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Retinal dysfunction in patients with congenital fibrosis of the extraocular muscles type 2

Arif O. Khan, MD[1], **Mohammed Almutlak, MD**[1], **Darren T. Oystreck MmedSci, OC(C)**[2,3], **Elizabeth C Engle, MD**[4], **Khaled Abu-Amero, PhD**[2], and **Thomas Bosley, MD**[2]

[1]Division of Pediatric Ophthalmology, King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia

[2]Department of Ophthalmology, College of Medicine, King Saud University, Riyadh, Saudi Arabia

[3]Division of Ophthalmology, Faculty of Health Sciences, University of Stellenbosch, Tygerberg, South Africa

[4]Divisions of Neurology and Ophthalmology, Children's Hospital, Boston, MA, USA

Abstract

INTRODUCTION—Congenital fibrosis of the extraocular muscles type 2 (CFEOM2) is a distinct non-syndromic form of congenital incomitant strabismus secondary to orbital dysinnervation from recessive mutations in the gene *PHOX2A*. The phenotype includes bilateral ptosis, very large angle exotropia, ophthalmoplegia, and poorly-reactive pupils. Other than amblyopia, afferent visual dysfunction has not been considered part of CFEOM2; however, we have repeatedly observed non-amblyopic subnormal vision in affected patients. The purpose of this study is to document this recurrent feature of the phenotype.

METHODS—Retrospective case series (2002–2012).

RESULTS—Eighteen patients (four families) were identified; all affected individuals had confirmed homozygous recessive *PHOX2A* mutations except one individual for whom genetic testing was not done because of multiple genetically confirmed family members. Age at assessment ranged from 5–62 years old (median 10 years old). All patients had decreased best-corrected visual acuity not completely explainable by amblyopia in both the preferred and non-preferred eye. In those patients who had further ancillary testing, visual fields (five patients) and electroretinography (10 patients) confirmed abnormalities not ascribable to amblyopia.

CONCLUSIONS—In addition to a distinct from of congenital incomitant strabismus, the phenotype of CFEOM2 includes subnormal vision consistent with retinal dysfunction. This could be the direct result of *PHOX2A* mutations or a secondary effect of orbital dysinnervation.

INTRODUCTION

Although congenital fibrosis of the extraocular muscles (CFEOM) was originally considered a primary disorder of extraocular muscle formation, CFEOM is now recognized as one of

Correspondence: Arif O. Khan MD, Division of Pediatric Ophthalmology, King Khaled Eye Specialist Hospital, Riyadh 11462 Saudi Arabia, arif.khan@mssm.edu.

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several rare forms of congenital incomitant strabismus secondary to orbital dysinnervation that are collectively known as congenital cranial disinnervation disorders (CCDDs).(1) The main clinical features of CFEOM type 2 (CFEOM2; Mendelian Inheritance in Man [MIM] #602078) are bilateral ptosis and absent adduction, supraduction, and infraduction, creating the appearance of bilateral oculomotor nerve palsies.(2) Abduction is present although often incomplete, and pupils generally are variable in size and shape and non-reactive to light and accommodative targets although they respond appropriately to pupillary pharmacologic agents and accommodative ability seems intact.(3) Neuroimaging shows absent oculomotor nerves bilaterally.(3)

CFEOM2 is caused by bi-allelic mutations in the gene *PHOX2A*,(2) which encodes a homeodomain transcription factor prominently expressed in developing oculomotor and trochlear motor neurons and is essential to their survival. In mice, *phox2a* also regulates the expression of two catecholaminergic biosynthetic enzymes essential for the differentiation and maintenance of the noradrenergic neurotransmitter phenotype.(4–6)

Subnormal visual acuity has sometimes been documented in CFEOM2 patients and has often been attributed to amblyopia(3, 7, 8); however, with longer follow-up and further investigations of affected patients, we have repeatedly observed subnormal vision that is not ascribable to amblyopia. The purpose of this study is to document this as a recurrent feature of the phenotype.

METHODS

Institutional review board approval was obtained for this retrospective study. Charts of patients with genetically-confirmed CFEOM2(2, 3) examined by the authors from 2002–2012 were reviewed for best-corrected visual acuities, cycloplegic refractions, and results of ancillary testing such as visual fields and standard electroretinography (ERG; ISCEVR standard [http://www.iscev.org/]), as well as other potentially relevant clinical details. All patients had multiple examinations performed over a period of years in multiple clinics. Patients without clearly documented visual acuities or cycloplegic refractions were excluded. Genetic sequencing of *PHOX2A* was by previously-described methods.(2)

RESULTS

Clinical data are summarized in Table 1. Eighteen patients (four families; 13 males, five females; age range of 5–62 years [median 10 years]) were identified, all with the classic CFEOM2 phenotype (Figure 1). Genetic results and neurological observations for some family members were previously reported(2, 3) except for the family of patient 18. Recessive homozygous *PHOX2A* mutations were confirmed in all patients except one who did not undergo genetic testing because several affected relatives had already been genetically confirmed (patient 9). Three families harbored the homozygous c.215C>T (p.A72V) mutation (families BD, BB, AL) while the fourth harbored a homozygous splice (IVS2, G>A, −1) mutation (Family Z).

No patient had 20/20 vision in either eye. Three patients had equally depressed best-corrected visual acuity in both eyes (20/40, 20/60, and count fingers). For the other 15

patients, two patients had 20/30 best-corrected vision in the preferred eye with better visual acuity but most were worse than 20/50. Subnormal vision was typically profound in the non-preferred eye of these 16 patients, often at the level of hand motion (five patients) or light perception (three patients). No patient had increased measured intraocular pressure. Crystalline lenses and ocular media were clear in all patients except for one older adult who had had unilateral cataract surgery with intraocular lens placement (Table 1, patient 14). The fundus examination was grossly normal in all patients with the exception of one patient who seemed to have narrowing of arterioles with questionable foveal discoloration (Table 1, patient 15) and another whose optic nerve heads appeared small (Table 1, patient 16). No patient complained of night vision loss, progressive visual loss, or color discrimination difficulties.

Visual fields were available for five patients, all of whom had abnormalities including mild constriction, arcuate defect, and residual island of vision. (Figure 2). ERG was performed for 10 patients, all of whom had delayed and depressed responses (both rod and cone for eight patients, only rod for two patients). An example of an abnormal tracing is provided in Figure 3.

DISCUSSION

In this cohort of 18 CFEOM2 patients, all had subnormal best-corrected visual acuity varying from 20/30 to light perception. This subnormal vision was not consistent with solely amblyogenic visual loss, as substantiated by visual field defects not consistent with amblyopia and abnormal ERGs in all patients who underwent such testing. These results suggest retinal dysfunction is a recurrent feature of the CFEOM2 phenotype.

Amblyopia is subnormal vision from abnormal visual experience during childhood. It can be strabismic, refractive, or occlusive in origin, and is not associated with significant structural or functional changes in the retina.(9) Previous reports of CFEOM2 did not emphasize visual acuities. Instances of subnormal visual acuity in CFEOM2 patients were typically considered amblyopia-related(3, 7, 8) although Wang and colleagues(7) did suggest subnormal retinal function as a possibility that deserved further investigation.

Strabismic amblyopia does not appear to explain visual loss in our cohort. All CFEOM2 patients were exotropic, even after strabismus surgeries. However, isolated exotropia typically does not cause strabismic amblyopia as the central visual fields of the two eyes do not overlap and strabismic amblyopia is unlikely to develop without competition between the two eyes when focusing on an object of regard.(10, 11) This is particularly true for large angle exotropia, which all of these patients had during early childhood.

Refractive amblyopia also does not adequately explain visual loss in our cohort. Many refractive errors in our cohort neither fit the commonly-observed refractive clinical profile of amblyopia(12) nor were in the range considered amblyogenic.(13) For those who did have larger anisometropias or absolute refractive errors, subnormal vision was lower than what would be expected from anisometropia alone. Light perception or hand motion vision was frequent in the non-preferred eye in this cohort, but uncorrected anisometropia by itself is

not associated with such severe visual impairment.(14) In addition, visual acuity was also typically subnormal in the less ametropic preferred eye of these CFEOM2 patients.

Ptosis-induced occlusive amblyopia is also not an adequate explanation for subnormal vision in this cohort, particularly in the preferred eye. Ptosis-related amblyopia is typically not occlusive(15, 16) but rather is usually associated with anisometropia and/or esotropia.(17) Moreover, amblyopia related to ptosis usually occurs in the setting of monocular ptosis rather than binocular ptosis(15) and is not typically to the degree of light perception or hand motion vision.

The five patients who underwent visual field testing had visual field loss not consistent with amblyopia. In amblyopia, standard monocular visual field testing generally shows depressed central sensitivity and occasionally milder depressed sensitivity into the near periphery.(18) However, in our CFEOM2 patients other visual field abnormalities and sometimes only residual islands of visual field were documented (Table 1, Figure 2). These visual field abnormalities may have been influenced by patient positioning given the typical large-angle exotropia and ophthalmoplegia of CFEOM2; however, they were still not the type of field defects expected in amblyopia-related visual loss.

ERG abnormalities are not typical for amblyopia,(9) but all 10 patients who underwent ERG testing in our cohort had abnormalities, i.e., delayed and depressed rod and cone function in eight and delayed and depressed rod function in two (Figure 3). No pigmentary changes were noted in the posterior pole of any patient but the peripheral retina could not always be completely assessed because of globe positioning. Repeat ERG testing was not performed, so it is unclear whether retinal dysfunction was stationary or progressive; however, no patient complained of progressive visual loss or had an unexplained change in visual acuity documented on repeat examinations. Additional ancillary testing to further characterize these findings such as color vision assessment, fundus autofluorescence, and ocular coherence tomography would have been ideal but was not performed.

PHOX2A is a homeodomain transcription factor gene expressed in certain differentiating neurons of the central and peripheral nervous system.(4) In the knockout mouse model, both oculomotor and trochlear nerve nuclei are absent,(5) consistent with the human CFEOM2 phenotype of ptosis, exotropia, ophthalmoplegia, and absent oculomotor nerves by neuroimaging.(3) *PHOX2A* does not appear to play a role in human strabismus phenotypes other than CFEOM2.(19) Unlike the human CFEOM2 phenotype, the knockout mouse dies soon after birth and has additional neurologic abnormalties such as absence of the locus coeruleus (the main noradrenergic center of the brain), atrophy of cranial sensory gangilia, and absence of parasympathetic ganglia of the head. Transient expression of dopamine beta-hydroxylase in neuroblasts is also abolished in the knockout mouse model. Thus *phox2a* in the mouse appears necessary for catecholamine function. This may be relevant to retinal dysfunction in patients with *PHOX2A* mutations, as dopamine has complex roles in retinal development, growth, and maintenance.(20–22) Another potential mechanism for abnormal retinal development in CFEOM2 patients is the orbital dysinnervation itself, as has been described for optic nerve development in the context of orbital dysinnervation.(23, 24)

There are several qualifications to this study. The severe exotropia of CFEOM2 meant that neither eye could be brought to primary position, which can sometimes complicate the examination of both visual acuity and the fundus. The coincidence of strabismus, refractive errors, and ptosis may have led to a unique, additive amblyogenic effect. These amblyogenic factors were difficult to treat in CFEOM2 patients because strabismus surgery was ineffective in bringing eyes into primary position, the extent of lid surgery was limited by the lack of a Bell phenomenon, and spectacles provided only partially effective correction of refractive errors because of strabismus with ophthalmoplegia. It is also possible that restricted positioning for Goldmann perimetry and ERG contributed to abnormal results on these tests. Nevertheless, no other amblyogenic circumstance is known to commonly result in light perception or hand motion visual acuity, and positioning is not expected to affect ERG implicit times. At the very least, CFEOM2 as a CCDD is distinctly unusual in that reduced afferent visual functioning is common. A retinal developmental abnormality due to *PHOX2A* mutations currently seems to be the most likely causative mechanism.

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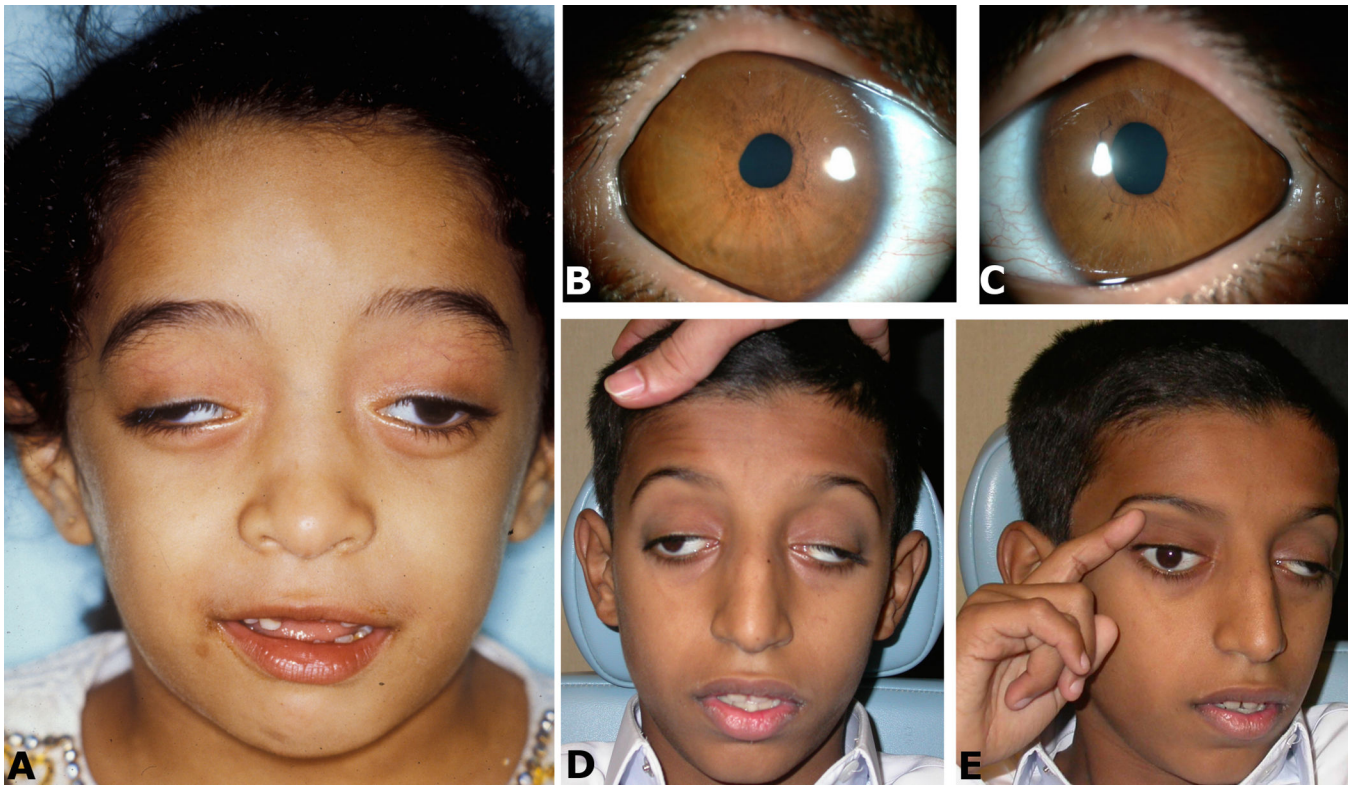

Figure 1. Clinical examples

A (patient 2): The typical ptosis and very large angle exotropia can be appreciated in primary position; (**B,C**: patient 9): Irregular pupils (not pharmacologically dilated) can be appreciated in both the right (B) and left (C) eyes; (**D,E**: patient 1): (D) The typical ptosis and very large angle exotropia can be appreciated in primary position; (E) The patient uses a finger to lift a ptotic lid and better visualize an object of regard, which is not an uncommon maneuver.

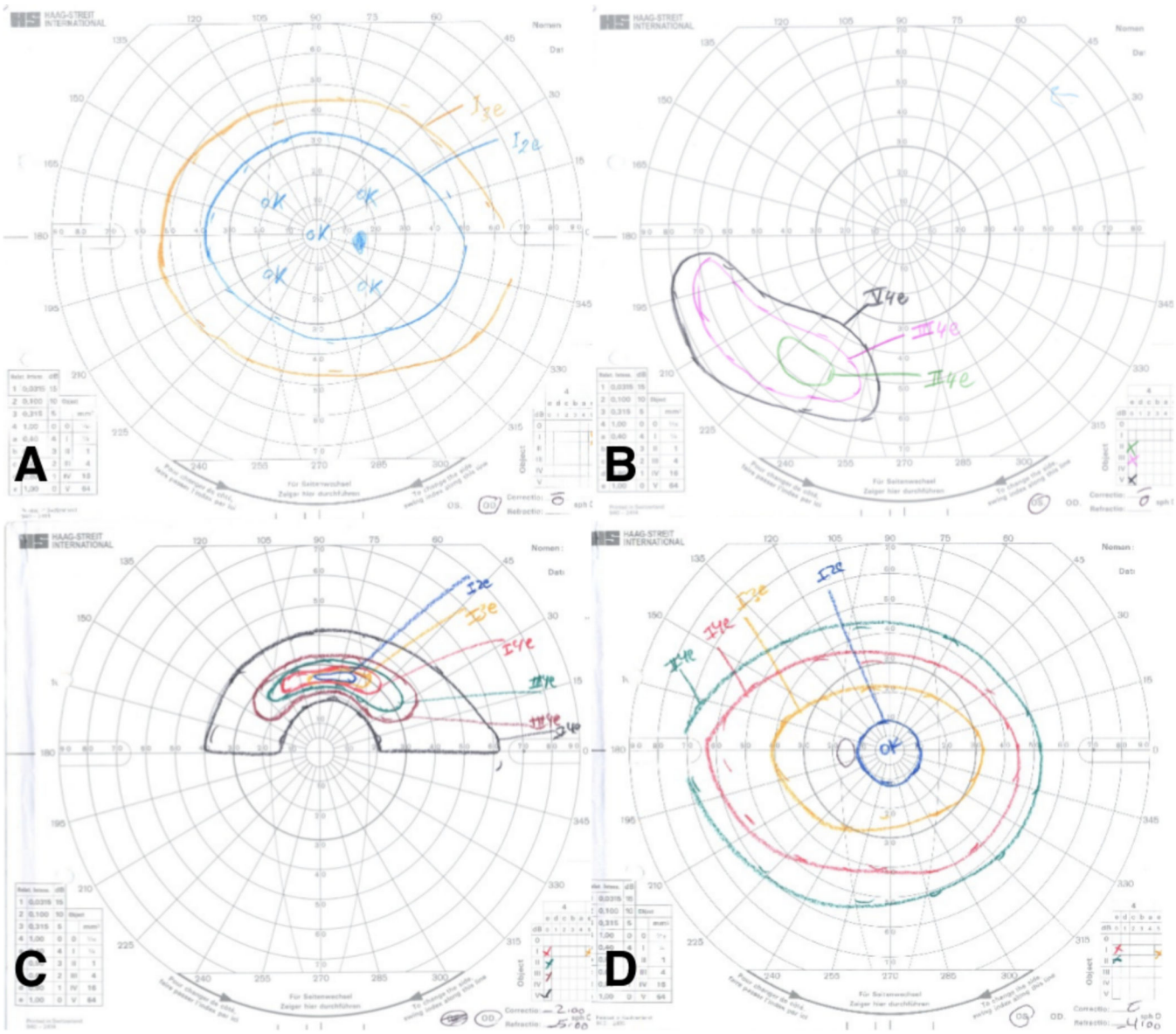

Figure 2. Goldmann visual field examples): (A,B: patient 9

A: The preferred right eye has a slightly constricted field that is otherwise normal; B: The non-preferred left eye has only an inferotemporal island of vision. (**C,D**; patient 16): C: The non-preferred right eye has only a superior arcuate island of vision; D: The preferred left eye has a slightly constricted field that is otherwise normal.

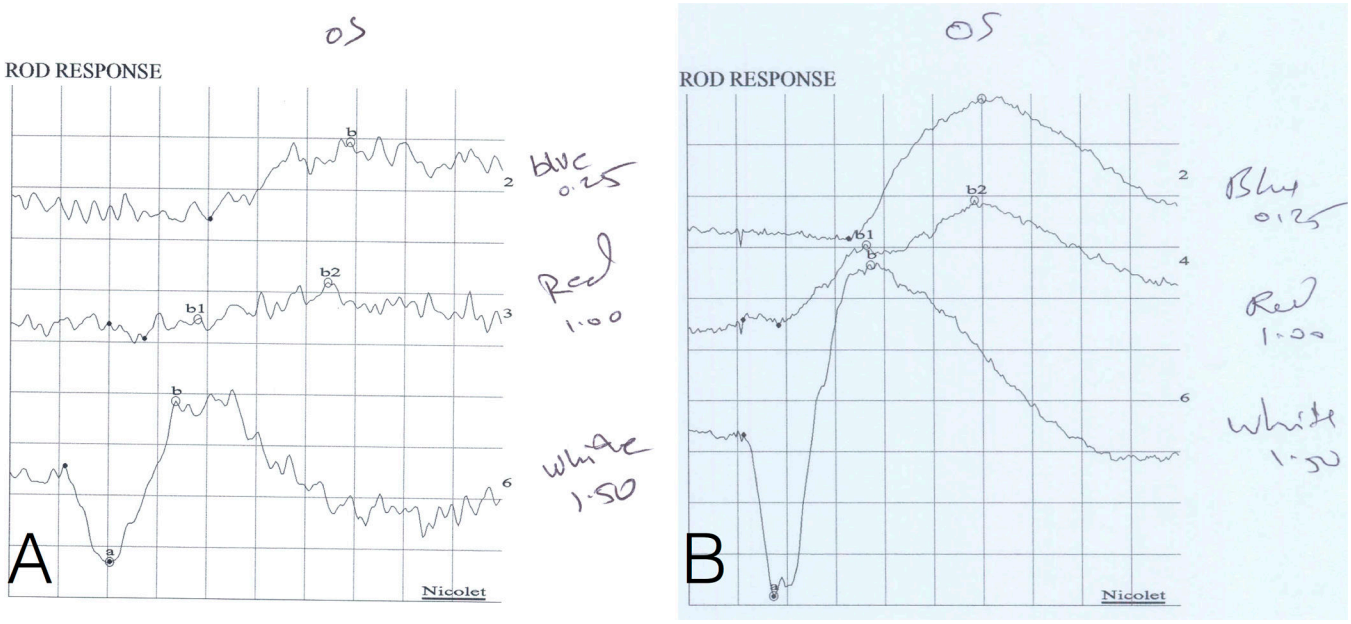

Figure 3. Scotopic electroretinography [ERG] example, patient 9

(**A,B**) The abnormal left eye (OS) of patient 9 and a normal control for comparison. (**A**) For the left eye of patient 9, the white flash a-wave (combined rod-cone response) implicit time was delayed (21 ms vs normal mean[range] 14 [11–17]) and its amplitude is at the low range of normal (169 millivolts [mv] vs 271 [164–378]). Responses to blue (rod isolated) and red (cone isolated) stimuli under scotopic conditions are also depicted, and both also show delayed implicit times (blue 118 ms vs 92 [69–115]; red 56 ms vs 47 [42–53]). In addition, the amplitude of the response to red is depressed (red 36mv vs 124 [51–197]). (**B**) A normal control is shown for comparison. The white flash a-wave implicit time was 14 ms. Each box corresponds to 100 mv and 20 ms and normal means (ranges) are as follows: a-wave implicit time 14 (11–17) ms; a-wave amplitude 271 (164–378) mv; b-wave implicit time 51 (42–60) ms; b-wave amplitude 242 (103–380) mv.

SUMMARY OF PATIENTS

ID	FAMILY	AGE	SEX	BCVA	REFRACTION	GOLDMANN VISUAL FIELD	ERG BOTH EYES	LID/EOM SURGERY	COMMENTS
1	BD (2)	5	M	20/40 20/40	+3.50+0.50×090 +3.50+0.50×090	--- ---	---	no	---
2	BD	8	F	20/60 20/60	−4.50+2.00×060 +3.00+1.50×180	--- ---	---	no	---
3	BD	5	F	HM 20/70	+1.00+1.50×020 −1.50+0.75×120	--- ---	---	no	---
4	BD	8	M	20/125 LP	−1.25+0.50×100 +0.50+1.00×150	--- ---	---	no	---
5	BB (4)	20	M	20/50 HM	−3.00 −8.00	nasal step ---	delayed & depressed rod & cone	yes	developing keratoconus
6	BB (5)	13	M	20/30 20/50	+1.00+1.00×090 plano+2.00×090	--- ---	delayed & depressed rod & cone	yes	---
7	BB (6)	7	M	20/50 20/70	plano+1.50×180 +0.75+1.50×180	--- ---	delayed & depressed rod & cone	yes	---
8	BB (7)	5	M	HM 20/60	+2.25 +1.50	--- ---	delayed & depressed rod & cone	yes	resolved childhood seizures; nystagmus right eye
9	BB (9)	14	M	20/50 HM	plano plano	slight constriction inferotemporal island	delayed & depressed rod	yes	---
10	BB (10)	6	M	20/200 20/30	+2.50+2.00×080 +1.50+1.00×040	---	---	yes	---
11	BB (11)	33	M	HM 20/50	plano plano	--- nasal step (HVF)	delayed & depressed rod & cone	yes	MRI suggests small optic nerves
12	BB (12)	11	F	LP 20/40	−7.00 −0.50+1.50×105	--- ---	---	no	---
13	BB	26	M	CF CF	−17.00 −17.00	--- ---	delayed & depressed rod & cone	no	---
14	BB	62	M	20/160 20/80	−4.50+5.00×095 −17.50+3.00×180	--- ---	delayed & depressed rod & cone	yes	high myope (30mm axial length); intraocular lens right eye
15	BB	11	M	20/60 20/100	−5.50+1.00×175 −4.50+4.50×170	--- ---	delayed & depressed rod	no	query retinal arteriolar attenuation and abnormal macular reflex
16	Z (13)	21	F	CF 20/50	−8.50+1.50×105 −2.00−1.50×170	superior arcuate island slight constriction	---	no	hypoplastic right optic nerve; question of frontal atrophy by CT
17	Z (14)	7	M	20/100 20/80	+4.00+2.50×090 +1.50+3.00×125	slight constriction superonasal arcuate defect	delayed & depressed rod & cone	yes	idiopathic scleritis left eye
18	AL	9	F	LP 20/80	+6.50 +4.50	--- ---	---	yes	---

BCVA: best-corrected visual acuity; ERG: electroretinography; EOM: extraocular muscle; M: male; F: female; HM: hand motion; CF: count fingers; LP: light perception; HVF: Humphrey visual field rather than Goldmann; MRI: magnetic resonance imaging scan; CT: computed tomography scan; "---": not available

"rod" refers to testing under scotopic conditions; "cone" refers to testing under photopic conditions

Where relevant, for a given patient top line refers to right eye and bottom line refers to left eye

For FAMILY column, number in parenthesis refers to patient identification in reference 3