Anomalous superior oblique muscles and tendons in congenital fibrosis of the extraocular muscles

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PURPOSE To evaluate the finding of anomalous superior oblique muscles in congenital fibrosis of the extraocular muscles (CFEOM), a feature not previously emphasized in this condition.

METHODS The medical records of all patients clinically or genetically diagnosed with CFEOM at Boston Children's Hospital between 2010 and 2018 were reviewed retrospectively. Those who underwent strabismus surgery during the study period were included in the analysis. Baseline patient characteristics, type of CFEOM, results of genetic testing, and intraoperative features of the superior oblique muscle or tendon were recorded.

RESULTS Of 24 patients identified (age range, 1 month to 62 years), 10 (42%) had genetically confirmed CFEOM, and 22 underwent strabismus surgery, 14 (64%) involving the superior oblique muscle. Of these, 7 (50%) had anomalously inserted tendons (most commonly attached nasal to the superior rectus muscle), whereas 7 (50%) had increased superior oblique muscle tension.

CONCLUSIONS Half of CFEOM patients who underwent superior oblique surgery had abnormally inserted superior oblique tendons, and 50% had tight muscles or abnormally thin tendons, findings that have not been well-characterized in this condition. The findings suggest that abnormal insertion of the superior oblique muscles and tendons are additional features of the disease process in CFEOM that have not been described previously. These features may contribute to the severe upgaze limitation in CFEOM and highlight the importance of superior oblique tenotomy in surgical management. (J AAPOS 2019;23:325.e1-6)

Congenital fibrosis of the extraocular muscles (CFEOM) is a rare genetic disorder characterized by nonprogressive ophthalmoplegia and strabismus. It is understood to be caused by abnormal axonal growth of the oculomotor nerve toward its target muscles during embryonic development. This leads to dysinnervation and subsequent hypoplasia and secondary fibrosis of the extraocular muscles and levator palpebrae. Three forms of CFEOM have been described in the literature (CFEOM types 1, 2, and 3), each categorized by its associated genetic mutation, degree of vertical or horizontal restriction, and other accompanying ocular or neurologic symptoms. The most common phenotype is bilateral ptosis, severe vertical gaze palsy, some element of horizontal gaze restriction, and compensatory chin-up head position.[1-3] Dysinnervation is also commonly observed. These symptoms tend to present as an isolated phenomenon in CFEOM type 1 but may be accompanied by retinal and pupil dysfunction in type 2[4] and by peripheral neuropathy, brain anomalies, and other systemic findings in type 3.[5,6]

Treatment of CFEOM involves surgery to correct functional deficits and to prevent the development of deprivation or strabismic amblyopia. Most patients require bilateral inferior rectus recessions to improve head position; some surgeons also recommend bilateral superior oblique tenotomies.[1,7] Mild or extensive horizontal strabismus surgery is also required, depending on the degree of limitation of horizontal gaze, along with eyelid surgery for correction of ptosis (taking care to prevent exposure keratopathy).[8,9] Many patients must ultimately undergo multiple surgical procedures to optimize ocular alignment and head position.[7]

In our experience performing superior oblique tenotomies in this population at Boston Children's Hospital, we have encountered several patients with abnormally inserted superior oblique tendons, a phenomenon only rarely reported previously[8,9] and not encountered in any of our other patient populations. The goal of this study was to review CFEOM cases where strabismus surgery involving the superior oblique tendon was performed to more rigorously characterize the prevalence and manifestations of this association.

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Subjects and Methods

This study was approved by the Boston Children's Hospital Institutional Review Board. The medical records of all patients evaluated for CFEOM at the Department of Ophthalmology, Boston Children's Hospital, between January 2010 and July 2018 were reviewed retrospectively. Patients diagnosed with restrictive strabismus were identified via review of hospital billing records. Those with a clinical diagnosis of CFEOM were included. The following information was extracted from the record: type of CFEOM, procedure(s) performed, genetic testing results, and previous surgeries prior to treatment at our clinic. The position and description of the superior oblique muscle and tendon were also noted in each case. Magnetic resonance imaging (MRI) examinations of the brain and orbits were reviewed when available to determine superior oblique muscle thickness and position.

Results

A total of 24 patients (13 males) with CFEOM were treated during the study interval. Mean age of presentation was 10.8 years (range, 1 month to 62 years). Of these, 12 (50%) were found to have mutations in known CFEOM target genes, including *TUBB3*, which encodes a class of B tubulin protein comprising microtubules involved in cell structure and growth,[5] and *KIF21A*, encoding a kinesin protein involved in the transport of substances along microtubules to the developing axonal growth plate.[10] Two patients had ptosis surgery performed at outside hospitals, with no strabismus surgery at the time of this review. The remaining 22 patients underwent strabismus surgery with or without ptosis repair. Of these, 14 (64%) had been treated with superior oblique tenotomy, tenectomy, or recession (in addition to vertical and/or horizontal muscle surgery), including 12 (9 bilateral and 3 unilateral procedures) treated by one coauthor (DGH) and 2 treated prior to presentation (both bilateral procedures). In 9 patients, the superior oblique tenotomy or tenectomy was performed during the same procedure as the vertical and/or horizontal muscle surgery. The remaining patients presented to our clinic after having undergone inferior rectus recessions at outside hospitals; they underwent superior oblique tenotomy as part of their further surgical management to correct residual vertical deviation or upgaze limitation. Baseline characteristics, surgical management, and intraoperative findings in the 14 patients who had superior oblique surgery are provided in Table 1.

Abnormalities in superior oblique tendon insertion and tension were documented intraoperatively in 13 of 14 patients (93%). Seven (50%) had an anomalously inserted superior oblique tendon, identified immediately adjacent and nasal to the superior rectus muscle rather than in its usual location in the superotemporal fornix. One patient was thought to have an absent right superior oblique muscle, apparently replaced by an abnormal band of connective tissue. Another was found to have abnormally thin tendons yet tight superior oblique muscles bilaterally. In both of these patients there were no clinical findings that indicated a weak superior oblique muscle. Additionally, 7 patients had increased superior oblique muscle tension, 3 of whom also had anomalous tendon insertions. All but 1 of the abnormal findings were bilateral in those who had bilateral procedures. Only 1 patient who had superior oblique surgery did not have mention of anomalously inserted or tight muscles in their operative report. Of those with anomalous insertions, 4 had confirmed mutations (2 in *KIF21A*; 2 in *TUBB3*). In all cases, the visualized superior oblique tendons were cut, including those that were anomalously thin. In the patient whose superior oblique tendon appeared to have been replaced by fibrotic bands, the fibrotic tissue was cut. In all patients, upgaze limitation and A pattern improved at postoperative visits.

Eight of 14 patients had adequate MRI imaging for review of the extraocular muscles. For each patient, the coronal area (mm^2) of the superior oblique muscle at the optic nerve–globe junction was calculated, as in the study by Yang and colleagues.[11] Angles of reflected tendons on axial imaging were also calculated, and other cranial nerve findings were recorded (Table 2). Mean area of the superior oblique muscle was 7.7 ± 3.3 mm^2 (range, 3.7–12.6 mm^2) on the right and 7.3 ± 2.8 mm^2 (range, 4.6–12.4 mm^2) on the left. Mean angle of the reflected tendon off of the muscle belly was $70° \pm 18°$ on the right and $74° \pm 16°$ on the left. All superior oblique tendons were visible on MRI, even in the patient who was initially believed to have an absent superior oblique muscle (patient 7). Several patients demonstrated aplastic or hypoplastic olfactory, oculomotor, and trochlear nerves.

Representative Case

A 4.3-year-old boy adopted from China at age 3 presented to Boston Children's Hospital for evaluation of crossed eyes, ptosis, and chin-up head positioning. He had previously undergone bilateral frontalis slings (subsequently removed because of corneal exposure) as well as injection of botulinum toxin into both inferior rectus muscles. On examination, binocular visual acuity by preferential looking test was 20/190. Cycloplegic refraction was +4.50 sphere in both eyes. On sensorimotor evaluation, his eyes were fixed in adduction and depression, with esotropia of 40^{Δ} at distance and near, increasing with attempted upgaze, and decreasing to 35^{Δ} with attempted downgaze. He had −4 limitation of elevation, −5 limitation of abduction, and a 25° chin-up head position (Figure 1). Genetic testing revealed a *KIF21A* R954W mutation consistent with CFEOM type 1 as well as a previously unreported but presumed pathogenic mutation for Coffin-Lowry syndrome, a rare disorder characterized by developmental delay and craniofacial and other skeletal abnormalities. He subsequently underwent bilateral medial and inferior rectus recessions,

Table 1. Demographics, genetic diagnoses, surgical management, and operative findings in patients undergoing SO tenotomy or tenectomy

Patient	Age at surgery, years	Sex	CFEOM type	Genetic mutation	Strabismus surgery performed[a]	Intraoperative findings (involving SO)	Other pertinent findings
1[b,c]	1.3	M	1	*KIF21A* (M947T)	R-SO/L-SO tenotomy (outside hospital); R-IR/L-IR rec; R-SR/L-SR rec	Tight (bilat)	
2[d]	4.5	M	1	*KIF21A* (R954W)	R-SO/L-SO 3 mm tenectomy; R-IR/L-IR rec; R-MR/L-MR rec	Anomalous insertion (bilat): both nasal to SR	R-IR/L-IR 2+ tight R-MR/L-MR 3+ tight
3	5	F	1[e]	NA	R-SO/L-SO tenotomy; R-MR/L-MR res	Tight (bilat)	R-SR/L-SR tight; R-IO weak
4	5.4	M	1[e]	NA	R-SO/L-SO tenotomy; R-IR/L-IR dis; R-MR/L-MR res; R-LR rec	Tight (bilat); abnormally thin (bilat)	R-IR/LIR very tight; R-LR tight; R-SR/L-SR moderately tight; R-IO/L-IO weak
5	15.3	F	1[e]	NA	R-SO/L-SO tenotomy; R-IR/L-IR rec; R-MR/L-LR res	Tight (bilat)	RIR/LIR 3+ tight
6	16	F	1[e]	NA	R-SO/L-SO tenotomy; dis of L-IR with lysis of adhesions; R-LR/L-LR rec; R-SR/L-SR plic	Anomalous insertion (bilat): R-SO tendon attached just nasal to the R-SR muscle insertion; L-SO superotemporally adjacent to L-SR insertion	R-IR/L-IR behind equator; Bilat SR tight (L > R)
7[c]	40.5	F	1	*KIF21A* (R954W)	R-SO/L-SO tenotomy; R-IR/L-IR dis and trans to lateral orbital rim; R-MR rec	R-SO absent, appeared as mostly connective tissue	Previous surgery (1996): no L-SR found
8[c]	63	M	1	*KIF21A* (R954W)	R-SO/L-SO tenotomy; R-IR/L-IR rec; R-MR/L-MR rec	Tight (bilat)	L-IR anomalously positioned 10 mm from limbus
9	0.7	M	3[e]	NA	R-SO tenotomy; R-IR rec; R-LR rec; R-MR res	Anomalous insertion; R-SO inserted under R-SR; R-SO tight	R-IR with anomalous insertion 8 mm from limbus; R-LR displaced downward; R-SR displaced laterally; R-IR displaced nasally
10	1.3	F	3[e]	NA	R-SO/L-SO tenotomy; R-IR/L-IR rec; R-SR/L-SR plic	Anomalous insertion (bilat): both inserted adjacent/nasal to SR; tight (bilat)	R-IR/L-IR 3+ tight; R-IO/L-IO weak
11[c]	1.3	M	3	*TUBB3* (E410V)	R-SO/L-SO rec (outside hospital); R-LR/L-LR rec	Anomalous insertion (bilat): inserted 3 mm posterior and 2 mm medial to SR	
12	6	M	3[e]	NA	R-SO/L-SO tenotomy; R-IR/L-IR rec; R-MR/L-MR res	*Normal tension (bilat)*	R-SR and L-IR very tight; R-IR tight and nasally displaced despite no prior surgery
13	10.2	F	3[e]	NA	L-SO tenotomy; L-IR dis; L-SR plic; L-MR res; R-LR rec; R-IR rec	Anomalous insertion: L-SO immediately adjacent to lateral corner of L-SR	R-IR tight; L-SR tight; L-IR very tight and previously recessed
14	42.3	F	3[e]	NA	L-SO tenotomy; L-IR dis; L-LR rec; L-MR res; L-SR plic	Anomalous insertion: L-SO inserted behind and immediately adjacent to L-SR	L-SR tight and adherent to the L-SO

Bilat, bilateral; *CFEOM*, congenital fibrosis of the extraocular muscles; *Dis*, disinsertion; *IR*, inferior rectus; *L*, left; *LR*, lateral rectus; *MR*, medial rectus; *Plic*, plication; *R*, right; *Rec*, recession; *Res*, resection; *SO*, superior oblique; *SR*, superior rectus; *Trans*, transposition.
[a]At BCH unless noted otherwise.
[b]Patient previously reported by Yamada et al[21] for association of CFEOM with Marcus Gunn jaw winking.
[c]Genetic mutations previously reported by Heidary et al.[7]
[d]On genetic testing, patient also found to have previously unreported but presumed pathogenic mutation for Coffin-Lowry syndrome.
[e]Not genetically confirmed: based on clinical presentation.

Table 2. MRI findings of the SO muscles and tendons in 8 of 14 patients

	SO coronal area,[a] mm^2			SO tendon angle,[b] degrees		
Patient	R	L	Tendon visible?	R	L	CN II, VI abnormalities
2	8.5	8.7	Y	91	86	Aplastic III VI (bilat)
4	7.2	4.6	Y	76	73	N/A
7	4.5	6	Y	50	91	N/A
9	3.7	5.3	Y	90	82	Small R III
10	7.9	5.7	Y	69	62	Hypoplastic III (bilat)
11	5.3	5.4	Y	42	45	Aplastic III, I (bilat)
12	12.1	10.2	Y	83	91	N/A
13	12.6	12.4	Y	61	63	N/A

Bilat, bilateral; *CN*, cranial nerve; *MRI*, magnetic resonance imaging; *SO*, superior oblique.
[a]Measured at optic nerve–globe junction.
[b]Angle of tendon reflected at muscle belly.

bilateral superior oblique tenectomies (3 mm), and placement of silicone rods for ptosis correction. Intraoperative findings included tight inferior and medial rectus muscles, with normal tension in superior rectus, lateral rectus, and inferior oblique muscles, and bilateral anomalous insertion of the superior oblique tendons at the nasal border of the superior rectus muscle (Figure 2 and Video 1). Postoperatively, he had improved upgaze and abduction and marked correction of head positioning, with a 5° residual chin-up position.

Discussion

The hallmark intraoperative findings in CFEOM include muscles with various degrees of hypoplasia, fibrosis, and globe attachment. Reports of deep orbital findings visualized by MRI include atrophic optic nerves, levator palpebrae, and extraocular muscles with bright T1 signal. The oculomotor and abducens nerves are often small or absent,[12,13] but little has been noted regarding the status of the superior oblique muscle/tendon or trochlear nerve. In addition, dysinnervation can at times produce unpredictable postoperative results. These features add substantial challenges to the surgical management of CFEOM, as detailed by others.[7-9,14,15] Less commonly, references to heterotopic tendons have been described in the literature; however, these findings are not discussed in detail.

There has been rare mention of abnormal superior oblique muscles as a feature of CFEOM: we have found only 2 references to an anomalously inserted superior oblique tendon in this population. Brodsky,[8] outlining the surgical challenges in CFEOM, provided a surgical vignette of tight and anomalously inserted superior oblique tendons "resembling muscle" in 1 patient and considered how recruitment of the superior oblique in downgaze might exacerbate an A pattern after inferior rectus recession. Sener and colleagues[9] described the surgical management of 52 cases of CFEOM; they mentioned 3 cases of heterotopic superior oblique muscles inserting 0–4 mm nasal and posterior to the superior rectus insertion. To our knowledge, these features have not been further commented on or recognized in subsequent reports.

We empirically noted heterotopic superior oblique muscles intraoperatively in several patients with CFEOM; we have not encountered the same findings in other patients undergoing strabismus surgery. On review, we discovered that almost all CFEOM patients undergoing superior oblique muscle surgery at our institution had an abnormal superior oblique muscle, most often with an anomalous tendon insertion or unexpectedly increased tension (Figure 3). We suspect that the high incidence of tendon misplacement may be underappreciated, given that tenotomies are often performed in the superonasal fornix, away from the tendon insertion on the globe. Early in our experience, we did not specifically track the insertion of the superior oblique tendon to the globe in all cases; thus, it is possible that the frequency of anomalous insertions is underestimated in this retrospective review.

MRI findings, where available, were also abnormal. For example, superior oblique cross-sectional area at the optic nerve–globe junction was approximately 7.5 mm^2, compared with 4.5 mm^2 in controls in one study[11] but smaller than reported at that location for controls in other studies (12 mm^2 by Gong and colleagues[16] and 14 mm^2 by Demer and Miller[17]). These findings are difficult to interpret, given that cross-sectional area differs significantly by the exact plane, measurement technique, and whether the muscles are actively contracting during image accession. MRI also demonstrated that a superior oblique muscle was present in a patient believed to have an absent superior oblique muscle, which may have correlated to the "connective tissue-like" structure identified intraoperatively.

These findings may have implications for the underlying pathophysiology of this condition. Mutations identified to date in CFEOM have been described mainly in relation to the oculomotor nerve and its innervation of the superior, inferior, and medial rectus muscles, the inferior oblique muscle, and the levator palpebrae superioris.[18] The abducens nerve has also been described as atrophic on orbital imaging in some cases, with the lateral rectus

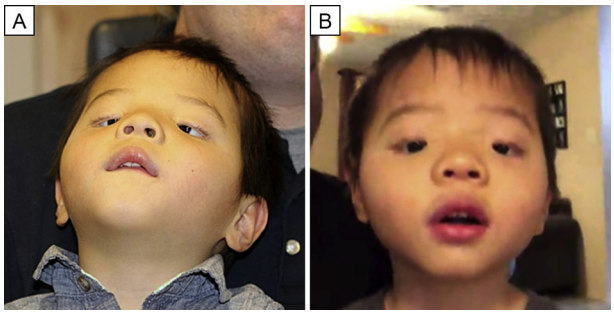

FIG 1. Change in head positioning before and after strabismus surgery. A, A 4-year-old boy presented with severely limited upgaze and 25° of compensatory chin-up head positioning. B, Photograph obtained during virtual postoperative visit showing marked improvement in upgaze and only 5° of residual chin-up positioning 2 months following bilateral medial and inferior rectus recessions, bilateral superior oblique tenectomies, and bilateral silicone rods.

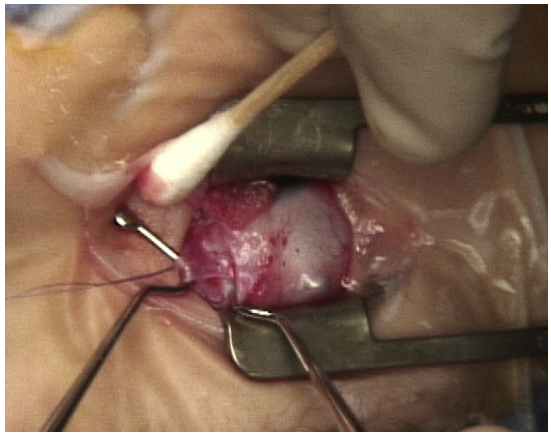

FIG 2. Anomalous superior oblique insertion identified intraoperatively. Right eye, surgeon's view. The Jameson muscle hook abutting the lid speculum has secured the superior rectus muscle. The other Jameson hook has secured the superior oblique tendon, which inserts at the nasal border of the superior rectus insertion. Similar findings were present in the left eye.

muscle often innervated by a branch of the oculomotor nerve.[12] The trochlear nerve and its innervated superior oblique muscle have not been as heavily emphasized in this condition, although Tischfield and colleagues' original paper describing mutant *TUBB3* mouse models did report stalling of trochlear nerve growth in addition to abnormal targeting of the oculomotor nerve and absent trigeminal nerve branching.[5] Issues relating to the trochlear nerve and superior oblique tendon are more commonly described as distinct features of Brown syndrome, which has been proposed to be a manifestation within the spectrum of congenital cranial dysinnervation disorders.[19,20] Thus, the finding of anomalous insertions in many of our patients indicates that superior oblique muscle and tendon abnormalities may be yet another manifestation of the disease process in CFEOM, resulting from a similar phenomenon of aberrant axonal guidance and subsequent dysgenesis of the trochlear nerve or superior oblique muscle.

We believe that our findings may help guide surgical management of CFEOM. Along with bilateral inferior rectus recessions, bilateral superior oblique tenotomies should be considered a key additional intervention for correcting upgaze limitation and restoring anomalous head postures in patients with CFEOM.[1,7] Although it may seem reasonable to leave the superior oblique tendon intact out of concern that the anomalous insertion of the superior oblique tendon may somehow benefit the otherwise-limited elevation of the eye, we have found that the restriction to elevation on forced ductions does not improve until both the inferior rectus muscles and the superior oblique muscles have been detached. We propose that the tight superior oblique muscles and misplaced superior oblique tendons may contribute to the severe upgaze limitation seen in CFEOM by causing a mechanical restriction similar to that observed in Brown syndrome but more severe, given the misplacement of the insertion. We found superior oblique tenotomies to be helpful in restoring elevation even in the case of abnormally thin tendons. Additionally, we found that cutting the fibrous tissue (which may or may not have represented the superior oblique muscle in patient 7) aided in restoring elevation as well. Furthermore, most patients with CFEOM 1 have an A pattern and thus, as noted by Brodsky,[8] gain additional benefit from the superior oblique tenotomy. We further recommend that surgeons performing superior oblique tenotomies for CFEOM should anticipate a possible anomalous insertion nasal to the superior rectus muscle and therefore consider 1) creating a larger incision for improved visualization and 2) approaching the superior oblique tendon from the superonasal rather than superotemporal fornix, taking care to track the insertion of the tendon onto the globe before performing the tenotomy.

This study was limited by its retrospective nature and relatively small sample size. Results were based on operative reports and diagrams, and the location and characteristics of the superior oblique muscle and tendon were subject to surgeon interpretation at the time of the procedure. All procedures at Boston Children's Hospital were performed by the same surgeon with consistency in annotation, while the two tenotomies performed at outside hospitals may have had discrepancies in documentation. Further, the superior oblique anomalies may be underappreciated and under-recorded due to the fact that in performing the tenotomy, surgeons do not always track the superior oblique tendon all the way to its insertion on the globe.

Future prospective studies may be warranted to systematically assess superior oblique tendon location with orbital MRI in all patients diagnosed with CFEOM compared with controls, followed by comparison with intraoperative findings. Additionally, the incidence of

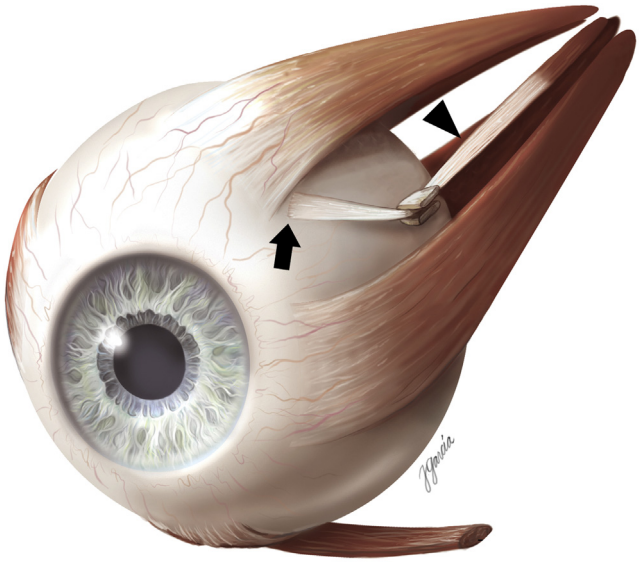

FIG 3. Schematic representation of the abnormalities of the superior oblique tendon in congenital fibrosis of the extraocular muscles (CFEOM). The arrow indicates the anomalous insertion of the superior oblique tendon nasal to the superior rectus muscle; the arrowhead, the abnormally tight superior oblique muscle creating a Brown syndrome–like restriction of elevation. Such anomalies were observed in 93% of CFEOM patients. Illustration by Juan R. Garcia © 2019 Johns Hopkins University.

anomalous superior oblique insertion in the CFEOM population may be compared to a control population of patients with other forms of congenital, incomitant strabismus such as Möbius syndrome or congenital oculomotor nerve palsy to determine whether this phenomenon is unique to CFEOM.

Literature Search

PubMed was searched on November 27, 2018, without date or language restriction, using the following terms: *CFEOM* AND *superior oblique*, *CFEOM* AND *trochlear nerve*, *congenital cranial dysinnervation disorders* AND *superior oblique*.

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