IMAGING WITH MULTIMODAL ADAPTIVE-OPTICS OPTICAL COHERENCE TOMOGRAPHY IN MULTIPLE EVANESCENT WHITE DOT SYNDROME: THE STRUCTURE AND FUNCTIONAL RELATIONSHIP

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Purpose: To elucidate the location of pathological changes in multiple evanescent white dot syndrome (MEWDS) with the use of multimodal adaptive optics (AO) imaging.

Methods: A 5-year observational case study of a 24-year-old female with recurrent MEWDS. Full examination included history, Snellen chart visual acuity, pupil assessment, intraocular pressures, slit lamp evaluation, dilated fundoscopic exam, imaging with Fourier-domain optical coherence tomography (FD-OCT), blue-light fundus autofluorescence (FAF), fundus photography, fluorescein angiography, and adaptive-optics optical coherence tomography.

Results: Three distinct acute episodes of MEWDS occurred during the period of follow-up. Fourier-domain optical coherence tomography and adaptive-optics imaging showed disturbance in the photoreceptor outer segments (PR OS) in the posterior pole with each flare. The degree of disturbance at the photoreceptor level corresponded to size and extent of the visual field changes. All findings were transient with delineation of the photoreceptor recovery from the outer edges of the lesion inward. Hyperautofluorescence was seen during acute flares. Increase in choroidal thickness did occur with each active flare but resolved.

Conclusion: Although changes in the choroid and RPE can be observed in MEWDS, Fourier-domain optical coherence tomography, and multimodal adaptive optics imaging localized the visually significant changes seen in this disease at the level of the photoreceptors. These transient retinal changes specifically occur at the level of the inner segment ellipsoid and OS/RPE line. En face optical coherence tomography imaging provides a detailed, yet noninvasive method for following the convalescence of MEWDS and provides insight into the structural and functional relationship of this transient inflammatory retinal disease.

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Multiple evanescent white dot syndrome (MEWDS) is an inflammatory retinal disease that predominately affects females between their second to fifth decade of life. First described in 1984 by Jampol et al.,[1] symptoms of MEWDS include decreased central vision and new blind spots in the peripheral vision as well as photopsias. The clinical signs include foveal granularity and deep outer retinal yellow-white lesions 100 μm to 200 μm in size. Both the symptoms and the clinical signs of the disease are transient with complete recovery occurring at a mean of 6 weeks after onset (range of 4.5 weeks–6 months).[2]

Since the identification of the MEWDS syndrome, the exact location of the disease pathology has been a source of debate. Initially, the retinal pigment epithelium (RPE) was thought to be the primary site of pathology. This finding was supported by evidence of late staining on fluorescein angiography (FA).[1] However, the evaluation of electroretinography (ERG) revealed photoreceptor (PR) dysfunction from decreased a-wave and early receptor potential (ERP) amplitudes, as well as prolonged ERP regeneration time.[1,2] Analysis with optical coherence tomography (OCT), first with time-domain technology in 2006,[3] and then with Fourier-domain (FD-) OCT in 2007 to 2009, also suggested that the primary location of inflammation was at the level of the PRs.[2] In 2013, Thomas et al.[4] displayed PR shortening during the acute phase of MEWDS with preservation of outer nuclear layer (ONL) in patients who had full vision recovery. However, use of choroidal imaging techniques sparked additional controversy with the delineation of multiple hypercyanescent lesions in the choriocapillaris during active disease on indocyanine angiogram (ICGA), which implied deeper extension of this disease.[5] Reports of choroidal thickening in MEWDS added support to the theory of choroidal involvement,[7] though not in all cases. Li and Kishi[2] found choroidal changes in only 3 out of 7 cases and those lesions showed no correlation with the visual field, multifocal ERG, or PR disruption. In 2012, Silva et al.[6] concluded that inflammation was present but not the initial cause of disease supported by their finding of more lesions on FA than ICGA. Today, there is still debate on whether this disease affects the RPE, PR or choroid, or a combination of all layers.

We present a case study of a patient with recurrent MEWDS who underwent structural analysis of the retina with multimodal imaging including adaptive optics, FD-OCT, infrared (IR) confocal scanning ophthalmology (cSLO), and blue-light fundus autofluorescence (FAF), which delineated the anatomical changes in MEWDS in the outer segments of the PRs.

**Methods**

Institutional review board approval from the University of Pittsburgh was obtained. Research adhered to the tenets set forth in the declaration of Helsinki and was conducted in accordance with regulations from the Health Insurance Portability and Accountability Act.

The 24-year-old female was evaluated under approved consent on 8 separate visits from January 2008 through February 2014 at a tertiary referral center. The diagnosis of MEWDS was based on clinical criteria from Jampol et al.[1] The fundus changes in the right eye showed foveal granularity as well as small, subtle, discrete, yellow lesions in the deep retina throughout the macula and the FA displayed typical wreath-like hyperfluorescence within the fovea (Figure 1). At each visit, the patient received a comprehensive examination including best-corrected visual acuity, pupillary reaction, intraocular pressures, slit lamp examination, and fundoscopic examination. On selected examinations, testing was performed with colored fundus photographs, FA, ICGA, FAF, and IR reflectance image from cSLO (Spectralis; Heidelberg Engineering, Heidelberg, Germany), FD-OCT (Cirrus; Zeiss, Dublin, CA), VF testing, ERG (Espion; Diagnosys, Lowell, MA), and with a multimodal adaptive optics (AO) system (Physical Sciences Inc, Andover, MA).

The multimodal AO system used in this study has both cSLO and OCT imaging channels. The cSLO and
OCT channels follow the same optical path, and images are acquired simultaneously such that each cross-sectional image (B-scan) acquired by the OCT corresponds to a cross-section perfectly registered in the center of the cSLO frame. The AO corrections enabled improved cSLO transverse resolution sufficient to resolve foveal cones in our subject. The scans were taken in sections of 4° by 4° at locations in the fovea identified as abnormal in the clinical examination. Hammer et al7 have previously detailed this system.

Choroidal thickness measurements were obtained using the native Cirrus software utilizing a ruler that was placed directly under the center of the foveal depression at the lower border of the hyper-reflective line of the RPE layer and then extended to the hyper-reflective surface of the inner sclera.

Fig. 1. A. Color fundus photo of the right eye, clear vitreous media, tilted myopic nerve with peripapillary atrophy, macula with foveal granularity and very subtle multiple white lesions in the retina. B. Early-phase fluorescein angiography during active inflammation (C) mid-phase FA with hyperfluorescence of macular lesions and central wreath-like staining.

Fig. 2. A. High-definition Fourier-domain optical coherence image (HD FD-OCT) of the right eye during an acute flare of multiple evanescent white dot syndrome (MEWDS) on December 1, 2011 that shows 3 large areas of disruption in the inner segment ellipsoid layer and complete absence of the outer segment/retinal pigment epithelial (OS/RPE) layer but intact RPE outer layer. The arrow shows the temporal edge of each segment of disruption. The external limiting membrane has few focal areas of mild disruption in the locations overlying the PR disturbance. The arrowheads show outer retina disruption from peripapillary atrophy. Changes resolved within 4 weeks for this image double-headed arrow represents locations used for choroidal measurements, which measured 180 (B) an HD FD-OCT image of the second flare that shows more extensive disruption in the ISe layer, still absence of the OS/RPE layer and intact outer RPE. Areas of recurrent disturbance of this flare are similar to the first flare. Double-headed arrow represents locations used for choroidal measurements, which increased to 205 (C) the arrows show improvement in the PR changes at 4 months after the third flare. The arrowheads show the only location still with disruption in the PRs. The double-headed arrow represents locations used for choroidal measurements, which decreased to 144. (D–F) HVF 30-2 from the right eye corresponding to the date shown. The visual fields show enlarged blind spot that correlates with the degree of ISe and OS/RPE changes observed in the FD-OCT. (G–I) show the corresponding en face C scan images from the same dates taken at the level of the PR, which delineates the degree of disruption at this level and highlights the correlation to the visual field if inverted to the same orientation.
Figure 2 shows representation of the location of choroidal measurements.

**Results**

Three distinct acute episodes of MEWDS occurred in the right eye on January 2008, December 2011, and August 2013. Visual acuity in the right eye in each flare was 20/30, 20/50, and 20/100, respectively (Table 1). Vision recovered to 20/20 at the end of follow-up. Time to recovery was between 2 weeks, 4 weeks, and 6 weeks, respectively. Visual field showed enlarged blind spot with each flare in the right eye with the largest depression seen on the most recent flare on August 8, 2013 (mean deviation –12.93 dB) and full recovery on February 14, 2014. The left eye visual field showed mild central depression with later flares that improved with follow-up (Figure 3).

The FD-OCT data collected on the second and third flares displayed recurrent focal disruption in the PR layer in 3 distinct areas in the macula (Figure 2). Careful analysis of the outer retina bands showed severe disruption of the inner segment ellipsoid (ISe) but also a striking absence of signal from the outer segment (OS)/RPE junction during acute flares. There was also mild focal disturbance in the external limiting membrane overlying a small area over the affected PRs (Figure 2, A–B). The RPE layer remained intact in the center macula, except for a subtle area of transmission defect seen subfoveally in each image, which suggested RPE irregularity in this location only. The outer retinal changes recovered over the course of follow-up (Figure 2C). The degree of PR disruption corresponded with the location and degree of visual field changes (Figure 2, D–F and Table 2). The en face image captures the correspondence between the degree and extent of the PR change with the VF depression (Figure 2, G–I). ERG testing obtained after the third flare was normal, confirming complete recovery of PRs.

A series of 4 en face images were obtained during the second flare at the level of the PRs (Figure 4). The images show multiple, discrete, dark patches with low reflectivity in the fovea and throughout the macula, with a large confluent dark areas around the optic nerve. During convalescence, each one of the hyporeflective areas became smaller with a decrease in the ratio of hyper-reflective border to hyporeflective core lesion, resolving centripetally. The large foveal lesion improved in the same pattern but also with central bridging areas of hyper-reflectivity that developed as an early sign of improvement from within the hyporeflective region.

In-depth assessment at the PR layer was made with the multimodal AO system during the second flare and then 2 weeks later. During the acute phase, the cone mosaic on the AO-OCT images showed discrete areas of decreased reflectivity that resolved in follow-up testing (Figure 5). This finding is not from poor signal or media opacities because the signal from the cones immediately adjacent to the disrupted area was in focus in the same image. Although a small decrease in the cone mosaic is expected to be seen outside the fovea due to the natural decrease in cone density in this location, in this case the decrease signal is seen in patches of disrupted signal that corresponds with the hyporeflectivity observed in the en face image (Figure 5C).

The en face image was also compared with the blue-light FAF from the same day and the IR image taken one month later. Each image showed focal disruptions of signal in corresponding areas (Figure 6). The FAF and IR image were strikingly similar even though they were taken at different time points. The FA image showed typical features of MEWDS with hyperfluorescence in the area of the retinal lesions and late foveal staining. ICGA was not done at the time of the FA image, but was normal at the one-month follow-up visit. Thickening of the choroid was also observed in each of the acute flares (Table 3).
Discussion

Imaging with FD-OCT and multimodal AO-OCT confirmed specific disruption within the PR layer and localized it to the ISe junction as well as the OS/RPE level. The dark patches on AO-OCT images in the PRs have been shown in previous reports on MEWDS. Localization of the primary insult of MEWDS to the level of the PRs has been supported by other reports that use ERG to validate their claim, whereas we used FD-OCT and AO-cSLO to verify the PR disruption, showing the precise location of the affected PR. Another important observation in this case study was the association between the visual field changes and the exact location and extent of damage within the PR layer, indicating that vision loss in MEWDS is directly related to PR damage and not to changes in other layers of RPE or choroid.
These PR OS changes can regenerate in a relatively short time period. In our case, each flare resolved twice over a 6-week period, which also agrees with the natural history of MEWDS. This turn-over of the PR OS can also explain the appearance of PR shortening previously described in MEWDS. Unique in this series is the elucidation of the degree of PR OS/RPE junction involvement as opposed to previous reports that localized the disease to the overlying band of retina, previously termed IS/OS line. We were also able to capture the method of convalescence of PR for the first time as depicted in the serial en face images that show the centripetal resolution of the lesion from the outside edges inward (Figure 4). The specific changes seen as an initial focus of hyporeflectivity outlined by a hyper-reflective ring that later equilibrates to a homogenous signal on en face FD-OCT may provide insight into the exact changes taking place within the PRs. More investigation into this pattern of healing may be important for understanding other retinal diseases as well.

The disruption in the PRs, specifically the severe changes in the OS/RPE, may even explain the findings of hyperautofluorescence on FAF, which has previously sparked controversy. FAF changes typically show disruption in the RPE and not PR changes, but it is important to note that this band corresponds to the interdigitation of the OS with the RPE and a significant disruption that starts in the PR OS can result in RPE alterations on imaging. This can occur by phagocytosis of the outer segments within the RPE and subsequent accumulation of the lipofuscin breakdown product or from disruption in the melanosomes in the apical RPE causing a release in melanin, which was previously described with IR imaging in acute macular neuroretinopathy (AMN). Both lipofuscin and melanin create a hyperautofluorescence signal on blue-light FAF, whereas accumulation of melanin creates a dark signal on IR imaging. A release of melanin is supported by our case, which shows correspondence of lesions on the FAF and IR images. This close interplay between PR and RPE is supported by the similar convalescence pattern that occurred in the PR layer (as documented in this case by the serial en face images obtained at the level of the photoreceptors during the second flare and capture the initial pathology affecting the photoreceptors, as well as, their changes during convalescence.)

| Date                | Visual Acuity | Visual Field (VF) Mean Deviation | VF Pattern Standard Deviation |
|---------------------|---------------|----------------------------------|-------------------------------|
| December 2, 2011    | 20/50         | -5.41                            | 6.14                          |
| August 8, 2013      | 20/100        | -12.93                           | 13.7                          |
| September 20, 2013  | 20/25         | -5.49                            | 6.25                          |
| February 14, 2014   | 20/20         | -2.66                            | 1.72                          |

Fig. 4. A series of en face images obtained at the level of the photoreceptors during the second flare and capture the initial pathology affecting the photoreceptors, as well as, their changes during convalescence.
Fig. 5. A. An AO image taken during the second acute flare of MEWDS (B) an AO image taken of the same spot 6 weeks later. The arrow heads in (A) show a discrete area of loss of resolution of the cone mosaic suggestive of diseased PRs. This is adjacent to areas with clear delineation of the cone mosaic in the same image denoted by the arrows. In the follow-up image in (B), the arrows point to the same cones that can still be resolved in the image, but in (B) there is improvement in the center of the image with more reflectivity seen from the cone mosaics then in (A) (denoted by the arrowheads). The fact that the surrounding cones are visible in both before and after images and the vessels can be resolved both before and after shows consistency between the images and supports the case that only the area denoted by the arrowheads has changed. The area of decrease in reflectivity of the cone mosaic correlates to the location of the disruption in PR on the en face C scan. Similar images can be seen on AO in other locations of active lesions (C) En face C scan image through PR outer segments with decrease reflectivity in same location of AO image. D. An AO image to serve as a control, taken in an area of unaffected retina during the acute flare and (E) then at follow-up. (C) shows that there was no blockage from media opacities that could have contributed to the focal disruption seen in (A).

Fig. 6. A. Fluorescein from the second active flare (December 1, 2011) that shows early phase imaging with delay in choroidal filling initially. The area of delayed filling, seen with arrowheads, corresponds with (B) the location of PR hyporeflectivity on en face OCT from the same day and with (C) hyperautofluorescence lesions on blue-light fundus autofluorescence (FAF) from the same day and (D) dark focal areas on the infrared (IR) reflectance image from confocal scanning laser ophthalmoscope scan of the macula taken one month later during follow-up. The lesions on FAF are not as numerous as those on FA or en face imaging, which may be due to the stage of the disease during image acquisition. The arrows indicate additional areas of overlap between the FAF and IR image. Increase melanin can explain both the hyperautofluorescence lesions and the dark lesions on IR which may be why the areas of pathology correlate better than in the other modalities. The delay in choroidal fill is also seen around the optic nerve, similar to the depression seen on OCT en face but the area is more clearly defined on OCT scan.
OCT images) and the pattern of convalescence of FAF signal (previously reported by Dell’omo et al in 2010).\textsuperscript{10}

In conclusion, although choroidal thickening and RPE alterations can be seen in MEWDS, multimodal imaging revealed that more significant changes of this disease are localized at the level of the PR. These transient retinal changes occur at the level of the ISe and OS/RPE line. AO-corrected en face cSLO imaging provides a detailed, yet noninvasive method for delineating this pathology, following convalescence of disease and distinguishing MEWDS from other retinal inflammatory conditions. Future studies should incorporate multimodal imaging evaluation in transient retinal diseases to help determine the pathological processes involved in these conditions.

Key words: adaptive-optics, autofluorescence, C-scan, dot, evanescent, imaging, MEWDS, multiple, syndrome, white.

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Table 3. Choroidal Measurements of Each Eye Throughout the Study. Measurements Were Taken by Using the Ruler Feature on Cirrus From the Retinal Pigment Epithelial Layer to the Inner Surface of the Sclera at the Center Point of the Macula Directly Under the Fovea. The Choroidal Thickness is Greater in the Right Eye During Flare and Compared to the Contralateral Eye

| Date               | Active Flare | Choroid Thickness Right Eye | Choroid Thickness Left Eye | Difference Between Active Right Eye and Quiet Left Eye |
|--------------------|--------------|-----------------------------|---------------------------|--------------------------------------------------------|
| December 1, 2011   | Yes          | 180                         | 172                       | 8                                                      |
| December 9, 2011   | Yes          | 188                         | 173                       | 15                                                     |
| December 11, 2011  | Yes          | 180                         | 172                       | 8                                                      |
| August 8, 2013     | Yes          | 205                         | 182                       | 23                                                     |
| December 20, 2013  | No           | 144                         | 160                       | −16                                                    |