Outcomes of strabismus surgery in genetically confirmed congenital fibrosis of the extraocular muscles

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PURPOSE To detail surgical strategy and strabismus outcomes in a genetically defined cohort of patients with congenital fibrosis of the extraocular muscles (CFEOM).

METHODS A total of 13 patients with genetically confirmed CFEOM (via genetic testing for mutations in *KIF21A*, *PHOX2A*, and *TUBB3*) were retrospectively identified after undergoing strabismus surgery at Boston Children's Hospital and surgical outcomes were compared.

RESULTS Age at first surgery ranged from 11 months to 63 years, with an average of 3 strabismus procedures per patient. Ten patients had CFEOM1, of whom 9 had the *KIF21A* R954W amino acid substitution and 1 had the M947T amino acid substitution. Of the 3 with CFEOM3, 2 had the *TUBB3* E410K amino acid substitution, and 1 had a previously unreported E410V amino acid substitution. CFEOM1 patients all underwent at least 1 procedure to address chin-up posture. Chin-up posture improved from 24° ± 8° before surgery to 10.0° ± 8° postoperatively ($P < 0.001$). Three CFEOM1 patients developed exotropia after vertical muscle surgery alone; all had the R954W amino acid substitution. Postoperatively, 1 CFEOM1 patient developed a corneal ulcer. All CFEOM3 patients appeared to have underlying exposure keratopathy, successfully treated with prosthetic replacement of the ocular surface ecosystem (PROSE) lens in 2 patients.

CONCLUSIONS CFEOM is a complex strabismus disorder for which surgical management is difficult. Despite an aggressive surgical approach, multiple procedures may be necessary to achieve a desirable surgical effect. Knowledge of the underlying genetic diagnosis may help to inform surgical management. (J AAPOS 2019;23:253.e1-6)

Congenital fibrosis of the extraocular muscles (CFEOM) refers to several rare strabismus disorders, generally characterized by nonprogressive blepharoptosis and ophthalmoplegia with restricted vertical gaze and variably restricted horizontal gaze. Three clinical phenotypes of CFEOM have been reported: CFEOM1, 2, and 3. CFEOM1 results primarily from heterozygous mutations in *KIF21A*[1]; CFEOM2, from homozygous mutations in *PHOX2A*[2]; and CFEOM3, from heterozygous mutations in *TUBB3* and rarely in *KIF21A* or *TUBB2B*.[1-5] Mouse models of CFEOM have revealed that the strabismus phenotype results from dysinnervation of the extraocular muscles that normally receive innervation from the oculomotor or trochlear nerves.[4,6,7] CFEOM thus falls within the broad spectrum of the congenital cranial dysinnervation disorders (CCDDs).[8-10]

Surgical management of strabismus in patients with CFEOM is difficult given the complexity of the disease process. Patients may have profound limitation of eye movements, severely anomalous compensatory head postures, and aberrant innervation that may lead to unexpected surgical results. Surgical treatments have varied dramatically, and, in the literature, few reports provide a detailed surgical approach and sensorimotor outcomes.[11-20] Furthermore, among the cohorts examined to date, patients have been defined on the basis of clinical criteria without genetic confirmation of diagnosis or stratification.

We hypothesized that knowledge of the mutation underlying the clinical presentation of an individual patient could provide additional information or perspective for a surgeon considering a corrective procedure on a CFEOM patient. The purpose of this study is to describe the surgical results in a genetically defined population of CFEOM patients in

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Table 1. Patient demographics and genetic diagnoses

Patient	Age at first surgery, years	Sex	Amino acid substitution	Total no. strabismus procedures	Eyelid surgery	Outcome AHP/strabismus[a]
CFEOM 1 patients						
1[b]	2	F	R954W	1	No	++/−
2[b]	46	M	R954W	1	No	+/−
3[c]	31	F	R954W	2	No	++/−
4[c]	63	M	R954W	1	No	+/+
5	3	F	R954W	2	Yes	+/NA
6	6	F	R954W	3	No	++/++
7	2	M	R954W	2	Yes	++/NA
8	1	M	R954W	2	Yes	+/++
9	5	F	R954W	1	Yes	++/++
10	1	M	M947T	12	Yes	−/++
CFEOM 3 patients						
11	2	M	E410K	5	Yes	−/−
12	1	F	E410K	2	Yes	NA/++
13	8	M	E410V	2	No	++/++

[a]Grading system for anomalous head posture (AHP): + indicates 10° of improvement; ++ indicates within 5° of primary position; − indicates no improvement; NA indicates that head posture was not a preoperative concern. Grading system for strabismus: + indicates 10^{Δ} of improvement; ++ indicates strabismus $\leq 10^{\Delta}$ of primary position; − indicates no improvement or overcorrection of $\geq 10^{\Delta}$; NA indicates that strabismus was not a preoperative concern.
[b]Patients 1 and 2 are from the same family.
[c]Patients 3 and 4 are from the same family.

an effort to examine whether genetic stratification was relevant for surgical planning or would lead to more predictable surgical outcomes. We evaluated this within each genetically defined subtype, that is, within the CFEOM1 group and the CFEOM3 group. Further, with this genetic categorization, we sought to determine the differences in surgical outcomes and specific surgical considerations between patients with CFEOM1 and CFEOM3, as such analysis has not been previously undertaken.

Subjects and Methods

This study was approved by the Boston Children's Hospital Institutional Review Board and was conducted in compliance with the US Health Insurance Portability and Accountability Act of 1996. The medical records of all patients with a diagnosis of CFEOM seen in the Department of Ophthalmology from January 1992 to September 2018 were reviewed retrospectively. Patients were included in the study if they had undergone at least one strabismus surgery for CFEOM at our institution and had a genetically confirmed diagnosis. Genetic testing for mutations in *KIF21A*, *PHOX2A*, and *TUBB3* had been undertaken either as part of clinical testing and/or through a research-based protocol, as previously described.[1,2,4]

The practice for clinical evaluation of CFEOM patients at our hospital included assessment of ocular alignment at both distance and near, using alternate prism and cover testing where appropriate. In cases of limited cooperation or extremely limited ocular motility, Krimsky light reflex testing was used to approximate the angle of strabismus. Anomalous head positions were measured in degrees, using a goniometer by evaluating the position when fixating at distance or using external photographs of the subject when goniometer measurements were not available. The goniometer was positioned to allow for measurements of chin-up or -down head positions as well as for right or left head turns.[21]

Statistical analysis of changes in head position was performed using IBM SPSS Statistics for Windows (version 23.0; IBM Corp, Armonk, NY). A *t* test was used to compare mean angle for pre- and postoperative head position.

Results

The genetic database record review identified 13 patients (7 males) who met inclusion criteria (Table 1). Age at first surgery ranged from 11 months to 63 years. Of these patients, 10 harbored a mutation in the CFEOM1 *KIF21A* gene; 3 patients harbored a mutation in the CFEOM3 *TUBB3* gene. No patients in our group had CFEOM2.

CFEOM1 Group

Of the 10 patients with CFEOM1, 9 carried the R954W amino acid substitution, which is the most commonly reported CFEOM1 substitution in the *KIF21A* gene.[1,22] The remaining patient had the less common M947T amino acid substitution, and details of this patient were previously reported by Yamada and colleagues[23] for the association of CFEOM and Marcus Gunn jaw winking. Prior to presentation at our institution, 2 patients (patient 3 and patient 10, see Table 1) had undergone strabismus surgery; one had 4 previous procedures and the other had 1 previous surgery.

The majority of the CFEOM1 cohort had a significant chin-up posture secondary both to inability to elevate the eyes to midline and to bilateral blepharoptosis. The surgical interventions to address this head position were varied and included large inferior rectus recessions, inferior rectus myectomies, superior oblique tenotomies, and superior

Table 2. Surgical treatments for chin-up head posture in CFEOM 1 patients

	Procedure				
Patient	Bilateral SO tenotomies	IR recession ≥11 mm	Bilateral IR myectomy	Other IR-weakening[a]	SR plication or resection
1	–	–	+	–	–
2	+	–	+	–	–
3	+	–	–	+	–
4	+	+	–	–	–
5	–	–	–	+	+
6	–	+	–	–	–
7	+	–	–	+	+
8	+	+	–	–	+
9	–	+	–	–	–
10	+	–	–	+	–
Total (%)	6 (60)	4 (40)	2 (20)	4 (40)	3 (30)

SO, superior oblique; *IR*, inferior rectus; *SR*, superior rectus.
[a]Other IR-weakening procedures included small recessions and transposition of the IR to the orbital wall.

rectus strengthening procedures. These details are listed in Table 2.

Head position data pre- and postoperatively were available for 8 CFEOM1 patients (Figure 1). Chin-up head position improved in these patients, from 24.4° ± 7.8° before surgery to 10.0° ± 7.5° postoperatively ($P < 0.001$).

With respect to preoperative horizontal alignment, 3 of the CFEOM1 patients had esotropia, 2 had exotropia (including the patient with the M479T substitution), and 5 had minimal horizontal strabismus (≤10$^{\Delta}$). Of those without initial strabismus, three developed a postoperative exotropia after vertical strabismus surgery, 2 of whom (patients 6 and 8) subsequently underwent horizontal strabismus surgery, with excellent postoperative alignment. Postoperative results are summarized in Table 1.

In our CFEOM1 cohort, surgery to address blepharoptosis was performed in half of the patients. Patients 7, 8, and 9 underwent frontalis slings with silicone rod suspension, and patient 5 underwent frontalis slings with autologous fascia lata. In addition, patient 10 underwent bilateral levator resections prior to seeking treatment at our institution. Patient 7 required removal of an infected silicone rod of the left upper eyelid prior to presentation at our institution. To date, no patient in our cohort has required a revision of eyelid surgery performed at our institution and no patient has experienced exposure keratopathy consequent to the eyelid procedure.

CFEOM1 patient 3 developed a post–strabismus surgery corneal ulcer despite having undergone no eyelid surgery. The development of the ulcer was noted approximately 5 weeks following strabismus surgery and was not associated with any perioperative injury. Rather, the patient appeared to have bilateral superficial punctate keratopathy of the inferior corneal surface noted in the immediate postoperative period and was treated with topical antibiotic ointment. Nevertheless, a small inferior and peripheral corneal ulcer developed in the right eye and was treated with topical antibiotic eye drops and ointment. The patient was followed closely with complete resolution of the ulcer by the 2-week follow-up after initiation of treatment. No other corneal complications were noted in this group.

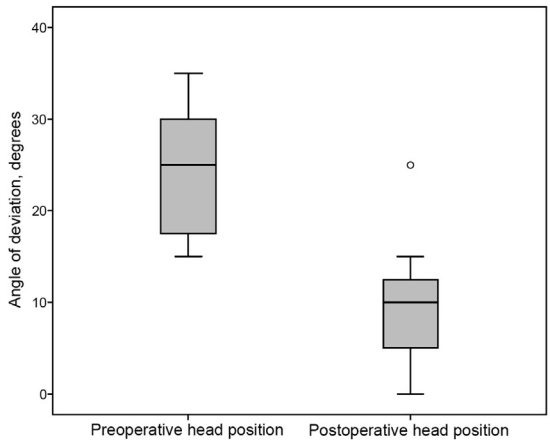

FIG 1. Change in head position after surgery for congenital fibrosis of the extraocular muscles, type 1. In these box-and-whiskers plots, the bottom and top of each box represent the 25th and 75th percentiles (the lower and upper quartiles, respectively); the band near the middle of the box is the 50th percentile (the median). The circle denotes an outlier.

CFEOM3 Group

Of the 3 patients with CFEOM3, patients 11 and 12 harbored the previously reported heterozygous TUBB3 E410K amino acid substitution,[4] and patient 13 harbored a previously unreported TUBB3 E410V amino acid substitution. Patient 13's presentation was similar to that described for the TUBB3 E410K amino acid substitution,[4,24] including CFEOM, facial weakness, Kallmann syndrome, and developmental delay; he had been presumed to have atypical Möbius syndrome prior to definitive genetic testing for CFEOM3 (see eSupplement 1, available at jaapos.org, for the full clinical report). Patient 11 underwent 11 mm bilateral inferior rectus recessions for a chin-up head position estimated at 20°, which improved postoperatively to head position of 0°. Patient

Table 3. Surgical treatments for exotropic CFEOM 3 patients

	Procedure				
Patient	LR recession	Fixation of LR to lateral orbital wall	Transpose SO to MR insertion	Botox to LR	MR resection
11	+	+	–	+	–
12	–	+	+	–	–
13	–	+	–	–	+
Total (%)	1 (33)	3 (100)	1 (33)	1 (33)	1 (33)

Botox, botulinum toxin; *LR*, lateral rectus; *MR*, medial rectus; *SO*, superior oblique.

13, with the E410V amino acid substitution and who presented elsewhere without a chin-up head posture, nonetheless underwent 10 mm superior oblique recessions at that center due to an anomalous superior oblique muscle found at the time of surgery. His head posture is excellent, within 5° of primary position (see Table 1).

All 3 CFEOM3 patients had large exodeviations at birth and underwent their initial surgeries at age 1 year or younger. Lateral rectus recessions alone were ineffective at correcting the horizontal alignment and in each case transposition of the lateral rectus muscle to the orbital rim was eventually performed.[25] Patient 11 had 14 mm bilateral lateral rectus recessions for an exotropia of 80$^{\Delta}$. This patient was treated with numerous botulinum toxin injections and finally a transposition to the orbital rim, with a modest improvement in the exotropia to 50$^{\Delta}$. He did not undergo any medial rectus strengthening procedures. At most recent follow-up, the exotropia had recrudesced to 80$^{\Delta}$, but the family was not interested in pursuing further surgery. Patient 12 had bilateral fixation of the lateral rectus muscles to the orbital rim. This was combined with nasal transposition of the superior oblique muscles. For this procedure, the superior oblique tendon was disinserted, transposed, and fixed immediately superior and anterior to the medial rectus insertion to bring the eye into an adducted position. This approach reduced the exotropia from 75$^{\Delta}$ to 16$^{\Delta}$ over 8 years' follow-up. Patient 13, with the E410V amino acid substitution, presented with a 90$^{\Delta}$ exotropia for which bilateral lateral rectus recessions of 7.5 mm were performed at an outside hospital at 1 year of age, followed at age 8 by resection plus transposition of the lateral rectus muscles to the orbital rim in combination with 4 mm medial rectus resections (see eSupplement 1). At most recent follow-up, the patient had an exotropia of 8$^{\Delta}$. A summary of the procedures performed for the exotropic CFEOM3 group is shown in Table 3.

The 2 patients harboring the E410K amino acid substitution underwent eyelid surgery. In patient 11, epiblepharon repair was performed for persistent corneal issues. In patient 12, multiple ptosis procedures were performed, including frontalis slings with silicone rod suspension followed by reoperation with banked fascia lata. Patient 13 did not have ptosis surgery as he already had evidence of corneal exposure.

All CFEOM3 patients experienced some degree of exposure keratopathy and/or corneal surface disease that may or may not have been a direct consequence of corneal exposure. Patients 11 and 12 were fitted with the prosthetic replacement of the ocular surface ecosystem (PROSE; BostonSight, Needham, MA [bostonsight.org]) lens,[26] with excellent results.

Discussion

CFEOM is rare, and prevalence data for CFEOM and its different subtypes are limited. One study focusing on CFEOM in the Wessex region of England estimated a minimal prevalence of 1/230,000 cases.[27] Because of the limited number of affected individuals, accumulating a number of cases sufficient to develop general principles of management is difficult; many patients have their first surgery performed by surgeons who have no experience operating on this condition. Consistent with this, initial surgical therapies for our 13 patients were quite variable, and their outcomes were also varied. Nevertheless, we have sought to develop a paradigm that uniquely focuses on genetic stratification. With this approach we identified several trends that we believe may guide surgical strategy or at least inform prognosis.

The CFEOM1 group included 9 patients with the *KIF21A* R954W amino acid substitution and 1 patient with the M947T amino acid substitution. Patients who harbored the most commonly seen R954W amino acid substitution underwent between 1 and 3 procedures; none had clinically significant exotropia at presentation. In contrast, the M947T patient presented with CFEOM1 with exotropia and Marcus Gunn jaw winking and has required 8 incisional strabismus procedures and 4 separate botulinum toxin injection procedures to date. The large number of procedures required occurred either because the M947T amino acid substitution conferred a more severe strabismus presentation or because the patient was first treated elsewhere with several small surgeries, and then at our institution in the early days of our experience treating CFEOM. To explore these possibilities more fully, we would require a larger cohort of patients with the M947T phenotype. After undergoing a definitive medial rectus resection, he has done well. The CFEOM1 patients all required inferior rectus muscle weakening, and most also had superior oblique tenotomies with the intent of weakening both depressors of the eye.[28] We now perform this procedure routinely in CFEOM patients with severe upgaze limitation and have begun adding adjustable superior rectus resections or plications in some

cases to obtain additional effect where needed. The rationale for superior rectus strengthening procedures is to provide an effect equivalent to that of a traction suture—even in patients with anomalous, dysinnervated superior rectus muscles. This overall approach is similar to that described by Ferrer.[14]

Patients who harbor the *KIF21A* R954W amino acid substitution appear to be at risk for developing exotropia after vertical rectus muscle surgery if they are not esotropic at presentation. One hypothesis that has been offered for this phenomenon is that, following inferior rectus recessions, there is a release of their adducting effect.[12] A second possibility is that dysinnervation contributes to this phenomenon. We commonly see convergence of both eyes in attempted upgaze in R954W patients. These patients try to elevate the eyes to minimize the chin-up head position during fixation. When this occurs in a patient with a propensity for exotropia, the exotropia is masked. When surgery improves the vertical limitation, the drive to elevate the eyes (and secondarily convergence) is reduced, allowing the underlying exotropia to become manifest. Thus, when an exotropia is noted in downgaze pre-operatively (probably a pseudo-A pattern secondary to the dysinnervation described above), we counsel the family that there may be an exotropia that develops after vertical rectus muscle surgery and that this may require an additional procedure. This finding also provides further support for performing superior oblique tenotomies, which will reduce or eliminate the A pattern and thus decrease the exotropia in downgaze.

The CFEOM3 patients differed from the CFEOM1 patients with respect to horizontal alignment and to ocular surface disease. For the CFEOM3 patients, large exotropias were present that required strong surgery involving fixation of the lateral rectus to the orbital wall and such measures were not needed to address horizontal strabismus in the CFEOM1 cohort. All 3 of the CFEOM3 *TUBB3* patients (both E410K and E410V) had corneal exposure problems, which we believe were secondary to the weakness of facial muscles that has been described as part of the phenotype associated with E410K substitution.[4,24] This feature likely predisposes patients to a poor blink, which may contribute to the vulnerability of the ocular surface. Alternatively, there may be corneal dysinnervation in the setting of the tubulin mutation, and preoperative corneal sensation testing may be helpful in this regard. In either case, the genetic confirmation of a *TUBB3* mutation would direct the ophthalmologist to be more cautious regarding blepharoptosis repair and more vigilant regarding the potential for ocular surface disease.

For all CFEOM patients, because of lack of a normal Bell's phenomenon combined with a propensity to develop corneal exposure, we recommend a modest blepharoptosis repair that uncovers enough of the pupil to allow the patient to be able to function without increasing the risk of vision loss from exposure. When both strabismus and ptosis repair were performed at our institution, we typically performed the ptosis surgery within 2 months of the strabismus surgery, and sometimes simultaneously with strabismus surgery to reduce the number of anesthetic administrations and travel requirements for families. This timing reflected that ptosis became much more symptomatic and required more urgent correction after strabismus surgery was successful in elevating the eyes. In our practice, we favor the frontalis sling with silicone rod suspension because this procedure results in a gentler lift of the eyelids that can be easily modified over time.

This study is limited in that it is a retrospective review of a limited cohort of patients treated with a variety of surgical approaches. By limiting this study to only patients with genetically confirmed CFEOM, the cohort is more uniform, but we caution that surgical decision-making for individual patients must be tempered by clinical judgment and experience. In our experience, knowledge of the genetic diagnosis provides us with at least some direction as well as perspective on areas of concern.

In conclusion, CFEOM is a complex strabismus disorder for which surgical management is difficult. In some patients, eye alignment may fail to respond even to bold surgical intervention. We found that surgical differences occurred within CFEOM subtypes as well as between patients with *KIF21A* vs. *TUBB3* mutations. Patients with *TUBB3* mutations tended to require more robust surgery to address horizontal strabismus and were particularly susceptible to issues regarding the ocular surface, while patients with *KIF21A* mutations required profoundly strong vertical procedures to address upgaze limitation. As more patients with genetic diagnoses are cared for in a more uniform manner over time, it may be possible to develop additional insights and more specific and directed recommendations for surgery.

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