LETTER TO THE EDITOR

Reply: Retinal pathology in multiple sclerosis: insight into the mechanisms of neuronal pathology

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Sir, We wish to acknowledge the insightful and constructive comments provided by Gundogan and colleagues regarding potential retinal disturbances that may occur in the setting of multiple sclerosis, in response to the scientific commentary (Calabresi et al., 2010) pertaining to the study, recently published in Brain, of ocular pathology in multiple sclerosis (Green et al., 2010).

Retinal nerve fibre layer thinning has been shown to occur in multiple sclerosis, both in eyes with and without a history of optic neuritis. This has been demonstrated pathologically (Toussaint et al., 1983) as well as in vivo with the use of optical coherence tomography (Parisi et al., 1999; Trip et al., 2005; Fisher et al., 2006). Retinal nerve fibre layer thinning in the absence of a history of clinical optic neuritis is thought to be the result of subclinical optic neuropathy. Optic neuropathy is thought to result in retrograde degeneration of constituent optic nerve axons (Trapp et al., 1998), in turn culminating in ganglion cell death (Shindler et al., 2008). Attenuation of the N95 amplitude (primarily regarded as a reflection of ganglion cell integrity) in pattern electroretinography, both in multiple sclerosis eyes with and without a history of optic neuritis, corroborates this hypothesis.

As pointed out, Hollander et al. (1984) observed that retinal changes are restricted to the inner retina following optic nerve transection. Indeed, several additional animal (Levkovitch-Verbin et al., 2001; Williams et al., 2001) and electrophysiological studies (Dawson et al., 1982; Seiple et al., 1983; Kaufman and Celesia, 1985) have likewise failed to demonstrate atrophy or dysfunction in retinal layers deeper than the ganglion cell layer, except for reorganization of the inner nuclear layer (but without accompanying cell loss) (Williams et al., 2001), following optic nerve transection. Such observations raise the possibility that retrograde degeneration of retinal layers resulting from optic nerve pathology may not extend beyond the ganglion cell layer. As such, findings from prior electrophotography studies in multiple sclerosis have suggested the possibility that outer retinal dysfunction may occur in multiple sclerosis (Papakostopoulos et al., 1989; Forooghian et al., 2006; Gundogan et al., 2007). Further, although the possibility of structural abnormalities within the inner nuclear layer of multiple sclerosis eyes has been previously suggested (Gills, 1966), this has not been demonstrated or studied in the same systematic fashion as the study by Green et al. (2010).

Gundogan and colleagues’ (2007) full-field electroretinography findings implicating outer retinal dysfunction in multiple sclerosis are interesting and consistent with findings from other electroretinography studies in multiple sclerosis, which have likewise implicated outer retinal dysfunction (Forooghian et al., 2006). It is not unreasonable to suggest that an immune-mediated mechanism may underlie outer retinal dysfunction in multiple sclerosis. Retinal periphlebitis occurs in up to 20% of multiple sclerosis cases (Kerrison et al., 1994; Green et al., 2010) and since the retina is essentially devoid of myelin, this suggests that myelin may not be necessary for establishing or maintaining retinal inflammation in multiple sclerosis. Furthermore, the occurrence of periphlebitis in multiple sclerosis emphasizes breakdown of the blood-retinal barrier as a feature of the multiple sclerosis disease...
process, which may facilitate retinal antigen exposure and the propagation of immune-mediated processes targeting retinal antigens. Indeed, anti-retinal antibody reactivity against retinal antigens including arrestin and α-enolase have been described in multiple sclerosis (Gorczyca et al., 2004; Forooghian et al., 2007), with highest anti-retinal activity associated with greatest electroretinography disturbances. These data may support a role for potential auto-immune mechanisms underlying outer retinal dysfunction in multiple sclerosis.

However, to date, there are no data supporting structural disruption within retinal layers deeper than the inner nuclear layer in multiple sclerosis. If multiple sclerosis affects the outer retina independent of optic nerve pathology this may imply that primary retinal neuronal pathology could be a feature of the multiple sclerosis disease process. However, it remains possible that detected outer retinal dysfunction in multiple sclerosis may represent heightened neuronal susceptibility to retrograde trans-synaptic degeneration resulting from optic nerve pathology in some patients with multiple sclerosis, as suggested by Green et al. (2010). Perhaps optical coherence tomography segmentation techniques (enabling quantitative assessment of individual retinal layers) in the future may help determine if patients with multiple sclerosis demonstrate structural abnormalities below the inner nuclear layer. Longitudinal in vivo optical coherence tomography segmentation studies following optic neuritis may shed light on retinal layer changes resulting from optic nerve pathology in multiple sclerosis and help discriminate which, if any, retinal changes in multiple sclerosis may not be the derivative of optic nerve pathology, but instead potentially represent primary retinal-mediated mechanisms of pathology.

References


