Morphologic Photoreceptor Abnormality in Occult Macular Dystrophy on Spectral-Domain Optical Coherence Tomography

Sang Jun Park,1,2 Se Joon Woo,1 Kyu Hyung Park,1 Jeong-Min Hwang,1 and Hum Chung2

PURPOSE. To investigate morphologic photoreceptor layer abnormalities and their correlation with visual function in occult macular dystrophy (OMD), by using spectral-domain optical coherence tomography (SD-OCT).

METHODS. This observational case series included 18 eyes of 9 patients with OMD. All patients underwent an ophthalmic evaluation, which included a fundus examination, fluorescein angiography, full-field electroretinography (ERG), multifocal ERG, time-domain optical coherence tomography (TD-OCT), and visual field testing. Morphologic photoreceptor layer abnormalities of the retinal layers were investigated with SD-OCT. The structure–function relationship was investigated regarding visual acuity, symptom duration, and multifocal ERG results.

RESULTS. Best corrected visual acuity ranged from 20/200 to 20/20. Four patients had a symmetric decline of acuity in both eyes (20/200–20/100), and five had unilateral vision impairment (20/200–20/50). TD-OCT showed foveal thinning in all patients, but revealed no other retinal layer abnormality. In 15 eyes of 8 patients, SD-OCT demonstrated a well-defined disruption of the inner segment–outer segment (IS-OS) junction of the photoreceptors and of the Verhoeff membrane (cone outer segment tips). SD-OCT showed that three of five patients with presumed unilateral OMD had bilateral OMD after initial or follow-up examinations. Degrees of abnormality in the photoreceptor layer varied and correlated with visual acuity and symptom duration.

CONCLUSIONS. SD-OCT can demonstrate the disruption of photoreceptors in most patients with OMD and the morphologic changes on SD-OCT correlate with visual function and disease progression. These morphologic abnormalities can be an important feature and cause of vision loss in patients with OMD. (Invest Ophthalmol Vis Sci. 2010;51:3673–3679) DOI:10.1167/ iovs.09-4169

Occult macular dystrophy (OMD) is an unusual macular dystrophy characterized by a progressive decline in visual acuity with a normal fundus appearance and normal fluorescein angiography (FA) and full-field electroretinography (ERG) findings.1,2 Several studies have verified abnormal foveal function by focal ERG and multifocal (mf)ERG in OMD.1–3 Two optical coherence tomography (OCT) studies have been undertaken to find morphologic abnormalities of the retina in OMD. Kondo et al.4 showed that patients with OMD had thinner foveal thicknesses by OCT, but failed to find a correlation between foveal thickness and visual acuity. According to a recent OCT study by Brockhurst and Sandberg,5 some patients with OMD have reduced foveal thickness with thinning of the outer nuclear layer (ONL), indicating that decreased visual acuity could be explained by foveal thinning as a result of photoreceptor loss. For patients with no ONL thinning, Brockhurst and Sandberg ascribed the pathologic mechanism of OMD to be a foveal malfunction.

Recently, spectral-domain (SD)-OCT, which has better axial resolution than conventional time-domain (TD)-OCT, was introduced, and several studies revealed that SD-OCT is better able than TD-OCT to visualize retinal layers, especially the inner segment–outer segment (IS-OS) junction of photoreceptors.6,7 Therefore, we hypothesized that, by using SD-OCT, we could better visualize the proposed photoreceptor abnormalities in OMD and shed more light on the pathogenesis of OMD. In the present study, we used SD-OCT to investigate photoreceptor status in nine patients with diagnosed OMD. To the best of our knowledge, no case report or case series about photoreceptor morphologic changes in OMD has been published.

METHODS

This case series was a retrospective study of nine consecutive patients with OMD diagnosed at Seoul National University Bundang Hospital from January 2005 to January 2009. The Institutional Review Board of Seoul National University Bundang Hospital approved the study.

The diagnostic criteria of OMD were a history of progressive decline in visual acuity, a normal fundus, normal findings in FA, a normal full-field standard ERG, and an abnormal mfERG amplitude. A normal fundus and a normal FA mean no abnormal pigmentation or depigmentation in the macula, normal fluorescein pattern in the early- and late-phase of FA, no vascular abnormality in the posterior pole and peripheral retina, and normal optic disc contour, cupping, color, and size.

In accordance with the Declaration of Helsinki, all patients provided informed consent after obtaining a full explanation of the examinations, and all underwent a full ophthalmic evaluation that included an ocular motor examination, a slit lamp examination, a manifest refraction, a fundus examination, a cycloplegic refraction, FA, full-field standard ERG,8 mfERG (VERIS II; ElectroDiagnostic Imaging 45 Inc, San Francisco, CA), and TD-OCT (Stratus OCT, Carl Zeiss Meditec, Inc., Dublin, CA).

Visual field testing was conducted with a retinal perimeter (Humphrey Field Analyzer; Carl Zeiss Meditec, Inc.) in seven patients and by...
Goldmann perimetry in two (cases 7 and 9). Abnormalities of foveal amplitude by mfERG were defined when local amplitudes were significantly lower than those of an age-matched normal population.

SD-OCT was performed in all patients: six (cases 1, 2, 3, 4, 5, and 9) by Cirrus OCT (Carl Zeiss Meditec, Inc.), two (cases 6 and 8) by scanning laser ophthalmoscope/OCT (SLO/OCT; Ophthalmic Technologies, Inc., Toronto, ON, Canada), and one (case 7) by Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany). Six to 12 months after the initial examination, follow-up SD-OCT with Spectralis was performed in three patients (cases 2, 6, and 7).

In SD-OCT images, the boundary between the photoreceptor inner and outer segments is visualized as a hyperreflective layer, and the dark band above the photoreceptor inner segments in OCT images is defined as the outer nuclear layer (ONL). The two reflective lines under the IS-OS junction of the photoreceptors indicate the Verhoeff membrane or cone outer segment tips (COST) and retinal pigment epithelium (RPE). In normal eyes, these layers were clearly visible in the SD-OCT images (Figs. 3A, 3B). A retina specialist (SJW) and an expert in OCT interpretation (SJP) inspected the SD-OCT images thoroughly in all nine patients, while magnifying the retinal structures, especially the photoreceptor layers.

To evaluate the structure-function relationship, we obtained quantitative data on structural abnormalities by measuring the horizontal length of photoreceptor disruption within the central 3 mm of macula on the horizontal scan of SD-OCT images. We then analyzed the correlation of the photoreceptor disruption with visual acuity, amplitudes of mfERG, and symptom duration using commercial software (SPSS v.15.0; SPSS Inc., Chicago, IL).

RESULTS

Seven patients were men and two were women, ranging in age from 24 to 48 years (mean, 33.3). Eight patients did not report a family history of similar visual problems, and hence, these cases were considered sporadic. Only one patient (case 2) was autosomal dominant. Best corrected visual acuities of patients ranged from 20/200 to 20/20. Four (cases 1, 2, 3, and 9) reported a symmetric decline in visual acuity in both eyes, and five had unilateral deterioration of vision. All patients had neither strabismus nor a history of surgery for strabismus. No patients had anisometropia (>2.0 D) or extreme hyperopia (>5.00 D) or myopia (<−6.00 D). All had a history of normal vision in both eyes and reported the deterioration of vision after certain time points in their lives. No patient had afferent pupillary defect and abnormality in the visual pathway.

Responses from the central retina in the mfERG were depressed in all patients except in the left eye of one patient (case 8; Fig. 1). To clarify the depression in the central retina in our patients, we grouped the mfERG responses as a function of eccentricity (5 rings), as shown in Figure 1.

Four patients had a deep central scotoma within 5° of fixation in both eyes (cases 1, 2, 3, and 9; Figs. 2E, 2G). One patient (case 4) had normal visual fields on Humphrey perimetry but subjectively reported a unilateral central scotoma. Another (case 5) had bilateral, small paracentral scotomas; one (case 6) had a unilateral central scotoma in the eye with poor vision, but normal visual fields in the opposite eye; and one (case 8) had a deep central scotoma and poor visual acuity (20/50) in the right eye and normal visual fields and visual acuity in the left eye at the time of presentation. Six months later, a visual field test showed a new central scotoma in the right eye that suggested a progression of disease.

TD-OCT showed reduced foveal thickness in our series (mean, 177.6 ± 18.9 μm, 8 patients, 15 eyes), but did not reveal a structural abnormality in the retinal layers, such as an attenuation of the ONL.

SD-OCT demonstrated morphologic changes in the photoreceptor layers. Of the nine patients, eight showed disruption in the photoreceptor layers in both eyes. The other retinal layers, including the ONL and RPE were normal in all patients. In case 1, SD-OCT showed a large nonvisualization of the IS-OS boundary line in the central retina. The patients in cases 2 (Figs. 3C, 3D) and 3 also manifested a dotted, obscured photoreceptor layer in the central retina. In patients with presumed unilateral OMD (cases 4 and 5), SD-OCT showed bilateral focal disruptions of the IS-OS junction in the photoreceptors. These disruptions were more noticeable in the severely affected eyes with worse visual acuity (Figs. 3G, 3H). However, in cases 6, 7, and 8, in which there was an asymmetric decline in visual acuity, SD-OCT revealed a disruption of the photoreceptor layer only in the eyes with worse visual acuity (Figs. 4A, 4B, 4E, 4F).

On follow-up examination of three patients (cases 2, 6, and 7), there were no changes in subjective symptoms, including...
However, at the 1-year follow-up, SD-OCT in one patient (case 6) showed new structural abnormalities that had been absent in the initial OCT images: focal disruption in the photoreceptor IS-OS junction, disruption of the Verhoeff membrane, and corresponding external limiting membrane (ELM) downsloping caused by the decreased thickness of the photoreceptor layers (Figs. 4E, 4F). Therefore, in case 6, a patient with presumed unilateral OMD turned out to have bilateral OMD. In cases 2 (Figs. 3E, 3F) and 7 (Figs. 4G, 4H), the patients showed no definite changes on follow-up SD-OCT images.

The structure–function relationship in OMD patients is illustrated in Figures 5 and 6. Visual acuity and symptom duration in the eyes with photoreceptor disruption correlated significantly with the severity of the photoreceptor disruption.
shown on SD-OCT (visual acuity, Spearman’s correlation coefficient = 0.846, $P < 0.001$; symptom duration, Spearman’s correlation coefficient = 0.864, $P < 0.001$; Table 1, Figs. 5, 6). However, the response densities from the innermost eccentric ring of the mFERG had no significant correlation with the size of photoreceptor disruption.

SD-OCT revealed morphologic abnormalities in the Verhoeff membrane (cone outer segment tips), as well as in the IS-OS junction of the photoreceptors. Cirrus OCT images did not visualize (case 1) or showed disruption (cases 2, 3, 4, and 5) of the Verhoeff membrane corresponding to the abnormality in the IS-OS junction of the photoreceptors. SLO/OCT and Spectralis OCT provided more detailed images of retinal layers than did Cirrus OCT, and they clearly showed obscuration of the Verhoeff membrane under the disrupted IS-OS junction. This abnormality was particularly evident in one patient (case 2), in whom Spectralis OCT (Figs. 3E, 3F) revealed more distinct disruptions of the photoreceptor IS-OS junction and Verhoeff membrane than did Cirrus OCT (Figs. 3C, 3D). The ELM was also obscured, and there was thinning of the IS and OS of the photoreceptors. There were no discernible abnormalities in the other retinal layers of the macula, including the ONL and RPE.

The patient in case 8, who had been considered to have unilateral OMD, experienced visual deterioration of the previously unaffected left eye (visual acuity from 20/20 to 20/50) 6 months later, which indicated the progression of unilateral to bilateral OMD, as in case 6.
### TABLE 1. Patient Demographic and Clinical Features

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Symptom Duration</th>
<th>Laterality</th>
<th>BCVA</th>
<th>SD-OCT</th>
<th>Foveal Thickness SD-OCT* (µm)</th>
<th>Foveal Thickness TD-OCT† (µm)</th>
<th>PR Disruption Size‡ (µm)</th>
<th>R1 Amp in mfERG§ (nV/deg²)</th>
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<td>20/200</td>
<td>210</td>
<td>203</td>
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**Notes:**
- BCVA, best corrected visual acuity; NA, data not available; No, no photoreceptor disruption in SD-OCT.
- * Cirrus: Cirrus OCT, Carl Zeiss Meditec Inc., Dublin, CA; SLO/OCT: Ophthalmic Technologies Inc., Toronto, ON, Canada; Spectralis: Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany.
- † Stratus OCT, Carl Zeiss Meditec Inc.
- ‡ Size of photoreceptor disruption within the central 3 mm of macula from a horizontal SD-OCT scan.
- § R1 (innermost ring) amplitude of the mfERG (Fig. 1).
- || Retinal thickness of central 1-mm zone.
- ‖ Retinal thickness of central 6-mm zone.
The remaining patient (case 9) had no disruption of the retinal layers, including the photoreceptors, ELM, and RPE in both eyes (Figs. 3I, 3J).

DISCUSSION

The structural abnormalities of the photoreceptor layers that are undetectable by TD-OCT were visualized by SD-OCT in most OMD patients. The photoreceptor layer was disrupted in the majority (8/9, 88.9%) of patients to various extents and degrees of severity. Furthermore, in eight patients showing photoreceptor disruption, the degree of photoreceptor abnormality correlated with the severity of vision deterioration, which demonstrates that the decline in visual acuity and foveal dysfunction is the result of structural disruption of the photoreceptor layer. The correlation between symptom duration and the degree of structural abnormalities explains the characteristic feature of OMD: progressive decline in visual acuity.1–5 Follow-up SD-OCT also revealed the progressive and bilateral nature of OMD in one of three patients.

Brockhurst and Sandberg7 examined the retinal layers by TD-OCT in OMD patients. They found thinning of the retina, especially the ONL in the fovea in OMD patients, and suggested that photoreceptor loss is the cause of visual impairment and that it can be predicted by OCT. In our study, although TD-OCT demonstrated foveal thinning in all patients, as has been reported,4,5 in none of our cases did we find ONL attenuation by TD-OCT or SD-OCT. On the other hand, we found that the foveal thinning in OMD was mostly due to the thinning of the IS and OS of the photoreceptors. Since OMD may include several disease entities,3,13,14 we and Brockhurst and Sandberg7 might have studied the different types of OMD. However, we are presenting morphologic evidence of photoreceptor abnormalities that Brockhurst and Sandberg proposed as a possible reason for the visual impairment in OMD patients.

By using a higher axial resolution and scan velocity of SD-OCT, investigators in several studies have already shown the structural abnormalities in the photoreceptor layer and their correlations with the functional status in various diseases (i.e., epiretinal membrane,15 macular hole,16 retinal detachment,17 retinitis pigmentosa,18 and hydroxychloroquine retinopathy19), as in our present study.

In addition, SD-OCT can visualize not only photoreceptor IS-OS junctional layers but also the Verhoeff membrane which corresponds to the boundary of the cone outer segment tips.9,10,12,19 In a recent study, Srinivasan et al.5 showed that the Verhoeff membrane corresponds to the photoreceptor outer segment tips. In our cases, SD-OCT revealed disruption in the Verhoeff membrane that corresponded to the area showing disruption of the IS-OS junction of the photoreceptors.

Some groups have reported that most OMD patients show bilateral visual decline. Five patients in our series (cases 4, 5, 6, 7, and 8) reported only unilateral deterioration of vision and had normal (20/20); cases 4, 5, 6, and 8) or near normal (20/25; case 7) visual acuity in the eyes with better vision. However, SD-OCT showed bilateral morphologic changes in the photoreceptor layers in cases 4 and 5, and in case 6, follow-up SD-OCT revealed new morphologic abnormalities in the photoreceptor layers in the eye with normal vision on initial examination. In addition, the patient in case 8 experienced visual deterioration in the previously unaffected left eye during follow-up. The observed morphologic abnormalities in eyes with normal visual acuity indicate that these eyes were at a subclinical stage and the patients would probably progress to bilateral OMD, although the abnormal findings in the photoreceptor layers were more distinct in the eyes with reduced vision. It is also noteworthy that deterioration of vision was less severe in these asymmetric cases than in the symmetric cases (20/50–20/70 in cases 4, 5, 6, 7, and 8 and 20/100–20/200 in cases 1, 2, 3, and 9), which also illustrates the progressive nature of OMD.

We could not find a morphologic abnormality in the photoreceptors in one patient (case 9). Several researchers have suggested that OMD includes various disease entities with different genetic bases and autoimmune pathophysiology.5,13,14 The heterogeneous pathogenesis of OMD could be one explanation of the dissimilarity in SD-OCT findings in our case series. Second, although SD-OCT provides better resolution and retinal visualization, a very small morphologic change in photoreceptors could have been undetected by SD-OCT. A future, new-generation OCT may be able to show a novel abnormality in the photoreceptor layer in OMD patients that cannot be detected by current SD-OCT technology.

Because our study was basically a cross-sectional study, it is hard to say whether the functional or the structural abnormality occurred first. Structural abnormality may precede functional abnormality, as in the patient in case 6, who had a new structural abnormality without functional impairment on follow-up examination. However, the patient in case 9 had only functional impairment without morphologic abnormality, showing that functional impairment may precede morphologic abnormality.

Up to now, mfERG has been known to be the most valuable instrument for revealing the localized central retinal dysfunction in OMD.3,21,22 However, mfERG has several limitations: Experienced physicians and a normative database in the laboratory are necessary for accurately interpreting the reduced amplitude in mfERG as abnormal data. In addition, mfERG has the potential for error in analyzing the topographic data because of the eccentric fixation, especially in patients with poor central vision such as OMD patients have, and it has relatively low spatial resolution.23 We think that those are the possible reasons that there was no correlation between the mfERG amplitudes and the severity of photoreceptor disruption in our results. SD-OCT, on the other hand, has advantages over mfERG, in that it is easy to interpret, causes no concern about eccentric fixation, and has high spatial resolution and good repeatability. Thus, we think that SD-OCT is indispensable for the diagnosis and evaluation of OMD.

There are limitations in our study. First, we used three different types of SD-OCT that yielded inconsistent data on image quality and foveal thickness. Second, we had only three cases with available short-term follow-up SD-OCT data. As the SD-OCT has been introduced recently, we could not obtain long-term follow-up images for all OMD patients in the present study. Future long-term SD-OCT studies of OMD patients may elucidate the disease’s characteristics and pathogenesis.

In conclusion, SD-OCT can show morphologic changes in the photoreceptor layer in most patients with OMD, and these structural changes detected by SD-OCT can predict the functional status and progression in patients with OMD. This new finding may not only facilitate clinical diagnosis of OMD, but also may accelerate the elucidation of the etiology of OMD.

References


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