Strabismus in Craniosynostosis

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ABSTRACT
Strabismus is common in craniosynostosis, with rates from 39% to 90.9% in Crouzon, Apert, Pfeiffer, and Saethre-Chotzen syndromes. This article reviews the epidemiology of strabismus in these disorders and discusses competing theories of the mechanism, including absent muscles, excyclorotation of muscles, and instability of muscle pulleys. The authors then review options for surgical treatment of the often complex ocular misalignment in these disorders.

INTRODUCTION
The cranial vault consists of several distinct bones, including the frontal, parietal, temporal, and occipital bone. The junctions between the bony segments are cranial sutures, which normally do not fuse until adult life to allow for an appropriate degree of skull expansion.1 A schematic of cranial vault anatomy is shown in Figure 1.

Craniosynostosis, premature fusion of one or more of the cranial sutures, results in a restricted growth pattern across the fused suture. A compensatory or accelerated growth pattern occurs along patent sutures, typically in the direction parallel to the affected suture. For instance, compensatory growth along the patent sutures causes brachycephaly, an abnormally wide head, in bilateral coronal synostosis. It causes scaphocephaly, a long and narrow head, in sagittal synostosis.1

Craniosynostosis occurs in approximately 1 in 2,500 children.2 Syndromic craniosynostosis often presents as bi-coronal synostosis or multiple suture fusion. More than 100 syndromes have been recognized, with the most common phenotypes being Crouzon, Apert, Pfeiffer, and Saethre-Chotzen syndromes.2 Common features of various craniofacial syndromes are highlighted in Table 1.3-7

The genetic mutations have been identified for these syndromes. Fibroblast growth factor receptor gene 2 mutations have been implicated in Crouzon syndrome,8 Apert syndrome,9 and Pfeiffer syndrome.10 Often, mutations arise de novo, indicating that fibroblast growth factor receptor gene 2 has a high mutation rate.11 Saethre-Chotzen syndrome is caused by mutations in the TWIST gene.12

Children with craniosynostosis syndromes can have a range of ophthalmic complications, including eyelid anomalies, proptosis, corneal surface issues due to exposure, refractive error, strabismus, and papilledema or optic atrophy related to increased intracranial pressure.13-19 The purpose of this article is to discuss strabismus related to craniofacial disorders, specifically the most common forms of craniosynostosis.

PREVALENCE AND TYPES OF STRABISMUS
Strabismus is common in patients with craniosynostosis, with a rate between 39% and 90.9% (Table 2),20-31 compared to 2.1% to 3.3% of children younger than 6 years in the general population.32,33
Specific genetic mutations have been identified that increase the rate of strabismus in patients with Apert syndrome even further: patients with Ser353Trp tend to have higher rates of strabismus than those with Pro253Arg.34,35

In addition to the above studies that detail the rates of strabismus in the population of patients with craniosynostosis, many case reports have discussed anomalous muscles found in these disorders. In Apert syndrome, several reports have document-
<table>
<thead>
<tr>
<th>Author</th>
<th>Disorders Studied</th>
<th>No. of Patients</th>
<th>No. With Strabismus</th>
<th>No. With Exotropia</th>
<th>No. With Esotropia</th>
<th>No. With Vertical Strabismus</th>
<th>No. With A- or V-Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelson et al.29 (1981)</td>
<td>Apert, Crouzon, Pfeiffer</td>
<td>4 (14 Apert, 21 Crouzon, 7 Pfeiffer)</td>
<td>35 (83.3%)</td>
<td>6 Apert, 11 Crouzon (1 patient with ET/XT), 3 Pfeiffer (1 patient with ET/XT)</td>
<td>6 Apert, 4 Crouzon (1 patient with ET/XT), 2 Pfeiffer (1 patient with ET/XT)</td>
<td>1 Apert, 0 Crouzon, 0 Pfeiffer</td>
<td>11 Apert V, 1 Apert A, 13 Crouzon V, 4 Pfeiffer V</td>
</tr>
<tr>
<td>Diamond &amp; Whitaker22 (1984)</td>
<td>Crouzon</td>
<td>44</td>
<td>20 (45.5%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Morax28 (1984)</td>
<td>Apert, Crouzon</td>
<td>11 (2 Apert, 9 Crouzon)</td>
<td>10 horizontal (90.9%), 10 vertical (90.9%)</td>
<td>0 Apert, 8 Crouzon</td>
<td>2 Apert, 0 Crouzon</td>
<td>10</td>
<td>–</td>
</tr>
<tr>
<td>Carruthers20 (1988)</td>
<td>Apert, Crouzon, Pfeiffer, hypertelorism</td>
<td>10 (4 Apert, 4 Crouzon, 1 Pfeiffer, 1 hypertelorism)</td>
<td>9 (90%) (&quot;in at least 1 field&quot;)</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>6 V</td>
</tr>
<tr>
<td>Cheng et al.21 (1993)</td>
<td>Apert, Crouzon, Pfeiffer, CFND/FND</td>
<td>63 (24 Apert, 15 Crouzon, 5 Pfeiffer, 19 CFND/FND)</td>
<td>68%</td>
<td>7 Apert, 5 Crouzon, 4 Pfeiffer, 3 CFND/FND</td>
<td>12 Apert, 3 Crouzon, 0 Pfeiffer, 6 CFND/FND</td>
<td>1 Apert, 0 Crouzon, 0 Pfeiffer, 2 CFND/FND</td>
<td>16 Apert V, 7 Crouzon V, 1 Crouzon A, 3 Pfeiffer V, 0 Pfeiffer A, 8 CFND/FND V, 1 CFND/FND A</td>
</tr>
<tr>
<td>Khan et al.24 (2003)</td>
<td>Apert, Crouzon, Pfeiffer, Saethre-Chotzen</td>
<td>141</td>
<td>76%</td>
<td>38%</td>
<td>32%</td>
<td>6%</td>
<td>62, 95% of those V</td>
</tr>
<tr>
<td>Gray et al.23 (2005)</td>
<td>Crouzon</td>
<td>71</td>
<td>39%</td>
<td>20</td>
<td>6</td>
<td>6</td>
<td>16 V</td>
</tr>
<tr>
<td>Khong et al.25 (2006)</td>
<td>Apert (before craniofacial surgery)</td>
<td>63</td>
<td>38 (60%)</td>
<td>21</td>
<td>11</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>Khong et al.26 (2006)</td>
<td>Apert (after craniofacial surgery)</td>
<td>49</td>
<td>36 (63%)</td>
<td>11</td>
<td>16</td>
<td>2</td>
<td>11 V</td>
</tr>
<tr>
<td>Tay et al.30 (2006)</td>
<td>Apert, Crouzon, Pfeiffer, Saethre-Chotzen, CFND</td>
<td>60</td>
<td>26 (43.3%)</td>
<td>18 (30.0%)</td>
<td>5 (8.3%)</td>
<td>12 (20.0%)</td>
<td>20 V</td>
</tr>
<tr>
<td>Tay et al.31 (2007)</td>
<td>CFND</td>
<td>9</td>
<td>8 (88.9%)</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>–</td>
</tr>
<tr>
<td>Kreiborg &amp; Cohen27 (2010)</td>
<td>Crouzon</td>
<td>60</td>
<td>46 (76.6%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

ET = esotropia at distance fixation; XT = exotropia at near fixation; V = V-pattern strabismus; A = A-pattern strabismus; CFND = craniofrontonasal dysplasia; FND = frontonasal dysplasia.
ed an absence of extraocular muscles. Pollard described 11 children with Apert syndrome who had bilateral superior oblique palsy, 5 of whom had no superior oblique tendon in either eye and 2 of whom had only a small fibrous band as a remnant of the muscle. For this reason, the author recommended that children with Apert syndrome should have computed tomography (CT) imaging of their extraocular muscles when they have a CT scan of the head. Similarly, Pinchoff and Sandall discussed two children, one with Apert syndrome and one with Crouzon syndrome, who also had congenital absence of the superior oblique tendon. Even after extensive surgical exploration, no evidence of a tendon or a fibrous band representing the tendon could be found. Bustos and Donahue described a child with agenesis of all four cyclovertical muscles in one eye. Cuttone et al. and Weinstock and Hardesty described children without superior rectus muscle tissue. Greenberg and Pollard described a child with bilateral absence of the superior rectus and superior oblique muscles.

Children with Crouzon syndrome can have similar problems. Coats et al. showed that 8 of 9 patients with Crouzon and Apert syndrome whose superior oblique muscle was explored had bilaterally absent or anomalous tendons. Snir et al. hypothesized that this agenesis occurs because an abnormal mutual stimulus between the orbital bones and the extraocular muscles arrests the growth of the ocular muscles. The medial rectus muscle can also sometimes be abnormal: Coats and Ou described a patient whose left medial rectus muscle had a Y configuration with two separate and distinct insertional heads, separated by 5 mm of bare sclera. The insertions were located 9 mm posterior to the limbus, and the total width of the double insertion was 13.4 mm. Captuo and Lingua described another patient whose medial rectus muscle was twice the normal size, with a bifid belly and footplate insertion 2.5 mm from the limbus. In the same patient, the lateral rectus insertion was also 2.5 mm from the limbus.

One report of absent muscles has been made in Pfeiffer syndrome. Greenberg and Pollard described a patient with an absent left superior rectus and inferior oblique, a vestigial left superior oblique, and an underdeveloped and misinserted left inferior rectus muscle.

### MECHANISM

Although it is well established that people with craniosynostosis have a higher rate of strabismus, the mechanism of the strabismus is not known. Several theories have been proposed.

The simplest explanation for the high rate of strabismus may be that the absence of muscles, as detailed above, may be more common than previously thought. Snir et al. hypothesized that this agenesis occurs because an abnormal mutual stimulus between the orbital bones and the extraocular muscles arrests the growth of the ocular muscles. In addition, even muscles that grossly look normal have structural alterations in mitochondria and myofibrillar organization as seen on light and electron microscopy.

The high rates of V-pattern strabismus have led to hypotheses about its etiology. The position of the orbit and muscles has been implicated as a cause of strabismus. Tan et al. described 10 patients with craniosynostosis (Apert, Crouzon, Pfeiffer, and Saethre-Chotzen syndromes), examining the association between presence of over-elevation in adduction and degree of excyclorotation of the extraocular muscle cone on CT or magnetic resonance imaging (MRI). They found that 7 of the 8 patients with over-elevation in adduction had more excyclorotation of the muscles than age-matched controls.

Velez et al. described a similar patient with V-pattern strabismus in whom CT demonstrated that the muscles in the left eye were rotated clockwise and the muscles in the right eye were rotated counterclockwise; surgical exploration confirmed that the lateral recti slanted inferiorly. This muscle heterotopy was thought to account for the V-pattern.

In Cheng et al.’s study of 63 patients, 4 patients had MRIs that showed varying degrees of orbital deformation and excyclorotation, and one patient had a CT that showed the same. Four patients were noted to have excyclorotation of retinal vessels on funduscopic examination. In three cases of Crouzon syndrome that had surgery, all had excyclorotation of the horizontal recti. Two were noted to have excyclorotation of the vertical recti; the final case was thought to have a missing inferior rectus and superior oblique muscle, but later MRI showed both muscles to be present, with the inferior rectus muscle displaced medially.

Cheng et al. explained how the excyclorotation can result in dissociated movements if Hering’s law still applied.
abduction of a fixing left eye requires the combined action of the superior rectus and lateral rectus muscles, whose vertical actions will cancel each other out. The contralateral synergists of these two muscles are the right inferior oblique and medial rectus muscles. In an excyclorotated position, both of these muscles will tend to elevate the eye, causing extreme upshoot. Similarly, adduction of a fixing right eye is the resultant action of the right medial rectus and inferior rectus muscles, whose vertical actions will cancel each other out. The contralateral synergists of the right medial rectus and inferior rectus muscles are the left lateral rectus and superior oblique muscles. When attempting to abduct, these muscles will cause the eye to move down and out, making it lower than the adducting eye. Clement and Nischal modeled the mechanics of excyclorotated muscles and verified the hypothesis that excyclorotated muscles will cause upshoots and downshoots based on Hering’s law.50

Another theory proposed by Gobin maintains that the V-pattern is caused by sagittalization of the oblique muscles, which disturbs the balance between the horizontal and vertical components of the muscles, causing torsional anomalies. Specifically, if the inferior oblique muscle’s insertion onto the globe lies further posterior than the superior oblique muscle or when its origin is anterior to the superior oblique muscle origin, the angle between the inferior oblique muscle and the visual axis is reduced. This reduction will cause a decreased extorsional and increased vertical action, leading to incyclophoria. This incyclophoria can be reduced by a contraction of the extorsional muscles (inferior rectus and inferior oblique) and an inhibition of the intorsional muscles (superior rectus and superior oblique). The contraction and inhibition of the vertical muscles to reduce the incyclophoria will produce an elevation in adduction and a V-pattern.51

More recently, instability of the connective tissue pulleys of the extraocular muscles have been thought to be related to incomitant strabismus52 and have been implicated in Y-pattern strabismus.53 A study of patients with unilateral coronal synostosis with ipsilateral hypertropia that simulated inferior oblique overaction examined the superior rectus muscle pulley using CT. The authors used a biomechanical model to simulate posterior displacement of the trochlea and superlateral displacement of the superior rectus muscle pulley. They determined that translation of the pulley creates an imbalance of pulling forces that better accounts for the hypertropia than posterior displacement of the trochlea. They believe that patients with complex craniofacial disorders or generalized craniosynostosis likely have complex displacements of multiple pulleys and additional pathologic abnormalities.54

There is also the possibility that abnormal sensory features may be at least a partial cause of anomalous eye movements and head positions. Tomac et al.55 reported a case in which a patient with unilateral craniosynostosis presented with right esotropia and hypertropia along with severe overaction of the right inferior oblique muscle and underaction of the right superior oblique muscle. She had a head tilt to the left shoulder. She underwent myectomy of the right inferior oblique muscle and a tuck of the right superior oblique muscle. This surgery resolved the vertical deviation, but the abnormal head position was unchanged. The torticollis disappeared on occlusion of the affected right eye, leading the authors to hypothesize that anomalous retinal correspondence with eccentric fixation may be playing a role in maintaining the anomalous head position.55 This theory has not yet been discussed in patients with syndromic craniosynostosis.

**IMAGING**

The position of the extraocular muscles in craniosynostosis can be determined with imaging. Tan et al. used CT and MRI techniques to assess extraocular muscle excyclorotation around the globe’s anterior-posterior axis.48 Using coronal views, they determined the position of the axes of the horizontal rectus muscles by drawing a line bisecting the lateral and medial rectus muscle on each side. The angle between this line and the horizontal plane was measured and classified as intorted or extorted; the angles from the two sides were added together. When comparing patients with craniosynostosis to age-matched controls, 88% had more excyclorotation of the extraocular muscles.

Another option for imaging is three-dimensional ultrasonography. Somani et al. compared the results of ultrasound to intraoperative findings.56 They found that this modality has good accuracy in assessing anatomic features of the rectus muscles, with a sensitivity of 80% ± 14% and a specificity of 88% ± 10%. The anatomic anomalies detected in their series included excessively thick, thin, scarred and fibrotic, and absent muscles. Three-dimensional ultrasound
was less accurate at determining position of muscles (sensitivity 48% ± 17%, specificity 85% ± 12%).

SURGICAL TECHNIQUES

Several studies have examined the best way to correct the V-pattern and over-elevation in adduction that is so common in patients with craniosynostosis. Coats et al. showed that this problem is complex and difficult to cure with surgery. Fourteen of their patients underwent 16 operations, including medial rectus infraplacement, inferior oblique recession, inferior oblique myectomy, inferior oblique anterior transposition, and inferior oblique denervation/extirpation. All patients had significant residual ocular motility dysfunction postoperatively, with better results after denervation/extirpation and myectomy than anterior transposition or medial rectus infraplacement. On the other hand, Hussein et al. did anterior and nasal transpositions of the inferior oblique muscle on nine children with missing superior oblique tendons, seven of whom had craniosynostosis, with all patients improving. Tan et al. suggested that preoperative orbital imaging, as described above, may help determine the appropriate surgery to address the V-pattern and over-elevation in adduction. They believe that transposing inferoplaced lateral rectus muscles may be a more appropriate operation than weakening the inferior oblique muscle in patients with extorted extraocular muscles. The model by Clement and Nischal indicates that transposition of the rectus muscles in combination with weakening of the oblique muscles should be effective.

Velez et al. described a different way to address the V-pattern. In their case described above, with the muscles of the left eye rotated clockwise and the right eye rotated counterclockwise, they first repositioned the lateral recti superiorly to a more horizontal position and sutured the superior border of the muscle belly to the sclera approximately 18 mm from the limbus, which improved the V-pattern somewhat. They then did a second procedure, recessing and nasally repositioning the superior recti, suturing the nasal border of the muscle belly to the adjacent sclera approximately 18 mm from the limbus. This second procedure resulted in good alignment in primary position and reduced the V-pattern and over-elevation in adduction.

Another option to address the V-pattern and over-elevation in adduction is to strengthen the superior oblique muscle. Holmes et al. did bilateral superior oblique tucks along with medial rectus resections with infraplacement for a patient with Saethre-Chotzen syndrome who had esotropia with apparent bilateral inferior oblique overaction and apparent bilateral superior oblique underaction, with good results at 2 years postoperatively. They stated that strengthening the superior oblique muscle directly addresses excyclotorsion of the globe, normalizing the vector forces of the rectus muscles.

Different surgical techniques have been used on the less common forms of strabismus seen in craniosynostosis. In a case series of 3 patients who had anomalous superior rectus muscles evidenced on clinical examination and orbital imaging, Rattigan and Nischal described their Foster-type modification of the Knapp procedure. They placed a non-absorbable suture at the upper border of each horizontal rectus muscle to draw it closer to the vertical midline. Hypotropia was reduced in all patients.

TIMING OF STRABISMUS SURGERY AND CRANIOFACIAL SURGERY

Another issue to consider is the changes that occur in patients after craniofacial surgery. There are several well-established procedures that are typically used in patients with syndromic craniosynostosis. During infancy, patients with syndromic craniosynostosis may undergo cranial vault remodeling, which consists of craniotomy with release of the fused suture, and fronto-orbital advancement, which decompresses the cranial vault and advances the posteriorly positioned supraorbital rim (also referred to as the supraorbital bandeau). These procedures are typically performed at age 6 to 12 months, but it is not uncommon for syndromic patients to require repeat cranial vault remodeling and fronto-orbital advancement as they continue to grow.

Patients with syndromic craniosynostosis also commonly have significant midface retrusion. Surgical correction of the midface is generally performed between the ages of 5 and 12 years. To separate the midface from the craniofacial skeleton, a “Le Fort III” osteotomy is performed; this includes bilateral osteotomies at the zygomatic arch, lateral orbital wall, orbital floor, medial orbital wall, frontonasal junction, and pterygomaxillary buttresses. In comparison to the fronto-orbital advancement, this procedure advances the lower half of the orbit.

In certain clinical scenarios, it may be advanta-
geous to correct the midface, orbital rim, and forehead simultaneously. The monobloc procedure, first described by Ortiz-Monasterio et al. and Wolfe et al., involves advancement of the Le Fort III segment and frontal bone. Table 3 summarizes the craniofacial procedures and Figure 2 displays a diagram of the bone movements in each procedure.

Because these procedures change the position of the orbit, they may be expected to alter ocular alignment. However, studies have shown varied results. Diamond and Whitaker and Diamond et al. examined 140 patients before and after craniofacial reconstruction and found that only 10 had a surgically induced alteration in primary position horizontal alignment. Only 2 had a new strabismus created by the surgery, which seemed to be cranial nerve palsies. On the other hand, a study by Morax of 11 patients reported more consistent changes in alignment after surgery. Nine patients with Crouzon syndrome and 2 with Apert syndrome were

<table>
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<tr>
<th>Procedure</th>
<th>Age of Surgery</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Fronto-orbital advancement and cranial vault remodeling</td>
<td>6–12 months</td>
<td>Movement of both the forehead and supraorbital rim. Corrects exorbitism and protects the globe. Repeat procedure may be required due to stunted growth.</td>
</tr>
<tr>
<td>Le Fort III osteotomy and advancement</td>
<td>5–12 years</td>
<td>Movement of the midface. Moves lower half of orbit forward. May be necessary to improve airway. Can be performed by conventional technique or distraction.</td>
</tr>
<tr>
<td>Monobloc advancement</td>
<td>5–12 years</td>
<td>Simultaneous movement of the forehead, orbit, and midface (combines the movements of fronto-orbital advancement and Le Fort III osteotomy as a single unit). Can be performed by conventional technique or distraction.</td>
</tr>
</tbody>
</table>
examined before and after sagittal expansion of the orbit. Eight of the patients with Crouzon syndrome had exotropia, which was reduced to orthophoria after surgery. The two patients with Apert syndrome both had esotropia, which was unchanged. The vertical deviation sometimes diminished but never resolved completely, and there was always over-elevation in adduction.

In addition to craniofacial surgery altering ocular alignment, prior surgery can also complicate strabismus surgery. Rattigan and Nischal described 2 patients who had severe diffuse subconjunctival scarring although they had not had prior strabismus surgery. The authors theorized that the fibrosis resulted from blood tracking into the orbit during frontal bone advancement or orbitotomy.

The issue of timing of strabismus surgery in patients with craniosynostosis has not been fully resolved. Based on their results, Diamond and Whiteker believe that strabismus surgery can be performed prior to craniofacial surgery. They advocate early surgery because it is more likely to result in attainment of binocularity and because motility surgery after orbital manipulation is technically harder. They do recognize that a second strabismus surgery may be necessary later. In contrast, Morax recommends performing strabismus surgery at least 6 months after major orbital translocation procedures. Resolving this question will require further study.

EXPERIENCE AND RECOMMENDATIONS

Our experience with strabismus in craniofacial disorders derives from the 35-year experience of one of the authors (NBM). In general, it parallels the experience of the literature. The incidence of strabismus is approximately 50%, with V-pattern exotropia being the most common form. The finding of abnormal muscles approaches 15%. The abnormalities seen include absent muscles (particularly superior oblique), abnormal insertions, bifid insertions, hypertrophic muscles, and atrophic muscles. For this reason, we strongly recommend preoperative evaluation of the muscles with MRI. Finding these abnormalities preoperatively aids discussions with families that secondary surgery may be needed.

The question of timing of surgery, as noted above, has not been fully resolved in the literature. We believe that strabismus deviations are not greatly changed after craniofacial surgery. Because of this, we tend to operate earlier if the deviations are large. In these cases, the need for amblyopia treatment can perhaps be lessened and the potential for binocularity increased. Our surgical treatment in these cases is the same as in cases without craniofacial disorders, with a higher rate of secondary procedures.

CONCLUSION

Strabismus is common in craniosynostosis. Correcting it surgically continues to present significant challenges, which may be compounded by prior craniofacial surgery. Advances in orbital imaging may help with surgical planning. Further study is needed to identify the optimal approach to correcting strabismus related to craniosynostosis and the optimal timing of the procedures.

REFERENCES


Journal of Pediatric Ophthalmology & Strabismus • Vol. 50, No. 3, 2013 147


42. Coats DK, Payse EA, Stager DR. Surgical management of V-pattern strabismus and oblique dysfunction in craniofacial dysos-