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Orbital and Eyelid Characteristics, Strabismus, and Intracranial Pressure Control in Apert Children Treated by Endoscopic Strip Craniectomy versus Fronto-Orbital Advancement

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Background: Apert syndrome is characterized by eyelid dysmorphology, V-pattern strabismus, extraocular muscle excyclorotation, and elevated intracranial pressure (ICP). We compare eyelid characteristics, severity of V-pattern strabismus, rectus muscle excyclorotation, and ICP control in Apert syndrome patients initially treated by endoscopic strip craniectomy (ESC) at about 4 months of age versus fronto-orbital advancement (FOA) performed about 1 year of age.
Methods: Twenty-five patients treated at Boston Children's Hospital met inclusion criteria for this retrospective cohort study. Primary outcomes were magnitude of palpebral fissure downslanting at 1, 3, and 5 years of age, severity of V-pattern strabismus, rectus muscle excyclorotation, and interventions to control ICP.
Results: Before craniofacial repair and through 1 year of age, none of the studied parameters differed for FOA versus ESC treated patients. Palpebral fissure downslanting became statistically greater for those treated by FOA by 3 ($P < 0.001$) and 5 years of age ($P = 0.001$). Likewise, severity of palpebral fissure downslanting correlated with severity of V-pattern strabismus at 3 ($P = 0.004$) and 5 ($P = 0.002$) years of age. Palpebral fissure downslanting and rectus muscle excyclorotation were typically coexistent ($P = 0.053$). Secondary interventions to control ICP were required in four of 14 patients treated by ESC (primarily FOA) and in two of 11 patients initially treated by FOA (primarily third ventriculostomy) ($P = 0.661$).
Conclusions: Apert patients initially treated by ESC had less severe palpebral fissure downslanting and V-pattern strabismus, normalizing their appearance. Thirty percent initially treated by ESC required secondary FOA to control ICP. *(Plast Reconstr Surg Glob Open 2023; 11:e4937; doi: 10.1097/GOX.0000000000004937; Published online 10 May 2023.)*

INTRODUCTION

Patients with Apert syndrome demonstrate anterior and posterior orbital dysmorphology, including a short anteroposterior orbit, downslanting of the orbital floor, a shallow lateral orbital wall, decreased orbital soft-tissue volume, and orbital excyclorotation.[1–3] Associated ophthalmic manifestations include hypertelorism, proptosis, downslanting of the palpebral fissures, exaggerated V-pattern strabismus, and papilledema or optic atrophy secondary to elevation in ICP.[3–5] Apert syndrome is most commonly associated with bicoronal synostosis, though it sometimes presents with pansynostosis and, least frequently, with other fusions.[6] Systemic associations include

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syndactyly of the hands and feet, developmental delay, high arched palate with midface hypoplasia, and elevated intracranial pressure (ICP).[7]

Fronto-orbital advancement (FOA), the traditional open vault intervention for craniosynostosis, is commonly performed close to 1 year of age.[8] Endoscopic strip craniectomy (ESC) is a less-invasive alternative recently reintroduced as a possible alternative for this population. Fused sutures are opened under endoscopic guidance at about 3–4 months of age, and orthosis is promoted by helmeting until age 1 year.[5,8]

Many retrospective studies have demonstrated less-severe V-pattern strabismus in patients with unicoronal synostosis treated by early ESC rather than by later FOA.[9–13] The apparent success in reducing ophthalmic morbidity in this population led to offering this alternative to appropriate patients with multisuture synostosis syndromes. Since 2012, ESC has been offered at Boston Children's Hospital as an alternative to FOA for children presenting with Apert syndrome by 4 months of age. The choice of craniofacial repair for this group was based entirely on time of presentation and family preference. Here, we compare orbital and eyelid characteristics, severity of V-pattern strabismus, rectus muscle excyclorotation, and procedures to control ICP in children with Apert syndrome initially treated by ESC and orthosis versus those initially treated by FOA.

Takeaways

Question: What are the eyelid and strabismus outcomes in Apert syndrome patients treated by early endoscopic strip craniectomy (ESC) versus fronto-orbital advancement?

Findings: There was a significant reduction in eyelid downslanting in patients treated by ESC rather than by fronto-orbital advancement, and an associated reduction in severity of strabismus. The majority of patients treated by ESC did not require additional surgery for intracranial pressure control.

Meaning: Early ESC may result in a more normalized external appearance and reduced strabismus severity than primary treatment by fronto-orbital advancement in Apert patients.

METHODS

Approval for the study was obtained from the Boston Children's Hospital institutional review board (IRB-P00040390). The study was performed in compliance with standards set forth by the Declaration of Helsinki. All patients treated for Apert syndrome at Boston Children's Hospital from December 2003 through October 2019 were considered for this retrospective cohort study. Inclusion required evaluation by neurosurgical, plastic surgical, and ophthalmic services with the presence of interpretable external photographs, complete sensorimotor examinations, CT imaging, and follow-up through a minimum of 3 years of age. Once data were extracted, all were deidentified, consistent with Health Insurance Portability and Accountability Act regulations.

For Apert patients whose initial craniofacial intervention was ESC, orthosis by helmeting had been carried out through the infant's first birthday. For Apert patients initially treated by FOA, a careful orbital dissection particularly around the peri-orbita superiorly and laterally had been performed to facilitate access to the orbital roof, the lateral orbital wall, and the zygomaticofrontal suture. In this manner, fronto-orbital bandeau osteotomies were made under direct visualization using a reciprocating saw and Midas Rex drill. The primary goal of both of these procedures was control of ICP and normalization of cranial morphology.

For our study, ImageJ (Bethesda, Md.) was used to analyze external photographs taken preoperatively in primary position, and postoperatively in primary position at ages 1, 3, and 5 years for angle of palpebral fissure downslanting, palpebral fissure length, inner canthal distance, outer canthal distance, and temporal to nasal interpalpebral fissure height ratio. Image-to-image measurements were standardized by using the global calibration setting on ImageJ. Measurements of both right and left eyes were included.

To measure inner canthal distance, a line was drawn between the two medial canthi. To measure outer canthal distance, a line was drawn between the two lateral canthi. For palpebral fissure length, a line was drawn between each medial and lateral canthus. To measure the angle of palpebral fissure downslanting, the angle between the line defining inner canthal distance and that defining palpebral fissure length was recorded (Fig. 1A). The slanting of the palpebral fissure was deemed positive if the axis was below the horizontal plane created by the medial canthi, and negative if above. This methodology has been previously reported by Traboulsi et al.[14] Temporal to nasal interpalpebral fissure height ratio was defined as the distance between the upper and lower eyelid at the temporal limbus divided by the distance between the upper and lower eyelid at the nasal limbus (Fig. 1B).

Head circumference and cephalic index at ages 1, 3, and 5 years were also recorded. For V-pattern strabismus, patients were placed in one of three severity groups based on change in horizontal alignment from down-gaze to upgaze, measured by alternate prism cover testing. Patients with a difference of less than or equal to 10 prism diopters (PD) were classified as mild, those with a difference of more than 10 PD and less than or equal to 30 PD were considered moderate, and those with a difference of more than 30 PD were classified as severe, as previously described.[3] The number of strabismus procedures performed on each patient was recorded.

CT imaging with sufficient views of the orbit was used to quantify the degree of anatomical cyclorotation of the horizontal rectus muscles in standard coronal view. Digital Imaging and Communications in Medicine (DICOM) images from the CT scans were exported and analyzed on a workstation equipped for advanced visualization (VOXAR, Toshiba Medical Visualization Systems, Edinburgh, Scotland), and measurements were performed by a board-certified pediatric neuroradiologist

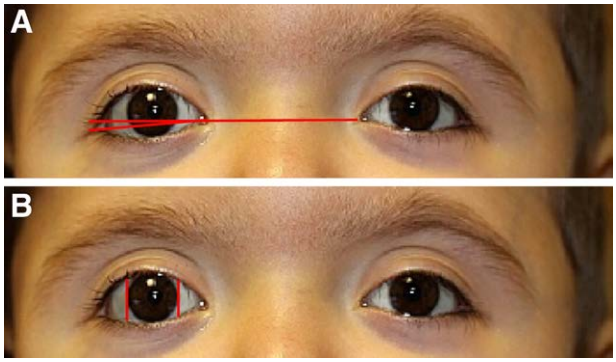

Fig. 1. A, Angle of palpebral fissure downslanting was measured as the angle between the inner canthal distance line and the palpebral fissure length line (positive value if axis below the horizontal and negative if above). B, Temporal to nasal interpalpebral fissure height ratio was defined as the distance between the upper and lower eyelid at the temporal limbus divided by the distance between the upper and lower eyelid at the nasal limbus.

blinded to clinical and surgical history of the patients. Cyclorotation was measured for each eye 1 mm posterior to the globe/optic nerve junction and within 6 mm of the rectus muscle pulleys.[15–17] Cyclorotation was ultimately expressed as the sum of cyclorotation in both right and left eyes ("net cyclorotation"), an approach that reduces error that could result from misplotting the horizontal plane.[3,18]

Measures of eyelid and cranial morphology were compared preoperatively and at ages 1, 3, and 5 years between those initially treated by ESC versus those by FOA. Severity of V-pattern strabismus and rectus muscle cyclorotation were compared at examinations closest to age 3 years.

Chart review identified secondary procedures performed for inadequate control of ICP recognized by presentation with papilledema, progressive optic atrophy, insufficient cranial growth, or volcano sign sometimes associated with headache or irritability. Measurements of eyelid morphology, strabismus, and rectus muscle excyclorotation from examinations after any secondary open vault craniofacial surgery were excluded from analysis. This methodology was chosen to prevent the possible confounding impact these secondary procedures might have had on our primary outcomes.

Continuous data are presented overall and within subgroups using medians and interquartile ranges, and categorical data are presented as frequencies and percentages. In Table 2, values are reported as means to facilitate comparison with reported values in the normal population. The number of nonmissing data values is expressed for each variable. Continuous data are compared between groups using the nonparametric Wilcoxon rank sum test and the Kruskal-Wallis test. Categorical data are compared using Fisher exact test. The Spearman correlation coefficient (rho) was calculated to determine the association between continuous variables. Stata (version 16.1; StataCorp LLC, College Station, Tex.) was used for all statistical analysis. A two-tailed *P* value less than 0.05 was implemented to determine statistical significance.

RESULTS

Twenty-nine patients with Apert syndrome treated by FOA or ESC were initially identified, but four were

Table 1. Palpebral Fissure Downslanting at Ages 1, 3, and 5 Years in Patients with Apert Syndrome Who Underwent FOA versus ESC and Helmeting

Age at the Time of External Photographs	Overall (n = 25 Patients)	FOA (n = 11 Patients)	ESC (n = 14 Patients)	*P*
Age at first surgery (mo)	3 (2, 11)	12 (8, 16)	3 (2, 3)	**<0.001**
	n = 25	n = 11	n = 14	
Age at preoperative external photographs (mo)	2 (2, 8)	9 (9, 15)	2 (1, 2)	**0.002**
	n = 14	n = 5	n = 9	
Age at 1 year postoperative external photographs (mo)	13 (11, 15)	15 (14, 15)	13 (12, 14)	0.066
	n = 15	n = 3	n = 12	
Age at 3 year postoperative external photographs (mo)	36 (35, 41)	36 (35, 41)	37 (30, 40)	0.490
	n = 23	n = 11	n = 12	
Age at 5 year postoperative external photographs (mo)	58 (54, 60)	58 (49, 61)	58 (53, 59)	0.748
	n = 14	n = 7	n = 7	
Angle of Palpebral Fissure Downslanting	**Overall (n = 50 Eyes)**	**FOA (n = 22 Eyes)**	**ESC (n = 28 Eyes)**	
Preoperative angle of palpebral fissure downslanting (degrees)	6.0 (1.2, 10.6)	8.1 (4.9, 14.9)	5.5 (2.6, 7.6)	0.179
	n = 28	n = 10	n = 18	
Age 1 year angle of palpebral fissure downslanting (degrees)	6.2 (1.6, 11.1)	9.7 (4.2, 14.9)	4.4 (1.5, 7.5)	0.057
	n = 30	n = 6	n = 24	
Age 3 year angle of palpebral fissure downslanting (degrees)	6.4 (1.4, 13.6)	8.8 (6.2, 14.2)	3.4 (-0.03, 4.7)	**<0.001**
	n = 46	n = 22	n = 24	
Age 5 year angle of palpebral fissure downslanting (degrees)	6.3 (1.3, 11)	10.1 (6.8, 12.8)	3.8 (1.3, 5.2)	**0.001**
	n = 28	n = 14	n = 14	

Of the 14 patients initially treated by ESC, three had eyelid, strabismus, and orbital outcomes from later examinations excluded from analysis correlating with timepoints after a secondary FOA was performed for ICP control. Data are presented as median (interquartile range). Sample sizes (n) show the amount of nonmissing data used for each calculation. *P* values were calculated using the Wilcoxon rank sum test, in bold when differences are significant.

Table 2. Inner and Outer Canthal Distances and Palpebral Fissure Length at Ages 1, 3, and 5 Years in Apert versus Typical Children

	Age 1	Age 3	Age 5
Inner canthal distance (mm)			
Apert	45.9±12.7	51.2±12.8	47±14.7
Typical	25±5	26.5±5	28±5.5
Outer canthal distance (mm)			
Apert	106±28.6	117.8±31	106.7±32.5
Typical	72.5±4	83±4.5	90±5
Palpebral fissure length (mm)			
Apert	29.7±8	33±9.1	29.4±8.8
Typical	22±2	25±2.5	26.3±3

Data are presented as mean ± standard deviation. Typical values were obtained from normal values reported in the literature.[19]

excluded on the basis of absent or incomplete sensorimotor examinations and/or external photographs of insufficient quality to extract the required information. Of the 25 patients included in this study, 14 had undergone ESC at a median age of 3 months (IQR 2, 3 months) followed by orthosis through a year of age, and 11 had undergone FOA at a median age of 12 months (IQR 8, 16 months). As expected, the age at initial craniofacial surgery was significantly higher for the FOA group compared with those treated by ESC ($P < 0.001$) (Table 1). The ESC group was composed of 12 White patients and two who identified as "other," whereas the FOA group was composed of eight White patients, one Asian patient, one Black patient, and one "other." Data obtained for the right and left eyes were not significantly different at each time point. (**See table, Supplemental Digital Content 1**, which displays the right versus left eye angle of palpebral fissure downslanting of patients treated by ESC and FOA, **http://links.lww.com/PRSGO/C542.**) Chart review of ESC patients' records did not reveal any lapse of helmeting therapy.

Before craniofacial repair, none of the studied parameters, including angle of palpebral fissure downslanting, palpebral fissure length, inner canthal distance, outer canthal distance, or temporal to nasal interpalpebral fissure height ratio, were different for patients initially treated by FOA versus by ESC. Age (in months) at which photographs were compared were not statistically different for outcomes noted at 1, 3, and 5 years of age (Table 1). Palpebral fissure length, inner canthal distance, outer canthal distance, temporal to nasal interpalpebral fissure height ratio, head circumference, and cephalic index were not statistically different between the two treatment groups at ages 1, 3, or 5 years of age. However, differences between our Apert population and typical children are noted in Table 2.

FOA- and ESC-treated patients had similar angles of palpebral fissure downslanting shortly after craniofacial repair at 1 year of age. However, by 3 years of age and continuing through 5 years of age, a statistically significant difference in angle of downslanting was present, with more severe downslanting noted in the FOA group (Table 1).

Of the 25 Apert patients, the vast majority had severe V-pattern strabismus (n = 14), with only eight classified as moderate and one in the mild group. Preoperatively, and at 1 year after craniofacial surgery, there was no correlation between angle of palpebral fissure downslanting and severity of V-pattern strabismus. By 3 years and 5 years of age, angle of downslanting was significantly correlated with strabismus severity (Table 3). Strabismus measurements included for this analysis were on 23 of 25 patients. Two patients in the ESC group were excluded because age-matched measurements were taken after secondary FOA had been performed. The median number of strabismus procedures performed by 5 years of age was 1±0.63 for the ESC group and 1±0.52 for the FOA group. Overall, eight of the 14 ESC patients and six of the 11 FOA patients had strabismus surgery.

All but one of the patients had CT imaging of sufficient quality to complete cyclorotation measurements. In patients who had strabismus surgery, measurements were taken from preoperative scans in all but three cases. These patients did not have adequate earlier imaging available, and postoperative measurements were used instead. The median age at the time of the measured scans was 29.5 months (IQR 24, 35 months). Overall, there was a trend associating greater net excyclorotation with greater net downslanting of the palpebral fissures ($P = 0.053$).

Four of the 14 patients initially treated by ESC and two of 11 initially treated by FOA required additional surgery to control ICP. The four patients initially treated by ESC had secondary FOA at a median age of 40.5 months (IQR 36.3–43.3); one of these patients also

Table 3. Angle of Palpebral Fissure Downslanting in Apert Syndrome Patients with Mild, Moderate, and Severe Strabismus

Severity of Strabismus	Mild (n = 2 Eyes)	Moderate (n = 16 Eyes)	Severe (n = 28 Eyes)	*P*
Preop angle of palpebral fissure downslanting (degrees)		2.6 (2, 4.9)	6.6 (5, 13.3)	0.098
	n = 0	n = 6	n = 19	
Age 1 angle of palpebral fissure downslanting (degrees)	-1 (-3.7, 1.6)	5.9 (-1.7, 6.3)	7.1 (3.4, 10.6)	0.068
	n = 2	n = 8	n = 18	
Age 3 angle of palpebral fissure downslanting (degrees)	1.1 (0.4, 1.7)	3.4 (-0.2, 5.4)	8.6 (3.5, 13.9)	**0.004**
	n = 2	n = 16	n = 28	
Age 5 angle of palpebral fissure downslanting (degrees)	-0.3 (-2, 1.3)	1.7 (-0.9, 5.1)	8.9 (5.2, 11.6)	**0.002**
	n = 2	n = 8	n = 18	

Data are presented as median (interquartile range).
Sample sizes (n) show the amount of nonmissing data used for each calculation. *P* values were calculated using the Kruskal-Wallis test for continuous variables and Fisher exact test for categorical variables. When differences are statistically significant, *P* values are set bold.

required an endoscopic third ventriculostomy, choroid plexus cauterization, and posterior cranial vault expansion with Chiari decompression. For the 11 patients initially treated by FOA, two required secondary third ventriculostomy, at ages 17 months and 128 months, one of these with choroid plexus cauterization. Four of the 11 initially treated with FOA had posterior vault expansion at the time of their FOA. There was no statistically significant difference between the number of patients initially treated by ESC versus FOA requiring additional surgery ($P = 0.661$) or number of additional procedures ($P = 0.234$) required for ICP control. It is noteworthy, however, that 30% of those initially treated by ESC required a later open vault, rather than endoscopic, intervention to control ICP.

DISCUSSION

We have shown a significant reduction in severity of V-pattern strabismus as well as eyelid downslanting for patients with Apert syndrome initially treated by ESC and helmeting rather than by FOA. Earlier studies have shown a reduction in severity of V-pattern strabismus in patients with unicoronal synostosis treated by early ESC rather than by later FOA.[9–13] Eyelid downslanting is not a primary characteristic of patients with unicoronal synostosis; thus, it was not relevant in these prior studies.

We have also shown that Apert syndrome patients with less palpebral fissure downslanting had less severe V-pattern strabismus. The difference in strabismus severity was significant at age 3 years and persisted at age 5 years. There was no statistically significant difference in V-pattern strabismus severity preoperatively, or in the early postoperative period. Severe V-pattern strabismus in Apert syndrome patients has been shown to correlate with extreme excyclorotation of rectus muscles originating near the orbital apex.[3] In this study we confirmed a trend of greater rectus muscle excyclorotation in patients with more downslanting of the eyelids. It is possible that significant downslanting of the eyelids serves as an anterior correlate of orbital excyclorotation and suggests a greater risk of severe of V-pattern strabismus.

In our entire cohort of 25 Apert syndrome patients, the median angle of palpebral fissure slanting was 6 degrees in the downward direction before craniofacial intervention. We found a reduction in eyelid downslanting for those treated by ESC compared with those treated by FOA by age 3 years that persisted though 5 years of age. In a prior study of 15 Apert syndrome patients, the average preoperative angle of downslanting was 10.7 degrees in right eyes and 12.4 degrees in left eyes.[19] In contrast, the average angle of palpebral fissure slanting in typical children at age 6 years has previously been reported as 3.4 degrees in the *upward* direction.[20] Compared with the general population, Apert patients in this study had longer inner canthal, outer orbital, and palpebral fissure lengths consistent with the orbital hypertelorism and eyelid downslanting known to mark Apert syndrome and thought to result from prolapse of the cribiform plate disturbing cranial base formation.[21,22]

Although we did not find a statistically significant difference in the need for secondary interventions to control ICP or in the number of procedures subsequently performed in our Apert population treated by FOA versus by early ESC, third ventriculostomy proved sufficient after initial treatment by FOA, with or without posterior calvarial expansion, whereas secondary FOA was required for those initially treated by ESC who developed recurrence of elevated ICP. Apert patients presenting early enough to be considered for ESC are made aware of this risk and the possible need for a later open vault intervention. As ESC is a far less-invasive surgery than fronto-orbital advancement and characterized by shorter operative time and hospital stay, and less blood loss,[13] parents of patients presenting early enough to consider this option often choose to proceed with endoscopic repair. In our population, 70% of those treated by ESC did not need a secondary open vault procedure to control ICP.

A notable limitation of this study is the modest sample size due to the rarity of this disorder exacerbated by the existence of different genetic variants of Apert syndrome. Apert is associated with at least two genetic variants with slightly different ophthalmic manifestations: point mutations Ser252Trp and Pro253Arg in the fibroblast growth factor receptor 2 gene.[23] In our cohort, nine patients had a confirmed Ser252Trp mutation (n = 5 ESC; n = 4 FOA), and two patients had a confirmed Pro253Arg mutation (both in the ESC group). The remaining patients either did not have genetic testing done, had inaccessible results, or had test results limited to confirming an FGFR2 mutation without the specific point mutation. Thus, there was insufficient genetic information to comment on the phenotypic differences between these two mutations and the impact on to V-pattern strabismus or any of the studied eyelid and orbital parameters. However, Figure 2 demonstrates quite disparate outcomes associated with treatment by FOA versus by ESC in two patients with the same genetic mutation (SER 252 TRP). The patient depicted in panels A, B, and C underwent ESC and shows a reduction in eyelid downslanting over time, whereas the patient depicted in panels D, E, and F underwent FOA and failed to show improvement in downslanting over time.

The possibility of unrealized selection bias for either treatment remains. Although all patients presenting early enough for consideration of ESC were offered both ESC and, later, FOA, it is possible that a less-severe presentation could have biased the craniofacial team toward treatment by ESC. However, it is also possible that those who presented later, thus limiting their option to FOA, may have been the group less severely affected early on. An unrealized selection bias in either direction seems unlikely, as we have demonstrated that none of the studied parameters were significantly different between the two groups preoperatively, or at about 1 year of age. An additional limitation of this study was that measurements were taken by one investigator not blind to patient history.

Of note, the morphologic values of eyelid and orbital characteristics are known to vary based on race.[24] Due to the small numbers present in our ESC and FOA groups, it

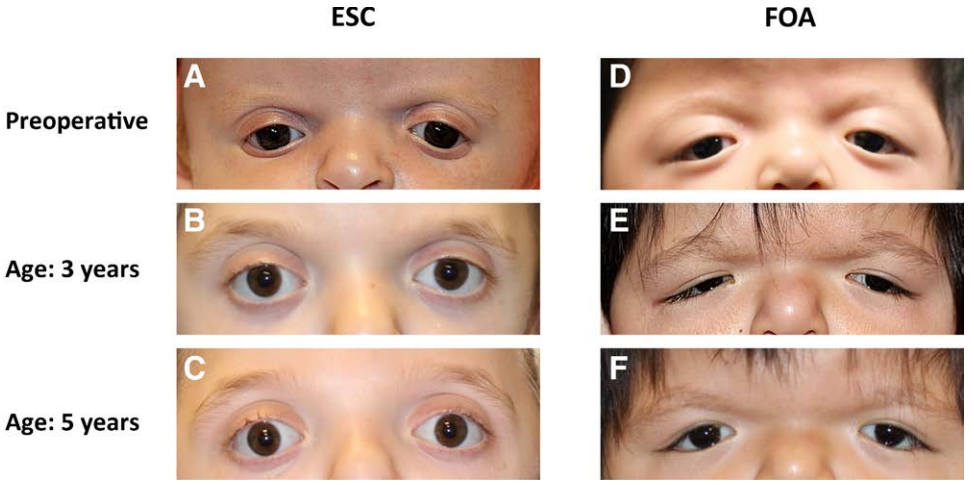

Fig. 2. Preoperative and early and late postoperative photographs of patients treated by ESC (A–C) and FOA (D–F). Both patients have the SER 252 TRP mutation.

was not possible to control for race, but each group consisted of a primarily White population. Future studies with a larger sample size and more genetic information might clarify how and when underlying point mutations affect orbital morphology and which groups might benefit most from early intervention with ESC.

An important question is whether the type of procedure or the timing of the intervention is more important in terms of the disparate outcomes shown for these two treatment groups. Early intervention with ESC and orthosis may help "normalize" some of the external orbital characteristics (eg, palpebral fissure downslanting) while the orbit is more pliable. However, it is also possible that FOA may not favorably address this particular orbital characteristic, regardless of timing. Concerning strabismus, FOA has sometimes been associated with evolution of superior oblique palsy where procedure-associated passive reinsertion of the trochlea may result in desagittalization of the trochlea, secondary superior oblique palsy and resultant V-pattern strabismus.[11]

In conclusion, in our study population, Apert patients demonstrated more severe palpebral fissure downslanting in those initially treated by FOA than ESC. Greater severity of palpebral fissure downslanting was associated with more severe anatomical excyclorotation and V-pattern strabismus. Surgeons and families of Apert children considering early intervention with ESC to improve these ophthalmic and orbital outcomes need be aware, however, that secondary FOA may prove necessary for intracranial pressure control in some cases. Over 70% of those treated initially with ESC did not require additional intervention to control ICP. Further studies are needed to understand how the underlying genetic mutations alter baseline characteristics of these patients and their response to these disparate surgical interventions.

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DISCLOSURES

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