Sir, we appreciate the thoughtful comments submitted in response to our recent article describing a new retinal phenotype (microcystic macular oedema) in a subset of patients with multiple sclerosis (Gelfand et al., 2012).

We thank Balk et al. and Abegg et al. for sharing similar observations of microcystic abnormalities of the inner nuclear layer in patients with optic nerve injury in the absence of multiple sclerosis. Clarification of the specificity of microcystic macular oedema will contribute towards understanding its aetiology, its relationship to optic neuropathy and its significance in multiple sclerosis.

As discussed in our article, we considered two separate, but not mutually exclusive, mechanisms that could contribute to the development of microcystic macular oedema in multiple sclerosis: retinal inflammation with associated blood-retinal barrier leakage and/or trans-synaptic degeneration. We appreciate the proposition by Balk et al. that distortion or loss of Mueller cells in the inner nuclear layer could be an additional contributory mechanism. This warrants more detailed investigation in future studies.

We agree that microcystic changes may occur strictly as a consequence of trans-synaptic degeneration; however, the individual cases highlighted by Balk et al. and Abegg et al. should be interpreted with caution. Balk et al. note an example of microcystic inner nuclear layer changes in a patient with recurrent unilateral optic neuritis without evidence of disseminated demyelination (relapsing isolated optic neuritis). This suggests that inflammatory demyelination in the optic nerve alone may be sufficient to induce microcystic macular oedema. However, it is worth highlighting that ~25% of eyes experiencing acute optic neuritis exhibit blood-retinal barrier breakdown, as evidenced by the presence of fluorescein leakage and/or uveitic features during the time of acute optic neuritis (Lightman et al., 1987). Since breakdown of the blood-retinal barrier is one of the important potential mechanisms underlying microcystic macular oedema, we would be cautious about drawing conclusions from a single patient with relapsing isolated optic neuritis (RION). In addition RION sometimes evolves into a more disseminated disease process such as multiple sclerosis or neuromyelitis optica.

Abegg et al. describe a case of microcystic inner nuclear layer abnormalities in an adolescent with neurofibromatosis type 1 (NF1) and associated optic nerve glioma. Although they characterize the lesion as a ‘compressive optic neuropathy’, it should be noted that NF1 is a complicated disorder, the pathobiology of which is not simply characterized by the development of tumours. White matter lesions, vascular abnormalities (including in the retina) and derangements in astrocyte function (including in the optic nerve in NF1-associated optic gliomas) have all been shown to occur in NF1 (Raininko et al., 2001; Bajenaru et al., 2003; Wu et al., 2006; Rodriguez et al., 2008). Therefore, the complex biology of NF1 needs to be considered carefully in the interpretation of their observation. It would also be useful to have a detailed description of the patient’s treatment history (i.e. history of radiation), to better understand the clinical context of their report.

We anticipate that microcystic macular oedema will be recognized in other disease states that involve the optic nerve—especially those in which inflammation plays a significant role. The fundamental question clinically, as it relates to multiple sclerosis, is not specificity, but rather the significance of these findings in the disease. Unlike Abegg et al., we do not think that microcystic...
macular oedema is an incidental finding in multiple sclerosis or that visual dysfunction in multiple sclerosis is better understood by evaluating the retinal nerve fibre layer or optic nerve atrophy alone. As we note in our article, one of the central findings from our work was that microcystic macular oedema was associated with visual dysfunction that could not be explained by retinal nerve fibre layer loss alone. Furthermore, microcystic macular oedema was associated with greater overall disability in multiple sclerosis, independent of retinal nerve fibre layer thickness. In our cohort of patients with multiple sclerosis, microcystic macular oedema of the inner nuclear layer was dynamic (which is different from the case reported by Abegg et al.). Establishing the exact prevalence, as well as the dynamic nature of microcystic macular oedema in multiple sclerosis, will require additional confirmation in larger data sets. Possible sources of variation could include differences in the underlying population of patients with multiple sclerosis studied as well as technical discrepancies, such as averaging of B-scans.

We appreciate that the microcystic inner nuclear layer pathology observed by Vanburen (1963) and Gills and Wadsworth (1966, 1967) has a similar appearance to the microcystic macular oedema phenotype we observed using optical coherence tomography in multiple sclerosis. However, we caution against presuming that retrograde trans-synaptic degeneration must necessarily be the sole operative mechanism, as some subsequent studies have been unable to confirm their findings (Darby et al., 1990; Komaromy et al., 2003). Moreover, it is interesting to note that Gills (1966) was one of the first investigators to propose that primary retinal pathology (distinct from optic nerve injury and its sequelae) is operative in multiple sclerosis.

Finally, Abegg et al. suggest that ‘microcystic macular degeneration from optic neuropathy’ may be a more appropriate term for this retinal abnormality. We elected to describe this phenotype as ‘microcystic macular oedema’ based on its microcystic, honeycombed appearance on optical coherence tomography and the increase in the volume of the macula associated with it. Similar appearing microcystic changes of the inner nuclear layer have been described in association with frank cystoid macular oedema (Brar et al., 2010). We added the qualifier microcystic to avoid confusion and distinguish this novel entity from conventional macular oedema. Terminology is evolving with advances in optical coherence tomography. The expression retinal ‘pseudocysts’ was recently proposed to describe scattered cystic-appearing lesions in the inner nuclear layer on optical coherence tomography in areas of geographic atrophy in age-related atrophic macular degeneration (the ‘pseudo’ added to distinguish these presumed ‘empty spaces’ from ‘walled’ fluid-filled structures; Cohen et al., 2010). The appropriate terminology for microcystic inner nuclear layer pathologies should be revisited when the underlying pathophysiology is better understood.

Funding

American Academy of Neurology Clinical Research Training Fellowship (to J.M.G.); National Institutes of Health (KL2 RR-024130), Howard Hughes Medical Institute Physician Scientist Early Career Award (57006497) and Debbie and Andy Rachleff Distinguished Professorship of Neurology (to A.J.G.).

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