Microcystic macular oedema confirmed, but not specific for multiple sclerosis

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Sir, a potentially new sign in multiple sclerosis was described in Brain (Gelfland et al., 2012). This new sign, microcystic macular oedema, is intriguing because it is considered to indicate breakdown of the blood-retinal barrier with or without microglial inflammation (Gelfland et al., 2012). There are earlier reports on vascular instability and leakage during inflammation in multiple sclerosis readily seen as sheathing of the retinal veins (Rucker, 1944). Not commented on in the article, but clearly visible from the images (Figs 1A, 3A, B and C in Gelfland et al., 2012), microcystic macular oedema occurs in areas without vascular sheathing. In fact, in most cases microcystic oedema is seen remote to the inner retinal vasculature (Figs 1A and 3A–C in Gelfland et al., 2012). Why does microcystic oedema predominantly affect retinal layers close to the very tight inner blood retinal barrier? Are there alternative pathological features to be considered?

One possibility could be Müller cell pathology. Like astrocytes in the brain, Müller cells are responsible for maintaining tissue homeostasis. Müller cells transverse all retinal layers orthogonal from the inner limiting membrane bordering the vitreous body to the external limiting membrane. Regulation of the retinal water content is a major role of Müller cells and controlled through aquaporin 4 (AQP4) water channels (Dyer et al., 2000). In the retina AQP4 is only expressed on Müller cells. In the macular area, regulation of water fluxes is highly dependent on Müller cell function because of the paucity of retinal vasculature. Therefore, an alternative pathological mechanism explaining microcystic macular oedema in multiple sclerosis may be Müller cell dysfunction.

To address this question we retrospectively reviewed a cohort of patients with multiple sclerosis (n = 129) and healthy controls (n = 81) from the MS Centre in Amsterdam. We included patients with relapsing-remitting, secondary progressive and primary progressive multiple sclerosis. All patients with multiple sclerosis had a disease duration of at least 15 years. All patients had retinal spectral domain optical coherence tomography performed using the same device and protocol as at the University of California, San Francisco. All retinal spectral domain optical coherence tomography scans fulfilled rigorous quality control criteria (Tewarie et al., 2012).

We identified a single case (1/129; 0.8%, 95% confidence interval 0.1–4.3%) in our cohort of patients with multiple sclerosis, in whom this newly described form of microcystic macular oedema was present. The macular spectral domain optical coherence tomography scan of this male patient showed several clear cystic areas of hyporeflectivity on multiple adjacent B-scans (Fig. 1A). The patient (with relapsing-remitting multiple sclerosis) suffered from optic neuritis in this eye 17 years ago. He experienced more than one relapse per year and was started on interferon β 12 years before the study. Ten years ago, he entered a natalizumab trial, after which he stayed on natalizumab, until 3 years ago. Currently, he is not using any medication and is clinically stable. His Expanded Disability Status Scale was 3.0 at the time of the spectral domain optical coherence tomography assessment. None of the healthy control subjects had microcystic macular oedema.

Of note, we have anecdotally seen microcystic macular oedema in patients who do not suffer from multiple sclerosis. One example is shown in Fig. 1B. This 53-year-old male did experience optic neuritis in his right eye 6 years ago. In subsequent years, he has suffered from another 10 episodes of visual loss in the same eye. Each episode was preceded by right-sided ocular pain on eye movements and scintillations. In between episodes he suffered from glare. On examination, there was a right relative afferent pupillary defect, reduced colour vision and visual acuity (0.4) on the right. Multiple MRI scans of his brain and spinal cord with gadolinium never revealed any lesions other than inflammation of...
his right optic nerve. The latency of visual evoked potentials (P100) on the right was severely delayed (right 137 ms, left 108 ms). He was given a diagnosis of relapsing isolated optic neuritis (Petzold et al., 2010).

In summary, we confirm the description of the presence of microcystic macular oedema using spectral domain optical coherence tomography in patients with multiple sclerosis, albeit in a substantially smaller proportion of patients. This new sign may not be specific to multiple sclerosis as we have also observed it in a patient with relapsing isolated optic neuritis (Fig. 1B). This patient also reported glare in the affected eye. Importantly, Müller cells minimize retinal light scattering, a cause for glare, by guiding light through their foot processes directly to individual photoreceptors (Agte et al., 2011). Our data are consistent with the hypothesis that Müller cell pathology may be relevant in patients with microcystic macular oedema. We are unable to tell whether or not glare may be part of the clinical phenotype in these patients. Likewise, we are not aware of any data relating targeted autoimmunity against Müller cells, for example via anti-AQP4 or anti-KIR4.1 antibodies to microcystic macular oedema. It would be interesting to hear the thoughts of Gelfland et al. on the hypothesis on Müller cell pathology and, if available, more information on the phenotype of their patients with regard to visual symptoms such as glare.

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**References**


