**IMPORTANCE** The value of imaging modalities remains unknown in occult macular dystrophy (OMD) because they have not been compared in previous studies to our knowledge. Furthermore, because most OMD imaging studies have been limited to a single imaging modality, information about retinal pathologic characteristics simultaneously obtained using multimodal imaging has not been provided for OMD to date.

**OBJECTIVES** To investigate the clinical and retinal pathologic features of OMD using multimodal imaging and to assess their value in OMD.

**DESIGN AND SETTING** Retrospective imaging study in an academic research setting.

**PARTICIPANTS** Forty-six eyes from 25 Korean patients diagnosed as having OMD.

**INTERVENTIONS** Detailed retinal morphologic abnormalities were evaluated using spectral-domain optical coherence tomography (SD-OCT), fundus infrared (IR) reflectance, autofluorescence (AF), and IR-AF imaging.

**MAIN OUTCOME MEASURES** Quantitative and qualitative morphologic features were evaluated for their association with visual and electrophysiologic function.

**RESULTS** All eyes showed abnormal outer retinal structures in the macula as assessed by SD-OCT. Abnormal round dark macular areas were detected with dark fundus IR reflectance imaging in 36 of 46 eyes (78%). This area corresponded to the area of photoreceptor disruption revealed by SD-OCT and was associated with visual acuity, perimetric results, and multifocal electroretinography responses. In 6 of 18 eyes (33%), IR-AF imaging showed central hypoautofluorescence within normal hyperautofluorescence. In 2 of 18 eyes (11%), fundus AF showed weak hyperautofluorescence. Progression of photoreceptor disruption was identifiable on SD-OCT, and hyporeflectance in IR images became more evident in eyes showing OMD progression.

**CONCLUSIONS AND RELEVANCE** Across multimodal imaging, SD-OCT was most valuable for diagnosis and for determining the outer retinal pathologic features of OMD. Outer retinal pathologic changes manifested different morphologic abnormalities, indicating that OMD is a heterogeneous disease. Fundus IR reflectance imaging is an easy and helpful adjunct for the diagnosis and detection of OMD progression.
Oc
cult macular dystrophy (OMD) is an uncommon he-
reditary macular dystrophy characterized by progres-
seive visual decline and abnormal macular function
found on focal macular electroretinography (ERG) in the
absence of full-field ERG or visible fundus abnormalities.1,2 Re-
gent genetic studies identified mutations in the RPL11 gene
(OMIM 608581) in Japanese families with OMD3 and in aspo-
radic patient.4 Previous studies1,2,5-10 described the physi-
ologic and structural abnormalities of the disease using mul-
tifocal ERG (mfERG) and spectral-domain optical coherence
tomography (SD-OCT). Several studies5,8-10 have shown mor-
phologic deformity of the photoreceptor layer using SD-OCT,
suggesting that photoreceptor abnormality is the main pre-
sentation of OMD. In addition to OCT, the results of a recent
study11 suggested that fundus autofluorescence (AF) is use-
ful for the differential diagnosis of OMD.

Fundus infrared (IR) reflectance and IR-AF imaging have
been used to delineate structural abnormalities, providing
novel information on retinal pathologic features in various
macular and retinal diseases.12-18 The value of these imaging
modalities remains unknown in OMD because they have not
been compared in previous studies to our knowledge. Fur-
thermore, because most OMD imaging studies have been lim-
ited to a single imaging modality, information about retinal
pathologic characteristics simultaneously obtained using mul-
timodal imaging has not been provided for OMD to date.

In this study, we aimed to investigate the clinical and reti-
nal pathologic features of Korean patients with OMD using mul-
timodal imaging, including IR-AF, SD-OCT, fundus IR reflec-
tance, and short-wavelength AF (SW-AF), and to correlate them
with functional factors to determine the structure-function re-
lation. We evaluated the usefulness of multimodal imaging
to diagnose OMD and to indicate visual and electrophysi-
ologic function. Notably, our study investigated the potential
use of fundus IR reflectance imaging in OMD, which has not
been evaluated in earlier studies to our knowledge.

Methods

Patients and Diagnosis
The medical records of 25 patients diagnosed as having OMD
at Seoul National University Bundang Hospital, Seongnam, Ko-
rea, between January 1, 2008, and January 1, 2012, were ret-
rospectively reviewed. The diagnostic criteria for OMD were
the following: (1) a progressive decline in visual acuity; (2) no
abnormal findings on fundus photography, fluorescein angi-
ography, or full-field standard ERG; and (3) a reduced foveal
mfERG response, defined as local amplitude significantly lower
than that of an age-matched healthy population. The institu-
tional review board of Seoul National University Bundang
Hospital approved this study, and our study complied with the De-
claration of Helsinki. Informed consent was obtained from all
patients before genetic analysis.

Multimodal Imaging
All patients underwent complete ophthalmic examinations,
including full-field ERG, fundus photography, fluorescein
angiography, best-corrected visual acuity, slitlamp and fun-
dus examination, and mfERG (VERIS II; ElectroDiagnostic
Imaging 45 Inc). Full-field ERG was performed using the pro-
cedures proposed by the International Society for Clinical
Electrophysiology of Vision, and mfERG was performed
using 61 scaled hexagons and procedures that conformed to
society guidelines. Visual field testing was conducted with a
Humphrey automated perimeter. High-resolution macula
imaging was performed using combined confocal scanning
laser ophthalmoscopy and SD-OCT (Spectralis OCT; Heidel-
berg Engineering). Fundus IR reflectance imaging (λ = 830
nm; field of view, 30° × 30°; and image resolution, 768 × 768
pixels) was obtained in all patients with simultaneous
SD-OCT imaging (λ = 870 nm; acquisition speed, 40 000
A-scans per second; image depth, 1.8 mm; and digital depth
resolution, approximately 3.5 µm per pixel).13 Short-
wavelength AF imaging, which was obtained using a 488-nm
wavelength of light with a barrier filter for detection of the
emitted light above 500 nm, was performed in 18 eyes. Infra-
red AF was obtained at a 787-nm excitation wavelength with
a barrier filter for detection of emitted light above 810 nm in
18 eyes. Automated eye tracking and image alignment based
on combined confocal scanning laser ophthalmoscopy
images enabled the correlation of the ophthalmoscopy
images and SD-OCT findings.

Image Analysis
All images were independently reviewed in a masked man-
ner by 2 of us who are retina specialists (S.J.A. and S.J.W.). Any
discrepancies were resolved by consensus. The SD-OCT im-
ages of all patients were investigated for abnormal findings for
structural integrity and reflectivity in each layer of the retina.
The digital caliper tool built into the OCT system was used to
measure the thickness of the outer nuclear layer (between the
internal limiting membrane and the external limiting mem-
brane [ELM]),19,20 thickness of the photoreceptor inner seg-
ment–outer segment (IS-OS) (between the ELM and the reti-
al pigment epithelium [RPE]),19 and foveal thickness (from
the internal limiting membrane to the RPE)19 at the central fo-
evea (Figure 1A).

A pixel-to-pixel correlation of combined confocal scan-
ing laser ophthalmoscopy and SD-OCT findings was per-
formed in all patients using available software (Heidelberg Eye
Explorer, version 1.6.2.0; Heidelberg Engineering). Abnormal
findings revealed by IR were correlated with structural changes
on SD-OCT. We matched the mfERG data with IR images by
merging mfERG trace arrays with fundus IR reflectance
images. Infrared images in which the field of view was 20° × 20°
were used for this process. The circle demarcating the central
20° visual field on mfERG trace arrays was exactly superim-
posed on the fundus IR reflectance images using software
(Adobe Photoshop CS3, version 10.0; Adobe Systems, Inc). By
combining the 2 images, we were able to investigate the elec-
trophysiologic properties of the abnormal retinal areas on IR
images.

The main obstacle to evaluating abnormalities in IR-AF
imaging is the diversity of IR-AF.18 Therefore, we evaluated
the macular area in IR-AF images of each patient with OMD

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by comparing the images of 2 age-matched healthy control subjects in which background fluorescence of the IR-AF images, except the macula, were similar. An abnormality in SW-AF was defined as the presence of hyperfluorescent lesions.

**Data Analysis**

Comparative analyses were performed using the Mann-Whitney test for continuous variables and the Fisher exact test for dichotomous variables. The agreement of fundus IR reflectance with other imaging modalities (IR-AF and SD-OCT) was evaluated. The κ statistic was calculated as an indicator of this agreement. Using linear regression analysis, the correlations of quantitative and qualitative morphologic features on SD-OCT were evaluated for their association with best-corrected visual acuity, the mean P1 amplitude of the involved segments on mERG, and the mean threshold value at the central 4 points in the total deviation numeric plot of the Humphrey visual field. Disease progression was evaluated by comparing the SD-OCT and IR images between the initial visit and the final visit in patients who were followed up for at least 12 months.

Continuous values are expressed as means (SDs). P < .05 was considered statistically significant. Statistical analyses were performed using available software (SPSS for Windows, version 17.0; SPSS Inc).

**Results**

The demographics of 25 patients (14 men and 11 women) are summarized in Table 1. Their mean age was 33.5 years (age range, 8–71 years). All patients reported good and symmetrical visual acuity in both eyes before the onset of visual de-
cline. Asymmetrical visual decline occurred in 11 patients, including 4 patients with unilateral involvement, while 14 patients reported symmetrical visual decline in both eyes. Best-corrected visual acuity in the affected eye ranged from 20/200 to 20/15. All patients denied any history of amblyopia, trauma, or extreme refractive errors (hyperopia exceeding +3.00 diopter [D] or myopia exceeding −6.00 D). Our study included 10 patients showing autosomal dominant inheritance from 6 families. Of 25 patients, 6 (patients 2, 7, 8, 10, 11, and 25) from 3 families with OMD had a known mutation of the RP1L1 gene, c.133 C>T (p.Arg45Trp), as determined by direct sequencing.

**SD-OCT Findings**

The abnormal findings of multimodal imaging in patients with OMD are summarized in Table 2. The qualitative features of OMD on SD-OCT (Figure 1) can be summarized as the following 4 findings based on disease severity: (1) central loss of the OS-RPE interdigitation zone (also termed cone OS tips),

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Laterality/Symptom Duration/Inheritance</th>
<th>Best-Corrected Visual Acuity</th>
<th>Fundus IR Reflectance Imaging</th>
<th>SW-AF</th>
<th>IR-AF</th>
<th>SD-OCT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>OD/OS</td>
<td>OD/OS</td>
<td>OD</td>
<td>OS</td>
<td>OD</td>
<td>OS</td>
<td>OD</td>
</tr>
<tr>
<td>1/M/24</td>
<td>OU/10 y/AD</td>
<td>20/100</td>
<td>20/100</td>
<td>LR</td>
<td>LR</td>
<td>Hyper NA</td>
</tr>
<tr>
<td>2/M/38</td>
<td>OU/10 y/AD</td>
<td>20/200</td>
<td>20/200</td>
<td>LR</td>
<td>LR</td>
<td>None None</td>
</tr>
<tr>
<td>3/M/29</td>
<td>OU/1 y/sporadic</td>
<td>20/20</td>
<td>20/70 None LR NA NA</td>
<td>1</td>
<td>1,3</td>
<td>65</td>
</tr>
<tr>
<td>4/M/36</td>
<td>OU/1 y/sporadic</td>
<td>20/20</td>
<td>20/80 None LR None None</td>
<td>1,2</td>
<td>1-4</td>
<td>105</td>
</tr>
<tr>
<td>5/F/33</td>
<td>OU/2 y/sporadic</td>
<td>20/120</td>
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<td>1,2</td>
<td>84</td>
</tr>
<tr>
<td>6/F/37</td>
<td>OU/5 y/sporadic</td>
<td>20/100</td>
<td>20/22 None None NA NA</td>
<td>1</td>
<td>1</td>
<td>66</td>
</tr>
<tr>
<td>7/M/21</td>
<td>OU/9 y/AD</td>
<td>20/60</td>
<td>20/60 LR LR None Hypo</td>
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<td>1-4</td>
<td>89</td>
</tr>
<tr>
<td>8/M/8</td>
<td>OU/5.5 y/AD</td>
<td>20/100</td>
<td>20/150 LR NA NA</td>
<td>1-4</td>
<td>1-4</td>
<td>80</td>
</tr>
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<td>9/M/11</td>
<td>OU/2 y/sporadic</td>
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<td>20/50 LR LR NA NA</td>
<td>1-3</td>
<td>1-3</td>
<td>38</td>
</tr>
<tr>
<td>10/M/34</td>
<td>OU/6 y/AD</td>
<td>20/200</td>
<td>20/200 LR LR None None</td>
<td>1-4</td>
<td>1-4</td>
<td>70</td>
</tr>
<tr>
<td>11/F/36</td>
<td>OU/2 y/AD</td>
<td>20/50</td>
<td>20/40 LR LR NA NA</td>
<td>1-3</td>
<td>1-3</td>
<td>83</td>
</tr>
<tr>
<td>12/F/47</td>
<td>OU/1 y/unknown</td>
<td>20/40</td>
<td>20/60 LR LR NA NA</td>
<td>1,2</td>
<td>1-3</td>
<td>107</td>
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<tr>
<td>13/F/50</td>
<td>OD/1 y/sporadic</td>
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<td>20/30 LR None None None</td>
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<td>None</td>
<td>94</td>
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<tr>
<td>14/M/21</td>
<td>OD/6 mo/AD</td>
<td>20/30</td>
<td>20/30 LR None None None</td>
<td>1-3</td>
<td>1-3</td>
<td>80</td>
</tr>
<tr>
<td>15/F/15</td>
<td>OD/1 y/sporadic</td>
<td>20/30</td>
<td>20/20 LR None NA NA</td>
<td>1,2</td>
<td>None</td>
<td>62</td>
</tr>
<tr>
<td>16/M/24</td>
<td>OD/2 y/sporadic</td>
<td>20/80</td>
<td>20/100 LR NA NA</td>
<td>1,2</td>
<td>1-3</td>
<td>74</td>
</tr>
<tr>
<td>17/F/40</td>
<td>OD/5 y/sporadic</td>
<td>20/100</td>
<td>20/100 LR None NA NA</td>
<td>1,2</td>
<td>1-2</td>
<td>69</td>
</tr>
<tr>
<td>18/F/42</td>
<td>OD/3 y/sporadic</td>
<td>20/60</td>
<td>20/60 None None NA NA</td>
<td>1-3</td>
<td>1-3</td>
<td>48</td>
</tr>
<tr>
<td>19/F/26</td>
<td>OD/4 mo/AD</td>
<td>20/200</td>
<td>20/25 LR NA NA</td>
<td>1-3</td>
<td>1,2</td>
<td>59</td>
</tr>
<tr>
<td>20/M/19</td>
<td>OD/3 y/AD</td>
<td>20/100</td>
<td>20/100 LR NA NA</td>
<td>1-4</td>
<td>1-4</td>
<td>88</td>
</tr>
<tr>
<td>21/F/58</td>
<td>OD/3 y/unknown</td>
<td>20/200</td>
<td>20/30 LR LR None Hypo</td>
<td>1-3</td>
<td>1-3</td>
<td>49</td>
</tr>
<tr>
<td>22/M/71</td>
<td>OD/2 y/sporadic</td>
<td>20/40</td>
<td>20/25 None None NA NA</td>
<td>1</td>
<td>1</td>
<td>99</td>
</tr>
<tr>
<td>23/F/53</td>
<td>OS/1 y/sporadic</td>
<td>20/20</td>
<td>20/100 LR None None None</td>
<td>1,2</td>
<td>None</td>
<td>82</td>
</tr>
<tr>
<td>24/M/14</td>
<td>OS/4 y/sporadic</td>
<td>20/15</td>
<td>20/40 None None NA NA</td>
<td>1</td>
<td>1</td>
<td>115</td>
</tr>
<tr>
<td>25/M/51*</td>
<td>OU/3 y/AD</td>
<td>20/200</td>
<td>20/40 LR LR NA NA</td>
<td>1,2</td>
<td>1-2</td>
<td>69</td>
</tr>
</tbody>
</table>

Abbreviations: AD, autosomal dominant; AF, autofluorescence; Hyper, hyperfluorescence; Hypo, hypofluorescence; IR, infrared; IR-AF, infrared reflectance autofluorescence; IS-OS, inner segment–outer segment; LR, low reflectance; NA, not applicable; SD-OCT, spectral-domain optical coherence tomography; SW-AF, short-wavelength autofluorescence.

*Patient 25 had a cataract in the right eye, which affected visual acuity.

Table 2. Abnormal Findings of Occult Macular Dystrophy in Multimodal Imaging

<table>
<thead>
<tr>
<th>Abnormal Finding</th>
<th>No./Total No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD-OCT</td>
<td></td>
</tr>
<tr>
<td>Central loss of the OS-RPE interdigitation zone</td>
<td>46/46 (100)</td>
</tr>
<tr>
<td>Low reflectivity of the IS-OS junction</td>
<td>39/46 (85)</td>
</tr>
<tr>
<td>Discontinuous IS-OS junction</td>
<td>29/46 (63)</td>
</tr>
<tr>
<td>Disruption of the ELM</td>
<td>12/46 (26)</td>
</tr>
<tr>
<td>Fundus IR reflectance imaging</td>
<td></td>
</tr>
<tr>
<td>Focal areas with low reflectance around the fovea</td>
<td>36/46 (78)</td>
</tr>
<tr>
<td>SW-AF</td>
<td></td>
</tr>
<tr>
<td>Weak hyperautofluorescence</td>
<td>2/18 (11)</td>
</tr>
<tr>
<td>IR-AF</td>
<td></td>
</tr>
<tr>
<td>Central hypofluorescence within normal hyperautofluorescence</td>
<td>6/18 (33)</td>
</tr>
</tbody>
</table>

Abbreviations: ELM, external limiting membrane; IR, infrared; IR-AF, infrared reflectance autofluorescence; IS-OS, inner segment–outer segment; OS-RPE, outer segment–retinal pigment epithelium; SD-OCT, spectral-domain optical coherence tomography; SW-AF, short-wavelength autofluorescence.
(2) low reflectivity of the IS-OS junction, (3) discontinuous IS-OS junction, and (4) disruption of the ELM. In order of frequency, central loss of the OS-RPE was noted in all 46 patients (100%), followed by low reflectivity of the IS-OS junction around the macula in 39 patients (85%), discontinuous IS-OS junction in 29 patients (63%), and disruption of the ELM in 12 patients (26%). In order of severity, the following 3 patterns of retinal involvement were observed in patients with OMD: (1) OS-RPE only, (2) OS-RPE plus IS-OS, and (3) OS-RPE plus IS-OS plus ELM involvement. However, no patients showed abnormal findings in the RPE layer on SD-OCT.
ings on SD-OCT included thinning of the following: central fovea (161.0 [32.1] μm, representing 80.5% of the mean thickness in healthy eyes of unilateral cases), photoreceptor layer (62.1 [13.7] μm, representing 75.1% of the mean thickness), and outer nuclear layer (75.8 [17.3] μm, representing 78.1% of the mean thickness).

A significant correlation was found between best-corrected visual acuity and ELM, IS-OS, OS-RPE, and the number of involved retinal layers (Pearson correlation coefficient, r = 0.457; P = .001) (Figure 2A). The thickness of the photoreceptor IS-OS (r = −0.540, P < .001) (Figure 2B), but not of the central fovea (r = −0.196, P = .19) (Figure 2C) or the outer nuclear layer (r = −0.217, P = .15) (Figure 2D), showed a significant correlation with visual acuity. Furthermore, a significant correlation was found between photoreceptor IS-OS thickness and the mean threshold value at the central 4 points on Humphrey perimetry (r = 0.464, P = .02) (Figure 2E) or the mean P1 amplitude on mfERG (r = 0.434, P = .03) (Figure 2F).

Fundus IR Reflectance Imaging
A round dark area with low fundus IR reflectance that was mostly centered on the fovea was observed in 36 of 46 eyes (78%) (Figure 3). In all patients with dark areas on fundus IR reflectance imaging, the area corresponded to low reflectivity or discontinuity in the IS-OS junction on SD-OCT (Figure 3D). The degree of low reflectivity on fundus IR reflectance imaging and corresponding changes on SD-OCT are shown in Figure 4. As the areas with low reflectivity on fundus IR reflectance imaging become more evident from Figure 4A to C, the IS-OS junction and photoreceptor OS appears more disrupted, and the reflectivity of the IS-OS junction layer seems more diminished. Compared with the right eye, the left eye of patient 8 (Figure 4C) had worse visual acuity, a more prominent decrease in fundus IR reflectance, and a lower reflectivity of the IS-OS junction (Figure 4B). The κ statistics between fundus IR reflectance imaging and other diagnostic tests were 0.642, 0.439, 0.179, and 0.000 for the discontinuous IS-OS junction, low reflectivity of the IS-OS junction, disruption of the ELM, and central loss of the OS-RPE, respectively. Among SD-OCT findings, discontinuous IS-OS junction, low reflectivity of the IS-OS junction, and disruption of the ELM were significantly associated with the presence of abnormal lesions on fundus IR reflectance imaging (P < .001, P < .003, and P < .03, respectively, by Fisher exact test).

The clinical features were compared between patients with and without abnormal lesions on fundus IR reflectance imaging. The mean (SD) visual acuity was significantly worse in eyes with an abnormal fundus IR reflectance finding than in those without (0.59 [0.28] vs 0.31 [0.27] log minimum angle of resolution, P = .01 by Mann-Whitney test) (Table 3). The mean (SD) foveal (ring 1) P1 amplitude on mfERG in eyes with notably decreased fundus
IR reflectance was 89.9 (28.7) nV per degree squared, and the mean (SD) amplitude in eyes without an IR hyporeflective lesion was 128.3 (25.5) nV per degree squared, which represents a statistically significant difference (P = .008). The combined fundus IR reflectance and mfERG images revealed that the amplitudes of these segments in a more hyporeflective area on fundus IR reflectance imaging were lower than those in segments with less hyporeflective infrared reflectance (D). The circle in both images indicates the central 10° of the retina. The numbers in D and E indicate the multifocal electroretinography amplitude in each trace array (in nanovolts per degree squared).

IR reflectance was 89.9 (28.7) nV per degree squared, and the mean (SD) amplitude in eyes without an IR hyporeflective lesion was 128.3 (25.5) nV per degree squared, which represents a statistically significant difference (P = .008). The combined fundus IR reflectance and mfERG images revealed that the amplitudes of the segments in a more hyporeflective area on fundus IR reflectance imaging were lower than those in a less hyporeflective area on the fundus IR reflectance image from an age-, sex-, and laterality-matched patient (Figure 4D and E).

Progression of photoreceptor disruption imaged by SD-OCT and fundus IR reflectance imaging in OMD is shown in Figure 5. Among 46 eyes, definite morphologic progression was seen in 7 (15%) on SD-OCT and in 8 (17%) on fundus IR reflectance imaging during the follow-up period of less than 2 years for all patients. The eyes that showed progression in SD-OCT images also showed progression in fundus IR reflectance images. The case in which the 2 investigators interpreted morphologic progression in fundus IR reflectance images (more distinguished hyporeflectance) and SD-OCT images (greater photoreceptor disruption) is shown in Figure 5A. The ELM line was intact at the initial visit but became barely discernible at the central fovea at the final visit, which indicates progression of photoreceptor disruption from OS-RPE plus IS-OS to OS-RPE plus IS-OS plus ELM involvement. However, in Figure 5B, one investigator interpreted progression, and the other investigator interpreted no progression on SD-OCT, whereas they both agreed on fundus IR reflectance progression. Functionally, this patient showed progression of OMD because he experienced a visual decline from an initial visual acuity of 20/100 to 20/200 during the follow-up period. In contrast, Figure 5C shows an example of no progression from either the fundus IR reflectance image or the SD-OCT image between the initial visit and the final visit.

IR-AF and SW-AF Imaging

The IR-AF and SW-AF images of 7 patients with OMD are shown in Figure 6. As summarized in Table 2, only patient 1 showed a faint hyperfluorescence ring resembling a bull’s-eye pattern on SW-AF, whereas the other patients had no remarkable findings. However, 6 of 18 eyes (33%) showed central hypoaufotofluorescence within normal hyperautofluorescence on IR-AF images (in patients 7, 10, and 21). As shown in Figure 3B and D, central hypoaufotofluorescence on IR-AF showed a good point-to-point correlation with severely disrupted photoreceptor IS-OS junction and OS-RPE; however, the k statistics indicated poor agreement between the abnormal findings of the SD-OCT images and those of the IR-AF images (k = 0.057).

Discussion

We used multimodal imaging to demonstrate the value of the modalities in OMD and the structure-function relationship of OMD among a large number of patients with the disease. Multimodal imaging, especially SD-OCT and fundus IR reflectance imaging, was useful for elucidating the abnormal features and progression of OMD.

Previously, an OMD diagnosis was based on clinical features and the exclusion of other macular diseases from diverse modalities, such as fluorescein angiography and full-field or focal macular ERG. These diagnostic tests are time consuming and require several types of equipment and resources. Patients with poor fixation from low vision often show variable results on mfERG and visual field testing. Although multimodal imaging cannot replace functional tests, such as ERG and perimetry, these modalities are noninvasive and quick and can greatly aid physicians in diagnosing OMD and understanding retinal pathologic features. Of these modalities, SD-OCT was most sensitive in detecting pathologic changes of OMD; macular photoreceptor abnormalities, such as photoreceptor disruption sparing the
RPE,5,9,10 were identified in all patients with OMD using SD-OCT. In addition, with fundus IR reflectance imaging we detected abnormal macular lesions in 78% (36 of 46) of eyes with OMD, which supports the value of this imaging modality for OMD diagnosis. The paradigm shift from OMD as a diagnosis of exclusion to a histologically determined retinal disease imaged with noninvasive instruments adds to our understanding of this disease.

In this study, we revealed the structure-function relationship in OMD by showing that photoreceptor thickness, the number of retinal layers involved, and the severity of photoreceptor pathologic features in the cross-sectional vertical dimension were also associated with visual acuity. Furthermore, photoreceptor thickness significantly correlated with foveal amplitude on mfERG and with threshold values in Humphrey visual field tests. Therefore, SD-OCT is also useful for correlating the outer retinal pathologic features with visual and electrophysiologic function in OMD.

In addition, our study findings suggest that progression of outer retinal pathologic features in patients with OMD advances from the photoreceptor OS to more internal retinal layers. For instance, ELM and IS-OS junction involvement was always accompanied by abnormalities in the photoreceptor IS-OS junction and OS-RPE, respectively. In addition, follow-up SD-OCT images revealed that photoreceptor disruption progressed in the vertical direction (Figure 5A).

Our finding of abnormal fundus IR reflectance images in OMD is notable and has not been reported previously to our knowledge. Of the photoreceptor layers in SD-OCT images, the IS-OS junction was associated with reduced fundus IR reflectance.
Figure 6. Short-Wavelength Autofluorescence (SW-AF) on the Left and Infrared Autofluorescence (IR-AF) on the right in Patients With Occult Macular Dystrophy

Patient numbers are indicated within the white boxes. Only patient 1 shows ringlike faint hyperfluorescence around the macula on SW-AF. Patients 7, 10, and 21 demonstrate central hypofluorescence within a round area of hyperfluorescence on IR-AF.
reflectance. Low reflectance on fundus IR imaging has been reported in other retinal diseases, such as age-related macular degeneration and pseudoxanthoma elasticum.\(^2,3,15\)\(^-\)22\) In OMD, the photoreceptor IS-OS junction disruption was associated with abnormal fundus IR reflectance based on the findings that (1) the dark area in IR images corresponded to the area with severe photoreceptor IS-OS disruption in SD-OCT images and (2) the association between IS-OS junction abnormalities and IR abnormalities was statistically significant.

The combined mfERG and fundus IR reflectance images (Figure 4) provide further evidence substantiating the structure-function relationship because the retinal areas showing lower fundus IR reflectance demonstrate decreased electrophysiologic function. In addition to the value of representing both visual and electrophysiologic function, fundus IR reflectance imaging has the advantage of simplicity in interpretation and image acquisition.\(^2,3\) Furthermore, fundus IR reflectance imaging may be helpful for monitoring progression. Our patient in Figure 5 showed that fundus IR reflectance imaging can detect progression of OMD more easily than SD-OCT.

Infrared AF has been used to detect several retinal diseases and is reportedly useful for diagnosing central serous chorioretinopathy.\(^10,18\) The fluorescence in IR-AF can originate from melanin in the RPE or choroidal tissue.\(^16,23,24\) In our patients with OMD, IR-AF provided additional information about the diagnosis and disease severity because the central hypautofluorescent lesion was correlated with an area of severe photoreceptor disruption on SD-OCT images. However, the few patients with abnormalities in IR-AF imaging limits its clinical usefulness in OMD.

Short-wavelength AF is an imaging modality that permits evaluation of the interaction between photoreceptors and the RPE in macular diseases.\(^2,3\) The predominant fluorophores of SW-AF are lipofuscin granules located within the RPE, outer retina, or intraretinal or subretinal fluid.\(^26,27\) Our SW-AF imaging results are consistent with the findings of a recent study\(^26\) on fundus AF in OMD in which few patients showed weak hyperautofluorescence on SW-AF. An intact RPE layer in OMD may explain why fundus examination reveals a normal fundus in patients with OMD.

A limitation of our study is the short follow-up period (<2 years). Therefore, although our study showed progression of photoreceptor abnormalities, a generalized conclusion for the long-term progression of OMD and the usefulness of IR imaging in its detection cannot be drawn from our study. The structure-function relationship and genotype-phenotype correlations should be investigated further in future studies with larger sample sizes.

In conclusion, multimodal imaging, including SD-OCT and fundus IR reflectance imaging, seem to be useful noninvasive diagnostic tools for patients with OMD. These imaging modalities provide in vivo, quasihistologic images demonstrating that OMD is characterized by progressive photoreceptor disruption and thinning. These findings can shift the paradigm of OMD from a diagnosis of exclusion to a specific pathologic diagnosis. In particular, fundus IR reflectance imaging is valuable for indicating visual and electrophysiologic function and for predicting disease progression.


