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LETTER TO THE EDITOR

Anisometropia and asymmetric *ABCA4*-related cone-rod dystrophy

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Case report

The patient is a 54-year-old woman with a past medical history of ulcerative colitis under mesalazine treatment and allergic rhinitis under inhaled fluticasone. Her parents were non-consanguineous. She was diagnosed with severe anisomyopic amblyopia in her right eye at the age of 5 years, which she maintained despite optical correction and patching.

She presented with a two-year history of progressive central vision loss on her left, non-amblyopic eye, which made her search for medical advice. She experienced nyctalopia and photophobia over the last 4 years, and more recently, she became aware of color and central vision loss. She had been submitted to bilateral cataract surgery the year before.

Best-corrected visual acuity (BCVA) was 0.05 at 1 m in the amblyopic eye and 0.6 "searching" in the left eye. Ophthalmoscopy disclosed myopic choroidopathy in her right eye, and extensive macular atrophy in the left eye with atrophic patches extending to the mid periphery (Figure 1(a, b)). Fundus autofluorescence (FAF) highlighted the asymmetry of macular atrophy with a strikingly larger hypoautofluorescent area in the non-amblyopic eye (Figure 1(c,d)). This difference was also remarkable on optical coherence tomography (OCT) imaging (Topcon Triton plus Ver.10.13), which showed central preservation of the ellipsoid layer in the amblyopic eye (Figure 2). Concerning ETDRS grid thickness map, the central thickness was inferior in the left, less myopic eye, but the average thickness was similar in both eyes (Figure 3).

Axial length (AL) measurements were performed (Anterion® optical biometry—Heidelberg engineering) to quantify the degree of anisometropia, revealing an AL of 28.84 mm and 25.64 mm, in the right and left eye, respectively.

Electroretinography based on ISCEV standards (Metrovision Vision Monitor MonPack3) showed subnormal photopic and scotopic responses with slightly more reduced amplitudes on the amblyopic eye (Figure 4).

Visual fields (EyeSuite™ Static perimetry, V3.6.1 OCTOPUS 900® Program N1 Standard 80°) revealed central and temporal defects in the amblyopic right eye, and an extensive central defect in the left eye (Figure 5). PV-16 Quantitative Color Vision Test® (Precision Vision) showed mild color vision defects in both eyes. Based on the clinical history and examination, the clinical diagnosis of cone-rod dystrophy was made.

Following informed consent from the patient, Whole Exome Sequencing (WES) and targeted Sanger sequencing were performed. Genetic analysis revealed two known heterozygous pathogenic variants in the *ABCA4* gene: one missense variant NM_000350.3: c.32T>C, p.(Leu11Pro) (rs62645946), which is particularly prevalent in the Portuguese population of STGD1 patients (1), and one altering splicing mutation NM_000350.3: c.5196 + 1137 G>A, p.? (rs778234759) (2). Both variants were previously associated with a spectrum of retinal dystrophy phenotypes in the clinical and genetic databases (ClinVar, https://www.ncbi.nlm.nih.gov/clinvar/) and have been classified as alleles of moderate severity (3). Although segregation analysis was not performed, the phenotype matched *ABCA4*-related disease spectrum and a presumptive diagnosis of *ABCA4* related cone-rod disease was made.

Discussion

Review of the literature identified a similar case published in 1996 by Lafaut *et al.*, describing an unusual asymmetric pattern of fundus flavimaculatus in a unilateral myopic patient. Although electrophysiologic testing yielded similar results for both eyes, fundus lesions were different, with myopic choroidopathy and lack of flecks in the myopic eye, and perifoveal pisciform flecks and a discrete bull's eye lesion in the non-myopic eye (4).

Generally, inherited retinal diseases have very symmetrical presentation and progression (5,6). Could therefore myopia and/or AL influence the natural history of *ABCA4*-related retinal disease? Clearly, the interest in *ABCA4*-related disease symmetry is growing since novel therapies are emerging and the fellow eye can be used as a control.

To better understand the mechanism underlying disease asymmetry in these two patients, and the potential role of AL on disease progression, we searched the literature and identified two studies evaluating inter-eye symmetry in Stargardt disease.

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