An update of ophthalmic management in craniosynostosis

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SUMMARY Craniosynostosis has a varied clinical spectrum, ranging from isolated single suture involvement to multisutural fusions. Syndromic and nonsyndromic patients require orchestrated and multidisciplinary care from birth to adulthood. Advances in our understanding of craniosynostosis over the last quarter-century have resulted in more systematic management of the problems associated with the syndromic and nonsyndromic forms of this condition. This review provides an update on the genetic basis of, management of strabismus and oculoplastic manifestations in, and visual surveillance of patients with craniosynostosis. (J AAPOS 2019;23:66-76)

Craniosynostosis is the premature closure of one or more cranial sutures. This common developmental anomaly affects 1 in 2,500 live births worldwide and is associated with more than 180 different syndromes.[1] Approximately 15% of patients are syndromic and typically have multisutural fusion, dysmorphism, and associated central nervous system, digital, and occasionally cardiac and tracheal anomalies.[2] Patients with nonsyndromic, isolated craniosynostosis typically have a single suture involvement and no additional anomalies. Monogenic mutations or chromosomal defects are typically found in 75%-80% of syndromic patients. Research in craniosynostosis has resulted in identification of specific DNA errors associated with nonsyndromic craniosynostosis.[3] Sagittal synostosis is the most frequent form of isolated craniosynostosis, accounting for 45%-58% of all nonsyndromic craniosynostosis. Metopic suture involvement is the second most common type of nonsyndromic craniosynostosis.[4-6] Of the syndromic types, Muenke syndrome is the most frequent, followed by Crouzon syndrome and Pfeiffer syndrome. Apert syndrome has the lowest prevalence.[1,7] Syndromic craniosynostosis is characterized predominantly by bilateral and unilateral coronal suture, and skull base suture fusion.

The skull can be divided into two parts, the calvarium or cranial vault and skull base, with each containing multiple sutures. The major sutures of the calvarium are the metopic, coronal, sagittal, and lambdoid (Figure 1). The sutures are joints between the skull bones, which contain osteoblastic foci, and function as growth centers for the developing skull, enabling rapid growth of the skull and underlying brain in the first 2 years of life. According to Virchow's law, normal cranial bone growth occurs parallel and perpendicular to the direction of the sutures. Premature fusion of the cranial sutures results in arrested skull growth perpendicular to the suture. The resulting growth parallel to the affected suture, along with compensatory skull overgrowth at unrestricted sutures induced by the developing brain, leads to characteristic and predictable skull and or facial deformities.

Metopic suture synostosis, or trigonocephaly (Greek, *trigonon*, "triangle"), leads to triangular shape to the forehead because a ridge runs down the central forehead and glabella to the anterior fontanelle, with accompanying bifrontal narrowing and hypotelorism (Figure 2).

Sagittal suture synostosis, or scaphocephaly (Greek, *scapho*, "boat"), leads to a long, narrow skull (Figure 3). Unilateral coronal suture synostosis, or anterior plagiocephaly (Greek, *plagio*, "slant"), leads to ipsilateral flattening of the forehead and superior orbital rim, with a higher orbit, wider interpalpebral fissure, and secondary bulging of the forehead with a lower supraorbital rim and orbit of the contralateral side (Figure 4). Bilateral coronal suture fusion produces brachycephaly (narrowing of the anterior to posterior skull length), a wide forehead, and bilateral forehead retrusion. Coronal suture synostosis leads to superior orbital rim retraction and vertical elongation of the lateral orbit, with extorsion of the orbit. This results radiologically in a "harlequin" appearance of the orbit (Figure 5).

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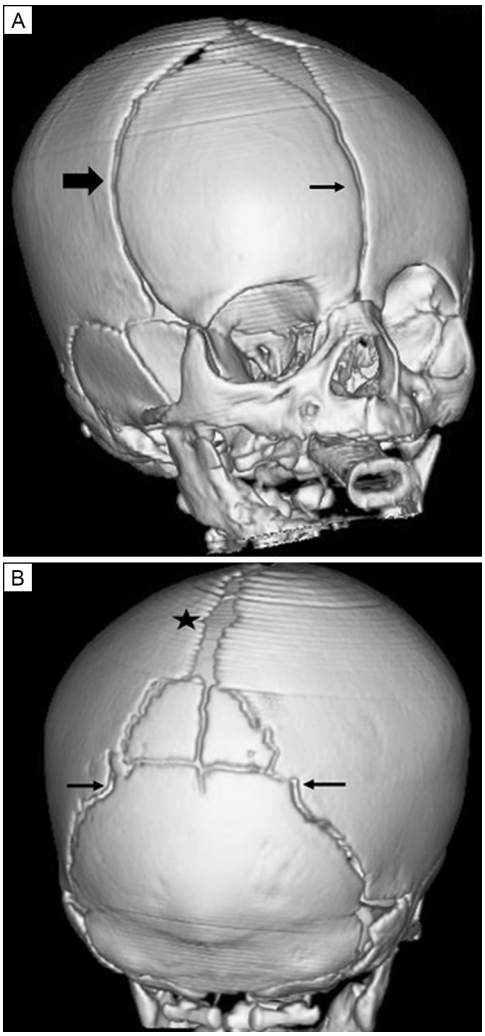

FIG 1. A 3D reconstruction computed tomography (CT) scan showing. A, Normal patent metopic (line arrow) and right coronal suture (block arrow) in a 1-month-old baby. B, Normal patent sagittal (star) and bilateral lambdoid (line arrows) sutures.

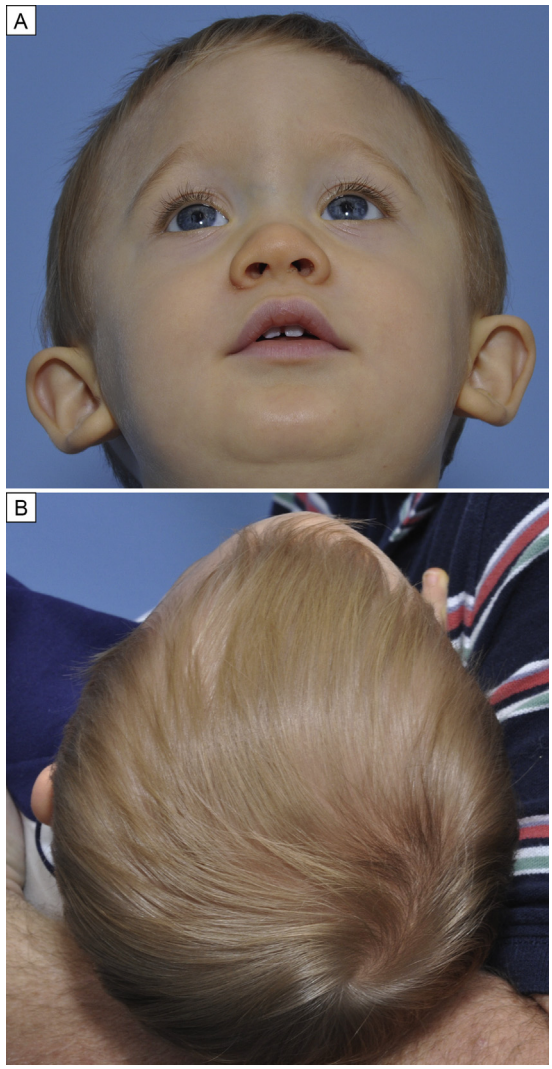

FIG 2. Patient with metopic suture synostosis resulting in trigonocephaly. A, Vertical forehead ridge. B, Triangular skull shape (aerial view).

There may be an ipsilateral harlequin eye deformity in pronounced cases of unilateral coronal suture synostosis. Lambdoidal suture fusion is rare in isolation and results in flattening of the occipital portion of the skull. Multiple sutures may be fused; an extreme and rare example is Kleeblattschadel (German, "clover-leaf" + "skull"), manifesting as a trilobed skull with frontal bossing, pronounced temporal bulging and exophthalmos, and acrocephaly (tower skull). The skull base, composed of the ethmoid, sphenoid, occipital, paired frontal, and paired parietal bones with intervening sutures, may be involved. Premature closure of the skull base sutures causes midface retrusion (or hypoplasia), beaked nose, shallow orbits, proptosis, exorbitism (or hypertelorism), high arched palate, and relative mandibular prognathism (Figure 6).

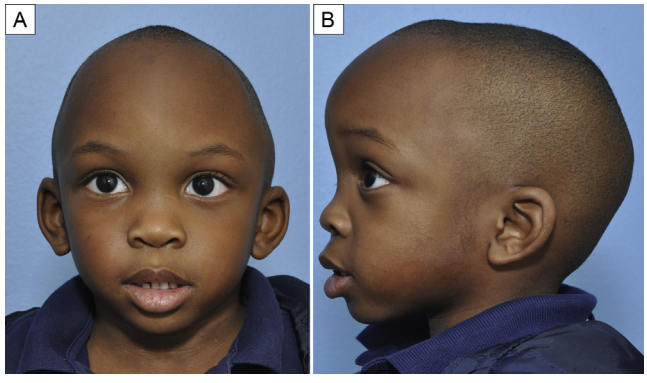

FIG 3. Patient with sagittal suture synostosis. A, Bony ridge at level of synostosed sagittal suture. B, Long, narrow skull.

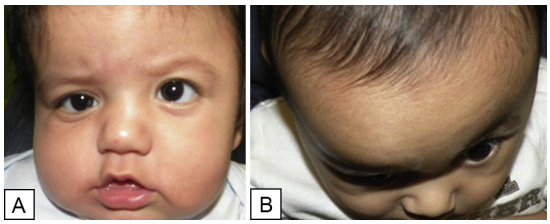

FIG 4. Patient with left unilateral coronal synostosis. A, Left forehead retrusion and right forehead protrusion. B, Higher left superior orbital rim and eyebrow, left hyperglobus, and widening of the left interpalpebral fissure, and lower right superior orbial rim and right hypoglobus.

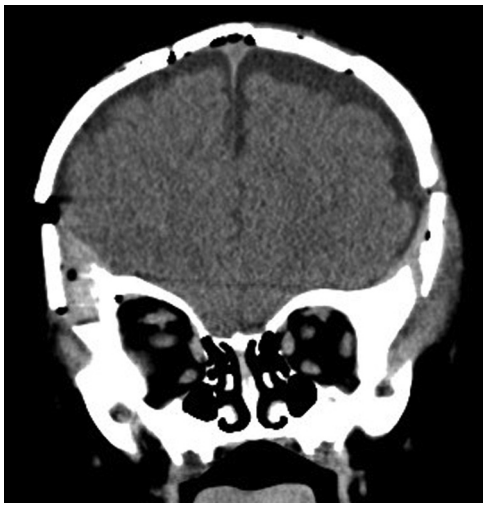

FIG 5. CT scan of the skull showing right unilateral coronal suture synostosis leading to peaking of the superolateral orbital rim and a consequent "harlequin" appearance of the orbit.

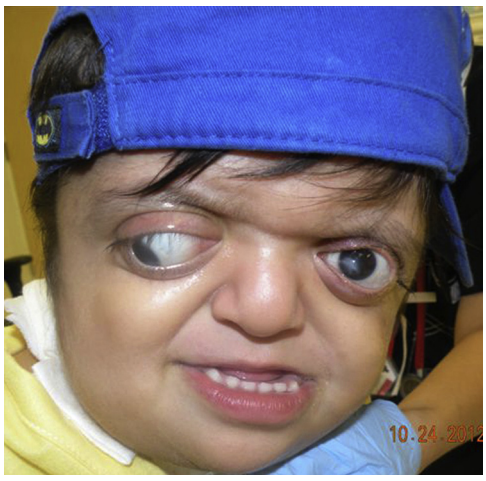

FIG 6. Patient with Apert syndrome with midface retrusion, exorbitism, and relative prognathism. Note the corneal scars from exposure and left hypertropia due to right superior rectus agenesis.

Genetics of Craniosynostosis

The skull sutures develop by a wedge-shaped proliferation of mesenchymal cells at the periphery of the extending bone fields that divide and differentiate into osteoblasts.[8] A fine balance between proliferation and differentiation is essential and is ensured by a complex molecular genetic network involving multiple signals, receptors, and transcription factors.[9] The transformation of multipotent mesenchymal cells into osteoblasts occurs under the influence of different developmental genes (Table 1). Mutations in these genes disturb coordinated bone growth and development and result in abnormal cellular proliferation and differentiation.

Apert syndrome, Crouzon syndrome, Pfeiffer syndrome, Muenke syndrome, and Jackson-Weiss syndrome are caused by genetic alterations in the fibroblast growth factor receptors *FGFR1*, *FGFR2*, and *FGFR3* (Table 1).[10] The Twist homologue 1 (*TWIST*) gene, a transcription factor strongly conserved during evolution, is an upstream modulator of the *FGFR*s. Mutations in this gene result in Saethre-Chotzen syndrome. Boston-type craniosynostosis and craniofrontonasal syndrome are caused by mutations in the *MSX2* (muscle segment homeobox 2) and *EFNB1* (ephrin B1) genes, respectively. Most genetically determined craniosynostoses have an autosomal dominant pattern of inheritance with the exception of craniofrontonasal syndrome (X-linked).

FGFR gene mutations result in gain-of-function properties, enabling the *FGFR* to become active without binding to its FGF ligand. This results in enhanced proliferation and differentiation of osteoblasts bordering the cranial suture mesenchyme, leading to premature fusion of sutures. Apert syndrome is characterized by hypertelorism, downslanting palpebral fissures, midface hypoplasia, and severe bony syndactyly of the hands and feet. Craniosynostosis most commonly involves the coronal suture. Apert syndrome may be caused by 2 mutations in *FGFR2*: the p.P253R and the p.S252W mutations. The p.P253R mutation (33% of cases) is associated with severe syndactyly, while the p.S252W (66% of cases) is commonly associated with cleft palate.[11] Crouzon syndrome, characterized clinically by shallow orbits, exorbitism, and maxillary hypoplasia, is associated with craniosynostosis involving the coronal suture.[12] Crouzon syndrome is caused by mutations in *FGFR2*. Crouzon syndrome with acanthosis nigricans has been associated with a specific mutation (A391G) in *FGFR3*.[2,13] Pfeiffer syndrome, characterized by variable proptosis, midface hypoplasia, broad and short medially deviated great toes, broad thumbs, and craniosynostosis of the coronal suture, is associated with mutations in *FGFR2*. A small number of patients have mutations in the *FGFR1*.[14] Muenke syndrome is characterized by coronal craniosynostosis, hypertelorism, midfacial hypoplasia, brachydactyly, carpal and/or tarsal bone fusion, and hearing loss. A single mutation in the *FGFR3* gene (p.Pro250Arg) is responsible for all cases of Muenke

Table 1. Some common craniosynostosis syndromes and their genetic basis

Syndrome (MIM#)	Main skull suture involved	Main clinical features	Inheritance	Gene (locus)
Pfeiffer syndrome (101600)	Coronal	CS; midface hypoplasia; broad, medially deviated halluces; and variable soft tissue syndactyly.	AD	*FGFR1* (8p11) *FGFR2* (10q26)
Apert syndrome (101200)	Coronal	CS; midface hypoplasia; cleft palate; symmetrical cutaneous and bony syndactyly of hands and feet	AD	*FGFR2* (10q26)
Crouzon syndrome (123500)	Coronal	CS; maxillary hypoplasia; shallow orbits; and prominent eyes (exorbitism)	AD	*FGFR2* (10q26)
Crouzon syndrome + acanthosis	Coronal	CS; maxillary hypoplasia; shallow orbits; and prominent eyes (exorbitism); acanthosis	AD	*FGFR3* (4p)
Jackson-Weiss syndrome	Coronal	CS; mandibular prognathism; Broad and medially deviated great toes, with normal hands; short first metatarsal, calcaneocuboid fusion, abnormally formed tarsals; normal intellect	AD	*FGFR2* (10q26)
Muenke syndrome (134394)	Coronal	CS; carpal, and/or tarsal bone fusion; and hearing loss	AD	*FGFR3* (4p)
Saethre-Chotzen syndrome (101400)	Coronal	CS; broad or bifid great toes; ptosis; characteristic appearance of the ear (small pinna with a prominent crus); and soft tissue syndactyly	AD	*TWIST1* (7p21.1) *FGFR2* (10q26)
Craniofrontonasal syndrome (304110)	Coronal	CS; frontonasal dysplasia; marked hypertelorism; broad or bifid nasal tip	X-linked	*EFNB1* (Xq13.1)
Carpenter syndrome (201000)	Coronal	CS; brachydactyly, syndactyly; aplasia or hypoplasia of the middle phalanges of the hands; preaxial polydactyly - feet	AR	*RAB23* (6p11)
Antley –Bixler syndrome (207410)	Coronal and lambdoid	Choanal stenosis or atresia; low-set dysplastic ears with stenotic external auditory canals; skeletal anomalies (radiohumeral synostosis, neonatal fractures, joint contractures, arachnodactyly); renal anomalies, developmental delay.	AR AD	*POR* (7q11.2) *FGFR2* (10q26)
Boston craniosynostosis	Coronal	CS; dysmorphism; short first metatarsal	AD	*MSX2* (5q34)

AD, autosomal dominant; *AR*, autosomal recessive; *CS*, craniosynostosis.

syndrome. Patients with Saethre-Chotzen syndrome typically present with ptosis and have characteristic appearance of the ear (small pinna with a prominent horizontal crus), prominent chin, broad or bifid great toes, and soft tissue syndactyly. Saethre-Chotzen syndrome is characterized by coronal suture craniosynostosis, but may also have involvement of the metopic or sagittal sutures.[15]

Chromosomal abnormalities have been detected in up to 30% of syndromic craniosynostosis.[16] Deletions of 7p21.1, which includes the *TWIST1* gene, cause Saethre-Chotzen syndrome.[17] The 22q11 deletion syndrome is also occasionally known to be associated with craniosynostosis.[18]

Genetic considerations and testing are an integral part of the management of patients with craniosynostosis, especially those with multisuture affectation, extracranial involvement, or associated family history. Given the highly variable phenotypic presentation of some of the syndromes, molecular genetic testing may be helpful in establishing the specific diagnosis in questionable cases.[19] An understanding of the hallmark features of particular syndromic forms of craniosynostosis leads to efficient diagnosis, management, and long-term prognosis of affected patients.

Up to 45% of patients with syndromic craniosynostosis have a genetic cause identified with current available genetic testing.[1,20] In one study, causative mutations were present in 11% of syndromic craniosynostosis patients with multisuture synostosis, 37.5% with bicoronal synostosis, and 17.5% with unicoronal synostosis, but they were absent in all sagittal, metopic, and lambdoid synostosis cases.[21] Thus, patients with isolated, nonsyndromic coronal craniosynostosis warrant genetic testing, whereas genetic testing is generally not advised for patients with isolated, nonsyndromic sagittal, lambdoidal, or metopic synostoses. Genetic testing strategies have been recommended, which will often lead to a specific diagnosis.[20] Initial performance of sequence analysis of recurrent mutations is recommended to increase efficiency and cost-effectiveness of molecular testing. Patients with apparently isolated unilateral or bilateral coronal craniosynostosis merit the testing of hotspots for *FGFR1*, *2*, and *3* and *TWIST1*.[22,23]

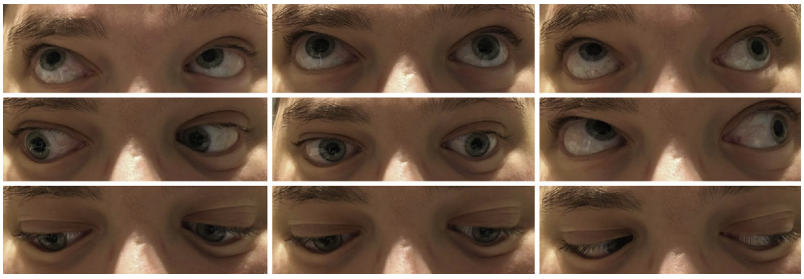

FIG 7. Patient with coronal suture synostosis with a large exotropia. There is an apparent overaction of the inferior oblique muscle (pseudo-inferior oblique overaction) due to excyclorotation of the orbits in both eyes (right more than left). Note the consequent V pattern and alternating hypertropia in adduction.

Identification of a mutation in a patient must be followed by testing in parents. Genetic work-up has immense value in predicting empiric recurrence risk. A recurrence risk of 2% for sagittal and metopic synostosis, 5% for unicoronal synostosis, and 10% for bicoronal and multisuture synostosis has been suggested in cases where no molecular or cytogenetic diagnosis is available and the family history is negative.[12]

Ophthalmic Management in Craniosynostosis

Historically, the care of patients with syndromic craniosynostosis focused purely on the surgical correction of the synostotic suture. In 2010 the National Foundation for Facial Reconstruction hosted an interdisciplinary meeting sponsored by the Centers for Disease Control to develop parameters of care for children with syndromic and nonsyndromic craniosynostosis.[24] This arose from the strong belief that the best care of these patients is delivered by teams of interdisciplinary specialists who are trained in the complex nature of these disorders, with management commencing immediately after birth in meeting short- and long-term goals.

Guidelines for ophthalmic care with isolated and syndromic craniosynostosis were created due to the high frequency of disorders of visual acuity, ocular alignment, and corneal and optic nerve health in this patient population.[24] It is recommended that all patients with syndromic and nonsyndromic craniosynostosis be examined by an ophthalmologist at the time of diagnosis, and before and after craniofacial surgery. In nonsyndromic craniosynostosis patients, annual examinations until age 7-9 and as needed thereafter is recommended. In syndromic craniosynostosis patients, biannual examinations until 7-9 years of age and yearly thereafter through adolescence is recommended, with particular attention paid to visual acuity, refractive error, ocular alignment, and corneal and optic nerve health. The frequency of follow-up examinations depend on the severity of the visual or ocular abnormality.

Strabismus

Ocular motor disturbances are frequently observed in patients with craniosynostosis. Depending on the syndrome, prevalence of strabismus can be as high as 100%, although an overall estimate for all craniofacial patients is 70%-75%, with exotropia being most frequently observed.[25] Patients with coronal suture synostosis commonly manifest a characteristic V pattern, with a large exotropia on upgaze, diminishing in downgaze. This pattern often accompanied by a marked apparent overaction of the inferior oblique muscle(s), also termed *pseudo-inferior oblique overaction*, with possible superior oblique underaction occurring ipsilateral to the fused coronal suture. This leads to a hypertropia of the involved eye, which increases in adduction (Figure 7). Various factors contribute to this characteristic strabismus including orbital and secondary globe extorsion, and retrusion of the superior orbital rim and trochlea leading to superior oblique underaction. Maldevelopment of the orbit, with consequent extraocular muscle and pulley displacement, and of the extraocular muscles are the main contributory factors in eventual development of strabismus.[26,27] Abnormal bony development at the orbital apex appears to initiate excyclorotation by displacing the superior rectus muscle laterally in the lateral rectus inferiorly at their origins in patients with more severe V patterns.[28] Agenesis, or anomalous insertions of extraocular muscles, and anomalous pulley system within the orbit may also play a role.[25,27,29,30] Amblyopia due to strabismus and high refractive errors are potential causes of visual loss in these children.

In general, early strabismus surgery is favored. Normal ocular alignment is beneficial in the development of stereopsis, and stable angle of deviation and correction of refractive errors and amblyopia are prerequisites for a successful outcome.[29] Craniofacial procedures may alter orbital contents and thereby the ocular alignment, and this has led to a conservative approach toward timing of strabismus surgery. It has been asserted that routine fronto-orbital advancement has little or no effect on the type or degree of strabismus[26,31]: although the trochlea is disinserted with periosteal stripping, it usually spontaneously reattaches, with no change in preoperative alignment. Intraorbital contents—including extraocular muscles, their nerve supply, and the globe—are usually unaffected by fronto-orbital advancement surgery. On the other hand, extensive manipulation of the orbital

contents may result in injury to the vascular and nervous structures in the posterior orbit. It is advisable to defer strabismus surgery if craniofacial surgery is planned.[32] Follow-up ophthalmic evaluation is performed 2 months after craniofacial surgery to assess for changes caused by the surgery. Subsequent evaluations are performed based on findings of the initial examination.

Another factor in the decision to offer strabismus surgery is the likelihood for binocular fusion postoperatively. Surgery should be considered in patients with an anomalous head posture or if there is a history of good alignment or fusion that has been lost because of decompensation or worsening strabismus.

Examination includes sensory testing of fusional status and measurements of ductions and versions and ocular alignment in all positions of gaze, right and left head tilt, and distance and near viewing. Imaging of extraocular muscles can be very helpful prior to strabismus surgery. The extraocular muscles are most easily identified on a coronal computed tomography (CT) scan or on magnetic resonance imaging. However, extraocular muscles that are observed on imaging may not be found attached to the globe at the time of surgery.[30,33] The role of 3D ultrasound in identifying the extraocular muscles in craniosynostosis has been shown to yield an acceptably accurate anatomic imaging of the extraocular muscles.[34] Preoperative awareness of structural variations and extraocular muscle anomalies in these patients provides the surgeon with valuable information for preoperative planning. A muscle that the surgeon was intending to operate on may be absent, malformed, or located in an aberrant position.

Standard surgical techniques for horizontal strabismus problems are generally effective in craniosynostosis patients. In most common forms of esotropia and exotropia, there is reported to be a 60%-70% success rate for alignment of the visual axis in the primary position with a single procedure.[29] However, in cases of incomitant strabismus due to abnormal orbital shape and extraocular muscle paths with or without anomalous muscle insertions and muscle agenesis, less satisfactory outcomes may be expected. Where muscles are absent, the risk of anterior segment ischemia must be kept in mind. There is no single agreed-upon surgical management for the V-pattern strabismus. Identifying the etiology of the overelevation in adduction is essential. If extorted extraocular muscles are confirmed in the presence of the eye movement pattern, muscle transposition surgery is more appropriate than inferior oblique weakening. One can transpose the medial rectus muscle down and the lateral rectus muscle up (with or without appropriate transposition of the vertical muscles), which treats the hypertropias in side gaze and the V pattern. Inferior oblique weakening alone can be performed, which treats the hypertropias in side gaze and V pattern and improves extorsion, although this is often an insufficient surgery. Additional anteriorization of the inferior oblique, which treats hypertropias in side gaze and V pattern, may hold the most promise for elimination of "pseudo inferior oblique overaction." Anterior and nasal transposition of the inferior oblique muscle reduces overelevation in adduction and helps eliminate or reduce divergence of the eyes in upgaze. However, the esodeviation may persist in downgaze.[34] This procedure is likely to benefit patients with absence of the superior oblique muscle/tendon.[35] Inferior oblique weakening with or without superior oblique strengthening, if the superior oblique is present, can also be useful in addressing the excyclotorsion that leads to apparent inferior oblique overaction and V-pattern strabismus associated with craniosynostosis.[36]

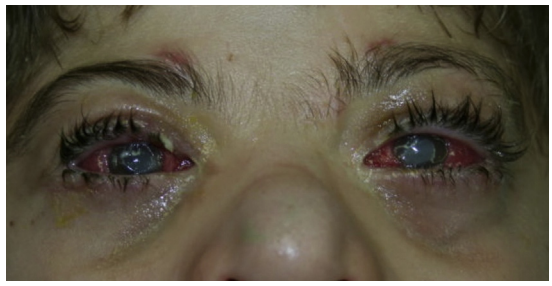

FIG 8. Patient with Saethre-Chotzen syndrome and corneal ulcers.

Many patients with vertical strabismus associated with craniofacial syndromes require multiple procedures, and comitancy is extremely difficult to obtain, especially when associated with absent and anomalous muscles. The most frequent complications are overcorrection and undercorrection, which occur more frequently in these patients because of anomalous anatomy. The lack of comitancy and high prevalence of amblyopia and refractive errors also make it difficult for these patients to attain binocularity, and without developing some sensory fusion, these patients are predisposed to recurrence of strabismus. More serious complications, such as infections, scleral perforations, slipped muscles, and retinal detachment, are observed no more frequently in this population than in patients without craniofacial abnormalities and strabismus.

Oculoplastics

Ophthalmologists are called on as part of a craniofacial team to perform oculoplastic procedures, ranging from urgent surgeries to preserve vision loss to reconstructive procedures to improve function and facial symmetry. The timing of these surgeries depends on a treatment plan that is ideally coordinated with craniofacial plastic surgeons and the rest the craniofacial team. Oculoplastic procedures are integral to the surgical management of patients with craniosynostosis and clefting syndromes.

Tarsorrhaphy

Patients with craniosynostosis can be challenged by dry eye due to corneal exposure either from shallow orbits, globe luxation, eyelid malformations, or eyelids malposition (Figure 8). If untreated, corneal exposure can

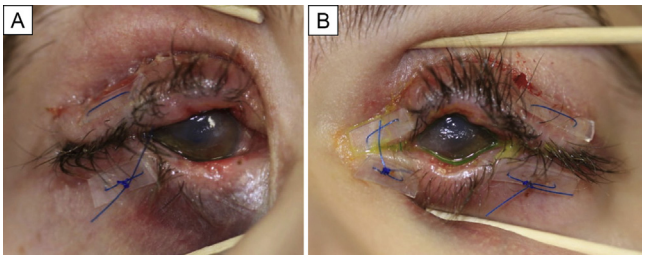

FIG 9. A, Lateral suture tarsorrhaphy with a bolster made of retinal band material (silicone). B, Left eye of the same patient with a lateral and medial tarsorrhaphy due to the severity of the ulcer and the need for better corneal coverage. Once again, the central eyelid is left untouched. This technique will most often allow for good corneal protection and central access for examination.

progress to ulceration and lead to permanent vision loss from corneal scarring and deprivation amblyopia.[37] A tarsorrhaphy can help preserve corneal and conjunctival health in the setting of acute and chronic corneal exposure and conjunctival prolapse. This can be encountered during infancy in patients with shallow orbits, such as in Pfeiffer, Crouzon, and Apert syndromes, or later in patients with chronic exposure due to poor eyelid closure. A tarsorrhaphy can either be temporary or permanent, partial or complete, and mechanical or pharmacologic. The type and timing of tarsorrhaphy depends on the treatment goals. For cases of acute exposure with an anticipated resolution, a temporary tarsorrhaphy can be placed; is chronic exposure is anticipated, a permanent tarsorrhaphy should be placed.

The most effective tarsorrhaphy involves suturing the eyelids, but other options are available. A tape tarsorrhaphy can be applied from the upper eyelid to the cheek. This is often used intraoperatively and by hospital staff; however, when applied poorly with persistent lagophthalmos, the cornea can come into direct contact with the adhesive of the tape with resultant grave consequences. A pharmacologic tarsorrhaphy is not typically used in craniofacial patients because of the amblyogenic risk of severe ptosis, but it is effective if surgery is contraindicated. Five units of reconstituted Botulinum toxin A can be injected into the levator aponeurosis under the preseptal skin to induce a temporary ptosis that usually will last up to 6 weeks.[38] A glue tarsorrhaphy with cyanoacrylate can also be used as a temporary tarsorrhaphy. This will typically last up to 1 week and can be performed in the office.[39] This procedure is effective when used with orbital expanders for patients with clinical anophthalmia and microphthalmia.[40]

Patients with corneal exposure who have nonsyndromic or syndromic craniosynostosis usually require a more robust tarsorrhaphy that must last months to years. This is accomplished with sutures and can be temporary or permanent, although in reality no procedure is truly permanent. Eyelid adhesions can separate from dehiscence or be surgically lysed.

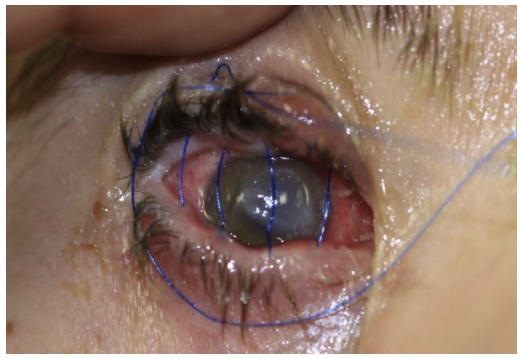

FIG 10. Complete tarsorrhaphy with a 4-0 monofilament polypropylene suture.

Temporary Tarsorrhaphy

An adhesion is usually not created between the eyelid margins. Some craniofacial surgeons (in anticipation of postoperative lagophthalmos after fronto-orbital surgery) place a suture tarsorrhaphy in the lateral one-third of the eyelids with an absorbable suture. This usually dissolves within a week and allows for adequate corneal protection. In the setting of corneal exposure that may require 1-12 weeks of closure, a suture tarsorrhaphy with a nonabsorbable suture (such monofilament polypropylene) can be placed over a synthetic bolster material to allow for a robust closure of the eyelids. A bolster will lower the risk of cheese wiring of the suture material through the skin. The most readily available bolster material is the tubing over a butterfly needle (Figure 9). The advantages of a single lateral tarsorrhaphy include good corneal coverage and easy access to the ocular surface for examination and application of medications or lubricants. In addition, only a mild ptosis is induced, allowing for good, functional vision. If the eyelids require complete closure, for example, for severe corneal ulceration, a complete tarsorrhaphy can be placed (Figure 10). The suture ends exit the skin in the upper eyelid are tied in a slip knot in the upper eyelid crease. Alternatively, the ends can be tied on loops with extra suture to allow for separation of the eyelids for examination. In both techniques excess suture can be taped to the brow.

Permanent Tarsorrhaphy

Some craniofacial patients who suffer from chronic exposure will benefit from a procedure to partly close the eyelids permanently. This is usually accomplished laterally; however, a medial and lateral permanent tarsorrhaphy can be performed as well. To accomplish this permanent adhesion between the upper and lower eyelids, a surgical debridement of the mucocutaneous junction of the eyelid is required. The anterior and posterior lamellae may also be separated to allow for direct anastomosis of each layer with the knots tied anteriorly. An early prophylactic tarsorrhaphy is an effective strategy in patients with large enough

lagophthalmos for which chronic exposure is anticipated (Figure 11).[41]

Orbital Procedures

Proptosis or exorbitism results from reduced orbital volume. Patients with extremely shallow orbits may suffer recurrent globe luxation, necessitating orbital volume expansion. Although most major orbital reconstructive procedures for craniofacial patients, including fronto-orbital advancement and repair of hypertelorism, are performed by craniofacial surgeons, an ophthalmologist must be aware of the impact these surgeries may have on the eye alignment, adnexal structures, and the lacrimal system. Any oculoplastic procedure should be timed with an individual's surgical plan in mind. The most commonly affected structures from craniofacial orbital surgery are the lateral canthi and the lacrimal system.[42]

Nasolacrimal System

There is a higher prevalence of nasolacrimal duct obstruction in patients with craniosynostosis.[43] Some patients may also have a poor lid-pumping mechanism. The nasolacrimal system can be damaged during Leforte III and other orbital advancement craniofacial procedures.[42] Some surgeons prefer to intubate the tear system during orbital advancement for protection.[44] A craniosynostosis patient with nasolacrimal symptoms of tearing and discharge can be treated conservatively with surgery delayed until at least the age of 1.[45] Ideally, any nasolacrimal surgery can be performed after craniofacial orbital surgery. Patients may require dacryocystorhinostomy surgery and even a secondary Pyrex glass bypass tube.[46]

Other Adnexal Abnormalities

Patients with craniosynostosis can have ptosis, lateral canthal dystopia, and epicanthal folds. The latter is often accentuated after repair of the hypertelorism. As previously mentioned, repairing these abnormalities should be timed with other planned procedures. In addition, craniofacial surgeons will often address canthal dystopia during fronto-orbital surgery. They will also attempt to address medial canthal epicanthal folds with either a midline nasal incision or a flap, such as a Y-V plasty. A Mustarde (or "jumping man") flap is helpful to address an epicanthal fold, as well as telecanthus.[47] Repair of ptosis and persistent epicanthal folds is best delayed until after frontal advancement surgery, unless early surgery is deemed necessary due to amblyopia that does not respond to nonsurgical therapy. Patients may experience a decrease in levator function after craniofacial surgery, thus necessitating frontalis sling surgery.[46]

Visual Surveillance

Visual loss in craniosynostoses may be due to amblyopia, uncorrected refractive errors, optic neuropathy, or exposure keratopathy, or any combination of these.[31,48,49]

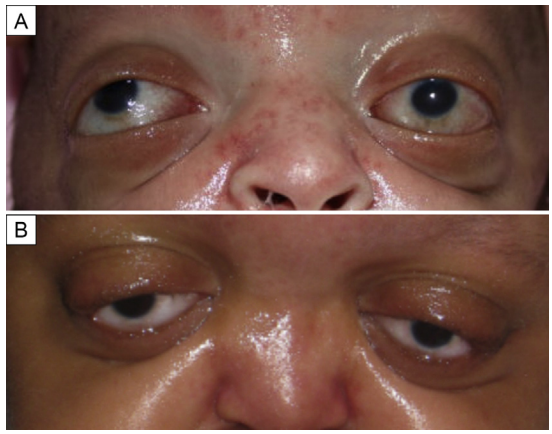

FIG 11. Infant with Pfeiffer syndrome with corneal exposure before (A) and after (B) bilateral permanent suture tarsorrhaphies. This patient had early signs of exposure and was treated with tarsorrhaphies before developing severe corneal disease.

Children with nonsyndromic or syndromic craniosynostoses may suffer from several factors that predispose them to amblyopia. In a review of 141 cases of craniosynostoses, the best-corrected visual acuity in the better-seeing eye was worse than 20/40 in 40% of cases.[49] Strabismus was seen in 70% of cases, anisometropia of greater than 1 D in 18% of cases, and astigmatism of greater than 1 D in 40% of cases.[49] Children with Apert, Pfeiffer, Crouzon, craniofrontonasal dysplasia, and nonsyndromic unicoronal synostosis were more likely to have greater than 1.25 D of astigmatism, while children with sagittal and metopic suture synostoses were much less likely. Children with Saethre-Chotzen syndrome often have asymmetric ptosis, which causes astigmatism. Exotropia was the most common type of strabismus seen. The types of amblyopia that may affect children with craniosynostoses therefore include strabismic, meridional, ametropic, anisometropic, and deprivational amblyopia (due to corneal scarring secondary to exposure keratopathy), or any combination of these.[49]

Children with syndromic craniosynostoses often have midface hypoplasia, and, as a consequence, narrow airways.[50] This results in an increased respiratory effort. The narrower the airway, the greater the respiratory effort, which leads to increased perspiration. Adhesive occlusive patches often don't adhere to perspiring faces; atropine penalization may be more effective in treating amblyopia in such instances. Another important issue is to have spectacles specially made to take into account the midfacial hypoplasia that may be seen in syndromic craniosynostoses. The shallow orbits these children exhibit often means that the lenses of spectacles are easily touched by the eyelashes and/or the globe, which often leads to spectacle noncompliance. Built-up nasal silicone nasal bridges can often help in this situation.

Exposure keratopathy is not uncommon[49] in children with syndromic craniosynostoses, but is rarely seen in

children with isolated synostosis such as sagittal, unicoronal, or metopic. Meticulous lubrication is important, and while tarsorrhaphy is helpful, the long-term solution is often expansion of the orbital volume via craniofacial surgery.

Optic neuropathy secondary to papilledema was formerly thought to occur secondary to raised intracranial pressure (ICP) due to craniocerebral disproportion. Many authors have shown that this is not the most common cause of raised ICP[51] and that there may be other causes of raised ICP and optic neuropathy, including hydrocephalus, upper airway obstruction and sleep apnea, and venous hypertension due to anomalous intracranial venous sinuses.[50,51]

Ophthalmologists are often asked to rule out papilledema in children with craniosynostoses,[49,52] but several authors have shown that in patients with craniosynostosis, the optic disk may not be swollen in the presence of raised ICP.[53]

A study comparing visual acuity, optic disk appearance, and visual evoked potentials (VEPs) as markers of visual dysfunction in 8 children with syndromic craniosynostosis showed that optic disk appearance or visual acuity measurements alone are unreliable markers of visual function in children with craniosynostosis. Of the children with syndromic craniosynostoses, 50% failed to show papilledema in the presence of raised ICP.[54,55] Only 1 case showed a linear decrease in visual acuity; the others either improved or fluctuated. This is not surprising because there is a learning curve for children with different visual acuity tests. However, all 8 cases showed a trend for the N80 to P100 to decrease in amplitude on serial pattern VEP testing prior to surgery. The decrease in amplitude was found to correlate with a rise in ICP prior to surgery. In all but 2 of the cases, after cranial vault expansion surgery, there was an opposite trend with an increase in the N80-P100 amplitude. Abnormal pattern VEPs were recorded in in 60% of patients in a study involving 114 patients with craniosynostosis,[56] suggesting that visual pathway dysfunction, as measured by electrophysiology, can affect a majority of patients with craniosynostosis. Since an anomalous skull shape may also lead to abnormal results on VEP testing, confounding the results, a baseline VEP should be obtained and conclusions based on serial measurements rather than an isolated VEP exam.[56] Pattern VEPs do not measure raised ICP but are a measure of visual pathway dysfunction due to elevated ICP.

Hayward and colleagues[50] have shown that a large proportion of children with syndromic craniosynostoses have absent or stenotic cerebral venous sinuses, leading to cerebral venous hypertension and development of venous collaterals, which are not thought to obey normal vascular autoregulation. This means that when these children have obstructive breathing problems (especially at night) and even get obstructive sleep apnea, the rise in pCO_2 results in vasodilatation of intracranial venous sinuses, causing raised venous ICP; the raised pCO_2 does not result in increased pulse rate if venous collaterals are present because of disordered autoregulation, resulting in cerebral hypoperfusion. Under these circumstances, the VEP is measuring the effect of hypoxia on the visual pathway.

One treatment modality for children with narrow airways and obstructive airways is adenoid tonsillectomy, and this has been reported to treat chronic papilledema in a child with obstructive sleep apnea and cranisoynostosis.[57] Again, the mechanism is presumably raised intracranial venous hypertension secondary to raised pCO_2. In all of these cases, the optic nerves were swollen. Continuous positive airways pressure can also be helpful but is often a short-term measure prior to midfacial distraction. It is important to note that pattern VEPs and flash VEPs are used for visual surveillance. Sweep VEPs have no place for such surveillance.

Recently it has also been suggested that ultrasound measurement of the optic nerve sheath would be a measure of raised ICP, but the reliability of such an examination in young children is unclear.[58,59] There has also been some work recently demonstrating the use of spectral domain optical coherence tomography (SD-OCT) to follow and look for optic nerve damage in craniosynostosis.[60] Peripapillary retinal nerve fiber layer thickness measured by SD-OCT was found to be a sensitive tool in identifying optic neuropathy in patients with craniosynostosis.

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