

LETTER TO THE EDITOR

Reply: Microcysts in the inner nuclear layer from optic atrophy are caused by retrograde trans-synaptic degeneration combined with vitreous traction on the retinal surface

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Sir, We appreciate the thoughtful commentary from Drs Lujan and Horton (2013) based on their patient with Kjer's dominant optic atrophy with retinal inner nuclear layer microcysts. Their case highlights an emerging understanding that inner nuclear microcysts are not specific to multiple sclerosis. We—and others—have now identified them in neuromyelitis optica (Gelfand *et al.*, 2013; Sotirchos *et al.*, 2013) and they have been reported to occur in neurofibromatosis 1-associated optic nerve glioma (Abegg *et al.*, 2012), dominant optic atrophy and Leber's hereditary optic neuropathy (Barboni *et al.*, 2013). Anecdotally, we have also heard of individual cases in patients with nerve atrophy following papilledema and traumatic optic neuropathy. However—other than for neuromyelitis optica—the frequency with which the microcysts occur in non-multiple sclerosis optic neuropathy remains unclear, and we are not aware of any cases of retinal inner nuclear layer microcysts that have been described in the most common optic neuropathy, glaucoma.

Lujan and Horton (2013) assert that these inner nuclear layer microcystic changes are related to trans-synaptic cell loss based on pathological reports that highlight inner nuclear layer cell loss in multiple sclerosis (Gills and Wadsworth, 1967; Green *et al.*, 2010) and after other forms of optic nerve injury (Van Buren, 1963). We strongly agree that the emerging evidence combined with the pathology data suggest that trans-synaptic cell loss is likely to be a significant contributory mechanism to the formation of these microcysts. However, we disagree with Barboni *et al.* (2013) that 'inner nuclear layer microcysts are simply a consequence of longstanding optic neuropathy'. Sigler *et al.* (2013) observed microcysts developing 2–4 months after internal limiting membrane peel. We have since observed a case of inner nuclear

layer microcysts in a 17-year-old female that developed 10 weeks after acute optic neuritis. These cases indicate that the injury does not necessarily have to be longstanding and the highly variable time interval observed for onset of microcysts suggests that there may be other important patient-specific factors driving the presence and pace of microcyst development. Furthermore, the short latency from onset of optic neuropathy to the development of microcysts observed on occasion suggests that direct injury may be contributory in some individuals rather than being solely dependent on a trans-synaptic process. We have seen mild capillary leakage on two of five fluorescein angiograms in patients with microcysts (10 eyes) although the areas of leakage could not be directly correlated to the location of an identifiable cyst. This result will require further investigation and replication.

In addition, we are concerned that our observation of an association between microcysts and disease severity in multiple sclerosis has been misunderstood. Our analysis identified an association between microcysts and disability from multiple sclerosis, independent of age and disease duration. This finding in multiple sclerosis has since been confirmed and extended by Saidha *et al.* (2012). Presuming the importance of trans-synaptic processes in the majority of patients with microcysts, this may imply that patients who are prone to trans-synaptic loss in the retina are more prone to trans-synaptic loss elsewhere in the CNS and that the variability of brain atrophy and disability that occurs in multiple sclerosis may in part be explained by variable propensity of patients to suffer trans-synaptic cell loss.

Lujan and Horton (2013) provide beautiful images to support their contention that the location and distribution of microcysts is explained by traction caused by incomplete separation of the

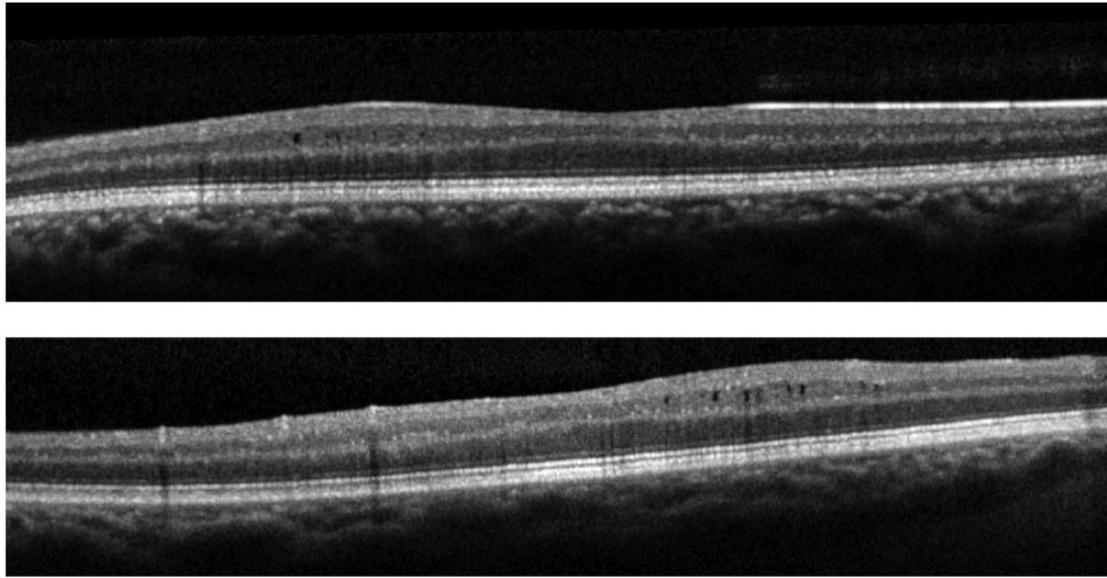


Figure 1 Examples of microcysts from two patients without incomplete separation of the posterior hyaloid membrane and no evidence for vitreomacular traction or vitreomacular adhesion. Panel A from the left eye of a 31-year-old man with progressive relapsing multiple sclerosis. Panel B is from the right eye of a 50 year old man with bilateral optic neuropathy secondary to seronegative neuromyelitis optica.

posterior vitreous from the internal limiting membrane. Based on the prevailing view that vitreoretinal traction requires evidence of sharp angulation of the internal limiting membrane at the point of vitreal insertion (Carpineto *et al.*, 2011)—and as detailed in our paper (Gelfand *et al.*, 2012)—we excluded subjects from our published analysis with evident hyaloid membrane traction as determined by our retinal expert (D.S.). However, in consideration of the proffered theory, we reviewed (or re-reviewed) 46 cases of inner nuclear microcystic change that we have now observed in our laboratory from all causes to assess (i) whether incomplete separation of the vitreous was evident (as an indication of milder traction from vitreomacular adhesion); and (ii) whether microcysts are strictly limited to the area around the area of posterior hyaloid membrane insertion. Analysis of these data did not support the hypothesis. Whereas some of the cases did have evidence of incomplete separation of the vitreous, nearly 80% had an intact posterior vitreous membrane or complete detachment (Fig. 1). Although the predominance of microcysts do appear to follow the C-shaped pattern identified by Lujan and Horton (2013), we also observed microcysts distributed throughout the macula including cysts as far as 12° from the foveola and a number of cases in which microcysts were most prominent—or only evident—on the temporal side of the macula.

We therefore do not believe that current evidence supports the contention that posterior hyaloid traction is a necessary precondition for the development of microcysts. As a consequence, we consider it likely that the microcysts in the case from Lujan and Horton (2013) were made more manifest by the presence of traction from an incompletely separated hyaloid membrane, but that this condition is not prerequisite in all cases.

Lastly, our paper demonstrated that after adjusting for the severity of optic neuropathy, microcysts were associated with vision loss (Gelfand *et al.*, 2012). Sigler *et al.*, (2013) also concluded that the morphologically similar inner nuclear layer cystic spaces that they identified had visual consequences. Therefore, the presence of microcysts may be visually significant. This should be the subject of additional study and evaluation.

In total, we greatly appreciate the contributions to this developing story from Lujan and Horton (2013) as well as other investigators who have significantly added to our understanding of retinal inner nuclear layer microcysts. We look forward to additional investigations on the topic that promise to extend our knowledge further.

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