New Insights Into Stargardt Disease With Multimodal Imaging

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ABSTRACT: A 20-year-old woman with bilateral mild blurring of vision presented with a bull’s eye maculopathy and was diagnosed with Stargardt disease, confirmed with genetic testing. The authors present several novel multimodal imaging findings including multicolor and multi-spectral imaging that enhanced visualization of perifoveal flecks, fundus autofluorescence that revealed both perifoveal and perimacular rings of hyperautofluorescence, adaptive optics imaging that revealed unprecedented visualization of cones at the fovea due to decreased cone density, and spectral-domain optical coherence tomography that identified thickening and increased hyperreflectivity of the external limiting membrane as a possible transient biomarker of early Stargardt disease.


INTRODUCTION

The large phenotypic variability of Stargardt disease or fundus flavimaculatus has become increasingly recognized since identification of the ABCA4 gene.1,2 The typical appearance of retinal flecks may be subtle in early or mild cases, and less common clinical manifestations such as a bull’s eye maculopathy,3,4 especially in the absence of abnormal electroretinography (ERG), may be misleading. With the advent of multimodal imaging techniques, features of Stargardt disease may be more easily characterized. This report aims to highlight several new imaging findings that may improve our understanding of this entity.

CASE REPORT

A 20-year-old woman with no significant medical or family history presented to her optometrist for a refraction. Her best corrected Snellen visual acuity was 20/25 bilaterally. She reported no photopsia or night or peripheral vision problems. Clinical examination revealed a bilaterally symmetric bull’s eye maculopathy. Visual field testing revealed bilateral incomplete central ring scotomas, and Ishihara pseudoisochromatic plates showed normal color vision. Full-field flash ERGs revealed essentially normal scotopic, photopic, and 30 Hz flicker responses. Genetic analysis detected a p.Arg602Trp:c.1804C > T mutation and a novel intronic variation at c.2743 + 12A > C of the ABCA4 gene.

The patient underwent comprehensive multimodal imaging including color fundus photography and fluorescein angiography (Topcon Retinal Camera 50DX; Topcon Corporation, Paramus, NJ), ultrawide-field color photography and fundus autofluorescence (AF) (Optos 200Tx; Optos, Dunfermline, UK), spectral-domain optical coherence tomography (SD-OCT), blue light or short-wavelength (488 nm) fundus AF and multicolor imaging (Heidelberg Spectralis; Heidelberg Engineering, Heidelberg, Germany), multi-spectral imaging (Annidis RHA; Annidis Corporation, Ontario, Canada), microperimetry (MP-1 Microperimeter; Nidek Technologies, Padova, Italy), and adaptive optics imaging (rtx1 prototype; Imagine Eyes, Orsay, France).

Multicolor (Figures 1D-E) and multispectral imaging (Figure 1F) enhanced visualization of perifoveal flecks compared to the standard or ultrawide-field color fundus photograph (Figures 1A-C). Fundus AF
(Figures 2D-E) revealed a perifoveal ring of hyperautofluorescence, whereas ultrawide-field AF (Figure 2A) revealed a wider perimacular ring of hyperautofluorescence that could be explained in part by increased lipofuscin deposition, confirmed by a “silent” choriocapillaris on fluorescein angiography (Figures 2B-C). SD-OCT imaging (Figures 2F-G) revealed outer retinal thinning at the perifoveal area that corresponded well to the perifoveal ring of hyperautofluorescence (Figures 2D-E). Hyperreflective accumulations on SD-
OCT (Figures 2F-G) involving the outer segments, interdigitation zone, and retinal pigment epithelium (RPE) band at the perifoveal area corresponded to the perifoveal flecks seen on multicolor and multispectral imaging (Figures 1D-F). SD-OCT also showed thickening and increased hyperreflectivity of the external limiting membrane (ELM) at the junction of the healthy and atrophic retina, a possible biomarker of early degenerating photoreceptors (Figures 2H-I). Microperimetry showed reduced sensitivity correlating well with the areas of cone loss on adaptive optics imaging (Figures 3A-B). More interestingly, we were able to visualize the foveal cones, which is usually not possible due to the normally high cone density at the fovea (Figures 3C-D).

**DISCUSSION**

We present a case of Stargardt disease with genetic confirmation that highlights several novel imaging findings and improves our understanding of the disease. This case was interesting because the patient presented clinically with a bull’s eye maculopathy, lacked typical prominent flecks, and had a normal flash ERG response. The G1961E mutant allele may manifest as a localized maculopathy with normal ERG; however, our patient did not carry this mutation but rather a p.Arg602Trp missense mutation and a novel intronic mutation.

In cases of early or mild changes, enhanced visualization of subtle flecks with multicolor and multispectral imaging may be helpful in making an early diagnosis of Stargardt disease, which is beneficial...

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Figure 2. (A) Ultrawide-field fundus autofluorescence (AF) showing two rings of hyperautofluorescence in both eyes, namely perifoveal and paramacular (white dashed ring on the right eye). (B, C) Fluorescein angiography of both eyes demonstrating a “silent” choroid. (D, E) Standard-field 488-nm fundus AF showing the perifoveal ring of hyperautofluorescence surrounding central hypoaufotofluorescence. (F, G) Spectral-domain optical coherence tomography (SD-OCT) of both eyes through the fovea showing perifoveal outer retinal thinning which corresponds to the perifoveal hyperautofluorescence ring on fundus AF. (H, I) High-magnification SD-OCT of both eyes at the junction of normal and atrophic retina showing thickening and hyperreflectivity of the external limiting membrane (white arrows) compared to that over the normal retina (white dashed arrow).
because there are ongoing FDA-approved clinical trials investigating effective therapies. The perifoveal flecks appeared primarily on the infrared reflectance, suggesting they were located at or close to the RPE layer. SD-OCT confirmed that these flecks were predominantly type A flecks, which involve the outer segments, interdigitation zone, and RPE layer. With multispectral imaging, these flecks could be seen on the shortest wavelength of 580 nm in addition to the longest wavelength of 940 nm, indicating that these hyperreflective lesions were not attributable to RPE disturbances alone.

The patient exhibited a type A fundus AF pattern with central hypoautofluorescence surrounded by a hyperautofluorescent ring. This hyperautofluorescent ring may likely be attributed in part to the increased lipofuscin deposition as well as an unmasking of the background AF of the RPE. This may be similar to the unmasking effect due to reduced photopigment density seen with photobleaching and entities such as central serous chorioretinopathy in which there is dysfunction or loss of photoreceptor outer segments. In addition, ultrawide-field fundus AF revealed a wider paramacular ring of hyperautofluorescence than may be present in a healthy individual but is accentuated in Stargardt disease. The normal ring of hyperautofluorescence can be attributed to variations of the RPE cell distribution and density in the retina, leading to a higher concentration of RPE lipofuscin at the fovea that decreases toward the peripheral retina. With the increased lipofuscin deposition in Stargardt, this paramacular hyperautofluorescent ring can be appreciated more readily.

With SD-OCT imaging, we were able to identify thickening and increased hyperreflectivity of the

Figure 3. (A,B) Microperimetry and adaptive optics images superimposed on color fundus images at the macula showing good correlation between the areas of decreased retinal sensitivity on microperimetry and areas of cone loss on adaptive optics. (C) Adaptive optics imaging of the patient at the fovea showing visualization of cones at the fovea and the appearance of reduced cone density in the perifoveal area. (D) Adaptive optics imaging of a normal fovea showing the inability of the device to resolve the cones at the fovea (white dashed circle) and normal cone mosaic at the perifoveal area.
ELM at the junction of the normal and atrophic retina, a phenomenon that has been described in early Stargardt disease.\textsuperscript{13,14} Although the observed ELM hyperreflectivity in achromatopsia was first suggested to be due to differences in refractive index,\textsuperscript{15} we propose an alternate explanation. We hypothesize that this phenomenon, which has been confirmed on histopathologic correlations with outer retinal tubulation, may be attributed to the migration and retraction of the inner segment ellipsoid back to the ELM during degeneration of the photoreceptor\textsuperscript{16} (also Litts KM et al, unpublished data). The densely packed mitochondria within the inner segment ellipsoid may be responsible for the thickening and hyperreflective appearance of the ELM on SD-OCT. This biomarker is likely transient but may precede photoreceptor atrophy and may be lost with further outer retinal degeneration. Awareness of this finding may be useful in screening patients at risk for Stargardt disease and for monitoring progression in clinical trials of future therapeutics.

With the advent of adaptive optics imaging, we are able to visualize the cone photoreceptor mosaic as a regularly spaced hexagonal array of hyperreflective discs across the retina.\textsuperscript{17} Under normal circumstances, foveal cones are usually not visible with adaptive optics imaging due to the normally high density of cones at the fovea, even in pathological eyes. In this case of Stargardt disease, adaptive optics was able to reveal cones at the fovea, which paradoxically indicates an abnormal reduction in cone cell density. This imaging finding could be useful for detecting early disease, but larger studies evaluating the sensitivity and specificity of this finding are necessary.

In summary, we present several novel multimodal imaging findings of Stargardt disease that may be useful in the diagnosis and monitoring of early disease.

REFERENCES