

Unilateral cone dysfunction with asymmetric maculopathy - Clinical features, multimodal imaging and genetic analysis of a novel phenotype

Poornachandra B, Bharathi Bhavaharan,
Sherina Thomas, Padmamalini Mahendradas,
Arkasubhra Ghosh, Chaitra Jayadev,
Anuprita Ghosh, Santosh G Krishna

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Cone dysfunction disorders are characterized by the loss of cone photoreceptors, which are responsible for central and color vision. Two distinct inherited pathologies which affect cone function include achromatopsia and progressive cone dysfunction.^[1,2] Complete or typical achromatopsia is congenital, typically does not show progression, is usually bilateral and symmetric.^[3] We report a case of asymmetric maculopathy with unilateral bull's eye macular lesion and severe cone dysfunction.

A 14-year-old male of Indian origin, noticed diminished vision in the right eye following an episode of fever with a corrected distance visual acuity (CDVA) of 20/200 and near vision of N36 in right and 20/30, N6 in the left eye on Snellen's chart. The patient failed to identify any of the plates on color vision testing by HRR (Hardy, Rand and Rittler) in the right eye but was normal in left eye. The anterior segment examination was normal in both eyes. On fundus examination, the right eye had a bull's eye macular lesion [Fig. 1a] and the left eye had mild retinal pigment epithelium (RPE) alterations at the fovea [Fig. 1b]. Multicolor images also documented asymmetric involvement [Fig. 1c and d].

Optical coherence tomography of the right eye showed foveal thinning with subfoveal loss of outer nuclear and photoreceptor layer [Fig. 1e], and disruption of the ellipsoid

zone in perifoveolar area with a poorly defined ellipsoid zone in the subfoveal region in the left eye [Fig. 1f]. Autofluorescence imaging showed a bull's eye configuration in the right [Fig. 1g] and very subtle changes in left [Fig. 1h], in foveal region. Fluorescein angiography did not suggest any active inflammation [Fig. 1i and j]. Patient was evaluated in Uvea clinic in view of history of fever prior to onset of symptoms, but there were no contributory findings from clinical and hematological work up for inflammation.

Full field electroretinogram (ERG) showed normal 'b' waves in both eyes after 20 minutes of dark adaptation in 0.01 ERG (rod driven response). Dark adapted 3.0 and 10.0 ERG (combined and maximal combined response) showed a mild reduction in the 'a' wave and normal 'b' wave in the right eye [Fig. 2a], but normal responses in the left eye [Fig. 2b]. Dark adapted oscillatory response was normal in the left and slightly reduced in the right eye. Light adapted response 3.0 (cone response to single white flash) and 3.0 flicker (cone response to 30Hz flicker) appeared to have mild reduction in the left eye but was 'un-recordable' in the right eye. The patient was followed up for two years and remained status quo [Fig. 3a-h]. Left eye light adapted response appeared near normal [Fig. 3h], so mild reduction on presentation was considered insignificant.

The patient was a product of a non-consanguineous marriage [Fig. 2c], both parents and sibling were normal. To study the gene sequence of this unusual phenotype, whole exome sequencing (WES) was performed on the DNA of the blood sample of the proband and unaffected family members. Heterozygous missense mutations of unknown significance were found in four different genes - USH2A, PDE6B, PRPF4, PDE6G [Fig. 2d]. In addition, a large heterozygous novel deletion in the CRX gene was identified in the proband, however the unaffected father also had same deletion.

Discussion

Asymmetric maculopathy with unilateral severe cone dysfunction is a rare entity. Though the ERG features resembled achromatopsia in the right eye of our patient, it was a unilateral manifestation. Nomura *et al.* reported a 20-year-old Japanese woman with unilateral cone dysfunction and bull's eye maculopathy.^[4] Our patient's manifestation was grossly asymmetric clinically, and even more so on the full field ERG. Sieving *et al.* has reported two cases with gradual color vision deficit, normal vision, and phenotypically normal macula but with subnormal response for rods, grossly abnormal response for cones, and an abnormally prolonged b-wave when long-duration photopic flashes were used.^[5] In contrast,

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Consultant VR Surgeon, Narayana Nethralaya Eye Institute, Bangalore, Karnataka, India

Correspondence to: Dr Poornachandra B, Consultant Vitreo Retinal Surgeon, Department of Electrophysiology, Retinal Dystrophy & Genetics Clinic, Narayana Nethralaya Eye Institute, Bangalore, Karnataka, India. E-mail: punith.poorna@gmail.com

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Figure 1: (a and b) Fundus and (c and d) multicolor photographs showing asymmetric maculopathy with a bull's eye lesion in the right. (e and f) OCT vertical scans showing foveal thinning with subfoveal loss of outer retinal layers in the right and poorly defined EZ in the left. (g and h) Fundus autofluorescence showing bull's eye configuration in the right and minimal alteration in the left. (i and j) Fluorescein angiography showing dot hyperfluorescence in the right and normal appearance in the left

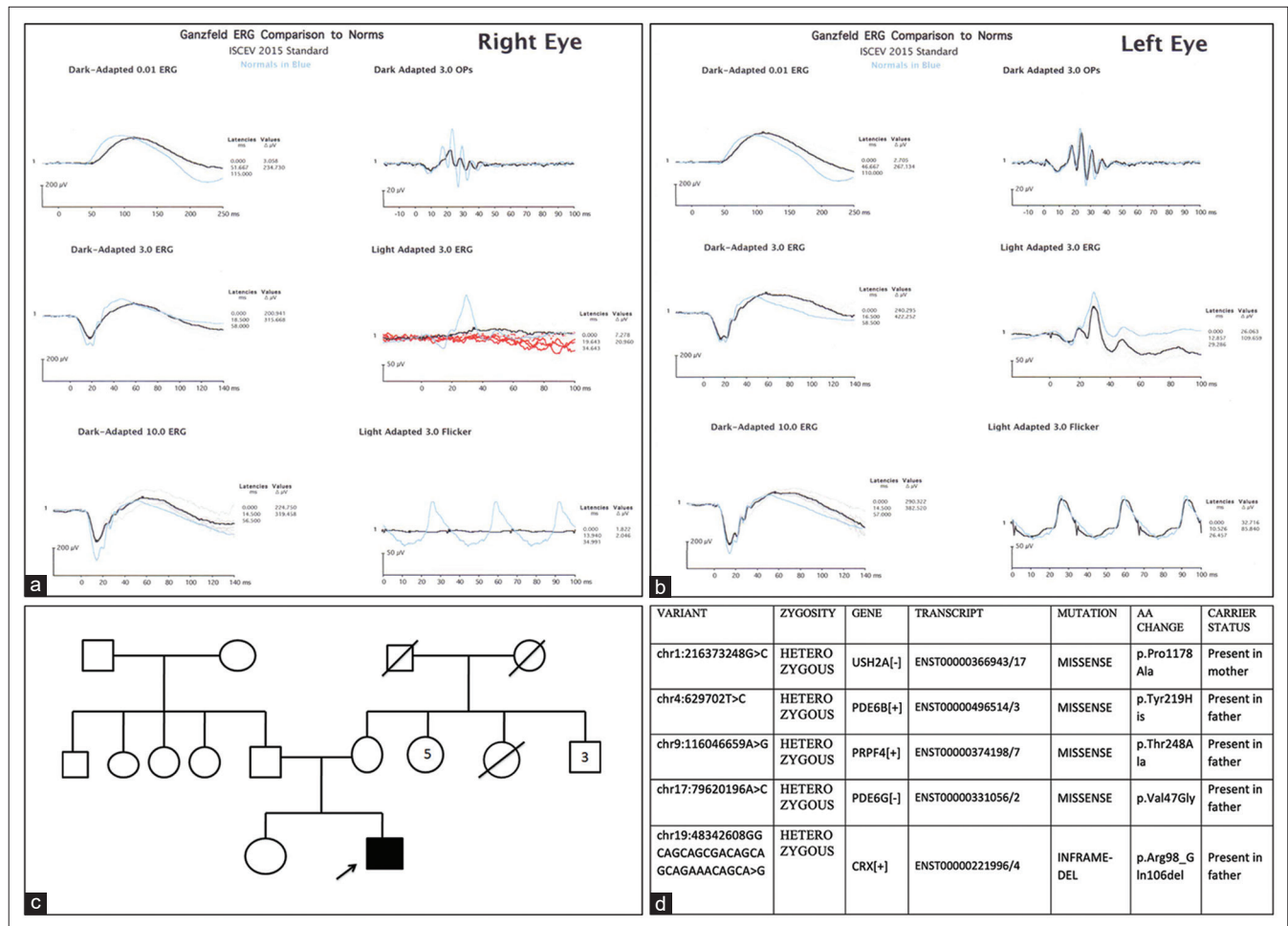


Figure 2: (a) Full field ERG of the right eye showing normal 'b' waves, mild reduction in 'a' wave and reduced dark adapted oscillatory response. Light adapted response 3.0 and 3.0 flicker was unrecordable. (b) Full field ERG of the left eye showing normal responses except for a mild reduction in light adapted responses. (c) Pedigree analysis of the proband (d) Table showing whole exome sequencing report of the proband

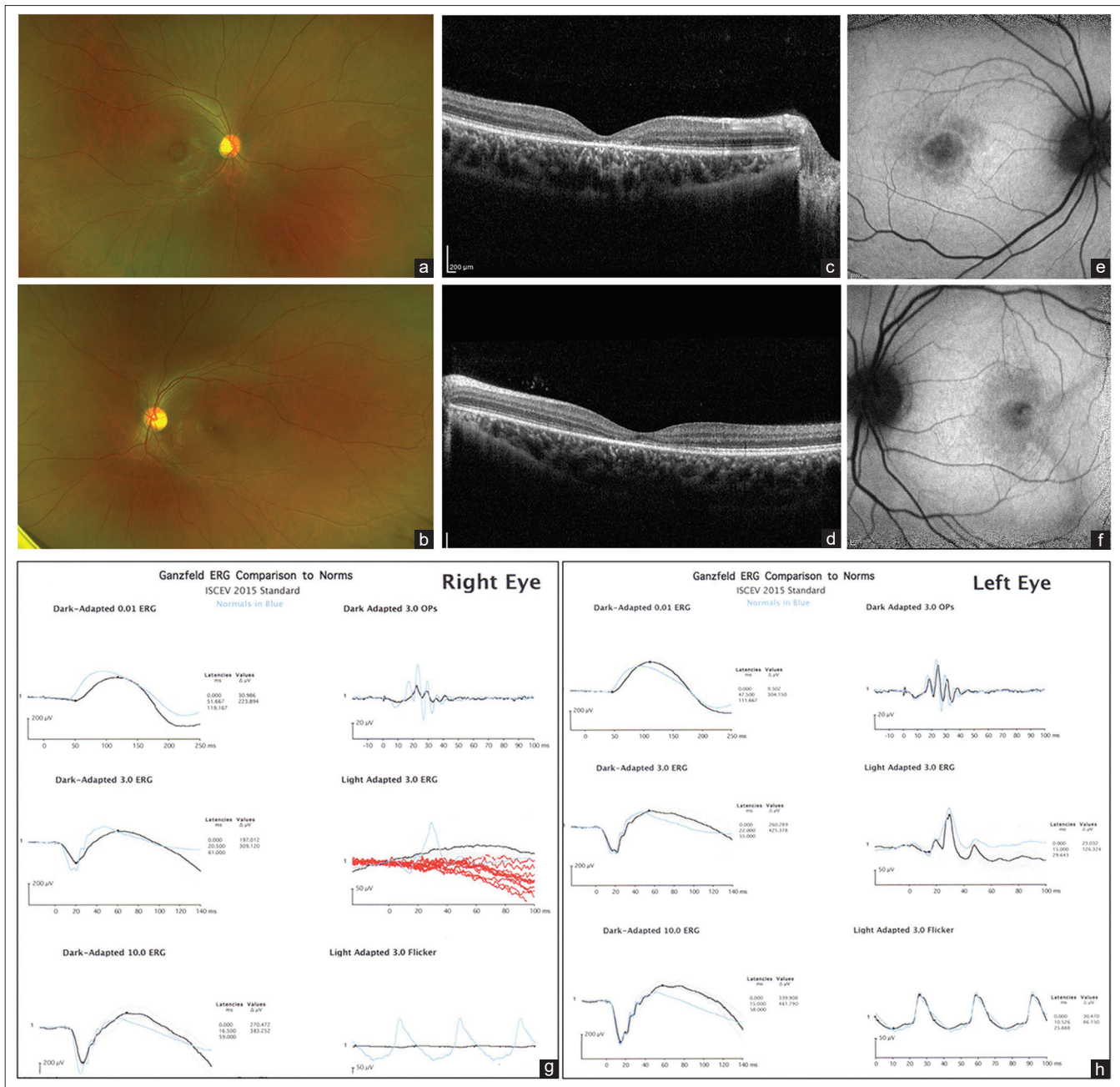


Figure 3: Follow up images (a and b) Fundus photographs showing asymmetric maculopathy. (c and d) OCT vertical scan images of the right and left eye showing no improvement or worsening. (e and f) Fundus autofluorescence images showing a bull's eye configuration in the right eye and minimal alteration of foveal autofluorescence in left eye. (g and h) Repeat full field ERG showing unrecordable photopic responses in right eye and near normal photopic response in left eye with unimpaired rod responses

our patient had low CDVA, near normal rod responses and no measurable full field photopic ERGs.

Two other similar cases reported also had good visual acuity and a clinically normal macula in the affected eye.^[6,7] Mochizuki *et al.* also reported a unilateral cone dysfunction, but was predominantly peripheral.^[8] Genetic analysis of none of these reported cases is available. One report of a novel nonsense mutation in the CRX gene (19q13.3) mimicked benign concentric annular macular dystrophy with bilateral symmetric bull's eye macular lesions in a mother and son duo.^[9]

Sequencing results of our patient did not suggest any pathogenic mutations since the identified variants were heterozygous in nature and was present in the unaffected parents. A possible reason could be because of the limitations of WES which does not determine epigenetic changes, copy number variants and epistatic interactions. The genetic cause of unilateral cone dystrophy may be incomplete penetrance, a novel gene mutation, a somatic genetic variation or a mutation in an epigenetic regulatory locus. It has also been suggested that a different unidentified mutation at a single locus or nonlinked

mutations in multiple loci could account for the unusual unilateral presentation in these diseases.^[10] These findings indicate that there could be a separate entity of asymmetric cone dysfunction, the pathogenesis and genetic variation for which is still unknown.

This is the first report of a patient of Indian origin with asymmetric maculopathy and unilateral bull's eye macular lesion and severe cone dysfunction in whom the possible genetic mechanism was studied.

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Conflicts of interest

There are no conflicts of interest.

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