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Multi –modality imaging on multiple evanescent white dot syndrome–A Spectralis Study

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Abstract

• AIM: To present retinal microstructure, metabolism and function abnormalities in the course of multiple evanescent white dot syndrome (MEWDS) by Heidelberg spectralis modality imaging platform and observe its outcome by EDI-SD-OCT and two wavelength autofluorescence.

• METHODS: A case of multiple evanescent white dot syndrome in a 23-year-old female presented initially with a 15-day history of floaters and a central scotoma in the right eye. To establish the diagnosis, multimodality imaging was performed, namely, blue light-fundus autofluorescence (BL-FAF, excitation 488nm, emission >500nm), near-infrared fundus autofluorescence (NIR-FAF, excitation 787nm, emission >800nm) using a confocal scanning laser ophthalmoscope, fundus fluorescein angiography (FFA), indocyanine green angiography (ICGA), spectrum-domain enhance depth imaging optical coherence tomography (SD-EDI-OCT), multifocal electroretinography (mf-ERG) and fundus photogragh were performed and followed up at the eighth month after initially visiting.

• RESULTS: Optical coherence tomography (OCT) showed a transient disruption of the foveal photoreceptor outer segments in correspondence to foveal granularity. NIR-FAF showed hypoautofluorescent areas, ≤ 40μ m in size, mostly concentrated around the posterior pole and its temporal side less than that in BL-FAF. Mf-ERG show pinnacle disappeared in fovea and macula and responses decreased markedly compared with the follow eye. At the eighth month follow up, hyperfluorescence in BL-FAF were disappear, while, NIR-FAF Hypofluorescent spots in early stage of such lesion were reduced. But OCT demonstrated the structure was recovered in residual Hypofluorescent area in NIR-FAF. The subfoveal choroidal thickness was decreased from 372μ m to 307μ m slightly and cost line was recovered.

• CONCLUSION: MEWDS is a benign self-healing disease and there is no pathological evidence to investigate the natural course of such disease. SD-OCT allows highly detailed images approaching histopathology to certify the microstructural changes. Two-wave length FAF and mf-ERG provide more information about metabolism in outer retina especial RPE and photoreceptor. Spectralis OCT combined with two-wavelength FAF and mf-ERG provide a new way to analyze this disease and offer more details for therapy and follow-up.

• KEYWORDS: MEWDS; Spectralis OCT; NIR-FAF; BL-FAF; mf-ERG

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INTRODUCTION

Multiple evanescent white dot syndrome (MEWDS) is a disease of unknown etiology that characteristically occurs in women in the second to fifth decades, and was first described in 1984 by Jampol *et al*[1] and Sieving *et al*[2]. It was most associated with autoimmune diseases and generally carried a good visual prognosis [3]. Ophthalmoscopic examination typically reveals multiple, 100μm to 200μm yellow-white dots deep to the retina as well as a unique foveal granularity, which may be the most specific feature of MEWDS with SD-OCT capable of localizing pathology to the outer retina-a historically controversial finding [4]. Fluorescein angiography (FA) and electrophysiologic studies suggest that the location of the disease process is in the outer retina and/or the retinal pigment epithelium (RPE)[2] and ICGA suggested pathologic choroidal nonperfusion or RPE inflammation[5,6]. Several methods such as FFA, ICGA, FAF had been performed to investigate such diseases, specially its pathogenic course. But there are rarely reports

about NIR-FAF of such lesion.

In this present study, we just focused on multi-modality imaging characteristics of MEWDS, especially for two wave-length FAF (BL-and NIR-FAF), indicating the material metabolism in this lesion, and observed the microstructural abnormalities by Spectralis SD-EDI-OCT with histology level imagination, which will provided a new view to explain the natural course of MEWDS.

Retinal imaging was performed using the Heidelberg spectralis modality imaging platform, including HRA and SD-EDI-OCT. The combination of high-resolution scanning laser imaging of the retina and SD-OCT enables real-time tracking of eyemove-ments and real-time averaging of multiple OCT B scans, thereby reducing the speckle noise of OCT images.

MATERIALS AND METHODS

Subjects A case of multiple evanescent white dot syndrome in a 23-year-old female presented initially with a 15-day history of floaters and a central scotoma in the right eye.

Methods To establish the diagnosis, multimodality imaging was performed, namely, blue light-fundus autofluorescence (BL-FAF,excitation 488nm, emission >500nm), near-infrared fundus autofluorescence (NIR-FAF, excitation 787nm, emission >800nm) using a confocal scanning laser ophthalmoscope, fundus fluorescein angiography (FFA), indocyanine green angiography (ICGA), spectrum-domain enhance depth imaging optical coherence tomography (SD-EDI-OCT), multifocal electroretinography (mf-ERG) and fundus photogragh were performed and followed up at the eighth month after initially visiting.

RESULTS

At the first visiting, best corrected visual acuity (BCVA) was 48/60 in the right eye. Examination of the left eye was remarkable for multiple, widely scattered, 100μm spots deep to the retina in the superior and temporal side of the macula and foveal granularity. OCT showed a transient disruption of the foveal photoreceptor outer segments in correspondence to foveal granularity and "COST line" (cone outer segment tip line between the IS/OS line and the retinal pigment epithelium) diappeared. At the junction between IS/OS disruption in fovea and lesion, OCT showed a high reflective line within the outer photoreceptor layer. At the margin of IS/OS disruption in fovea, the ONL shrinked and attracted into PR layer and OLM disupted at this site. The corresponding RPE separated from Bruch membrane. The RPE layer in lesion became thicker. NIR-FAF showed hypoautofluorescent areas, ≤40μm in size, mostly concentrated around the posterior pole and its temporal side less than hyperautofluorescent dots in BL-FAF. BL-FAF demonstrated that areas of increased autofluorescence usually found in correspondence to the white dots seen ophthalmoscopically and the site of the focal hypocyanescent spots seen on ICG but less numerous, although they were not visible clinically. FA demonstrated typical early hyperfluorescence corresponding to hypoautofluorescent spots in NIR-FAF which was in correspondence to hypofluorescent areas in the late phase of ICGA. The hypofluorescent areas in the late phase of ICGA were demonstrated moderately reflective focal lesions within the outer photoreceptor layer, where the inner and outer segment junction was disrupted by Spectralis OCT. mf-ERG show pinnacle disappeared in fovea and macula and responses decreased markedly compared with the follow eye. Amplification density of P1 wave was 30.9nV/deg^2 and reduced significantly compared with the follow eye. A diagnosis of MEWDS was determined based on the clinical feature and visual field results

At the second visiting, the eighth month follow up, (BCVA) improved to be 60/60 in the right eye.While, the foveal granularity and "COST line" was recovered by Spectralis OCT and the subfoveal choroidal thickness was decreased from 372μm to 307μm slightly. Hyperfluorescence in BL-FAF of early stage of such lesion were disappear,while, NIR-FAF Hypofluorescent spots in early stage of such lesion were reduced. But OCT demonstrated the structure was recovered in residual Hypofluorescent area in NIR-FAF (Figure 1).

DISSCUSION

MEWDS is a kind of primary inner capillary choroidalpathy (PICCP), considered as RPE inflammation and acute choroidal ischemia, mainly involving macula. The value of ICG angiography remains significant for Multiple Evanescent White Dot Syndrome (MEWDS) or Birdshot chorioretinitis [7]. Furthermore, RPE is beneficial for the metabolism and nutrition of photoreceptor and RPE-Bruch complex produce a markedly effect on connecting the retina and choroid. Thus, several uveitis usually involve this complex and affect photoreceptor.

Schmitz-Valckenberg *et al* [8] noted that the FAF was dependent on outer segment renewal and could be used as an indicator of the health of the retinal pigment epithelium. Early in MEWDS, multifocal choroidal inflammation may lead to increased phagocytosis of photoreceptor outer segments with increased production of lipofuscin, resulting in increased observed FAF. As the inflammatory response subsides, photoreceptors regenerate their outer segments and decrease their release to the retinal pigment epithelium, resulting in decreased production of lipofuscin and FAF. The photoreceptors at the center of larger lesions may be more severely affected by the inflammation than the smaller lesions. One important component of lipofuscin in retinal pigment epithelium cells is A2E [9],whose autofluorescent precursors (A2PE-H2, A2PE, and A2-rhodopsin) form in outer segments before phagocytosis by the retinal pigment epithelium[10,11]. These fluorophores, which are precursors to

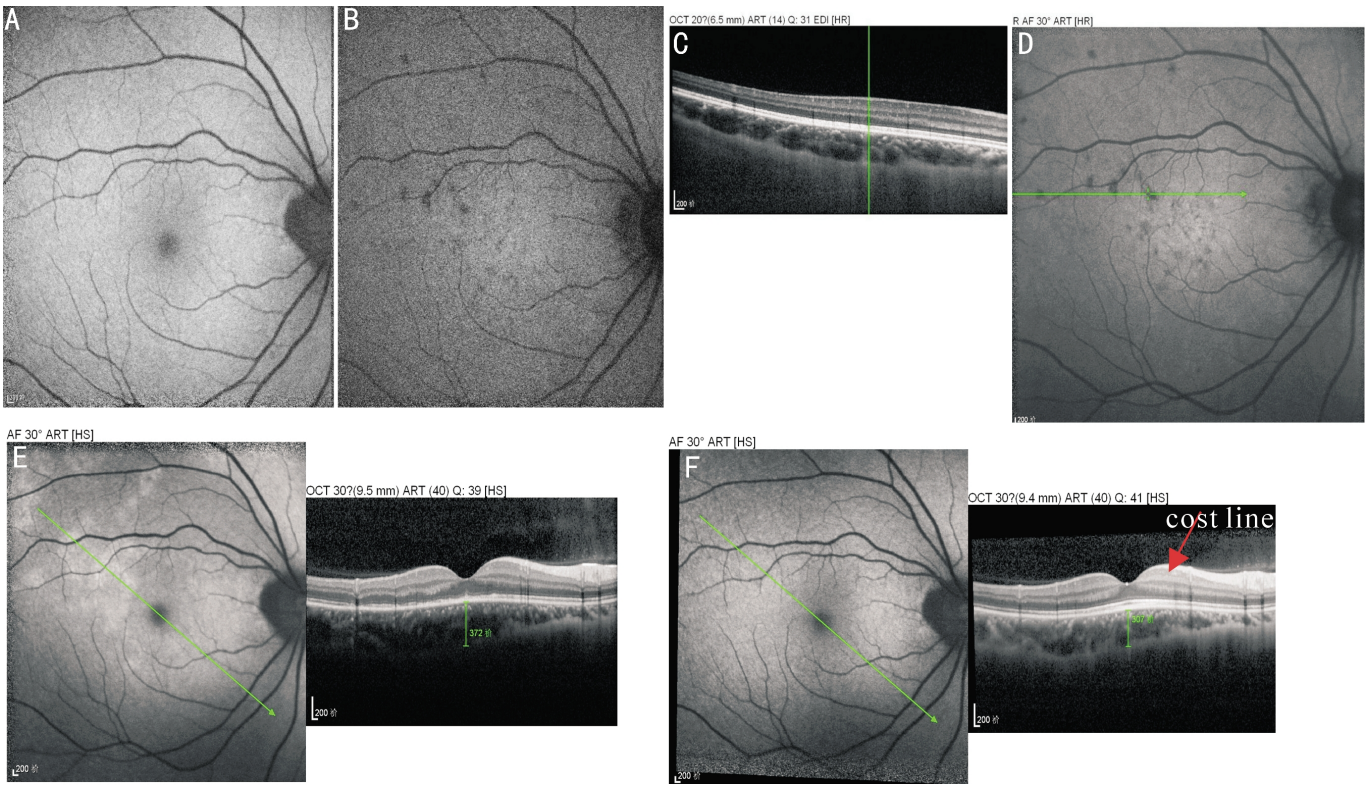

Figure 1 At the eighth month follow up, BL−FAF hyperfluorescence in early stage of the lesions were disappear (A), NIR-FAF hypofluorescent spots in early stage were reduced (B). EDI-SD-OCT demonstrated the structure was recovered (C) in residual Hypofluorescent area in NIR-FAF (D). The foveal granularity was recovered by Spectralis OCT and the subfoveal choroidal thickness was decreased from 372μm (E) to 307μm (F) slightly,the foveal granularity and "COST line" was recovered (red arrow) .

A2E that accumulate in the retina, show peak fluoresce at longer wavelengths than lipofuscin. So, except for BL-FAF whose fluorophore is mainly lipofuscin, NIR-FAF of non-lipofuscin and melanin (oxidation) at longer wavelengths was recorded.

Areas of increased autofluorescence in BL-FAF usually found in correspondence to the site of the focal hypocyanescent spots seen on ICG but less numerous, which were demonstrated moderately reflective focal lesions within the outer photoreceptor layer, where the inner and outer segment junction was disrupted by Spectralis OCT, according to Penha FM`s study [12]. NIR-FAF showed hypoautofluorescent dots less than hyperautofluorescent areas in BL-FAF, which suggested that the RPE was in a high metabolism stage with lipofuscin accumulated.

On the other hand, the hypoautofluorescent spots in NIR-FAF were in correspondence to severely damaged RPE cells with melanin involved, where the inflammation mass penetrate OLM or not and involved ONL. Thinning of the outer nuclear layer was seen by Spectralis OCT, suggesting that MEWDS may result in permanent photoreceptor atrophy. But at the eighth month follow up, the different pattern between BL and NIR-FAF, especially that OCT demonstrated the structure was recovered in residual Hypofluorescent area in NIR-FAF, may indicate the difference metabolism pathway between lipofuscin and melanin, which need further study to verify.

The a-wave on ERG, representing photoreceptor function[13], was not markedly reduced. This can be explained by the localised macular involvement. Mf-ERG shows pinnacle disappeared in fovea and macula and amplification density of P1 decreased significantly compared with the follow eye. P1 wave demonstrated depolarization of dipolar cells which induced transfer through Na^+/Ca^+ and K^+ channel in Rod outer segment plasma membrane. Thus, low level of P1 wave suggested disfunction of photoreceptor and its nutrition cell--RPE.

The malfunction of IS/OS, RPE-Bruch membrane complex was certified in microstructural abnormalities by Spetralis OCT was used in this study. Using a novel OCT-based method of quantitatively measuring photoreceptor outer segment length, Forooghian *et al* [14] showed that photoreceptor outer segment length decreased acutely with restoration to normal following disease resolution.

Spectralis OCT, capable of 3μm axial resolution, revealed a transient disturbances and signal attenuation in the photoreceptor IS/OS junction, especially the photoreceptor outer segments across the macula in MEWDS. A high reflective line within the outer photoreceptor layer was observed by Spectralis OCT at the junction between IS/OS disruption in fovea and lesion indicated inflammation in photoreceptor and RPE. We compared the subfoveal

choroidal thickness before and after recovery and got the result that it decreased. Aoyagi *et al*[15] had first reported the relationship between subfoveal choroidal thickness and MEWDS that the choroid was thicker in the acute phase than the convalescent phase in both the affected and opposite eyes of both patients, suggesting that an inflammatory reaction might occur in the choroidal stroma in addition to the choriocapillaris and might be bilateral rather than unilateral.

Healthy cones show a strong directional reflex towards the centre of the pupil, the so called "optical Stiles Crawford" effect. A foveal reflection analysis (FRA) measurement provides a parameter rho as a quantitative measure of the cone directionality. In addition, it provides estimates of the densities of lens, macular pigment and melanin. FRA, showed disarray of the foveal cones and indicated that in MEWDS the cones are temporarily in disarray, which is in agreement with our study, but regain their original orientation in a matter of weeks[16].

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[17,18], retinitis pigmentosa, repaired retinal detachment, closed macular hole, and re-solved central serous chorioretinopathy.

RPE disturbances are normally visualized as an increase in OCT signal penetration into the choroid. Spectralis OCT findings suggest that MEWDS is more likely associated with RPE inflammation. Swollen but intact RPE cells would likely appear thicker on OCT imaging, as well as RPE separated from Bruch membrane was seen in part of lesions. On the other hand, inflammation of the RPE cells could interrupt the orientation of photoreceptor outer segments acutely, causing attenuation of OCT signal from the IS/OS junction as the outer segments become misaligned, which demonstrated IS/OS structure changes mentioned above. At the eight month follow up, the "COST line" was recovered, considered as the better progression. The abnormality of the COST line was considered a subclinical sign for acute zonal occult outer retinopathy (AZOOR)[19], another subtype of PICCP.

MEWDS is a benign self-healing disease and there is no pathological evidence to investigate the natural course of such disease. SD-OCT allows highly detailed images approaching histopathology to certify the microstructural changes and two-wave length FAF and Mf-ERG provids more information about metabolism in outer retina especial RPE and photoreceptor. Spectralis OCT combined with two-wavelength FAF and mf-ERG provide a new way to analyze this disease and offer more details for therapy and follow-up.

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