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Congenital Fibrosis of the Extraocular Muscles Type 1, Distinctive Conjunctival Changes and Intrapapillary Disc Colobomata

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Abstract

Purpose—To describe the ocular features and genetic mutation of a 6 month old male with congenital fibrosis of the extraocular muscles Type 1 (CFEOM1) with distinctive conjunctival changes and small intrapapillary disc colobomata.

Materials & Methods—Clinical examination of the proband, his parents and sister, with DNA mutational analysis of the proband and parents.

Results—In addition to CFEOM1, the patient had the unusual clinical findings of bilateral optic disc colobomata. Ophthalmic examination of his parents and sibling were normal. The patient but neither of his parents harbored the most common CFEOM1 mutation, 2860 C>T, in *KIF21A*, resulting in the R954W substitution.

Conclusion—This is the first report of bilateral optic disc colobomata in a patient with a confirmed mutation of the CFEOM1 gene.

Keywords

Congenital fibrosis of the extraocular muscles; *KIF21A* gene; R954W mutation; conjunctival changes; optic disc coloboma

Introduction

Congenital fibrosis of the extraocular muscles (CFEOM) describes a group of congenital non-progressive eye movement disorders characterised by ptosis and a variable restrictive external ophthalmoplegia, confirmed with positive forced duction testing. It is classified within a broader spectrum of congenital neuromuscular disorders due to cranial nerve

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A 6 month old boy presented with a congenital eye movement disorder consistent with congenital fibrosis of the extraocular muscles type 1 (CFEOM1). Mutational analysis confirmed the most common mutation in the CFEOM1 gene *KIF21A*. In addition to the typical findings in CFEOM1, distinctive conjunctival changes and small bilateral optic disc colobomata were also noted. It is suggested that optic disc colobomata represent a new association of CFEOM1.

dysgenesis, including other conditions such as Duane and Moebius syndromes, and congenital ptosis. These disorders are collectively known as the Congenital Cranial Dysinnervation Disorders (CCDD) {1}.

It is now believed that cranial dysinnervation leads to secondary changes in the target muscles including muscle thinning and fibrosis, anomalous muscle insertion and **occasionally**, in congenital fibrosis, absence of a muscle {2,^{3,4,5}}.

The classification of CFEOM is evolving from one based on phenotypic manifestations to a genetic classification based on molecular analysis. OMIM currently lists seven forms and four genetic loci for CFEOM. CFEOM1, CFEOM2, CFEOM3 and Tugel syndrome have been mapped, and mutations in *KIF21A* and *PHOX2A* have been demonstrated to underlie CFEOM1 and CFEOM2 respectively {6,7}. CFEOM Type 1 (CFEOM1) is characterised by autosomal dominant inheritance, bilateral ptosis and hypotropic eyes with chin up position. Horizontal eye movements are often involved and frequently there is aberrant innervation. Patients typically have convergent-type nystagmus movements with attempted upgaze (synergistic convergence) and an A pattern with divergence of the eyes in downgaze {1,8}. Penetrance appears complete and there is generally little variation between the families. CFEOM1 has been found to be due to mutation in the *KIF21A* gene, which encodes a kinesin motor protein involved in the anterograde transport of cargo along the cellular cytoskeleton of microtubules, and is likely to be “essential to the development of the oculomotor axons, neuromuscular junction or extraocular muscles” {6}.

Occasionally *KIF21A* mutations have been reported in families who clinically have CFEOM type 3 {9,10}. CFEOM3 is an autosomal dominant disorder with incomplete penetrance which commonly maps to 16q24.4 - q24.3 {11,12}. Clinically some overlap between CFEOM1 and CFEOM3 occurs, but CFEOM3 is more variable, ranging from mild involvement with limitation of upgaze to a more severe disorder with bilateral ptosis and complete external ophthalmoplegia. The condition can be unilateral or asymmetric and ptosis may be absent.

Developmental anomalies of the eyes such as microphthalmos {4} and choroidal coloboma {2} have been rarely reported in CFEOM but have not been documented in association with any genetically defined cases. Ocular colobomas result from an arrest in the normal development of the eye during the 5th to the 7th week of gestation with failure of the fetal fissure to close. A coloboma of the optic disc is due to non closure at the most anterior portion of the optic stalk {13}. Ocular colobomata may be sporadic, although they may occur by autosomal dominant transmission with incomplete penetrance or autosomal recessive inheritance. Systemic associations have been reported e.g. CHARGE syndrome, as well as chromosomal anomalies, especially trisomy 13 and teratogens such as thalidomide.

The following is a case report of a 6 month old male with CFEOM1 resulting from the most common *KIF21A* mutation with distinctive conjunctival changes and small bilateral optic disc colobomata.

Case Report

A six-month old boy presented with bilateral ptosis and restricted eye movements. He was born full term following a normal pregnancy and birth, and growth and development were normal. His parents noted that his eyelids remained closed at birth but had opened a little further with time. He would tend to follow objects by moving his head. Torticollis was noted early, with a face turn to the right associated with a tight left sternomastoid muscle, which improved with physiotherapy. He was otherwise well, apart from severe eczema, particularly of his face. He had a tendency to hold himself with knees and hands flexed but

no joint abnormalities were noted and a hip ultrasound was normal. Marked plagiocephaly was noted. A head ultrasound was normal. Skull X-rays showed the cranial sutures to be patent, excluding a diagnosis of craniosynostosis. He was the second child of non-consanguineous parents. Both parents were myopic and there was no family history of ptosis or any eye movement disorder.

On examination head circumference and weight were just under the 50th percentile and height was along the 50th percentile. Marked plagiocephaly was present with mild facial asymmetry with the left side of the face being slightly smaller.

Severe eczema was noted, especially on his face, and the mouth was held open (Fig 1). Bilateral ptosis, worse on the right side, associated with a chin up position was present as was epicanthus inversus. The eyes were “locked in downgaze” and he could not elevate or depress the eyes from this position.

There was no evidence of a squint and little horizontal movement beyond the jerky convergent-type nystagmus seen with attempted upgaze. He could fix and follow objects by moving his head. Cycloplegic refraction showed a normal degree of hypermetropia in each eye (+1.50DS OU). The media were clear but fundoscopy showed large discs, suggesting the presence of either bilateral small coloboma or glaucomatous disc cupping. An examination under general anaesthesia was subsequently performed to exclude glaucoma. Pulsair tonometry (at the time of induction) measured the intraocular pressures at 10 and 7mmHg respectively. The horizontal corneal diameters measured 11mm across both eyes and slit lamp examination of the corneae was normal. Eversion of the lids showed shortening of the upper and lower fornices with a horizontal ridge of elevated conjunctival tissue extending onto the globes (Fig 2). Fundoscopy showed bilateral small disc colobomas within the boundaries of each disc with an intact neural rim (intrapapillary coloboma) and this was more evident on the right side (Fig 3). The retinal vessels were seen to extend from the edge of the colobomata. There were no other abnormal fundal findings. Forced duction tests showed mild restriction of vertical rotations but horizontal eye movements were normal.

The family was reviewed in the Genetic Eye Clinic at The Childrens's Hospital at Westmead. Both parents had vision of 6/6 or better in each eye with correction. The parents had otherwise normal eye exams with no evidence of ptosis or restricted eye movements. The older sister, aged two years and ten months, also did not show any ptosis or abnormality of eye movements and all three had normal discs on fundoscopy.

Blood was taken for chromosomal and DNA analysis from the proband and his parents. **G banded karyotype was performed at 550 band level and** was normal, **46,XY**. The *KIF21A* Hotspot exons (exons 8, 20 and 21) and their exon-intron boundaries were PCR amplified from genomic DNA from the proband using HotStar Taq DNA polymerase (Qiagen, Germany). The resulting amplicons were then purified (Exosap-it, USB Corporation, Cleveland, OH) and directly sequenced on an ABI 3730 Sequence Analyzer (Applied Biosystems, Foster City, CA). The most common *KIF21A* hotspot mutation, 2860 C>T; R954W, was identified in the proband. DNA from both parents of the proband was then sequenced and they were both wildtype 2860C.

Neuroimaging was not done as the family relocated overseas shortly after assessment.

Discussion

The present case is clinically consistent with CFEOM1 in displaying bilateral ptosis and hypotropic eyes, lack of vertical (and horizontal) eye movements, chin up position, jerky

convergent nystagmus movements with attempted upgaze and positive forced duction testing. Molecular analysis confirmed the most common mutation in the *KIF21A* gene, the gene responsible for CFEOM Type 1 {6}.

This patient also had distinctive conjunctival changes. Apt & Axelrod {14} described the clinical histopathological findings in four patients with generalised fibrosis of the extraocular muscles. In one patient “the lower fornices were foreshortened and contracted by the subconjunctival fascial adhesions extending to the globe”. This is similar to what we have seen in our case and emphasises the disease process within the orbit extends beyond the extraocular muscles. Conjunctival and orbital fascia changes, including inelasticity of the conjunctiva, fibrosis of Tenon's capsule and adhesions between the extraocular muscles, Tenon's capsule and the globe occur frequently in unclassified CFEOM {2,4,15} but it is not known whether these are non-specific changes due to the primary innervational anomaly or whether these changes are due to a direct effect of the CFEOM genes, such as *KIF21A*. Optic disc / nerve involvement has been reported previously in genetically undefined CFEOM. Harley {3} described a series of seven patients with CFEOM, including one patient with bilateral optic nerve hypoplasia. This patient was a 4 year old girl with partial blepharoptosis with extremely limited motility of the right eye, with a right esotropia and hypertropia. Ocular motility was normal in the left eye. Forced duction tests were positive under anaesthesia, although it is not clear from the report whether this was just for the right eye or for both eyes. It appears this girl would most likely fit into the CFEOM3 phenotype.

Khawam {16} reported an autosomal dominant family consisting of an affected father and four out of five affected children with what was described as a “progressive” congenital familial ophthalmoplegia. However, this familial disorder was almost certainly CFEOM, particularly in view of the bilateral ptosis with absent upper lid folds, typical chin up position with hypotropic eyes, minimal or no elevation and limited depression. In addition they had the typical “spastic convergent movement” with attempted upgaze, an A pattern and positive traction test to passive duction movements, especially elevation. The “progressive” nature of the condition was thought to be due to gradual progressive limitation of ocular rotations (not personally observed by the authors), the more severe restriction seen in the father and the milder limitation of eye movements seen in the youngest child and the presence of an A pattern. However, an A pattern is known to occur in CFEOM {17} and has been reported as a frequent finding in patients with CFEOM due to mutations in the *KIF21A* gene {8}. Clinically the family would best fit into the phenotype of CFEOM Type 1. In all affected family members bilateral optic disc coloboma with excavation of the optic nerve head of 0.9 disc diameter was noted, but with healthy neural rim tissue and normal intraocular pressures (as measured in the father and one affected son).

Since the description of genetically defined patients, Demer et al have conducted high-resolution orbital MR imaging of a series of patients with *KIF21A* mutations and CFEOM1 {8}. Many of these patients had small optic nerves within the orbit despite a normal appearance on fundoscopy. Only one patient was noted clinically to have small optic nerves associated with a double ring sign, typical of optic nerve hypoplasia. Small optic nerves were also found on neuroimaging in Duane syndrome patients from families whose disease gene maps to the DURS2 locus on chromosome 2. None, however, have had colobomata described {18}.

The mechanism of optic disc coloboma formation is unclear. It could arise as a result of nerve loss, secondary to inappropriate axoplasmic transport or indirectly through disruption of signals important for optic cleft closure. Our patient had CFEOM1, confirmed with mutation analysis. The family reported by Khawam is also likely to have CFEOM1. Both our patient and Khawam's family have similar descriptions of small intrapapillary disc

colobomata and it is likely that this represents an association of CFEOM1. Our findings of conjunctival changes and disc colobomas again highlight the fact that the ocular findings of CFEOM1 are not limited to the extraocular muscles as the name suggests.

References

1. Gutowski NJ, Bosley TM, Engle EC. 110th ENMC International Workshop: The congenital cranial dysinnervation disorders (CCDDs) Naarden, The Netherlands, 25–27 October 2002. *Neuromuscul Disord* 2003;13:573–578. [PubMed: 12921795]
2. Brown, HW. Congenital Structural Muscle Anomalies.. In: Allen, JH., editor. *Strabismus Ophthalmic Symposium*. CV Mosby; St Louis: 1950. p. 205-236.
3. Harley RD, Rodrigues MM, Crawford JS. Congenital Fibrosis of the Extraocular Muscles. *J Pediatr Ophthalmol Strabismus* 1978;15:346–358. [PubMed: 739362]
4. Hertle RW, Katowitz JA, Young TL, et al. Congenital Unilateral Fibrosis, Blepharoptosis, and Enophthalmos Syndrome (Case Report). *Ophthalmology* 1992;99:347–355. [PubMed: 1565446]
5. Engle EC, Goumnerov BC, McKeown CA, et al. Oculomotor Nerve and Muscle Abnormalities in Congenital Fibrosis of the Extraocular Muscles. *Ann Neurol* 1997;41:314–325. [PubMed: 9066352]
6. Yamada K, Andrews C, Chan W-M, et al. Heterozygous mutations of the kinesin *KIF21A* in congenital fibrosis of the extraocular muscles type 1 (CFEOM1). *Nat Genet* 2003;35:318–321. [PubMed: 14595441]
7. Nakano M, Yamada K, Fain J, et al. Homozygous mutations in *ARIX (PHOX2A)* result in congenital fibrosis of the extraocular muscles type 2. *Nat Genet* 2001;29:315–320. [PubMed: 11600883]
8. Demer JL, Clark RA, Engle EC. Magnetic Resonance Imaging Evidence For Widespread Orbital Dysinnervation in Congenital Fibrosis of Extraocular Muscles Due to Mutations in *KIF21A*. *Invest Ophthalmol Vis Sci* 2005;46:530–539. [PubMed: 15671279]
9. Yamada K, Chan W-M, Andrews C, et al. Identification of *KIF21A* Mutations as a Rare Cause of Congenital Fibrosis of the Extraocular Muscles Type 3 (CFEOM3). *Invest Ophthalmol Vis Sci* 2004;45:2218–2223. [PubMed: 15223798]
10. Lin L-K, Chien Y-H, Wu J-Y, et al. *KIF21A* gene c.2860C>T mutation in congenital fibrosis of extraocular muscles type 1 and 3. *Mol Vis* 2005;11:245–248. [PubMed: 15827546]
11. Doherty EJ, Macy ME, Wang SM, et al. CFEOM3: A New Extraocular Congenital Fibrosis Syndrome that Maps to 16q24.2-q24.3. *Invest Ophthalmol Vis Sci* 1999;40:1687–1694. [PubMed: 10393037]
12. Mackey DA, Chan W-M, Chan C, et al. Congenital fibrosis of the vertically acting extraocular muscles maps to the *FEOM3* locus. *Hum Genet* 2002;110:510–512. [PubMed: 12073023]
13. Onwochei BC, Simon JW, Bateman JB, et al. Ocular Colobomata. *Surv Ophthalmol* 2000;45:175–194. [PubMed: 11094243]
14. Apt L, Axelrod RN. Generalized Fibrosis of the Extraocular Muscles. *Am J Ophthalmol* 1978;85:822–829. [PubMed: 677209]
15. Laughlin RC. Congenital Fibrosis of the Extraocular Muscles – A Report of Six Cases. *Am J Ophthalmol* 1956;41:432–438. [PubMed: 13302348]
16. Khawam E, Azar D, Shami M, et al. Progressive Congenital Familial Ophthalmoplegia with Optic Nerve Coloboma. Report of a Family. *Binoc Vis* 1987;2:223–231.
17. Brodsky MC. Hereditary External Ophthalmoplegia, Synergistic Divergence, Jaw Winking, and Oculocutaneous Hypopigmentation. A Congenital Fibrosis Syndrome Caused by Deficient Innervation to Extraocular Muscles. *Ophthalmology* 1998;105:717–725. [PubMed: 9544647]
18. Demer JL, Clark RA, Lim K-H, et al. Magnetic Resonance Imaging Evidence For Widespread Orbital Dysinnervation in Dominant Duane's Retraction Syndrome Linked to the *DURS2* Locus. *Invest Ophthalmol Vis Sci* 2007;48:194–202. [PubMed: 17197533]

Fig 1.
Face photo showing typical bilateral ptosis and chin up position of CFEOM, and eczema

Fig 2.
Upper (A) and lower (B) fornices of left eye showing horizontal ridge of conjunctival tissue.
The right eye showed similar changes

Fig 3.

A - fundus of right eye showing small intrapapillary disc coloboma

B - fundus of left eye showing more subtle intrapapillary disc coloboma