Editorial

MEWDS, Common Cold of the Retina

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Multiple Evanescent White Dot Syndrome (MEWDS) was first described by Jampol and colleagues in 1984 as an acute, idiopathic, and typically unilateral disturbance in vision.[1] It manifests as transient small gray-white dots in the outer retina and retinal pigment epithelium (RPE) with foveal granularityas the most characteristic feature.[1,2] Other features include an edematous appearing optic nerve head and the presence of cells in the vitreous. No known racial or hereditary predilections have been reported.[3] Associated clinical findings include a flu-like prodrome, predisposition to involve young females, blurred disc margins, and temporal scotomata.[1] Although the precise pathogenesis remains unknown, a viral-like infection with a possible immune-mediated mechanism and genetic susceptibility is suspected.[4] In all of the MEWDS variants, a predilection for inflammation seems to exist in the peripapillary circulation. In this location, a plentiful source of ciliary arteries communicates axially with the retinal circulation and accounts for the characteristic enlargement of the blind spot that is observed in patients with this disorder.[5]

Based on their clinical and angiographic evidences,[2] the lesions are best characterized on fluorescein angiography (FA) as "wreath-like" punctate areas of early hyperfluorescence (window defects in the RPE, retinal vascular abnormalities, or a combination of both).[5] On indocyanine green angiography (ICGA), numerous hypocyanescent lesions significantly outnumber those visible on clinical examination and FA.[5-7]

The MEWDS lesions of the fundus are variable in size, ranging from dots (small lesions approximately 100 μm) to spots (larger lesions 200 μm). Small lesions (dots) are anterior to the larger lesions (spots).[5] Dots are superficial to spots in a seemingly dual-layered pattern at the level of the middle retina and the deep retina and RPE. Dots appear to be localized in the middle retina, and occur in larger numbers around the optic nerve head and the nasal retina. High magnification reveals that each dot is composed of many smaller lesions arranged in clusters. Occasionally, the dots align beneath retinal vessels, and patchy venous sheathing is observable.[4] In contrast, spots are localized to the deep retina and RPE and extend to the midperipheral fundus. Dots and spots seem to be absent in the foveal area in MEWDS, despite the foveal granularity typically seen on clinical examination. During the acute phase of the disorder, new dots and spots appear in a cluster as older lesions disappear, with spots resolving before dots. The combination of dots and spots produces a pattern on ICGA that appears to be pathognomonic for MEWDS.

The ICGA imaging modality most clearly demonstrates the multifocal spots and a zonal hypocyanescence in the peripapillary area. Such findings correspond to enlargement of the blind spot on visual field testing.

Ultra-high resolution optical coherence tomography (OCT), capable of 3-μm axial resolution, has clearly identified pathologic disruptions of the ellipsoid zone (EZ) in cases of MEWDS, without evidence of RPE disturbances or photoreceptor cell body loss.[7,8]

At the fovea, OCT shows disruption of the EZ and accumulations of hyperreflective material of variable size and shape. These accumulations vary from dome shaped deposits over the RPE, to linear and vertical aggregations, and other irregular formations centered at the EZ.

The accumulations of hyperreflective material resting on the RPE extend inward through the interdigitation zone (IZ), EZ, and outer nuclear layer (ONL) towards the inner retina. Irregularities of the RPE are also observed.

External to the fovea, OCT imaging also reveals the presence of discontinuities or disruptions centered on the EZ, including the IZ and, occasionally, the ONL. The spots observed with FA and ICGA correlate with these OCT findings. Vertical extension of the ellipsoid abnormalities could be correlated to the dots on FA and ICGA.[9] Peripapillary subretinal fluid and pigment epithelial detachment (PED) can be seen on OCT.[10]

En face OCT imaging demonstrates an unremarkable choroid and choriocapillaris and unaffected RPE layer.[8] The EZ and IZ are disrupted in areas corresponding to spots as well as dots. The *en face* OCT

of the outer portion of the ONL shows accumulations of hyperreflective material, which correspond to the dots visible on FA.

Enhanced depth imaging OCT (EDI-OCT) measurements suggest a transient choroidal thickening; however, the changes are not statistically significant.[9]

Short-wavelength fundus autofluorescence (SW-AF) of the foveal area reveals hyporeflective dots and hyperreflective areas that correlate to spots observed on FA and ICGA, as well as to areas of disruption of the EZ on OCT.[9]

There is no evidence of choroidopathy; however, nonspecific choroidal thickening, common in many chorioretinal inflammatory diseases, is seen in some patients. In spite of some nonspecific secondary mottling and proliferation of the RPE, there is no evidence of primary RPE disease either.

The classic "wreath-like" retinal lesion best seen on FA may be due to middle or deep retinal capillary hyperfluorescence, perhaps from dilation of the retinal microcirculation by inflammation. Inflammatory mediators may extend from the outer and inner layers to the middle retina to affect the deep retinal capillaries. Another explanation for the early hyperfluorescence of these lesions on FA may relate to the excitation of microglia which have been implicated in immune mediated inflammatory processes of the retina. The stellate configuration of microglial cells in the retina resembles the wreath-like lesions seen on FA in MEWDS. Activation of microglia by inflammation, in conjunction with dilation of the deeper retinal circulation, may contribute to the presenting signs of MEWDS.[11] Similar observations have been made in retinal microglia of transgenic mice expressing the green fluorescent protein (GFP). The GFP from the jellyfish *Aequorea victoria* is the most widely used fluorescent reporter in biological research. Transgenic mice and zebra fish expressing GFP in specific cell lineages or whole tissues have been extensively used for *in vivo* microscopy (IVM) experiments over the past few decades.[12]

In the adult retina, microglial cells are distributed primarily in the middle to inner retina: the plexiform layers, ganglion cell layer, and nerve fiber layer. They display highly motile protrusions in all directions, unaccompanied by soma migration. This suggests that the process dynamics may also serve to exchange signals between neighboring microglia, and may help to explain laminar retinal microglia distribution. Interestingly, in the adult retina, microglial cells have varying morphologies throughout the different layers. Activation of microglial cells plays a key role in the initiation and perpetuation of the retinal inflammatory response. Activated microglial cells can proliferate and migrate to the site of injury, where morphological alterations are usually accompanied by changes in signaling and gene expression.[13]

In acute MEWDS, the EZ is disrupted but is restored during recovery. No abnormalities are seen in the ONL and the RPE during follow-up. These OCT findings suggest that there is disruption in outer segments and EZ but photoreceptor cell bodies are intact, which may contribute to almost complete recovery of the photoreceptor outer segments. The reduced full field electroretinography (ffERG) and multifocal electroretinography (mfERG) amplitudes during the acute stage, which recover with restoration of the EZ, support the presumption that the main lesion of MEWDS involves damage to the photoreceptor outer segments and the EZ, but not the RPE or choriocapillaris.[6,8]

MEWDS is a disease of the photoreceptors and is almost completely reversible. The vitreous, RPE, and choroid are only secondarily and transiently involved. Therefore, MEWDS can be considered a "Common Cold" of the retina.

Protrusion of the hyperreflective material from the EZ towards the ONL corresponds to the location of dots visualized with photography, ICGA, and FA. The presence of a plaque of outer retinal involvement from confluent spots appears to be pathognomonic for MEWDS, differentiating it from idiopathic multifocal choroiditis. MEWDS is predominantly a disease of the outer retina, centered on the EZ, but also involving the IZ and the ONL. Minor changes in the acute and healed stages also occur in the RPE and choroid.[9]

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