Ocular Manifestations of Two Filipinos with Congenital Fibrosis of the Extraocular Muscles

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ABSTRACT

Congenital fibrosis of the extraocular muscles (CFEOM) is a rare, congenital, non-progressive disorder presenting with partial or total ophthalmoplegia, with variable degrees of ptosis in both eyes. We present the clinical manifestations of congenital fibrosis of the extraocular muscles in two patients.

Both patients presented with bilateral ptosis and variable ophthalmoplegia with a chin-up posture. The ocular deviations have been noted since birth. No patient demonstrated a Marcus-Gunn jaw-winking phenomenon. Both patients had a mild refractive error with with-the-rule astigmatism. Deviation for both patients revealed exotropia with varying amounts of hypotropia and limitations in the movement of extraocular muscles. Both patients presented no abnormalities in the pupils. Neuroimaging revealed atrophy of the extraocular muscles.

Diagnosis of CFEOM in a resource-poor setting is also challenging due to inaccessible gene testing. Manifestations of CFEOM vary across affected patients. CFEOM proposes challenges to the ophthalmologist with regards to management.

Keywords: congenital fibrosis, extraocular muscles, CFEOM, congenital cranial dysinnervation disorders

INTRODUCTION

Congenital fibrosis of the extraocular muscles (CFEOM) is a congenital restrictive ophthalmoplegia causing restriction of globe movement in one or more fields of gaze and primarily affecting extraocular muscles innervated by the oculomotor nerve (cranial nerve III) and/or the trochlear nerve (cranial nerve IV).[1] It is part of the Congenital Cranial Dysinnervation Disorders (CCDD) which encompass syndromic disorders affecting the extraocular muscles. The various forms of CFEOM are included in the CCDDs.[1] CFEOM is a rare syndrome and little has been reported in the Philippines. In this paper, we presented the clinical ocular manifestations in two patients with congenital fibrosis of the extraocular muscles.

CASE REPORTS

Two unrelated patients presented with ophthalmoplegia. Both patients underwent full ocular examination and imaging of the orbits and brain. A diagnosis of CFEOM was made.

The first patient is a 4-year-old male, Filipino with a chin up posture and drooping of both upper lids since birth. After an uneventful delivery to a 28-year-old mother with no fetomaternal complications at birth, this patient was born with bilateral ptosis. At 3 years of age, cranial CT

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scan was unremarkable. Family history is unremarkable. No similar ophthalmoplegia was noted in siblings and up to second degree relatives. Development was at par for his age.

The second patient is a 29-year-old male, Filipino with inability to move his eyes in all directions. This inability of movement was noted at birth. He had neither diplopia nor blurring of vision. Family history is unremarkable. No similar ophthalmoplegia noted with siblings and up to third degree relatives.

Both patients had an unremarkable past medical history, unremarkable review of systems and no intellectual disabilities. No patient demonstrated a Marcus-Gunn jaw-winking phenomenon.

Clinical Manifestations

On physical examination, the first patient showed no gross facial deformities or facies on head and neck examination. Examination of the chest, abdomen, and extremities was unremarkable.

Ocular examinations revealed uncorrected visual acuity in both eyes at 20/50 using Lea chart. Grossly, the patient had bilateral severe ptosis (margin reflex distance (MRD) 1 of -2 mm), with absent levator function. No nystagmus was present. There was a poor Bell's phenomenon. Patient had 3 mm pupillary diameters with no relative afferent pupillary defect for either eye. There was 30-35 prism diopter of near esotropia by modified Krimsky. Motility evaluation revealed absence of bilateral upgaze (Figure 1). Patient presented with chin up position (Figure 2). Patient's refraction revealed a hyperopic refractive error of +2.00 diopters (D) with -2.50 D cylinder with axis at 180 degrees, and +0.50 D with -1.50 D cylinder with axis at 180 degrees on the right and left eye, respectively. With spectacle correction, the best corrected visual acuity was 20/30 in both eyes. Anterior segment and posterior pole evaluations were unremarkable.

Given the risk of amblyopia for his age, contemplated surgery was a combined large inferior rectus recession with ptosis surgery. Surgery was delayed due to quarantine protocols during the 2020 Coronavirus pandemic.

The second patient showed no evident gross facial and body deformities. Ocular examinations revealed uncorrected visual acuity of 20/20 in both eyes. Grossly, the patient has moderate ptosis on the right (MRD 1 of 2) with poor levator function (4 mm) and severe ptosis on the left (MRD 1 of 0 mm) with poor levator function (3 mm). No nystagmus was present. Patient had 3 mm pupillary diameters with no relative afferent pupillary defect noted for either eye. Deviation exam showed 20 prism diopter exotropia by modified Krimsky. Motility evaluation showed absence of movement in all gazes (Figure 3). Refraction was a myopic

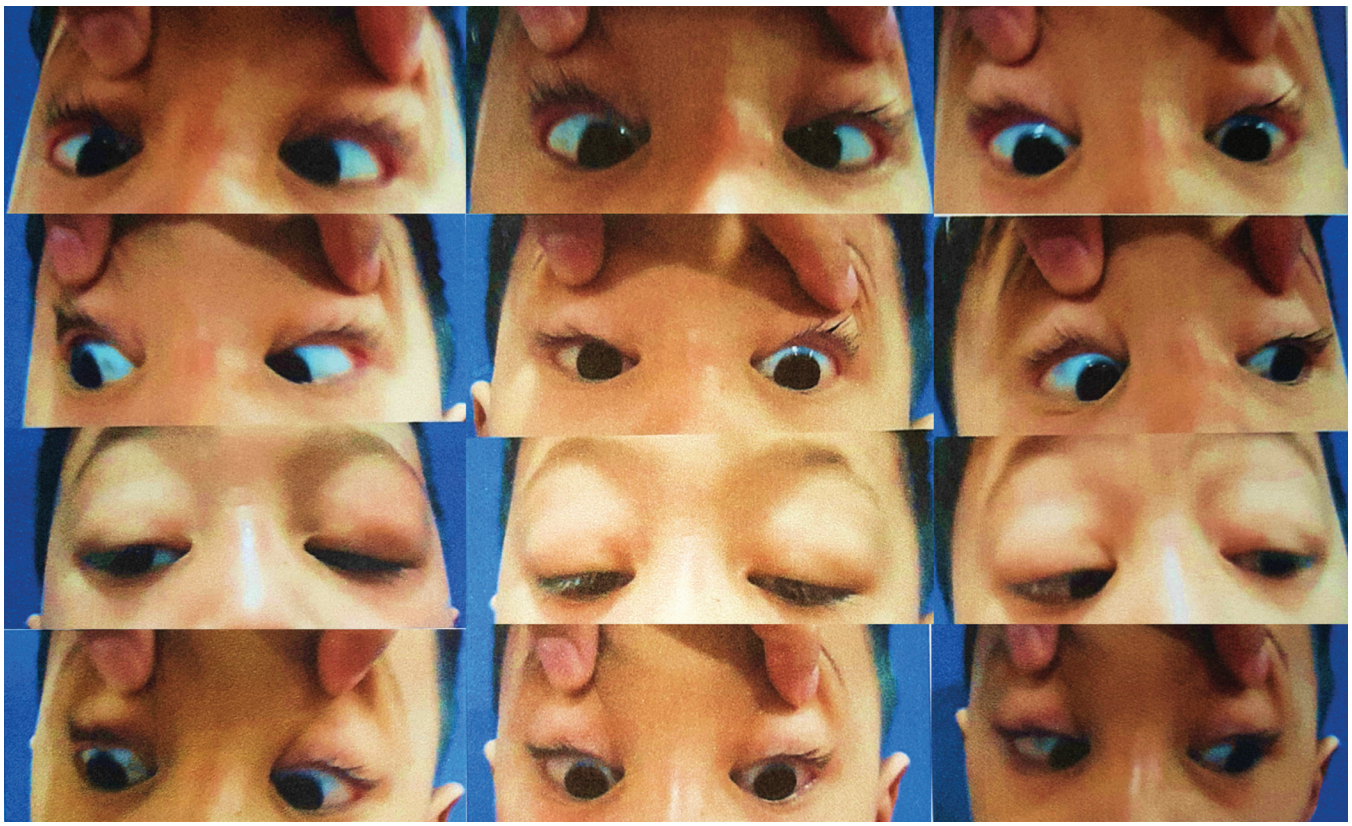

Figure 1. Gaze composite pictures showing bilateral severe ptosis with a 35 prism diopter esotropia and 35 prism diopter hypotropia on primary gaze. There is bilateral absence of upgaze and abduction.

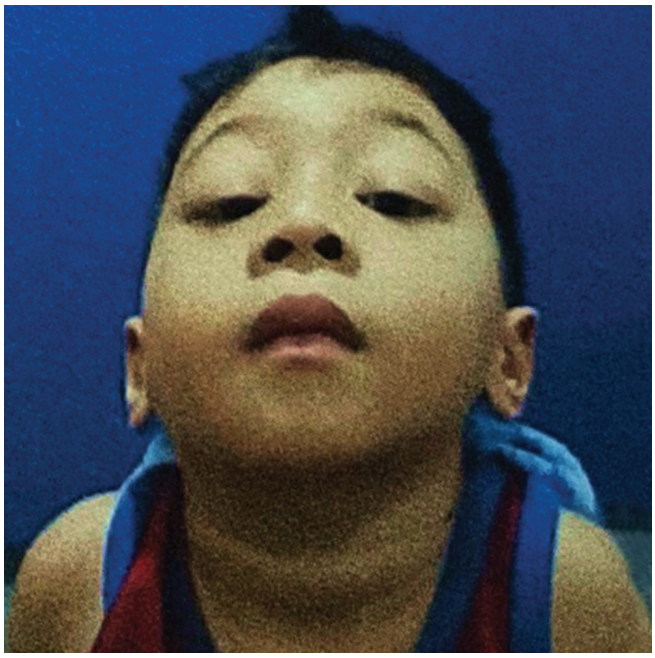

Figure 2. Chin up position.

refractive error of -0.50 diopter and -1.00 diopter spheres on the right and left, respectively without cylinder components. Anterior segment evaluation, intraocular pressures and indirect ophthalmoscopy were all unremarkable.

Both patients underwent imaging of the brain and orbits as part of evaluation for patients with CFEOM. Cranial imaging for both patients was unremarkable. Orbital imaging revealed hypoplasia of bilateral superior rectus in the first patient and hypoplasia of all extraocular muscles for the second patient (Figure 4). Ideally identification of the cranial nerves and their nuclei is important in CCDD spectrum. However, in this patient, a CT imaging was not sufficient to identify the status of the cranial nerves and their nuclei.

Given the fibrotic presentation of the muscles, further manipulation of these muscles might push to possible atrophy, hence no surgery was done. Given the good vision and absence of diplopia, observation and regular follow up monitoring were done. Spectacles with prisms were reserved for cases with intolerable diplopia.

CFEOM is non-progressive, therefore the pathology does not worsen nor improve.

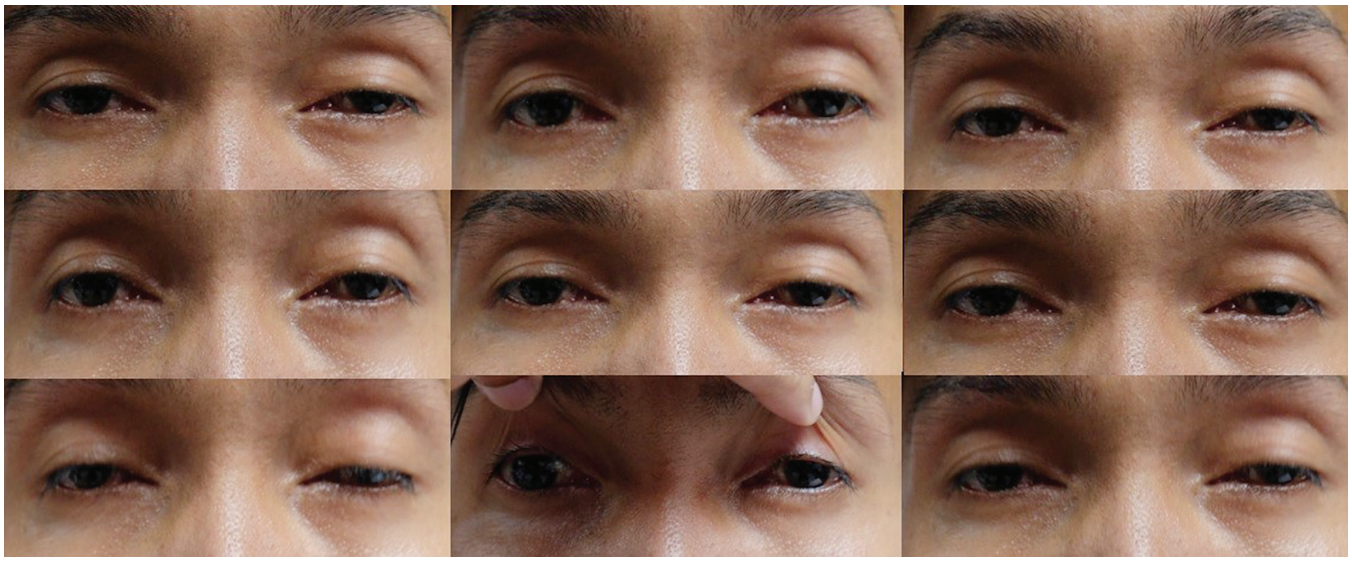

Figure 3. 9-gaze composite of patient 2 showing absence of movement in all gazes. There was bilateral ptosis.

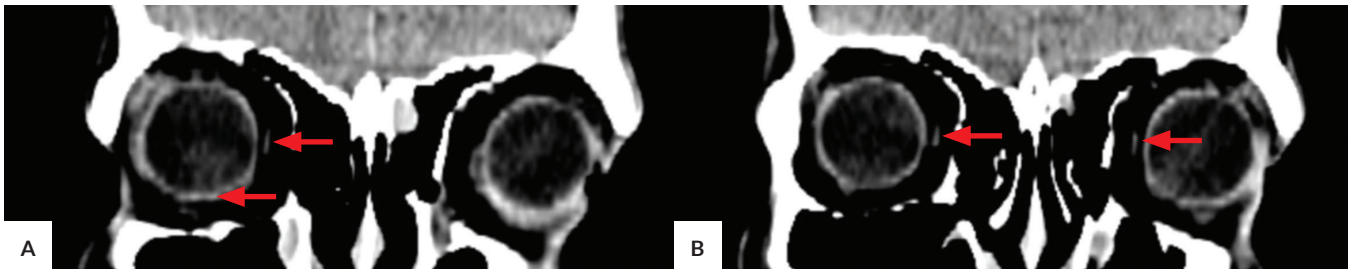

Figure 4. Orbital imaging photos of the second patient showing hypoplasia of all the extraocular muscles *(red arrows)*. Shown here are cuts from the anterior orbit **(A)** and posterior orbit **(B)**.

DISCUSSION

This paper described local presentations of CFEOM in two unrelated patients. CFEOM is a rare, congenital, and non-progressive disorder[1] characterized by ophthalmoplegia affecting one or more of the oculomotor nucleus and nerve (cranial nerve III) and its innervated muscles (superior, medial, and inferior recti, inferior oblique, and levator palpebrae superioris) and/or the trochlear nucleus and nerve (cranial nerve IV) and its innervated muscle (the superior oblique).[1,2] Patients may present with or without bilateral ptosis. Individuals with CFEOM are noted at birth with a severe form of incomitant strabismus caused by dysfunction of specific extraocular muscles. In general, affected individuals have variable limitations of vertical and horizontal gazes. Individuals with CFEOM compensate for the ophthalmoplegia by maintaining an anomalous head position at rest.[3]

CFEOM has been classified into three types and has been related to ocular and systemic syndromes. Type 1 patients present with bilateral ptosis, hypotropia, restrictions in upgaze, horizontal gaze may or may not be involved, uninvolved pupils and a restriction noted forced duction testing. Type 2 patients, on the other hand, present similarly with bilateral ptosis with restriction on duction testing but with exotropia, severe restrictions in horizontal and vertical gazes, and miotic pupils. Type 3 presents with variable strabismus, may be unilateral or bilateral, with or without ptosis. The diagnosis of CFEOM is made from the clinical manifestations, radiological examinations and genetic testing.[1] Clinically, patient 1 demonstrates a Type 1 classification due to the presence of bilateral ptosis, hypotropia with restrictions in upgaze and bilateral horizontal movement deficit. Patient 2 clinically presents as a Type 2 classification due to its pronounced, severe restrictions in all gazes. CFEOM can be associated with various neurologic abnormalities, and neuro-imaging is recommended as part of the evaluation.[2] Etiologies vary and correlate with affected extraocular muscles: for example, in type 1, etiology arises from the absence of the superior division of the oculomotor nerve leading to abnormalities in the levator palpebrae superioris and superior recti actions. For type 2, the absence of the motor neurons in all of the oculomotor and trochlear nuclei with abnormalities of the innervated muscles gives rise to the observed strabismus restrictions. For type 3, a variable developmental anomaly of the oculomotor nerve is noted.[1,3]

The minimum prevalence of CFEOM is 1:230,000.[4] The few individuals reported with CFEOM2 have been offspring of consanguineous unions reported in Saudi, Turkish, and Iranian families.[5] In the Philippines, no reports have been made on the prevalence of these cases.

Genetics plays a role in the pathogenesis of the syndrome.[5,6] Recent studies noted that mutations from the *HOX* and *PHOX* families contribute to the emergence of CFEOM. Both of these genes are both essential in the neural crest development. Ideally, to fully classify a patient with CFEOM into its types, a genetic study should be performed. Diagnosis of CFEOM in a resource-poor setting is also challenging due to inaccessible gene testing.

There are currently no treatment guidelines to restore the full range of motion to the extraocular muscles. Treatment is individualized per patient. Any refractive error and amblyopia should be corrected.[1] The surgical correction of strabismus and ptosis in CFEOM remains challenging. This is primarily because of varying degrees of EOM dysinnervation and EOM fibrosis in some cases which entail the unpredictability of the surgical outcomes.[7] A tailored surgical approach is advised to achieve satisfactory alignment and improvement in head posture.[7] Strabismus surgery is always attempted prior to ptosis correction. The expectations of strabismus surgery should be realistic, and parents and patient should be well informed about these expectations.[8] The aim of ptosis correction should be to provide a clear visual axis to prevent deprivation amblyopia, transfer null point to functional positions of gaze as close to primary as possible, partly eliminating head posture.

CONCLUSION

We have presented two cases of clinically and radiologically confirmed congenital fibrosis of the extraocular muscles. A constellation of total ophthalmoplegia with ptosis, mild to profound, should raise suspicion for CFEOM. Diagnosis of CFEOM in a resource-poor setting is also challenging due to inaccessible gene testing. Manifestations of CFEOM vary across affected patients. This paper presented two unrelated patients with varying manifestations. Management of CFEOM is symptomatic, and varies among patients.

Statement of Authorship

All authors contributed in the conceptualization of work, acquisition of data and analysis, drafting and revising and approved the final version submitted.

Author Disclosure

The authors declared no conflicts of interest relevant to the conduct of the study. All of the authors secured consent from the parents of the patient from Case 1 and from the patient himself in Case 2 for the publication of the report.

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