Features and Function of Multiple Evanescent White Dot Syndrome

Masanori Hangai, MD; Masahiro Fujimoto, MD; Nagahisa Yoshimura, MD

Objective: To describe and compare the tomographic features and macular abnormalities of multiple evanescent white dot syndrome (MEWDS) during the disease course.

Methods: In 5 patients (5 eyes) with characteristic MEWDS lesions (hypofluorescent in the late phase of indocyanine green angiography [IA]), results of microperimetric retinal sensitivity examination and IA were compared with findings from enhanced spectral-domain optical coherence tomography (SD-OCT) at diagnosis and until clinical resolution.

Results: Enhanced SD-OCT revealed moderately reflective focal lesions within the outer photoreceptor layer, where the inner and outer segment junction was disrupted, that corresponded with hypofluorescent areas in the late phase of IA. Areas of decreased retinal sensitivity on microperimetric examination matched areas of disruption in the inner/outer segment junction on SD-OCT images. In the first month after diagnosis, microperimetric examination and enhanced SD-OCT showed a shift in areas of decreased retinal sensitivity and disruption in the inner/outer segment junction from around the optic disc to the temporal macula. Retinal sensitivity and the inner/outer segment junction returned to almost normal in all eyes about a month after diagnosis of MEWDS.

Conclusion: Enhanced SD-OCT revealed abnormalities in the photoreceptor layer that were specific to MEWDS and that, with retinal shape and function, seemed to change location during clinical recovery from MEWDS.


Multiple evanescent white dot syndrome (MEWDS), a disease of unknown origin that occurs mostly in young women, was first described in 1984 by Jampol et al and Sieving et al. Patients with MEWDS typically develop an enlarged Marriott scotoma and decreased visual acuity but most recover fully in 1 to 2 months.

Ophthalmoscopic examination of an eye with MEWDS typically reveals multiple, 100- to 200-µm yellow-white dots in the deep retina and a unique foveal granularity. Results from fluorescein angiography and electrophysiologic studies suggest that the disease process occurs in the outer retina and/or the retinal pigment epithelium (RPE). On indocyanine green angiography (IA) images, multiple hypofluorescent spots are seen in eyes with MEWDS. Some authors propose that these lesions indicate involvement of the choroid in the MEWDS disease process, specifically choroidal ischemia resulting from inflammation, whereas others propose that the dots represent a blockade resulting from inflammation of the RPE without choroidal ischemia. The precise pathogenesis of MEWDS remains unknown.

Nguyen et al observed disruptions in the highly reflective line representing the photoreceptor inner and outer segment (IS/OS) junction on ultra–high-resolution optical coherence tomography (OCT) images in 5 patients (6 eyes) with MEWDS. Sikorski et al found areas of reduced IS/OS junction reflectivity on 3-dimensional spectral-domain OCT (SD-OCT) images of eyes with MEWDS that matched hypofluorescent spots on IA images. These findings indicate that the photoreceptor layer is involved in the disease process. However, disruptions in the IS/OS junction seem to be a common feature of various diseases in which the photoreceptor layer is damaged, including acute zonal occult outer retinopathy–complex diseases, retinitis pigmentosa, repaired retinal detachment, closed macular hole, and resolved central serous chorioretinopathy.
Spaide et al10 reported 1 case of MEWDS in which spontaneous improvement in an IS/OS junction abnormality was associated with improvement in symptoms and shrinking of the blind spot on perimeter testing, whereas disruptions in the IS/OS junction and the size of the blind spot were not improved in eyes with other acute zonal occult outer retinopathy–complex diseases. Therefore, if morphologic characteristics specific to MEWDS lesions exist, they need to be clarified.

In this study, we used enhanced (multiple B-scan averaged) SD-OCT B-scan images to clarify morphologic characteristics of MEWDS lesions.12-14 We used Spectralis HRA + OCT (Heidelberg Engineering, Heidelberg, Germany) for simultaneous IA and enhanced SD-OCT examinations. By performing enhanced SD-OCT and microperimetric examinations periodically from the time of clinical disease course, but it improved without treatment in all 5 eyes, with a return to normal (20/20) in 4 eyes and to 20/25 in 1 eye (Table 1).

Table 1. Clinical Findings in 5 Patients With MEWDS

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Eye</th>
<th>BCVA</th>
<th>Initial Examination</th>
<th>Lowest</th>
<th>Final</th>
<th>Enlargement of Blind Spot</th>
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<th>Yellow-White Lesions on IA</th>
<th>Findings From FA</th>
<th>Hyperfluorescent Lesions on IA</th>
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<tr>
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Abbreviations: +, present; –, absent; BCVA, best-corrected visual acuity; FA, fluorescein angiography; IA, indocyanine green angiography; L, left; MEWDS, multiple evanescent white dot syndrome; R, right.

During the disease course, the size of the blind spot decreased for all patients after resolution of fundus changes. Best-corrected visual acuity worsened in 2 of 5 eyes during the disease course, but it improved without treatment in all 5 eyes, with a return to normal (≥20/20) in 4 eyes and to 20/25 in 1 eye (Table 1).

ENHANCED SD-OCT AND MICROPERIMETRIC EXAMINATION

Retinal imaging was performed using the Spectralis HRA + OCT. The combination of high-resolution scanning laser imaging of the retina and SD-OCT enables real-time tracking of eye movements and real-time averaging of multiple OCT B-scans, thereby reducing the speckle noise of OCT images. At each location of interest on the retina, 50 SD-OCT images were acquired and averaged to reduce the speckle noise.

Fundus-monitored microperimetric examination was performed with the MP-1 Microperimeter (NIDEK, Vigonza, Italy). The MP-1 software automatically tracks fundus movements on 10 channels, evaluating every acquired frame for shifts in the x- and y-directions of the fundus with respect to a reference frame obtained by an infrared camera at the beginning of the examination. A 4-2 staircase strategy with a Goldmann III stimulus was used for MP-1 examination of 57 stimulus locations covering the central 10º. Each stimulus is located according to the measurement points used in Humphrey 10-2, with some additional points. The white background illumination was set at 1.27 candelas (cd) per meter squared. The differential luminance, defined as the difference between stimulus luminance and background luminance, was 127 cd/m² at 0 dB stimulation, and the maximum stimulus attenuation was 20 dB. The duration of the stimulus was 200 ms.

Three patients underwent weekly examinations, including SD-OCT and MP-1 examinations, until signs and symptoms of MEWDS resolved. The other 2 patients underwent examinations twice a month.

METHODS

All investigations adhered to the tenets of the Declaration of Helsinki and the study was approved by the Institutional Review Board and Ethics Committee of Kyoto University Graduate School of Medicine. Informed consent for all examinations was obtained from all patients.

PARTICIPANTS

Participants for this study were the most recent 5 patients at Kyoto University Hospital diagnosed as having MEWDS who had clinical manifestations characteristic of MEWDS and hypofluorescent lesions in the late phase on IA images. A diagnosis of MEWDS was based on the patient’s medical history; the results of routine examinations, including the ophthalmic examination; fluorescein angiography; IA; and automated static perimetric examination (Humphrey visual field testing; Carl Zeiss Meditec, Dublin, California). All patients had unilateral MEWDS. Findings from the initial examination and best-corrected visual acuity values are given in Table 1.

At the initial visit, patient 1 had a 5-day history of pericentral visual field defects, and patient 3 had a 9-day history of pericentral visual field defects followed by a central scotoma of 5 days’ duration. The other 3 patients (patients 2, 4, and 5) complained of central scotomas of 3, 4, and 5 days’ duration, respectively. At initial examination, all patients had enlargement of the blind spot on Humphrey visual field testing, and 4 of 5 eyes had a unilateral decrease in best-corrected visual acuity. Biomicroscopic examinations revealed several 100- to 200-µm yellow-white lesions in the deep retina unilaterally in all patients and foveal granularity in 3 patients (Table 1). The patients had characteristic early wreathlike hyperfluorescence on fluorescein angiographic images, and no patients had staining of the optic nerve (Table 1). All of the patients showed hypofluorescent lesions in the late phase of IA. This peculiar hypofluorescent pattern on late IA was the basis for selecting these cases.7

during the clinical disease course. If morphologic characteristics specific to MEWDS lesions exist, they need to be clarified.

In this study, we used enhanced (multiple B-scan averaged) SD-OCT B-scan images to clarify morphologic characteristics of MEWDS lesions.12-14 We used Spectralis HRA + OCT (Heidelberg Engineering, Heidelberg, Germany) for simultaneous IA and enhanced SD-OCT examinations. By performing enhanced SD-OCT and microperimetric examinations periodically from the time of diagnosis to recovery from MEWDS, we could correlate changes in lesions in the photoreceptor layer, disruptions in the IS/OS junction, the appearance of hypofluorescent lesions on IA images, and retinal sensitivity during the clinical disease course.

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Abbreviations: +, present; –, absent; BCVA, best-corrected visual acuity; FA, fluorescein angiography; IA, indocyanine green angiography; L, left; MEWDS, multiple evanescent white dot syndrome; R, right.
Table 2. Macular Findings From OCT and MP-1

<table>
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<tr>
<th>Patient No.</th>
<th>IS/OS Disruption</th>
<th>Recovery of IS/OS Junction</th>
<th>Focal Lesions</th>
<th>RPE Abnormalities</th>
<th>IS/OS Disruption</th>
<th>Recovery of IS/OS Junction</th>
<th>Focal Lesions</th>
<th>RPE Abnormalities</th>
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<td>+</td>
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<td>(Complete)</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>(Irregular)</td>
<td></td>
<td>+</td>
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<tr>
<td>4</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
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<td>(Incomplete)</td>
<td></td>
<td>–</td>
<td>NT</td>
<td>NT</td>
</tr>
</tbody>
</table>

Abbreviations: +, present; –, absent; complete, complete resolution of the photoreceptor inner and outer segment (IS/OS) junction defects; defect, IS/OS line almost recovered with small defects remaining in focal regions; irregular, IS/OS line was visible in all scan areas but slightly varied in thickness and reflectivity in focal regions; MP-1, MP-1 Microperimeter-1 (NIDEK, Vigonza, Italy); NT, not tested; OCT, optical coherence tomography; RPE, retinal pigment epithelium.

OCT FINDINGS IN THE RETINA

Disruptions in the IS/OS junction were seen in the fovea in 4 of 5 eyes and in the extrafoveal region of the macula in all 5 eyes (Table 2). Where the IS/OS junction was disrupted, the external limiting membrane was visible, and moderately reflective focal lesions were evident within the photoreceptor layer (Table 2). The focal lesions were located primarily in the IS/OS layers (Figure 1 and Figure 2). There were some focal lesions that crossed the external limiting membrane line to involve the outer nuclear layer, both in the foveal and extrafoveal regions (Figures 1 and 2). No apparent abnormalities were seen in the inner portion of the retina anterior to the outer plexiform layer.

These abnormalities in the photoreceptor layer changed remarkably during the clinical course of MEWDS. At the initial visit, the disruptions in the IS/OS junction and moderately reflective focal lesions appeared at the same foci on the macula (Figures 1, I and 2, C-1, C-2, and D-1). Then the areas of the disruption in the IS/OS junction became wider, and moderately reflective focal lesions spread as small spots over the area where the IS/OS line was disrupted (Figures 1, K and L, and 2, C-2, C-3, D-2, and D-3). Finally, in all eyes, the disruptions in the IS/OS junction disappeared from almost all macular regions, and moderately reflective focal lesions disappeared as well (Figure 2 and Table 2).

The outer photoreceptor layer (IS/OS layers, which can be discerned on SD-OCT images posterior to the external limiting membrane) was thicker where there were focal lesions in the acute phase of MEWDS and thinner where the IS/OS junction was disrupted compared with the neighboring region, where the IS/OS junction was visible (Figure 2). The outer photoreceptor layer seemed to finally recover its normal thickness when the IS/OS junction line reappeared (Figure 2).

SIMULTANEOUS FINDINGS FROM IA AND OCT

At the initial visit, simultaneous IA and OCT examinations using the Spectralis HRA + OCT showed hypofluorescent lesions in the late phase of IA that seemed to correspond to moderately reflective focal lesions on SD-OCT. For example, at the initial visit of patient 1, hypofluorescent areas in the late phase of IA (Figure 1, D and G) and disruption in the IS/OS junction and moderately reflective lesions evident on SD-OCT (Figure 1, E-I) appear to be in the same location, and it is difficult to determine which features on OCT correspond to the hyporeflective lesions in IA. However, 13 days later, the areas with disruptions in the IS/OS junction on SD-OCT were seen in wider regions of the macula, and the small moderately reflective focal lesions appeared as scattered small spots over the region where the IS/OS junction was disrupted (Figure 1, K and L). The hypofluorescent lesions seen on IA seemed to correspond not to the disruptions in the IS/OS junction but to the small, moderately reflective focal lesions at this later stage of MEWDS (Figure 1, J-L).

MICROPERIMETRIC EXAMINATION AND OCT FEATURES

Both OCT and MP-1 examinations were performed in 3 patients at the initial visit, which was 5 days (patient 1), 3 days (patient 2), and 9 days (patient 3) after onset of the initial symptoms, and were repeated on the same day every week until clinical recovery (Figure 2 and Table 2). In patient 3, the initial examinations were 5 days after onset of central scotoma. At the initial examination, all eyes had decreased retinal sensitivity in the vicinity of the optic disc and in the nasal extrafoveal region of the macula. Regions of decreased retinal sensitivity seemed to shift gradually from around the optic disc to the temporal side of the macula. When retinal sensitivity was...
Figure 1. Images of the left eye of patient 1 obtained at the initial diagnostic visit for multiple evanescent white dot syndrome (A-I) and 13 days later (J-L).

A, Color fundus photograph showing multiple yellow-white lesions in the deep retina. B and C, Simultaneously obtained late-phase dynamic fluorescein angiography (B) and indocyanine green angiography (IA) (C) images. D-H, Simultaneously obtained late-phase IA and enhanced spectral-domain optical coherence tomography (SD-OCT) images. Horizontal (E) and vertical (H) scan images through the fovea are shown. Green arrows in D and G indicate the scan lines. Magnified (>4×) view of areas outlined (red, F; blue, I) in the vertical SD-OCT image (H). J-L, Both IA and enhanced SD-OCT images obtained 13 days after diagnosis. Green lines in J indicate the vertical (K) and horizontal (L) scan directions. BM indicates Bruch membrane; ELM, external limiting membrane; IS/OS, photoreceptor inner and outer segment junction; ONL, outer nuclear layer; RPE, retinal pigment epithelium.
severely decreased in the temporal region, retinal sensitivity in the vicinity of the optic disc was recovering. The regions with decreased retinal sensitivity demonstrated disruptions in the IS/OS line (Figure 2). Retinal sensitivity normalized concurrent with the disappearance of disruptions in the IS/OS line and the disappearance of moderately reflective focal lesions (Figure 2).

During the shift in locations of lesions in the extrafoveal region, retinal sensitivity remained decreased at the fixation point and foveal findings remained abnormal on enhanced SD-OCT imaging. At the visit when the entire macular region had almost recovered normal retinal sensitivity and the photoreceptor layer seemed to be normal on enhanced SD-OCT, retinal sensitivity at the

Figure 2. Microperimetric examination and enhanced spectral-domain optical coherence tomography (SD-OCT) results in the left eye of patient 1 at initial (1, diagnostic) and follow-up (2, day 4; 3, day 13; 4, day 20; 5, day 34) visits for multiple evanescent white dot syndrome. A, Retinal sensitivity maps obtained with the MP-1 Microperimeter (NIDEK, Vigonza, Italy). The directions of horizontal (B) and vertical (C) enhanced SD-OCT scans are indicated by the white arrows. Horizontal sectional (B) and vertical cross-sectional (C) images through the fovea obtained by enhanced SD-OCT. D, Magnified (×4) views of the area outlined by dashed red line boxes in the vertical SD-OCT image in C. Areas with decreased retinal sensitivity corresponded to disruptions in the photoreceptor inner and outer segment (IS/OS) junction and shifted from the nasal to the temporal region of the macula during recovery. ELM indicates external limiting membrane; ONL, outer nuclear layer; RPE, retinal pigment epithelium.
fixation point and best-corrected visual acuity had also returned to normal or within the reference range.

**OCT FINDINGS IN THE RPE**

The highly reflective line representing the RPE on enhanced SD-OCT images looked normal over most of the macula in all eyes. However, in 4 patients, the RPE had areas of undulation with a thin straight line appearing underneath. However, these abnormal features were not evident in all regions where the photoreceptor layer was abnormal.

**COMMENT**

In this study, weekly examinations with enhanced SD-OCT and MP-1 showed that, in eyes with MEWDS, photoreceptor layer morphologic characteristics and retinal sensitivity were abnormal at diagnosis and that the abnormalities resolved concurrently with clinical recovery. The apparent depths (photoreceptor layer–affected) of abnormalities seen on SD-OCT relative to those seen on IA are concordant with biomicroscopic and angiographic observations, and the results of electrophysiologic studies that suggest the disease process of MEWDS occurs in the outer retina and/or the RPE.1,2 On SD-OCT, changes over time in the transverse extent of the abnormalities are consistent with the transient and benign nature of the disease.

Nguyen et al,3 the first to report on the tomographic features of MEWDS, found subtle disruptions of the photoreceptor IS/OS junction on scans of eyes with this disease. Sikorski et al4 showed that the areas of reduced IS/OS junction reflectivity matched areas of hypofluorescence on IA. These findings support the assumption that the outer retina and/or the RPE are involved in the MEWDS disease process. However, such disruptions in the IS/OS junction on OCT images are often seen in eyes with a variety of diseases affecting the photoreceptor layer. Our study, which demonstrated by enhanced SD-OCT that there are moderately reflective focal lesions within areas where the IS/OS line is disrupted in eyes with MEWDS, is the first, to our knowledge, to report a feature that may be specific to MEWDS.

In MEWDS, vision typically returns to normal by 1 to 2 months after onset, and the size of the blind spot also typically returns to normal. Dot lesions seen on biomicroscopic and angiographic examination usually disappear, and electrophysiologic measurements also normalize with clinical recovery.2-7 Spaide et al8 reported 1 case of MEWDS in which spontaneous improvement in an IS/OS abnormality was associated with improvement in symptoms and shrinking of the blind spot on perimeter evaluation. Consistent with these findings, we demonstrated a change during clinical recovery in the areas affected by decreased retinal sensitivity and photoreceptor damage. This shift in affected areas may be another characteristic of MEWDS and could account for its typically benign course.

Sikorski et al4 found a correlation between areas of reduced IS/OS junction reflectivity seen on 3-dimensional SD-OCT and hypofluorescent spots on IA. In this study, performing enhanced SD-OCT simultaneously with fluorescein angiography and IA showed that, at the initial visit for MEWDS, the moderately reflective focal lesions and areas of disruption in the IS/OS junction seen on OCT corresponded to hypofluorescent lesions seen on IA images; later, 13 days after the initial visit of patient 1, for example, there were more areas of disruption in the IS/OS junction than focal lesions, and, as clinical recovery progressed, only moderately reflective focal lesions corresponded with hypofluorescent areas on IA. These results indicate that areas of disruption in the IS/OS junction correspond to hypofluorescent spots on IA only when the areas of disruption in the IS/OS junction are identical to the areas of moderately reflective focal lesions, which, in our study, was at the initial visit.

Based on studies of the angiographic features of MEWDS, the inflammatory changes responsible for the disease are thought to occur in the RPE and choroid.3,7 However, cross-sectional ultra–high-resolution OCT images in a previous study did not reveal any clear abnormalities in the RPE layer or the choroid in 5 patients with MEWDS.6 In the present study, in 4 of 5 patients, undulations of the line representing the RPE and the appearance of a thin straight line under the undulations representing the Bruch membrane were seen in focal areas in the acute phase of MEWDS. These findings are consistent with previous reports that the visibility of the Bruch membrane is enhanced by speckle-noise reduction via multiple B-scan averaging.14 The undulations of the line representing the RPE and the appearance of the Bruch membrane are not specific to MEWDS but have been reported in other diseases, such as central serous choriotenopathy,14-16 and age-related macular degeneration with occult choroidal neovascularization or drusen,14-16 which are thought to involve RPE abnormalities. Therefore, our results support the assumption that the MEWDS disease process occurs in the RPE. However, our results do not provide direct evidence of involvement of the choroid in the disease process or determine whether the choroid and RPE are ischemic in MEWDS.

A limitation of previous studies and the present study was the small number of cases reported. Nevertheless, we think our study contributes important information about the correlation between tomographic and IA features characteristic of MEWDS and their correlation with clinical and functional changes during the disease course. Histological studies of the lesions shown in this study in eyes with MEWDS as well as studies of larger numbers of cases to discover what triggers the appearance and disappearance of these lesions would advance the understanding of the origins of MEWDS.

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REFERENCES


Correction

Error in Text. In the Letters: Research Letters article titled “Atypical Infectious Nodular Scleritis” by Kesen et al, published in the August 2009 issue of the Archives (2009; 127[8]:1079-1080), an error occurred in lines 12 through 16 of the third paragraph on page 1079. The text should have read, “Despite 3 months of tuberculosis therapy and treatment with oral prednisone, new nodules developed (Figure 1A). Because the infectious disease service was convinced that the scleritis did not represent infection with tuberculosis, treatment with cyclophosphamide (150 mg/d) was started but was discontinued after 10 days because of worsened scleritis.” This article was corrected online for typographical errors on August 10, 2009.