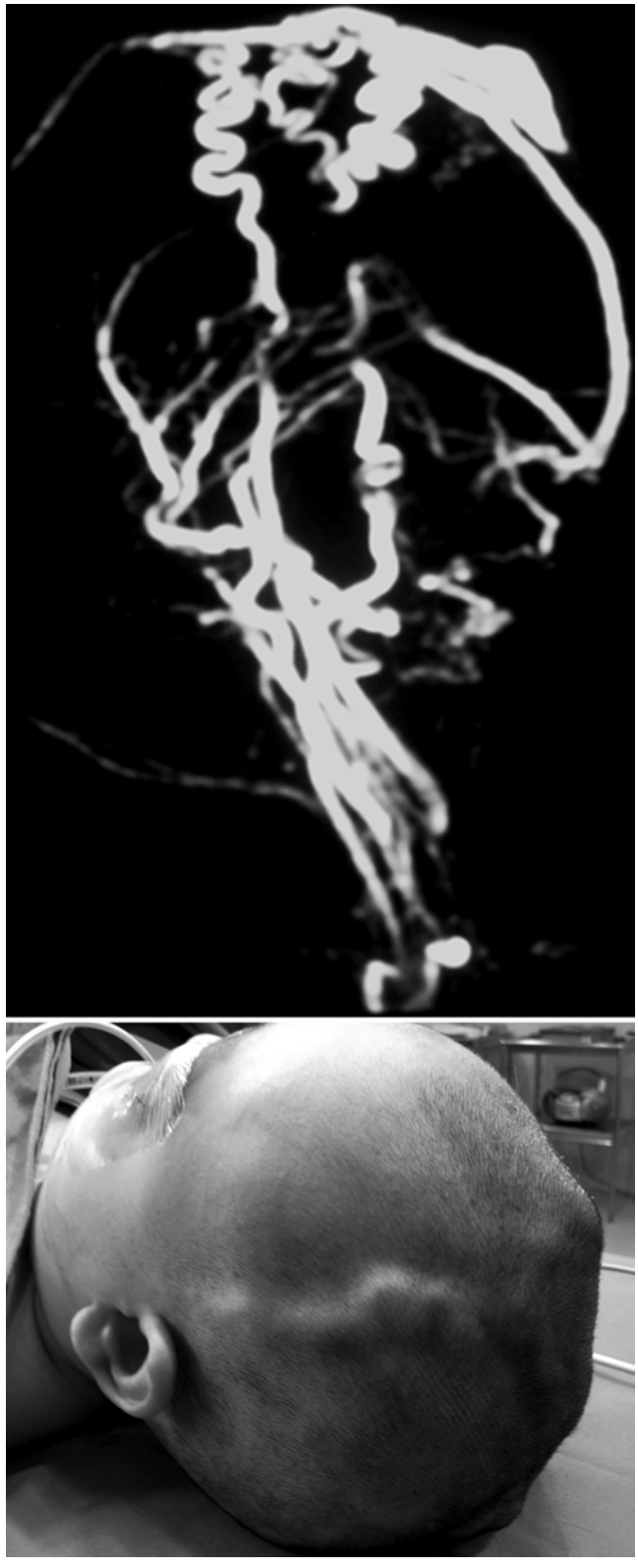

Fig. 4. Case 2. Magnetic resonance angiography showing an abnormal venous drainage pattern from the superior sagittal sinus into dilated subcutaneous veins **(upper)**, mimicking sinus pericranii shown in the photograph **(lower)**.

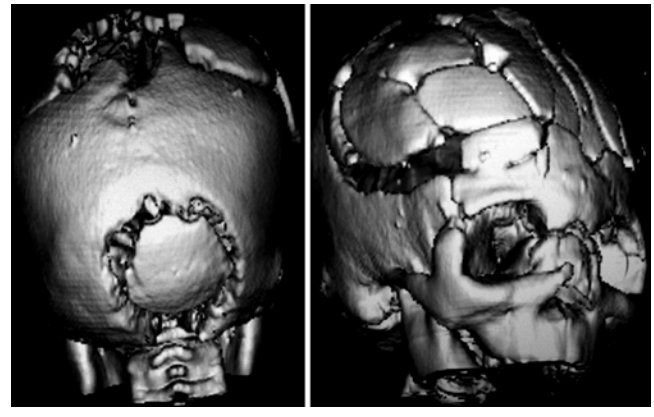

Fig. 5. Case 2. Three-dimensional cranial CT scans showing bilateral osteotomies in frontal, parietal, and temporal bones, orbital bar advancement, and superior sagittal sinus decompression **(left)**, as well as surgical decompression of the posterior fossa **(right)**.

size may be normal. The patient also presented with Chiari malformation Type I.[2,7] As a result of all these events, the origin of hypertension became multifactorial and the treatment became more complex: an increase in skull thickness and dolichocephalic morphology caused cranioencephalic disproportion, diminution in the skull foramina diameter (including the jugular foramen), and resistance to venous return. As a result, superior sagittal sinus pressure increased, as later confirmed on cerebral MR angiography. In view of these events, we decided to perform internal cranial expansion to release the superior sagittal sinus and both optic foramina. However, the result of this procedure was determined to not be effective, because CSF flow obstruction at the foramen magnum was also present. Diffuse bone sclerosis and diminution of the posterior fossa diameter led to the Chiari malformation, explaining the disturbances observed in CSF flow. At that point, posterior fossa expansion was achieved, as well as resection of the arch of C-1 (Fig. 5). After this second surgical intervention, the ventricles increased in size but the CSF leak remained. Consequently, a lumboperitoneal shunt was placed. At discharge from the hospital, the ventricles were bigger in size than in previous studies as a result of surgical cranial expansions, which led to an increase in intracranial capacity and diminution of venous congestion, and resulted in the disappearance of diffuse brain edema and improvement in cerebral compliance.

Intracranial findings determined surgical treatment in each case. In Case 1, a shunt was placed because there was hydrocephalus without a Chiari malformation; in Case 2, with decreased intracranial volume, small ventricles, Chiari malformation Type I, and intracranial hypertension, the chosen treatment was whole cranial vault expansion in 2 phases (frontoorbital advancement and suboccipital decompression; Fig. 5).

Despite presenting with the same pathological entity, patients who suffer from CMD and chronic intracranial hypertension may manifest a wide variety of signs and symptoms that can be managed by means of different therapies, varying from shunt placement to cranial expansion.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Rivero-Garvía, Márquez-Rivas. Acquisition of data: Rivero-Garvía, García-Iglesias, Gutiérrez-González. Drafting the article: Rivero-Garvía, García-Iglesias, Gutiérrez-González. Critically revising the article: Márquez-Rivas. Reviewed submitted version of manuscript: Márquez-Rivas, García-Iglesias, Gutiérrez-González. Approved the final version of the manuscript on behalf of all authors: Rivero-Garvía.

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Molecular signaling in pathogenesis of craniosynostosis: the role of fibroblast growth factor and transforming growth factor–β

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The interplay of signals between dura mater, suture mesenchyme, and brain is essential in determining the fate of cranial sutures and the pathogenesis of premature suture fusion leading to craniosynostosis. At the forefront of research into suture fusion is the role of fibroblast growth factor and transforming growth factor–β, which have been found to be critical in the cell-signaling cascade involved in aberrant suture fusion. In this review, the authors discuss recent and ongoing research into the role of fibroblast growth factor and transforming growth factor–β in the etiopathogenesis of craniosynostosis. *(DOI: 10.3171/2011.5.FOCUS1197)*

Key Words • craniosynostosis • fibroblast growth factor • pathogenesis • transforming growth factor–beta • molecular signaling

Regulation of suture fusion in craniosynostosis is a complex process involving the interplay of multiple signaling pathways, which results in premature and aberrant fusion of cranial sutures. Ongoing research in recent years has shown that most important among these pathways are those involving signaling mediated by fibroblast growth factor (FGF) and transforming growth factor (TGF)–β. In this review, we discuss the role of genetic mutations in the pathogenesis of craniosynostosis as well as recent and ongoing research into the physiological basis of normal and premature suture fusion mediated by FGF and TGF-β signaling.

Fibroblast Growth Factor Receptor Signaling

Genetics of FGFR Signaling

Fibroblast growth factor receptor (FGFR) signaling has been shown to be vital in many areas of skeletal development, with mutations in various craniosynostosis and dwarfism syndromes mapped to genes encoding for the extracellular domain, transmembrane domain, or tyrosine kinase domain of FGFRs.[36,56] The majority of these mutations are gain-of-function mutations, suggesting a role for FGFRs in normal regulation of bone growth.

The 4 FGFRs (1–4) are part of a larger family of single-pass transmembrane tyrosine kinase receptors, with binding of FGF to FGFR in the presence of heparan sulfate proteoglycan as a cofactor leading to receptor dimerization at the cell surface and subsequent autophosphorylation that leads to phosphorylation of downstream signaling proteins.

FGFR2 is the most common receptor wherein mutations have been associated with craniosynostosis syndromes (Table 1). Crouzon syndrome was initially mapped to chromosome 10, position 10q25–26, in 1994 and linked to mutations in FGFR2.[45,47,53] Most of these mutations lead to creation or destruction of cysteine residues. Other craniosynostosis syndromes subsequently linked to FGFR2 mutations include Apert syndrome,[57] Pfeiffer syndrome,[27,49] Jackson-Weiss syndrome,[27] Antley-Bixler syndrome,[4] and Beare-Stevenson cutis gyrata syndrome.[46] In Crouzon, Apert, and Pfeiffer syndromes, de novo mutations have been shown to arise only on the paternal chromosome.[9,30] Interestingly, advanced paternal age was noted as a risk factor for mutations leading to Crouzon and Pfeiffer syndrome,[9] suggesting that older men either accumulate or are more susceptible to a number of germline mutations.

Mutations in FGFR1 and FGFR3 have also been linked with craniosynostosis syndromes. Mutations in FGFR1 have been associated with Pfeiffer syndrome,[37,51] while FGFR3 mutations have been linked with Crouzon syndrome with acanthosis nigricans[28] and with Muenke

Abbreviations used in this paper: FGF = fibroblast growth factor; FGFR = FGF receptor; TGF = transforming growth factor.

TABLE 1: Fibroblast growth factor receptor subtypes and synonyms associated with common syndromic craniosynostosis

Subtype	Synonyms	Syndromic Craniosynostoses
FGFR1	basic fibroblast growth factor receptor 1, Flg protein, N-SAM, OGD, HBGFR, fms-related tyrosine kinase 2, FLT-2, CD331, CEK	Pfeiffer syndrome
FGFR2	Bek, K-Sam, CEK3, CFD1, BFR-1, CD332, ECT1, hydroxyaryl-protein kinase, JWS, keratinocyte growth factor receptor, soluble FGFR4 variant 4, TK14, TK25	Crouzon syndrome, Apert syndrome, Pfeiffer syndrome, Jackson-Weiss syndrome, Antley-Bixler syndrome, Beare-Stevenson cutis gyrata syndrome
FGFR3	Sam 3 protein, heparin-binding growth factor receptor, Mfr3	Crouzon w/ acanthosis nigricans, Muenke syndrome

syndrome.[35] The C749G (Pro250Arg) mutation in the gene for FGFR3 has also been attributed as a frequent cause of nonsyndromic coronal synostosis.[31] While a number of mutations in FGFR1, FGFR2, and FGFR3 have been associated with craniosynostosis, analysis of FGFR4 showed that this receptor was unlikely to contribute significantly to craniosynostosis in humans.[8]

A large number of mutations (more than 50, mostly missense mutations) have been identified in *FGFR*, which all lead via different mechanisms to gain-of-receptor function. These functions include constitutive activation of the receptor in a ligand-independent fashion or loss of ligand specificity, allowing the *FGFR* to be activated by splice variants, which do not normally have this function. Most mutations in *FGFR2* localize to just 2 exons (IIIa and IIIc), confirming the IgIIIa/IIIc region as a mutation hotspot.[19]

Loss of ligand specificity of FGFR2 has serious implications. Tissue-specific alternative mRNA splicing of *FGFR2* normally creates 2 receptor isoforms, FGFR2b and FGFR2c, with specific ligand-binding properties. FGFR2b expression is restricted to epithelial lineages, with only FGF7 and FGF10 being able to activate FGFR2b.[17] FGFR2c expression is normally restricted to mesenchymal lineages, with FGF2, FGF4, FGF6, FGF8, and FGF9 being specific for FGFR2c.[43] This specificity of ligand binding allows directional epithelial-mesenchymal signaling to occur during organogenesis and limb development. Loss of ligand-binding specificity toward different FGF isoforms may lead to varying severity of limb abnormalities. An example of loss of ligand specificity of FGFR2 was shown for Apert syndrome, with the S252W mutation allowing the mesenchymal splice form of FGFR2 (FGFR2c) to bind FGF7 and FGF10.[59] It is thought that limb abnormalities in Apert syndrome result from autocrine activation of FGFR2c by FGF7 or FGF10.[16] Hence, inability to bind FGF7 in other FGFR mutations for other craniosynostosis syndromes such as FGFR1 and FGFR3 mutations resulting in Pfeiffer and Muenke syndrome may explain mild limb pathology as opposed to Apert syndrome.[16]

Mechanisms of Action Leading to Suture Fusion

Development of cranial sutures is highly reliant on cross-talk between different FGFRs, resulting in a balance between osteogenic cell proliferation and differentiation. At 6 weeks of development in human embryos, FGFR1 and FGFR2 are found in mesenchyme of the cranial vault, while FGFR3 is almost undetectable. Later in development, all three FGFR2s are coexpressed in preosteoblasts around osteoid and in osteoblasts forming mineralizing tissue.[7] Signaling mediated through FGFR1 appears to regulate osteogenic differentiation, while signaling mediated through FGFR2 regulates stem cell proliferation.[18] FGFR3 could play a cooperative role during the process of cranial suture development.

The exact mechanism by which mutations in FGFR result in aberrant suture fusion is as yet unclear. In vitro studies have shown that under different culture conditions FGF signaling leads to either increased osteoblast differentiation[22] or decreased osteoblast differentiation with subsequent apoptosis.[25] One mechanism is suggested by a study focused on analysis of gene expression profiles, where downregulation of a number of Wnt target genes with simultaneous induction of the transcription factor Sox2 was found in osteoblasts expressing FGFR2-activating mutations as well as in osteoblasts treated with exogenous FGF.[24] Wnt signaling has been shown to promote osteoblast differentiation and function,[14] while Sox has been shown to interfere with Wnt signaling.[61] Wnt signals also cooperate with bone morphogenetic proteins to induce osteoblast differentiation. Hence, a block in Wnt signaling induced by FGF might result in decreased osteoblast differentiation with subsequent apoptosis.[23]

Other pathways have been implicated in pathogenesis of abnormal suture fusion downstream of FGFR. Noggin, an antagonist of bone morphogenetic proteins, has been found to be expressed in suture mesenchyme of patent but not fusing cranial sutures, with noggin expression suppressed by FGF2 and syndromic FGFR signaling.[55] Hence, syndromic FGFR-mediated craniosynostosis may result from inappropriate downregulation of noggin expression. Epidermal growth factor receptor (EGFR) and platelet-derived growth factor (PDGF)–α receptor expression were also recently found to be increased downstream of FGFR2 through activation of PKC-α–dependent AP-1 transcriptional activity in Apert craniosynostosis.[29] FGF2/FGFR signaling has also been shown to upregulate expression of the pyrophosphate generating enzyme (PC-1) and pyrophosphate channel (ANK), leading to increased mineralization of osteoblastic cells in culture.[15] Clearly, a number of mechanisms must be responsible for downstream signaling of FGFR to result in the craniosynostosis phenotype. However, at present, there is insufficient evidence

to implicate one as a dominant mechanism of action in the pathogenesis of craniosynostosis.

Twist is a transcription factor that acts upstream of FGFR and has also been implicated in the pathogenesis of Saethre-Chotzen syndrome, with localization of a genetic mutation to the short arm of chromosome 7.[3] Mutations resulting in altered protein-DNA binding lead to loss of protein function. Twist underexpression has been shown to result in differentiation of osteoblasts and premature fusion of sutures in a murine model.[2] Increased osteoblast and osteocyte apoptosis has been found in coronal sutures of patients with Saethre-Chotzen syndrome,[58] an effect of Twist haploinsufficiency resulting in increased TNF-α expression and caspase-2 activation. Mechanisms of action by which Twist regulates FGFR expression include one in which Twist interacts with NF-κβ to control FGFR expression[54] and also one in which Twist directly interacts with histone acetyltransferase p300/CBP, resulting in negative regulation of FGFR3 expression.[13]

Another transcription factor that may act upstream of FGFR signaling is muscle segment homeobox 2 (MSX2), which has been implicated in Boston-type craniosynostosis.[5] MSX2 appears to maintain preosteoblastic cells of the osteogenic front in an undifferentiated condition and to stimulate proliferation. MSX2 mutation and overexpression in humans leads to premature suture fusion by increasing the pool of osteogenic cells.[21]

Transforming Growth Factor–β Signaling

Transforming growth factor-β consists of a superfamily of growth factors, 3 of which have been found to be relevant in cranial suture fusion and craniosynostosis. These growth factors include TGF-β1, TGF-β2, and TGF-β3. They exert downstream effects through binding to cell surface receptors with a single transmembrane domain and intracellular serine-threonine kinase domain.[6] These receptors are divided into types I and II. Typically, TGF-βs bind to TGF-β receptor II, which recruits TGF-β receptor I through phosphorylation, with subsequent activation of downstream cascades.

Different isoforms of TGF-β are upregulated to varying extents in patent and fused sutures. In rat models of suture fusion using the posterior frontal suture (the only suture that fuses physiologically), TGF-β1 and particularly TGF-β2 expression was upregulated.[34,48] In contrast, TGF-β3 was found to be associated with patent sutures.[41] In a rabbit craniosynostotic model, a similar pattern was seen, with TGF-β2 significantly upregulated in the osteogenic front, dura mater, and periosteum of synostosed sutures compared with other isoforms.[44]

One mechanism postulated for regulation of suture fusion is by individual isoforms modulating access of other isoforms to cell surface receptor sites. TGF-β1, β2, and β3 all use the same cell surface receptors yet interestingly have opposite effects of suture patency and cell proliferation in the suture. TGF-β3, being a more potent competitor than TGF-β2 for binding to cell surface receptors, was found to bind and downregulate the number of TGF-β receptor I–positive cells in a rat suture model,[40] suggesting that TGF-β3 could regulate tissue responsiveness to TGF-β2 by modulating access of TGF-β2 to receptors.

A model has been proposed for downstream regulation of suture fusion whereby TGF-β2 induces suture closure through phosphorylation of Erk1/2 (Fig. 1).[39] This effect is both direct and indirect, with indirect effects involving boosting Erk1/2 protein expression and inhibiting Smad2/3 protein expression. Smad2/3, conversely, has been associated with suture patency. As Erk1/2 is also a substrate for FGFR signaling, upregulation of Erk1/2 may also result in facilitation of FGFR-induced suture fusion. The importance of Erk1/2 in TGF-β2–mediated suture fusion has demonstrated in a study where TGF-β2–mediated suture closure and cell proliferation were nearly completely inhibited by an Erk blocker, PD98059.[20]

The primacy of the TGF-β2 isoform in regulating suture fusion has been shown in studies in which treatment with TGF-β2 neutralizing antibodies inhibited postoperative resynostosis and enhanced growth of the cranial vault following surgical removal of the coronal suture in a craniosynostotic rabbit model.[32,33] In TGF-β2 knockout mice, there was calvarial bone dysgenesis and sutural agenesis in addition to cardiac, lung, limb, eye, spinal column, and urogenital defects.[50] There was no phenotypic overlap with TGF-β1 and TGF-β3 null mice, suggesting that noncompensated functions are mediated through individual TGF-β isoforms.

The mechanisms by which TGF-βs regulate suture patency are becoming clearer from ongoing research. In the rodent model, the posterior frontal suture fuses during skeletal development, whereas all other cranial sutures remain patent. Using this model, alteration of normal cranial suture development has been achieved by manipulating TGF-β signaling in the tissues adjacent to the developing suture.[60] Dura mater has been found to be essential in mediating suture fusion, likely through cellular mechanisms[42] involving paracrine signaling mediated by FGF-2 and TGF-β1,[11,26] among other cytokines. A model[38] was proposed whereby approaching bone fronts secrete various growth factors to induce formation of a cranial suture. Once the bone fronts overlap, a signal arising from dura mater maintains patency of the newly formed suture. Upon stabilization of the suture, suture mesenchyme signals underlying dura mater not to produce osteogenic signals and maintains the suture in a patent state. A balance between TGF-β1 and TGF-β3, which likely secrete inductive or stabilizing suture signals, and TGF-β2, which secretes osteogenic signals promoting recruitment of osteoblasts and osteogenesis at the bone fronts, is essential for normal suture morphogenesis. These signals allow cranial vault growth to be coordinated with growth of the underlying brain. Therefore, an imbalance between the different TGF-β isomers would result in craniosynostosis. Promising work has been done to demonstrate that TGF-β1 levels can be manipulated in vitro using short interfering RNA, which may provide a mechanism by which suture development can be modulated nonsurgically in the future.[10,12]

Conclusions

Craniosynostosis is a condition that has significant

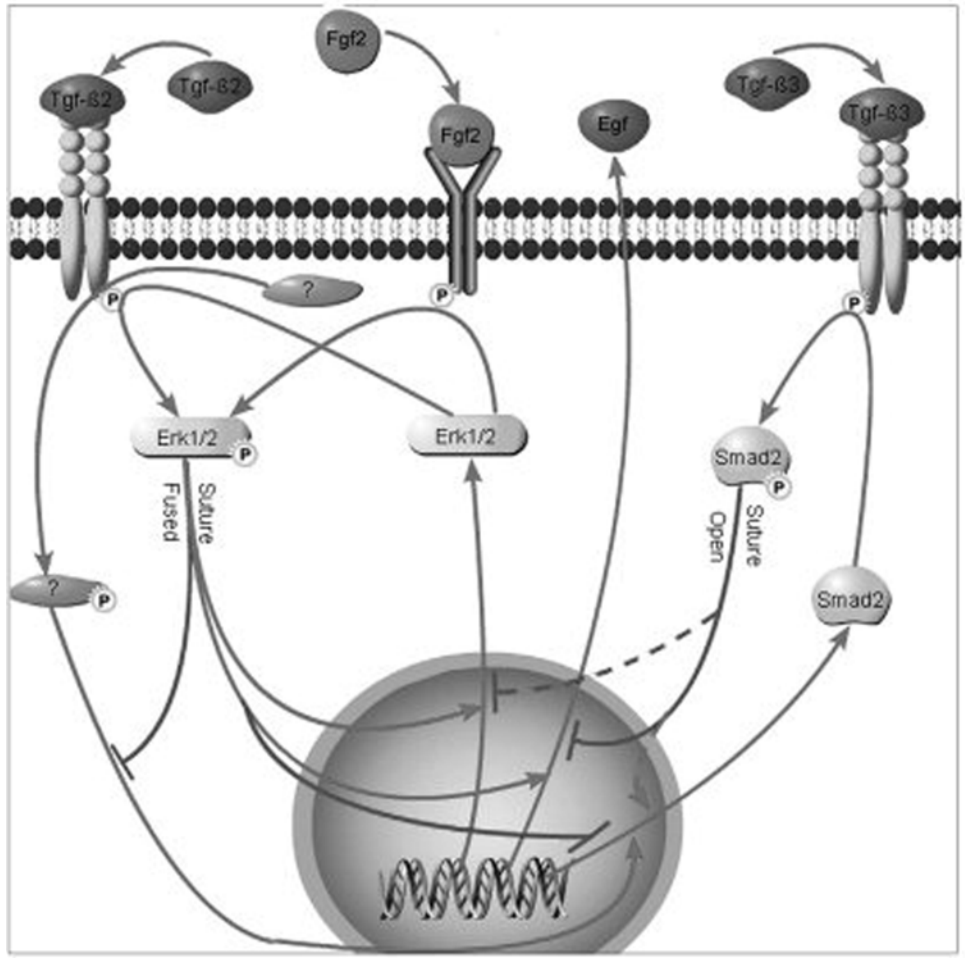

Fig. 1. Model of TGF-β2 signaling in sutures. TGF-β2 regulates suture patency and fusion through phosphorylation of Erk 1/2 and Smad2 proteins. *Solid lines* indicate proven signaling events and the *dashed line* indicates predicted signaling events based on this model. Reproduced with permission from Opperman LA, Fernandez CR, So S, Rawlins JT: Erkl/2 signaling is required for Tgf-beta 2-induced suture closure. **Dev Dyn 235:**1292–1299, 2006.

impact on the practice of neurological and craniofacial surgery. Advances in research have led to valuable insights into the critical role of FGFR- and TGF-β–mediated signaling in the pathogenesis of premature suture fusion. Normal suture fusion is dependent on a complex signaling cascade that can be disrupted by a large number of genetic mutations or perturbations in cell signaling. The present review has focused on cytokine regulation of suture fusion; however, many other mechanisms for sutural fusion and patency have been proposed, including increased apoptosis observed in patent sutures[1] and the potential for force-induced craniosynostosis secondary to events in utero.[52] Understanding how growth factors influence suture fusion allows development of new therapies for treatment.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Cohen, Chim, Gosain. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: Cohen, Manjila, Chim.

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