Loss of Photoreceptor Outer Segment in Acute Zonal Occult Outer Retinopathy

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Objective: To describe retinal changes in acute zonal occult outer retinopathy (AZOOR).

Methods: We investigated retinal function and morphologic changes in 5 patients (mean age, 33.6 years) with AZOOR and acute visual field loss in 1 or more zones using Stratus optical coherence tomography, multifocal electroretinograms, full-field electroretinograms, and Goldmann perimetry.

Results: Goldmann perimetry showed enlarged blind spots of Mariotte bilaterally in 2 patients and unilaterally in 3 patients. Another scotoma was seen in the nasal paracentral area, the inferior midperiphery, and centrally. No visible retinal lesions corresponded to these scotomas except for inferior midperipheral retinal pigment epithelium atrophy and peripapillary depigmented lesions. The multifocal electroretinograms showed a markedly decreased response from the blind spots and scotomas. Optical coherence tomography showed loss or irregularity of the inner segment–outer segment line in the areas of decreased response on multifocal electroretinography and those with visual field defects. The outer nuclear layer disappeared in 2 cases. Areas of visible retinal pigment epithelium atrophy showed an irregular retinal pigment epithelial reflex, increased choroidal reflectivity, and retinal attenuation.

Conclusions: Photoreceptor outer segment dysfunction and/or degeneration seem to be the primary lesion in AZOOR. Optical coherence tomography is an important tool for detecting morphologic changes in this occult retinopathy.

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Detailed patient histories were recorded. The patients underwent examinations in which the best-corrected visual acuity (BCVA) was measured, and Goldmann perimetry (GP), fFERG, mFERG, and Stratus OCT were performed in addition to a routine oculus examination for fundus diseases. Fluorescein angiography was performed in cases 1 and 3.

Before the fFERGs and mFERGs were recorded, the pupils were fully dilated with 1% tropicamide and 2.5% phenylephrine hydrochloride. Using the protocol of the International Society for Clinical Electrophysiology of Vision (Tomey Base software; Tomey, Nagoya, Japan), we measured the rod response and the maximal response using fFERG under dark adaptation. Cone response and responses to a 30-Hz flickering stimulus were examined under light adaptation. The mFERGs were recorded with the Visual Evoked Response Imaging System (VERIS 4.1; Mayo, Nagoya). The central 50° of the fundus were recorded with the Visual Evoked Response Imaging System (VERIS 4.1; Mayo, Nagoya). The central 50° of the fundus were stimulated by an array of 103 black-and-white hexagonal elements displayed on a monochromatic monitor; the pattern alternated according to a binary m-sequence at a rate of 75 Hz. The amplifier was set at a gain of 100 K, and the bandpass filters were set from 10 to 300 Hz. Residual refractive errors were corrected to monitor fixation. Ocular responses were acquired with a bipolar contact lens (Kyoto Contact Lens, Kyoto, Japan), and the visual stimulus for each m-sequence lasted approximately 4 minutes (8 segments of 30 seconds each). The VERIS algorithm was used to extract the local retinal responses. Stratus OCT was performed after the pupils were fully dilated. The cross-sectional images were obtained by scan lines 5 to 10 mm in length that passed through the fovea, optic disc, or other areas with visual field loss. Because dysfunction of the outer neurosensory retina and RPE atrophy are suspected in AZOOR,1–3 we paid particular attention to the outer nuclear layer (ONL), IS-OS junction, and RPE when evaluating the OCT images. The integrity of the IS-OS line was evaluated as a continuous reflective line immediately anterior to the RPE reflective line, with optical empty space in between. We defined loss of the IS-OS line as the absence of a reflective line immediately anterior to the RPE line and an irregularity of the IS-OS line as interrupted or a barely visible IS-OS line.

REPORT OF CASES

Case 1

A 29-year-old woman noticed a visual field defect in her left eye in February 2001. Her symptoms gradually improved after treatment with oral prednisolone for 2 months. In August 2003, she complained of a sudden temporal visual field defect with a windmill-like photopsia in both eyes. After 2 1/2 months of treatment with prednisolone, the patient was referred to us in November 2003. Her BCVA was 1.2 bilaterally. The refractive error was −1.0 diopter OD and −2.0 diopters OS. The anterior segment was normal in both eyes. Annular depigmentation of 1 disc diameter was present around the optic disc OD and 2 disc diameters in the midperiphery superior to the macula. The GP showed enlarged blind spots bilaterally and an inferior scotoma in the left eye. Fluorescein angiography showed a window defect in the peripapillary annular depigmented lesion. The retinal arteries passing through those depigmented lesions were narrower than those in the distal. Late-phase indocyanine green angiography revealed peripapillary hypofluorescence (Figure 1). The fFERG findings were normal bilaterally, although the left eye had a slightly reduced rod response. After 1 year, it remained in a normal range. The mFERG examination showed markedly decreased responses in the peripapillary region (Figure 1E and F).

Optical coherence tomography showed loss of the IS-OS line and attenuation of the ONL but intact RPE reflectivity in the peripapillary annular depigmented lesions in both eyes (Figure 1G). The IS-OS line and the ONL, which is normally depicted as a layer of low reflectivity, were preserved in the adjacent normal temporal retina. The retinal thickness was decreased in these peripapillary regions compared with the adjacent normal retina. In the temporal crescent of the optic disc, the outer retinal structure was not identified with increased chorioidal reflectivity. The oval depigmented lesion in the midperiphery of the left eye showed retinal thinning with loss of the ONL and the IS-OS line, an irregular RPE reflex, and in-
creased choroidal reflectivity in the central area (Figure 1H).

In the periphery of the midperipheral oval lesion, although the RPE line was intact, the IS-OS line disappeared. During 31 months of follow-up, the BCVA and GP results were unchanged. Apart from these findings, results of roentgenography of the chest and magnetic resonance imaging (MRI) of the

Figure 1. Left eye of case 1. A, Fundus photographs show annular depigmentation 1 disc diameter wide around the optic disc. The left eye has an oval depigmented lesion 3 disc diameters in the midperiphery superior to the macula (white arrows). The retinal arteries passing through those depigmented areas (a, white arrowhead) are more attenuated than those in the distal portion (b, white arrowhead) of the normal retina. The yellow arrows indicate the scan lines. B, Early-phase fluorescein angiogram shows window defect in the peripapillary annular depigmented lesion. C, Late-phase indocyanine green angiogram shows hypofluorescence in the peripapillary area. D, Goldmann perimetry visual field shows enlarged blind spots and an inferior scotoma. E and F, Multifocal electroretinograms show markedly reduced responses in the area of the peripapillary lesion in 3-dimensional plots and traces. G, Optical coherence tomography (OCT) image (5-mm horizontal scan) shows that the junction between the photoreceptor inner and outer segments (IS-OS line) has disappeared (white triangles) and attenuation of the outer nuclear layer (ONL); the retina is thinner in the lesion zone. H, A 10-mm OCT image of an oval atrophic retinal lesion (the upper yellow scan line in part A) shows that the normal IS-OS line (white arrow) has abruptly disappeared in the area of the lesion (white triangles). The retinal pigment epithelial (RPE) line is preserved in the peripheral area of the atrophic lesion while the normal retinal structure and the RPE have been destroyed centrally (black triangles).
brain were normal. Test results for syphilis, cytomegalovirus, herpes zoster and simplex were negative, and antinuclear antibody and rheumatoid factor titers were normal.

Case 2

A 34-year-old man had a visual disturbance of acute onset and a temporal visual defect in his left eye associated with flashes of light, which persisted about 1 week. After 2 weeks, he was referred to us. His BCVA was 1.2 OD and 0.9 OS. The anterior segment and ophthalmoscopic findings appeared normal bilaterally. The GP revealed an enlarged blind spot and nasal paracentral scotoma in the left eye (Figure 2). On the ffERG, cone and flicker responses were severely reduced in the left eye and normal in the right eye, while the rod responses in the left eye were reduced slightly compared with the right eye, though they were in the normal range. The mfERG from the left eye showed markedly decreased responses in the paramacular area, but a normal response in the macular area (Figure 2B and C). Optical coherence tomography showed a normal IS-OS line in the macula but irregularity or loss of the IS-OS line in the paramacular and peripapillary areas that corresponded to the areas of decreased response on the mfERG and the defective visual field (Figure 2). The retinal thickness appeared normal despite the IS-OS abnormalities (Figure 2E). During 8 months’ follow-up, the BCVA OS returned to 1.2 one week after the initial visit, and the visual defect was slightly improved (Table). The brain MRI and routine blood examination findings, including a test for syphilis, were normal.

Case 3

A 40-year-old man noted abrupt darkening of the vision in his right eye 2 weeks before his initial visit. He complained of floaters and flashes of light in both eyes. His BCVA was 1.2 bilaterally. His anterior segment was normal. The fundus showed a smaller optic disc and slightly dilated retinal vein in both eyes. The GP revealed an enlarged blind spot bilaterally. The I-2-e isopter shrank to the central 5° in the right eye but assumed an arcuate shape because of an enlarged blind spot and superior depression in the left eye (Figure 3). The mfERG showed markedly decreased responses on most examined retinal areas in the right eye but mainly in the inferior and nasal retina in the left eye. These areas of decreased responses corresponded to the abnormal GP findings (Figure 3). On the ffERG, rod and maximal responses were slightly reduced in the right eye and normal in the left eye.

Optical coherence tomography with 5-mm scan showed a normal IS-OS line only in the fovea but irregularity or loss of the IS-OS line in the other areas of the right eye; in the left eye, there was loss of the IS-OS line in the area of the enlarged blind spot. Despite loss of the IS-OS line, the ONL, RPE, and retinal thickness were normal (Figure 3E). During 1 month of follow-up, the BCVA and the visual field defect were unchanged. Symptoms of photopsia persisted. The brain MRI findings were normal. Serologic test results were negative for syphilis, cytomegalovirus, and herpes zoster and simplex, and antinuclear antibody and rheumatoid factor titers were normal.

Case 4

A 34-year-old lactating woman occasionally noted a floater and light sensitivity in her left eye. After 1 month, a temporal scotoma was detected by GP examination performed by a local ophthalmologist. Two months after the onset of the initial symptoms, she came to us. Her BCVA was 1.2 bilaterally. The anterior segment and ophthalmoscopic findings appeared normal bilaterally. In her left eye, a temporal scotoma of about 15° horizontally and 30° vertically, shaped (15° × 30°) like a horse bean,
was measured by the I-4-e test object (Figure 4). Over the following 15 months, the size of the temporal scotoma enlarged to 20° × 60° (horizontal × vertical diameter). On the ffERG, all responses in the left eye were reduced to two-thirds the level of that in the right eye. The mfERG from the left eye showed markedly decreased responses in the temporal scotoma but a normal response in the macular area (Figure 4). Optical coherence tomography showed a normal IS-OS line in the macula but irregularity or loss of the IS-OS line in the nasal area, which corresponded to the areas of decreased response on the mfERG and the defective visual field. The retinal thickness, ONL, and RPE appeared normal despite the IS-OS line abnormalities.
Case 5

A 31-year-old woman who was 4 months' pregnant awoke with a central scotoma in her right eye. She noted photopsia in her right eye. When she entered into dark from a bright site, an ameboid object appeared and soon disappeared in her visual field. She was referred to us 2 weeks later. Her BCVA was 0.01 OD and 1.2 OS. The anterior segment and fundus appeared normal bilaterally. The brain MRI and routine blood examination findings, including a serologic test for syphilis, were normal. The GP showed a central scotoma in the right eye (Figure 5).

Although retrobulbar neuritis was suspected, steroid pulse treatment was not prescribed because of the pregnancy. Because her BCVA remained 0.03 for 3 months, we examined the mfERG, ffERG, and OCT findings. The mfERG revealed a severely reduced response (Figure 5). The ffERG showed flat cone and flicker responses but normal rod and maximal responses. Optical coherence tomography showed loss of the IS-OS line and attenuated ONL in the macular area. The retinal thickness decreased to 83 µm at the fovea (reference range, mean±SD, 140±19 µm) (Figure 5E).

RESULTS

All 5 patients had acute loss of 1 or more zones of the visual field unilaterally (cases 2, 4, and 5) or bilaterally (cases 1 and 3) and photopsia or light sensitivity in the areas of the symptomatic visual field defects. The BCVAs in cases 1 to 4 were 1.2 in all eyes except those of case 2, which was 0.9 at the initial visit but recovered to 1.2 one week later, while in case 5, the final BCVA increased to 0.03 from the initial 0.01. The GP showed an enlarged blind spot of Mariotte bilaterally in cases 1 and 3 and unilaterally in cases 2, 4, and 5. Another scotoma was present in the nasal para-central area in case 2 and in the inferior midperiphery in the left eye of case 1. In case 3, although a central scotoma was not detected by GP, the I-2-e isopter shrank to the central 5° in the right eye. In case 5, GP showed a central scotoma with a stimulus I-4-e. The clinical characteristics of the 5 cases are shown in the Table.

The mfERG showed a markedly decreased response from the areas of the enlarged blind spot and scotomas in all cases. The mfERG from the superior midperipheral lesion in the left eye of case 1 was unrecordable because it was outside the area examined by the mfERG. The ffERG showed decreased rod and maximal responses in the right eye of cases 3 and 4, decreased cone and flicker responses in cases 2 and 4, and flat cone and flicker responses in case 5. The ffERG showed normal responses in case 1 and the left eye of case 3. The ffERG findings are shown in the Table.

Optical coherence tomography showed loss or irregularity of the IS-OS line in the areas of decreased response on the mfERG and in the areas with visual field defects. The extent of the deteriorated IS-OS line corresponded precisely to the visual field defect or the decreased response on the mfERG. In the affected lesions with no visible fundus abnormality or occult lesions, the IS-OS line disappeared or was disrupted, but the reflectivity of the RPE appeared normal in cases 2, 3, 4, and 5. Despite the abnormalities of the IS-OS line, the ONL was preserved in these occult lesions except in case 5, who had a central scotoma. In case 1, a peripapillary depigmented annular lesion showed loss of the ONL and retinal attenuation. In the midperipheral atrophic focus, loss of the outer retinal structure and increased reflectivity of the choroid were observed.

Figure 5. Right eye of case 5. A, Goldmann perimetry visual field shows a central scotoma. B and C, Multifocal electroretinograms show markedly reduced responses on 3-dimensional plots and traces. D, Posterior fundus is normal. The yellow arrow indicates the scan line. E, Optical coherence tomography image of a 5-mm horizontal scan (the yellow scan line in part D) shows loss of the junction between the photoreceptor inner and outer segments (IS-OS line) (white triangles) and attenuation of the outer nuclear layer (ONL). The retinal thickness has decreased to 83 µm at the fovea. RPE indicates retinal pigment epithelium.
COMMENT

Optical coherence tomography revealed loss or irregularity of the IS-OS line in the occult retinal lesion, which was characterized by visual field defects and markedly decreased responses in mFERG in all patients. The areas of IS-OS line abnormality corresponded well to those of the visual field defects and decreased responses on mFERG. These data suggest that the primary lesion of AZOOR is degeneration of the photoreceptor outer segment where the electrical response to light stimulation is generated. Characteristic photopsia or photophobia in the defective visual field can be explained by an insult to the photoreceptor outer segment.

The IS-OS line, first depicted by Stratus OCT with 10 µm of axial resolution, represents the junction between the photoreceptor inner segment and the outer segment, which was further confirmed by ultrahigh-resolution OCT.1,2 In human eyes, the length of the photoreceptor outer segment, or the length between the IS-OS line and the RPE, is 30 µm at the macula and 20 µm peripheral to the macula. Theoretically, the IS-OS line is detectable with Stratus OCT if the outer segment is higher than 10 µm. Thus, loss of the IS-OS line represents loss of the outer segment and shortening less than 10 µm at the photoreceptor outer segment.

In addition to loss of the IS-OS line, the ONL was attenuated at the macula in case 5, who had a central scotoma that was examined only 3 months and 2 weeks after the onset of symptoms. Because of the short duration of the disorder, late RPE alteration may yet develop despite the attenuation of ONL on OCT.

A long-term follow-up study of AZOOR reported that the visual field defect remained in all cases during follow-up and occult lesions in the subacute or chronic phase developed pigmentary changes in the RPE and retina in 48% of 90 eyes.3 In the current series, case 1 had a depigmented peripapillary lesion and midperipheral atrophy and had had an episode of photophobia and visual field defect 1 year previously. Thus, loss of the ONL and the outer retina and RPE reflex may reflect secondary degeneration after loss of the outer segment. It is known that AZOOR begins with very minimal fundus changes and the area of involvement can often have a curvilinear edge and involve the area around the disc. With time, this area will often show pigment epithelial atrophy, intraretinal bone spicule pigmentation, and choroidal atrophy. Loss of the outer segment and secondary atrophy of the photoreceptor and RPE in our cases explain the fundus changes of the disease.

Several authors1-5 have recorded ffERGs or mfERGs in patients with AZOOR and similar diseases. These ERG examinations are valuable adjuncts in diagnosing AZOOR. The studies showed that cone function may be affected more than rod function during the early phases, but during the end stage of the disease, both cone and rod function may be severely impaired. In the current cases, there was no predisposed susceptibility between the rods or cones, and susceptibility depended on the location of the affected lesion. In case 5, the cone response was severely decreased because the posterior pole, including the macular area, was affected. Since regional loss of the photoreceptor outer segment occurs in AZOOR, the mFERG is more sensitive for detecting the affected area. In conclusion, the primary abnormality of AZOOR appears to be loss of the photoreceptor outer segment. Optical coherence tomography provides morphologic evidence in the diagnosis of this occult retinopathy.

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