CASE REPORT

A child with unilateral restrictive ophthalmoplegia

Ka-Wai Kam, MBBS, MRCSEd (Ophth), Henry Hing-Wing Lau, M.Med, FRCSEd (Ophth), Wilson Wai-Kuen Yip, MBChB, FCOphth HK, Alvin L. Young, MMedSc (Hons), FRCS (Irel)
Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong SAR, China.

Correspondence and reprint requests:
Dr. Wilson Wai-Kuen Yip, Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong SAR, China.
Email: ywk806@ha.org.hk

Abstract

We report the case of a child with a rare condition of congenital restrictive ophthalmoplegia affecting the right eye. The condition comprised unilateral fibrosis, blepharoptosis and enophthalmos but without the intraorbital mass typical of congenital orbital fibrosis which was once considered a rare form of congenital fibrosis of extraocular muscles. The history, clinical features of the condition, and current understanding of congenital fibrosis of extraocular muscles were reviewed.

Key words: Blepharoptosis; Child; Eye diseases, hereditary; Ophthalmoplegia; Strabismus

Introduction

Congenital orbital fibrosis is a rare condition. Although the condition is associated with a typical constellation of features with limited eye movement, blepharoptosis, eyelid retraction, enophthalmos, proptosis and presence of orbital mass, it is a poorly understood condition due to its rarity.[1-3] While some consider it to be a distinct clinical entity,[2,4] it has traditionally been considered a rare form of congenital fibrosis of the extraocular muscles (CFEOM).[5] Typical clinical features of CFEOM include a fixed downgaze, presence of horizontal strabismus, ptosis of varying degree, and an abnormal chin-up head posture. The inferior recti are the most commonly involved muscles, followed by levator palpebrae and medial recti. Heuck[6] reported the first family of CFEOM and Laughlin[7] later published the first case series of six cases in 1956. In 2002, Gutowski et al[8] described a term "congenital cranial dysinnervation disorders"(CCDDs) at a European Neuromuscular Centre (ENMC) international workshop to encompass a spectrum of congenital, nonprogressive anomalies affecting one or more cranial nerves or their nuclei characterized by abnormal eye, eyelid and/or facial movements; CFEOM is considered a type of CCDD. With the advance of genetics, more and more conditions are being categorized under CCDD which is a concept in evolution.[9]

Case report

The baby was born full-term at 39 weeks' gestation with a birth weight of 4095 g via an uneventful Cesarean section. Perinatal history and past health were unremarkable. The child was referred to us at 2 months of age in June 2010 for a complaint of left divergent squint noted by parents since birth. He was otherwise healthy, and overall development was age-appropriate.

On examination, the child displayed a right exotropia and hypotropia alongside partial ptosis of the right upper eyelid rather than a left divergent squint as perceived by the parents. The right upper lid crease also appeared relatively fixed and right enophthalmos was apparent with a deep superior sulcus. Extraocular motility showed limited adduction, elevation and depression of the right eye, and was normal over the left eye (**Figure 1**). Corneal diameters were bilaterally normal, and both corneas were clear. Pupils were equal and reactive to light; there was no anisocoria. Posterior segment examination revealed pink optic discs and normal macula. A preliminary diagnosis of congenital orbital fibrosis was made. In view of the right partial ptosis, occlusion therapy was commenced at half an hour daily since then and

adjusted according to clinical response. Magnetic resonance imaging (MRI) of the brain and orbit revealed no intracranial lesion and no intraorbital mass which is typically seen in congenital orbital fibrosis (**Figures 2** and **3**).

At 4 months of age, the visual acuity was 20/300 in the right eye and 20/400 in the left eye. Examination findings were deemed unreliable because of poor cooperation and persistent crying. However, right partial ptosis remained evident with occasional chin-up. At 6 months of age, the mother reported presence of nocturnal lagophthalmos with poor Bell's reflex.

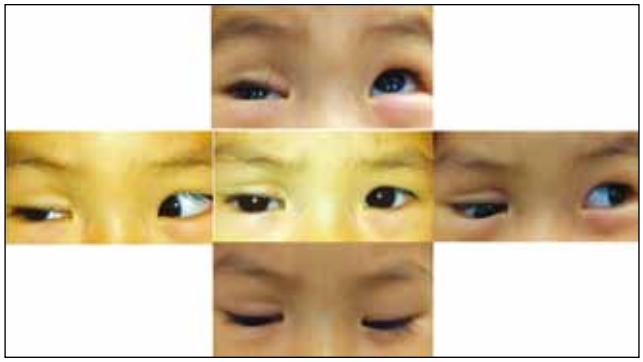

Figure 1. A composite picture showing mild exotropia in primary position with deep set sulcus and ptosis; and limited adduction and vertical gaze, especially upgaze.

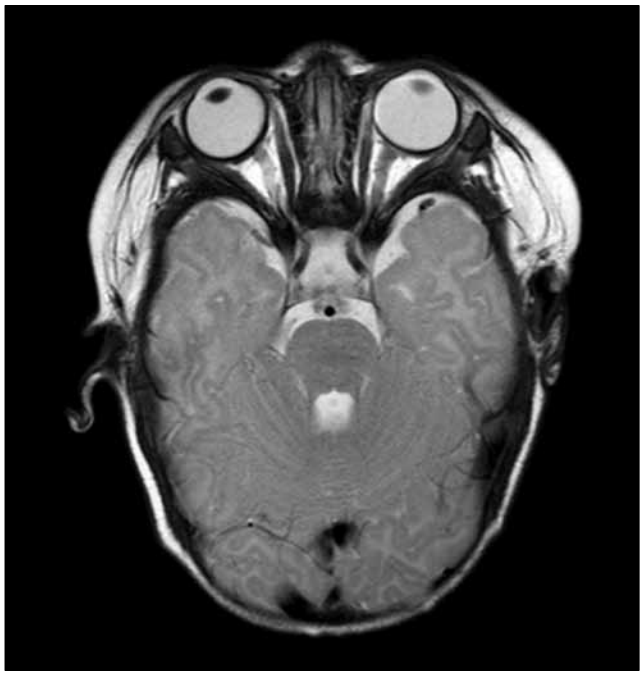

Figure 2. Magnetic resonance imaging of the brain showing normal horizontal rectus muscles in both eyes and no intraorbital mass.

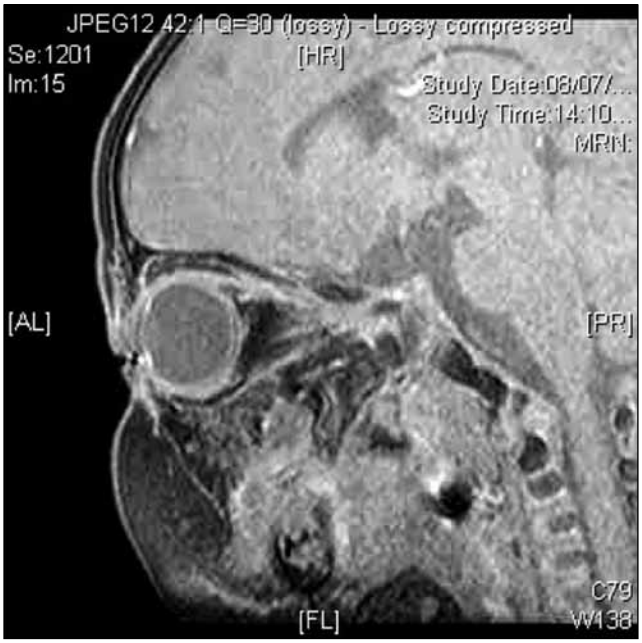

Figure 3. Sagittal magnetic resonance imaging of the orbits does not reveal abnormal recti muscles.

Cycloplegic refraction at 17 months of age showed bilateral moderate hyperopia with asymmetrical astigmatism, more severely in the ptotic eye. Spectacle correction was prescribed. Visual acuity in the right eye gradually improved from 20/200 to 20/32 at 3 years of age, which was equivalent to that in the left eye.

During this period, the strabismus and motility of right eye remained stable. In view of good visual improvement with amblyopia therapy, reasonable appearance in primary position, and the significant risks of postoperative lagophthalmos and exposure keratopathy due to the absence of Bell's reflex, it was decided to adopt a conservative approach of observation rather than surgery.

Discussion

In our patient, the combination of limited eye movement in both horizontal and vertical gazes, deep sulcus with ptosis, and enophthalmos would suggest a diagnosis of congenital unilateral fibrosis, blepharoptosis and enophthalmos. However, MRI of the orbit did not reveal any intraorbital mass, which is very common in this condition and existed in all four patients reported by Hertle et al[10] and in 13 out of 14 patients in Xiao et al's series.[3] The diffusely infiltrating intraobital mass may also involve the extraocular muscles.[2,11]

Congenital orbital fibrosis is a rare condition and there is only a limited number of cases in the literature on the condition. The pathogenesis remains unknown. Congenital orbital fibrosis was considered a rare subtype of CFEOM.[5] However, some considered it a distinct condition as it is non-

Table. Clinical classification of CFEOM[12,13]

	Type 1	Type 2	Type 3
Ptosis	Bilateral ptosis	Bilateral ptosis	Ptosis may be absent/variable
Primary position	Hypotropia	Exotropia	Variable, may be above midline
Restriction	Upgaze + variable horizontal	Severe vertical and horizontal Abduction variable	-
Laterality	Bilateral	Bilateral	Unilateral
Pupil	Small and non-reactive / normal	Small and non-reactive	Normal
Pathogenesis	Absence of superior div of CN 3, and abnormal LPS and SR	Absence of all motor neurons of CN 3 & 4 and the affected muscles	Variable developmental anomaly of CN 3 (superior branch more often involved than inferior branch)
Association	-	-	3A – neuropathy, developmental delay and MRI abnormalities; 3C – dysmorphism, developmental delay
Inheritance	AD with full penetrance and variable expression	AR	AD with incomplete penetrance and variable expression

Abbreviations: AD = autosomal dominant; AR = autosomal recessive; CFEOM = congenital fibrosis of extraocular muscles; CN = cranial nerves; LPS = levator palpebralis superioris; MRI = magnetic resonance imaging; SR = superior rectus.

familial, non-progressive, unilateral and diffusely involves the orbit[2,4] in contrast to the common subtypes of CFEOM, typically types 1 and 2 which are bilateral and familial and have a more well-defined genetic basis. Bosley et al[9] gave a very good review of the current understanding of CFEOM and the **Table**[12,13] gives a summary of the individual features. However, these features might be absent and/or unilateral in some type-3 CFEOM cases which may have variable penetrance and no family history. Yazdani and Traboulsi[14] also considered some CFEOM cases as sporadic and simplex without family history.

In 2002, the ENMC international workshop described CCDD to encompass a spectrum of congenital, non-progressive developmental anomalies affecting one or more cranial nerves or their nuclei characterized by abnormal eye, eyelid and/or facial movements.[8] Among these individual entities within the spectrum of CCDD, CFEOM was the earliest and most well described in the literature and was classified into CFEOM types 1, 2 and 3.

Advances in the genetic field have helped to identify genes that are accountable for this spectrum of congenital disorders, all of which are, in fact, responsible for the development of cranial nerves, at either the nuclear, brainstem, or at the peripheral nerve level. For instance, the *KIF21A* gene, which is responsible for the most commonly reported phenotypes of CFEOM, encodes a Kinesin-like motor protein KIF21A that is expressed during early development and involved in anterograde axonal transportation. It has been proposed that mutation of a gene may give rise to neuropathy due to disruption in the axonal transportation of a cargo that is critical to the development of ocular motor nerves.[15] Besides the *KIF21A*, there are other genes, namely, *PHOX2A, TUBB3* and *TUBB2B*, that are related to different subtypes of CFEOM which are now mainly subdivided into types 1A, 1B, 2 and 3A, B, C[9]; the classification is evolving with further understanding of underlying genetic mechanisms.

A typical case of congenital orbital fibrosis with classical features and intraorbital mass may well be a separate entity, but for those without the intraorbital infiltrating mass, it is debatable whether it should be considered an atypical case of congenital orbital fibrosis or a sporadic unilateral case of CFEOM without systemic features. Further advances in genetic study of the condition in future may be able to elucidate the underlying pathogenesis.

Clinical management of children suffering from congenital orbital fibrosis, CFEOM or other forms of CCDD is challenging and should be as individualized as possible. In a Tianjin study, high incidence of astigmatism was reported, resulting in an alarmingly high rate of amblyopia in up to 95% of the 60 eyes studied.[16] Hence, it is important to perform refraction examination in these children and detect any refractive error. One should treat amblyopia, if detected, with full refractive correction with or without occlusion therapy. As the muscles are fibrotic and stiff, large recession of tight muscles is the preferred operation, if necessary, as compared to resection surgery. Repositioning of the globe after squint surgery may necessitate a secondary ptosis operation. In children who have poor Bell's reflex, the postoperative risk of exposure keratopathy and lagophthalmos would be high; thus, the condition should generally be undercorrected to slightly above the pupil.[14] The decision to undertake primary strabismus operation should be carefully evaluated and discussed with the parents. Last but not least, we should refer these children to a pediatrician or pediatric neurologist for comprehensive examination to search for any coexisting anomalies.

References

1. *Leone CJ. Orbital fibrosis with enophthalmos. Ophthalmic Surg. 1972;3:71-5.*
2. *Mavrikakis I, Pegado V, Lyons C, Rootman J. Congenital orbital fibrosis: a distinct clinical entity. Orbit. 2009;28:43-9.*
3. *Xiao LH, Wang Y, Lu XZ, et al. Clinical analysis of 14 cases of congenital orbital fibrosis [in Chinese]. Zhonghua Yan Ke Za Zhi. 2012;48:679-82.*
4. *Athanasiov PA, Prabhakaran VC, Selva D. Unilateral orbital fibrosis with blepharoptosis and enophthalmos. Ophthal Plast Reconstr Surg. 2008;24:156-8.*
5. *Vijayalakshmi P, Jethani J, Kim U. Congenital unilateral ocular fibrosis syndrome secondary to benign congenital tumor. Indian J Ophthalmol. 2006;54:123-5.*
6. *Heuck G. Ueber angeborenen vererbten Beweglichkeits — Defect der Augen. Klin Monatsbl Augenheilkd. 1879;17:253-78.*
7. *Laughlin RC. Congenital fibrosis of the extraocular muscles; a report of six cases. Am J Ophthalmol. 1956;41:432-8.*
8. *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;13:573-8.*
9. *Bosley TM, Abu-Amero KK, Oystreck DT. Congenital cranial dysinnervation disorders: a concept in evolution. Curr Opin Ophthalmol. 2013;24:398-406.*
10. *Hertle RW, Katowitz JA, Young TL, Quinn GE, Farber MG. Congenital unilateral fibrosis, blepharoptosis, and enophthalmos syndrome. Ophthalmology. 1992;99:347-55.*
11. *Li Y, Han J, Yan H, Li J, Wang D, Xu S. Congenital orbital fibrosis associated with fibrosis of extraocular muscle. BMJ Case Rep. 2012;2012.*
12. *Luk HM, Lo IF, Lai CW, et al. Congenital fibrosis of extraocular muscle type 1A due to KIF21A mutation: first case report from Hong Kong. Hong Kong Med J. 2013;19:182-5.*
13. *Cooymans P, Al-Zuhaibi S, Al-Senawi R, Ganesh A. Congenital fibrosis of the extraocular muscles. Oman J Ophthalmol. 2010;3:70-4.*
14. *Yazdani A, Traboulsi EI. Classification and surgical management of patients with familial and sporadic forms of congenital fibrosis of the extraocular muscles. Ophthalmology. 2004;111:1035-42.*
15. *Assaf AA. Congenital innervation dysgenesis syndrome (CID)/congenital cranial dysinnervation disorders (CCDDs). Eye (Lond). 2011;25:1251-61.*
16. *Chen X, Guo X, Ma HZ. A clinical analysis of 40 cases with congenital fibrosis of extraocular muscles [in Chinese]. Zhonghua Yan Ke Za Zhi. 2011;47:978-82.*