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Cone Photoreceptor Abnormalities Correlate With Vision Loss in a Case of Acute Posterior Multifocal Placoid Pigment Epitheliopathy

In Hwan Hong, MD, Sung Pyo Park, MD, PhD, Ching Lung Chen, MD, Hyoung Kyun Kim, MD, Stephen H. Tsang, MD, PhD, and Stanley Chang, MD

Department of Ophthalmology, Kangdong Sacred Heart Hospital, Hallym University Medical Center, Seoul, South Korea (IHH, SPP, HKK); the Department of Ophthalmology, Columbia University, New York, NY (SPP, CLC, SHT, SC); the Department of Ophthalmology, Chang Gung Memorial Hospital, Chiayi, Taiwan (CLC); and the Department of Pathology & Cell Biology, Columbia University, New York, NY (SHT).

Abstract

The authors report adaptive optics scanning laser ophthalmoscopy (AO-SLO) findings in a case of acute posterior multifocal placoid pigment epitheliopathy. The right eye showed an island of coarse, hyperreflective speckles surrounded by a dark annulus lacking cone cells, which were associated with reduced MP1 sensitivity and abnormal findings in other imaging modalities. Although dark lesions were also detected in the left eye, the correlated spectral-domain optical coherence tomography images were normal. AO-SLO allowed for the direct observation of retinal disruptions and the ability of this technology to detect abnormalities in the left eye demonstrates a superior ability for in-depth retinal imaging.

INTRODUCTION

Acute posterior multifocal placoid pigment epitheliopathy (AMPPE) was first described by Gass¹ as a rare eye disease that typically affects the choriocapillaris, retinal pigment epithelium (RPE), and outer retina. The pathophysiology and the level of posterior segment involvement in AMPPE were unclear,¹⁻³ with few histopathologic studies reported due to the condition's transience. Also, current ophthalmic imaging modalities have provided additional information, but none of these can provide information at the level of single cells.⁴⁻⁶

Adaptive optics (AO) provides a means for dynamically correcting natural optical aberrations, allowing visualization of microstructures in the retina.⁷ Combining AO with scanning laser ophthalmoscopy (SLO) has provided insight into the structure of the cone cells in living eyes.⁷⁻¹⁰ In the present study, we report a case of AMPPE studied with an

Address correspondence to Sung Pyo Park MD, PhD, Kangdong Sacred Heart Hospital, Hallym University Medical Center, Department of Ophthalmology, Seoul, Korea; 82-2-2224-2274; fax: 82-2-470-2088; sungpyo@hanafos.com..

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AO-SLO. The aim is to elucidate the pathological consequences of AMPPE as related to organization of the cone mosaic and currently proposed etiologies.

CASE REPORT

A 16-year-old girl was referred for further evaluation of AMPPE. Visual acuity was normal with a silent anterior chamber and vitreous. Cream-colored lesions were scattered throughout the posterior fundus in both eyes. Hyperpigmentation, atrophy, and RPE mottling were observed, predominantly in the right eye (Figure 1A-B). Fluorescein angiography revealed hypofluorescent lesions with hyperfluorescent borders in the early phase. The degree of hyperfluorescence increased over the course of the angiogram, with late staining (Figure 1C-D). Such a presentation was compatible with old lesions and mild active inflammation of the AMPPE. Over the next 3 years, the lesions appeared to be fading, replaced by hyperpigmentation and atrophy (Figures 2A and 2D, page 76). Fundus autofluorescence (FAF) imaging of the right eye revealed areas of decreased fluorescence with absent autofluorescence areas corresponding to the pigmented lesion, indicating decreased visual function (Figure 2B). A spectral-domain optical coherence tomography (SD-OCT) scan of the fixation point revealed a disruption with partial disappearance of the inner/outer segment (IS/OS) line (Figure 2C). Although slightly decreased autofluorescence and foveal sensitivity were noticed in the left eye, the SD-OCT findings were nearly normal (Figure 2E-F).

AO-SLO of the right eye revealed an island of coarse, hyperreflective speckles surrounded by a dark annulus without any cones (Figure 3A-B, markers b2-b4, page 77), indicating a reduction of foveal sensitivity corresponding to the pigmented lesions (Figure 3A). An SD-OCT scan through the dark annulus revealed a disrupted IS/OS junction. Dome-shaped hyperreflective deposits could be seen elevating or penetrating the external limiting membrane in or on the RPE layer. These deposits co-localized with highly reflective structures on AO-SLO images (Figure 3B-C). AO-SLO images of the left eye included some dark areas where the cone cells were damaged or lost (Figures 4A and 4C, page 78). These patterns were not observed in areas of the retina that were less affected and were clearly differentiated from artifacts or blood vessels (Figure 4B). SD-OCT images of the dark lesions showed intact IS/OS junctions and macular structures with a grossly normal appearance (Figure 4C) that were not associated with decreased foveal sensitivity (Figure 4A).

DISCUSSION

Since the initial report by Gass in the late 1960s, there has been debate regarding the cause of AMPPE.¹⁻³ However, the histopathological evidence has been limited to that obtained during autopsy studies, which was insufficient to explain the pathophysiology of AMPPE. Thus, high-resolution retinal imaging is warranted to settle these debates.

SD-OCT allows for better visualization of the retinal architecture with high resolution. Our patient's right eye showed disruption with partial disappearance of the IS/ OS junction and thickening with an accentuated RPE hyperreflectivity during the resolved phase. These

results were consistent with previous studies in a patient with AMPPE,^{4,11,12} spurring us to investigate the microstructural abnormalities. The AO-SLO images obtained throughout these lesions revealed an island of coarse, hyperreflective cones surrounded by a dark annulus devoid of wave-guiding cones. As would be expected by the reflectance of the normal cone mosaic in AO-SLO, which is thought to represent reflectance from both the IS/OS junction and the OS,¹³ the dark annulus co-localized with disruptions of the IS/OS junction on SD-OCT images. The hyperreflective regions showed reduced sensitivity, which was consistent with disruptions of the outer retinal layer by the dome-shaped hyperreflective deposits seen on SD-OCT. These regions did not include normal cone cells because they were not arranged in a continuous mosaic and were not correlated with an intact IS/OS junction on the corresponding SD-OCT scan. These results are in accordance with those of previous studies,^{9,10} in which the dark areas seen on AO images corresponded with disruptions to the IS/OS junction. Similarly, hyperreflective areas were observed in the flecks corresponding to dome-shaped deposits in the RPE layer as seen on SD-OCT.¹⁰

Notably, we observed dark areas in the left eye, in areas where SD-OCT images had demonstrated an apparently intact IS/OS junction. Furthermore, the patient's visual acuity was normal, and foveal sensitivity was only mildly reduced in the areas surrounding the dark lesions. As the normal appearance of cone cells external to the dark lesions, these lesions may not alter overall visual acuity, which is a function of the entire retina.¹⁴ Also, the dark lesions were too small to be detected by microperimetry. Nonetheless, the decreased autofluorescence on FAF images likely represented a mild reduction in sensitivity attributable to RPE dysfunction. The inability of SD-OCT images to detect areas of cone loss as represented by AO-SLO images may be explained by differences in lateral resolution between SD-OCT without AO (20 μ m) and AO-SLO (3 μ m).

Many previous studies focused on quantitative analyses of cone cell density and cone optical properties.^{8-10,14} Presumably none of the cones in either the hyperreflective lesions or the dark areas were detected. Unfortunately, neither manual nor automatic calculation methods for cone density have been developed for our second prototype of AO-SLO. Although the pathogenesis of AMPPE remains unclear, the RPE has been hypothesized to play a major role¹⁻³ and the recently developed fluorescence AO-SLO allows individual RPE cells to be imaged.¹⁵ But the AO-SLO system employed in the present study is limited to visualizing individual RPE cells. In spite of those limitations, our study is significant because it is the first in vivo study to document the pathologic findings associated with AMPPE using AO-SLO and compare these results with those of standard clinical and functional tests. Although this study involved only one patient with late-stage AMPPE, AO-SLO allowed us to directly observe disruptions to the retina structure that previously had only been investigated indirectly through reductions in visual function. Furthermore, the dark, cone-less areas in the left eye were detected only with AO-SLO. This suggests that AO-SLO provides a sensitive method for the detection of cone mosaic disruptions in AMPPE patients. The technique would be particularly helpful in the treatment of patients in the late stages of the disease who cannot be examined using conventional imaging modalities.

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Figure 1. Initial presentation. (A,B) Color fundus photograph shows white multifocal placoid lesions with atrophic and pigmentary retinal pigment epithelium changes, predominantly in the right eye. (C) Fluorescein angiography of the right eye in the early phase. (D) Fluorescein angiography of the right eye in the late phase.

Figure 2.

Follow-up at 3 years. (A) Fundus appearance of the right eye shows central pigmented lesions with diffuse retinal pigment epithelial atrophic changes. (B) Fundus autofluorescence reveals diffuse areas with decreased autofluorescence and centrally located lesions with absent autofluorescence, corresponding to the marked reduction of retinal sensitivity. (C) Spectral-domain optical coherence tomography at the fixation point indicated by the white dashed line in B shows hypertrophic lesions with accentuated hyperreflectivity at the level of the retinal pigment epithelium and partial disruption of the inner segment/outer segment junction. (D) Fundus photography of the left eye shows that the cream-colored lesions have resolved, leaving a diffuse area of pigmentary and atrophic changes. (E) Diffuse areas of decreased autofluorescence that co-localized with slight reductions in sensitivity are observed. (F) Spectral-domain optical coherence tomography reveals normal macular structure with an intact outer retinal layer.

Figure 3.

(A) A montage of adaptive optics scanning laser ophthalmoscopy images from the right eye is superimposed on the fundus autofluorescence image with MP1 sensitivities. (B) Enlarged composite adaptive optics scanning laser ophthalmoscopy images of the regions outlined with a dashed white line in A reveal hyperreflective regions with dark annuli. (b1-b4) Higher-magnification views of the boxed regions of the larger montage images in A. (b1) A nearly continuous and regular cone mosaic pattern. (b2-b4) Dark areas devoid of normal wave-guiding cones and highly reflective regions are observed in the magnified image. (C) Spectral-domain optical coherence tomography at the point indicated by white dashed line in B, demonstrating dark areas correlate with the absence of an inner/outer segment junction and hyperreflective regions consistent with the dome-shaped hyperreflective deposit. The area with disrupted and/or abnormal cells in b2 is depicted by a white dashed line, and the left side of the white dashed line shows a less compact distribution of cones including dark lesions which are indicated by white lines. Through the comparison with other images, b3 may only include the disrupted and/or abnormal cells. Typical dark lesions in b2 and b4 are indicated by white lines.

Figure 4.

(A) A montage of adaptive optics scanning laser ophthalmoscopy (AO-SLO) images from the left eye is superimposed on the fundus autofluorescence image with MP1 sensitivities. (B) Enlarged composite AO-SLO images of the regions outlined with dashed white lines in A. Markers b1-b3 indicate higher-magnification views of the boxed regions of the larger montage images in A. (b1 shows grossly continuous and normal cone mosaic patterns, but b2 and b3 reveal that normal cone cells are not observed within the dark lesions because they have been damaged or lost. (C) Spectraldomain optical coherence tomography at the point indicated by the white dashed line in B shows normal macular structure with an intact outer retinal layer. Typical dark lesions in b2 and b3 are indicated by white lines.