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Disruption in Bruch membrane in patients with Stargardt disease

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Abstract

Purpose—To describe the spectral domain-optical coherence tomography (SD-OCT) findings of two patients with complete defects in the retinal pigment epithelium (RPE) with disruptions in Bruch membrane in Stargardt disease (STGD1).

Methods—Two patients with STGD1 were referred to our clinic for further evaluation. Fundus autofluorescence (FAF), spectral domain optical coherence tomography (SD-OCT), electroretinography (ERG) and Microperimetry (MP-1) were performed to assess the retinal anatomy and function. Screening for mutations in the ABCA4 gene was carried out and detected mutations were confirmed by direct sequencing.

Results—Both patients had bilateral macular geographic atrophy (GA) and yellowish subretinal pisciform flecks and mutations were detected in the ABCA4 gene by chip screening. SD-OCT revealed marked atrophy of the retina in the central macula, with focal defects in the RPE with disruptions in Bruch membrane and herniation of the retina through the defect in three of four eyes.

Conclusion—This case report highlights the necessity for a detailed ophthalmic examination including SD-OCT of patients with STGD1.

Keywords

Stargardt disease; Bruch membrane; spectral domain-optical coherence tomography; retinal pigment epithelium; geographic atrophy

INTRODUCTION

Initially described by Karl Stargardt in 1909,¹ Stargardt disease (STGD1) is the most common cause of juvenile macular dystrophy and leads to a progressive loss of central

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visual function usually beginning in the teenage years. STGD1 is an autosomal recessive dystrophy caused by mutations in the gene encoding the photoreceptor cell-specific ATP-binding cassette transporter ABCA4.² Fundus findings reveal a range of pathology from a beaten-bronze appearance at the fovea to the development of extensive geographic atrophy (GA). The most recognizable feature of the disease is yellow-white subretinal pisciform flecks, and the phenotypic appearance has been previously described in four stages.³ Briefly, in stage I disease the pathology is confined to the central macula, while in stage II disease the pathology extends anterior to the vascular arcades or nasal to the optic disc. In stage III and IV there is increasing atrophy of the retina, retinal pigment epithelium (RPE) and choriocapillaris. On FAF, flecks appear hyperautofluorescent, while regions of GA appear hypoautofluorescent.^{4,5}

Patients may also be sub-divided based on the results of the full-field electroretinogram (ERG). Those with normal cone and rod responses have ERG group I disease, while those with isolated cone abnormalities have ERG group II disease. Patients with combined cone and rod abnormalities have ERG group III disease, ie a cone-rod dystrophy pattern of dysfunction.⁶

SD-OCT provides cross-sectional images of the retina and information consistent with that obtained from histologic sections.⁷ The Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany) allows simultaneous acquisition of an en face infrared (IR) or FAF image, together with high resolution SD-OCT images, thus allowing point-to-point correlation between the appearance of pathology using multiple imaging modalities. *In vivo* visualization of the RPE as well as the inner segment/outer segment junctions of the photoreceptors (IS/OS) provides novel insights into STGD1 process.^{8,9} Using SD-OCT, the authors describe two patients (three eyes) with complete RPE defects with disruptions in Bruch membrane in STGD1. Screening for mutations in the ABCA4 gene was carried out using the ABCR 600 micro-array chip which detects all known mutations in the ABCA4 gene. Detected mutations were confirmed by direct sequencing.

CASE REPORTS

Case 1

A 32-year-old woman with a previous diagnosis of STGD1 was referred for evaluation. She had an onset of visual symptoms in her early twenties and was diagnosed with STGD1 at age 32 years. Her past medical history was unremarkable. At examination the patient's best-corrected visual acuity (BCVA) was OD: 20/200 and OS: 20/40. Refractive error was OD: $-5.25/-0.75 \times 4^\circ$ and OS: $-5.75/-0.50 \times 133^\circ$. Anterior segment examinations were normal. Following pupil dilatation, pigmentary changes in the macular area were observed together with RPE atrophy. Flecks extended anterior to the vascular arcades and the optic disc in both eyes on fundus examination in keeping with a diagnosis of Fishman stage II disease (Fig. 1A and B). On FAF, the atrophic macular lesions demonstrated profound hypoautofluorescence with surrounding heterogeneous patterns of alternating hypo/hyperautofluorescence bilaterally (Fig. 1C and D).

Microperimetry (MP-1 microperimeter; Nidek Technologies, Inc.), performed on the left eye only, detected an absolute scotoma (ie total deviation -20 dB) in the regions of GA, with detectable but reduced visual sensitivity in regions of abnormal FAF across the macula (Fig. 1D). Poor fixation precluded performing accurate microperimetry on the right eye. A single mutation, IVS40 + 5G→A, was detected in the *ABCA4* gene by chip screening. Normal amplitudes and implicit times in both rod and cone photoreceptor systems were detected by ERG in keeping with a diagnosis of ERG group I STGD1.

SD-OCT imaging of the macula revealed focal absence of the IS/OS junction and thinning of the entire retina in the central macula. Furthermore, a complete defect in the RPE/Bruch membrane complex was observed on SD-OCT in both eyes in the central macula. There was herniation of the retina through these defects into the sub-RPE/choroidal space. The defects in the RPE-Bruch membrane complex measured OD: 332 μ m and OS: 266 μ m in maximum horizontal diameter (Fig. 2A and B). There was no evidence of sub-RPE choroidal neovascularization (CNV), pigment epithelial defects (PED) or subretinal fluid (Fig. 2C and D).

CASE 2

A 48-year-old man with a clinical diagnosis of STGD1 was referred for electroretinogram testing. He had an onset of disease at 13 years of age. Medical and family histories were unremarkable. At examination, BCVA was 20/200 bilaterally and refractive error was OD: $-1.50/+0.50 \times 149^\circ$ and OS: $-1.50/+0.25 \times 161^\circ$. Anterior segment examinations were normal. Dilated fundus examination revealed pigmentary changes, with a beaten-metal appearance of the fovea and a discontinuous ring of flecks encircling the fovea in keeping with a diagnosis of stage I STGD1 (Fig. 3A and B). FAF demonstrated GA with central hypoautofluorescence. This was surrounded by a hyperautofluorescent transitional zone in each eye, though this finding was more pronounced in the right eye (Fig. 3C and D). This patient had normal cone and rod responses on ERG, and so was diagnosed with ERG group I STGD1. Genetic screening revealed that the patient was compound heterozygous for the H1406Y and G1961E mutations in the *ABCA4* gene.

SD-OCT imaging demonstrated thinning of the retina and absence of the IS-OS junction in the central macula in both eyes. The left eye showed a complete defect of the RPE-Bruch membrane complex with herniation of the outer retina through this defect (Fig. 3D). The maximum horizontal diameter of this RPE-Bruch membrane complex defect was 266 μ m (Fig. 3F). In the right eye there was RPE atrophy in the central macula with focal thickening of the RPE in the parafoveal region (Fig. 3D and E). However, there was no defect observed in the RPE and Bruch membrane in this eye. Importantly, the size of GA lesion in the eye with the RPE defect (the left eye) was greater than that of the right eye.

DISCUSSION

In this study, SD-OCT findings of three eyes in two patients with STGD1 revealed a complete RPE-Bruch membrane complex defect. To our knowledge, this is the first description of this finding in patients with *ABCA4* disease.^{4,5-8,11,12} Our patients did not demonstrate CNV or PED which are known causes of disruption of the RPE layer. While in

case 1 RPE-Bruch membrane complex defects were detected in both eyes, in case 2 a full-thickness defect of the RPE-Bruch membrane complex layer was seen only in the left eye on SD-OCT. Both patients had normal ERGs in keeping with a diagnosis of ERG group I STGD1.

Atrophy of the photoreceptors and RPE layer are characteristic of STGD1.^{7,10} The exact sequence of events in this process remains to be fully elucidated. High resolution retinal imaging is essential for a better understanding of the morphology of the retina in STGD1, facilitating earlier diagnosis and monitoring of disease progression.¹⁰ FAF enables visualization of A2E and other bis-retinoid components of lipofuscin in the RPE. This non-invasive technique has been clearly demonstrated to be useful in evaluating the extent of STGD1. Studies using SD-OCT in patients with STGD1 have previously demonstrated IS/OS junction loss and photoreceptor thinning, as well as atrophy of the choriocapillaris.^{4-8,10,11} Gomes demonstrated that changes in the photoreceptors, detected by SD-OCT, may precede changes detected by FAF in the RPE in STGD1.⁵

A defect in the RPE layer has been previously reported in a 60-year-old woman with solar maculopathy.¹² Neither of the cases reported here had any history of trauma nor evidence of vitritis, retinitis and choroiditis. Although Fryczkowski reported a spontaneous RPE tear in a patient with high myopia (refractive error -10.0 D), the refractive errors detected in the cases reported here were not so severe, suggesting that axial length was not likely to be a contributing factor to the SD-OCT findings.¹³ Given the small number of cases and the known genetic variability in STGD1, it was not possible to determine if the mutation type played a role in the development of the RPE-Bruch membrane complex defect.

Marcus et al. reported a focal RPE coloboma, which may give rise to a complete focal RPE defect similar to those observed in this series, in the animal model for retinal disease caused by mutations in the adenomatous polyposis coli (APC) gene. APC is critical in the regulation of RPE proliferation and development, and RPE hypertrophy is the most common pathologic finding associated with APC mutations.¹⁴ The mechanism and outcome of APC gene mutation is different to that of mutation in the ABCA4 gene, but this study suggests that further investigation of the ABCA4/RPE relationship is warranted as it may provide insight into the pathophysiology of STGD1.

Our study demonstrates that SD-OCT can detect complete defects of the RPE-Bruch membrane complex layer in patients with STGD1. This suggests that in certain cases disease progression continues within regions of GA, to give rise to further pathology in STGD1. Longitudinal monitoring of these patients will be necessary to check for development of CNV.

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FIGURE 1.

Fundus color photographs of the right (A) and left (B) eyes of patient 1 showing atrophic lesion in the macula with flecks observed across the posterior pole. Complete absence of autofluorescence was observed in the central macula on FAF, and a speckled pattern of alternating hypo/hyperautofluorescence was observed in the right (C) and left (D) eyes. MP-1 results were superimposed and registered to the left FAF image (D). Infrared images of the right (E) and left (F) eyes of patient 1 are presented with corresponding SD-OCT images (G and H). Magnified SD-OCT images (I and J) show IS/OS junction loss and focal absence of the RPE-Bruch membrane complex layer (double-headed horizontal arrows) in the central macular area bilaterally. As the RPE disappears, the outer retina and inner nuclear layer encroach on the RPE-Bruch membrane complex defect and herniate into the sub-RPE space. The positions of SD-OCT line scans on the corresponding infrared images are indicated by the white dashed lines. The white arrows indicate the borders of the intact RPE-Bruch membrane complex.

FIGURE 2.

Fundus photographs of patient 2 showing bilateral geographic atrophy with pigmentary changes in the central macula. (A and B) Central hypoautofluorescence surrounded by hyperautofluorescence is seen in both eyes on the FAF (C and D). SD-OCT images of the right eye show IS/OS loss and RPE atrophy in the central macula with abnormal thickening of the RPE in the parafoveal region. There was no focal defect of RPE layer in the right eye on the SD-OCT (E). SD-OCT of the left eye revealed a defect in the RPE-Bruch membrane complex layer (F). Magnified views reveal prolapse of the outer retina through this defect in the RPE-Bruch membrane complex layer (G and H). The position of corresponding SD-OCT line scans on the infrared fundus images are indicated by the white dashed lines. The double-headed horizontal arrows indicate regions where the RPE and Bruch membrane are absent. White arrows indicate the borders of the intact of RPE-Bruch membrane complex.