BRAIN
A JOURNAL OF NEUROLOGY

SCIENTIFIC COMMENTARY

# The expanding spectrum of aetiologies causing retinal microcystic macular change

In this issue of *Brain*, John Kisimbi *et al*. (2013) describe spectral domain optical coherence tomography (OCT) findings in a cohort of patients with Tanzanian endemic optic neuropathy, a disorder of unknown aetiology, leading to severe bilateral subacute optic neuropathy. They describe severe retinal nerve fibre layer (RNFL) thinning and concomitant microcystic macular changes in 12.5% of this cohort. The authors describe a parafoveal annular or semi-lunar pattern of the microcystic (perhaps a misnomer but the term will be used for consistency in the literature) changes with a predilection for the nasal aspect of the macula visible using *en face* infrared imaging. This distribution of microcystic macular change is consistent with that described in previous contexts (Abegg *et al*., 2012; Kaufhold *et al*., 2013; Wolff *et al*., 2013). The current study by Kisimbi *et al*. (2013) adds Tanzanian endemic optic neuropathy to a growing list of aetiologies causing microcystic macular changes.

Histopathological changes similar in appearance to microcystic macular change were described as early as 1963 by John Van Buren, who observed cystic changes in the retinal inner nuclear layer of non-human primates following optic nerve injury. Similar changes to the inner nuclear layer of human eyes with optic nerve lesions were subsequently demonstrated by Gills and Wadsworth (1966). A more recent study demonstrated inner nuclear layer cavitation and cystic changes in rhesus macaques with bilateral idiopathic optic atrophy (Fortune *et al*., 2005).

Microcystic macular changes on OCT were described in patients with multiple sclerosis and correlated with disease severity (Gelfand *et al*., 2012; Saidha *et al*., 2012). These studies were followed by a flurry of Letters to the Editor demonstrating morphologically similar microcystic macular changes in a variety of inflammatory and non-inflammatory optic neuropathies. Microcystic macular changes have now been described in multiple sclerosis, neuromyelitis optica, Leber's hereditary optic neuropathy, dominant optic atrophy, isolated relapsing optic neuropathy, NF-1-related optic chiasmal glioma, glaucoma, trauma and hydrocephalus (Abegg *et al*., 2012; Balk *et al*., 2012; Barboni *et al*., 2013; Kaufhold *et al*., 2013; Sotirchos *et al*., 2013; Wolff *et al*., 2013). Furthermore, microcystic changes are also described in patients undergoing internal limiting membrane removal for epimacular membrane—possibly secondary to damage to the RNFL and the ganglion cell layer (Sigler *et al*., 2013).

Several different theories have been advanced to explain the pathophysiology of retinal microcystic changes. One of the most attractive explanations, is retrograde trans-synaptic degeneration. Retrograde trans-synaptic degeneration in the visual pathways secondary to occipital lobe damage was demonstrated by Jindahra *et al*. (2012). By extension, this could be hypothesized to occur in the retina, and hence ganglion cell dropout in optic neuropathies, or direct damage secondary to surgery, and could lead to loss of bipolar cells and subsequent formation of microcystic cavities. Providing more convincing proof for this theory is the appearance of microcystic change in localized areas of the retina where the RNFL and ganglion cell layer are injured during surgery for epimacular membranes (Sigler *et al*., 2013). However, it must be noted that, in most studies the prevalence of the microcystic macular change has been a small fraction of the total number of patients with optic neuropathy (5–25%). Thus, it appears that retrograde trans-synaptic degeneration alone is not sufficient to cause microcystic macular change. A caveat would be that it is possible that some changes are too small to be picked up by current OCT technology, leading to under-estimation of the true occurrence of microcystic macular change. Another feature not explained by retrograde trans-synaptic degeneration, is the predilection of the microcystic change for the inner nuclear layer. The relative absence of cystic change in the ganglion or outer nuclear layers is not explained by this theory.

Another interesting hypothesis is that of traction. In a beautifully illustrated Letter to the Editor, Lujan and Horton (2013) show how traction on the retina can produce microcystic macular change. They also demonstrate that traction seems to be greater on the nasal, rather than the temporal aspect of the retina, thus helping to explain the nasal predominance of the microcysts. However, many cases with microcystic macular change do not have evidence for traction, and several studies have specifically excluded this group of patients, although prior traction cannot entirely be excluded at the time of scanning (Sotirchos *et al*., 2013; Wolff *et al*., 2013). Thus, although in some cases traction likely plays a role, and may explain the nasal distribution of the microcystic macular changes, it is probably not the primary cause in most optic neuropathies.

Glial cells found in the retina include astrocytes and Müller cells (Bringmann and Wiedemann, 2012). Astrocytes are found only in

the RNFL and ganglion cell layer. The Müller cells span the entire thickness of the retina, however, their cell bodies reside predominantly in the inner nuclear layer. Their location in the inner nuclear layer and the predilection of microcystic change to this layer, makes Müller cell dysfunction a very promising theory for microcyst production. Müller cells express aquaporin 4 and the potassium channel Kir4.1. They help maintain the ionic and osmotic homeostasis of the retina, and respond to various stressors that perturb the retina including stretch, hypo-osmolarity, ischaemia and inflammation. In these pathological conditions, Müller cells downregulate Kir4.1 and upregulate and redistribute aquaporin 4. This leads to accumulation of potassium and water in the Müller cells resulting in cell oedema. Concomitantly, reduction of Kir4.1 current leads to reduction in glutamate reabsorption by these cells (Reichenbach *et al*., 2007). Increased glutamate concentrations can lead to neuronal damage by excitotoxicity, whereas elevated potassium concentrations affect the osmotic homeostasis of the retina.

Also consistent with the hypothesis of Müller cell dysfunction are findings seen in disorders, such as epiretinal membranes, that cause traction on the retina. These lead to thickening of the retina especially in the inner nuclear layer (Koo *et al*., 2012). Thickening of that structure has also been described in other inflammatory causes of optic nerve disease such as multiple sclerosis (Saidha *et al*., 2012). Recently, a study of early diabetic retinopathy also noted swelling of the inner nuclear layer compared with controls (Vujosevic and Midena, 2013). Müller cell swelling may initially produce cytotoxic oedema—water primarily within the cells leading to thickening of inner nuclear layer. Subsequently Müller cell drop-out or dysfunction may lead to disruption of retinal homeostasis and movement of fluid out of the vessels or vitreous into the retina leading to cyst formation. The fluctuation of microcystic macular changes in some situations but not others may also point to the occurrence of different pathologies with similar appearances—a phenomenon commonly experienced with other imaging modalities such as MRI. As a corollary to MRI, inner nuclear layer thickening equates to $T_2$ lesions (oedema), and microcystic change to $T_1$ black holes (tissue loss).

Longitudinal studies of patients with acute optic neuropathy involving careful clinical, OCT and fluorescein angiography follow-up may provide further insight into the development and natural history of these microcystic macular changes. Incorporation of *en face* infrared imaging and development of automated cyst detection algorithms may help increase the identification of these changes. Besides this, newer techniques may also help sort out the contribution of different retinal elements to microcystic change. Precise estimates of the effect of microcystic change on vision may be obtained by correlating OCT findings with microperimetry. Adaptive optics is a new technique that allows visualization of individual photoreceptors. Use of this technique may help assess loss of photoreceptors in areas of microcystic change.

Although a great deal of information has emerged regarding microcystic macular change, there are still several unanswered questions regarding natural history, pathophysiology and prognostic relevance. Future longitudinal studies combining different imaging and functional approaches may help us understand this phenomenon. Studies such as that reported by Kisimbi *et al*. (2013) are very useful in broadening our understanding of the incidence and prevalence of microcysts. One hopes that through a better understanding of the aetiology and pathophysiology, this destructive pathology might be treated or prevented. It is indeed of note that improving nutritional status, in other countries, has led to dramatic reductions of endemic optic neuropathies that predispose to this process.

# Funding

This investigation was supported in part by a Sylvia Lawry Physician Fellowship from the National Multiple Sclerosis Society (P.B). P.A.C. is supported by R0-1 NS082347.

*Pavan Bhargava and Peter A. Calabresi*
*Johns Hopkins University, Baltimore*

Correspondence to: Peter A. Calabresi, M.D.,
Johns Hopkins Hospital,
600 N Wolfe Street, Pathology 627
Baltimore, MD 21287, USA
E-mail: calabresi@jhmi.edu

doi:10.1093/brain/awt295

# References

Abegg M, Zinkernagel M, Wolf S. Microcystic macular degeneration from optic neuropathy. Brain 2012; 135: e225.

Balk LJ, Killestein J, Polman CH, Uitdehaag BM, Petzold A. Microcystic macular oedema confirmed, but not specific for multiple sclerosis. Brain 2012; 135: e226; author reply e227.

Barboni P, Carelli V, Savini G, Carbonelli M, La Morgia C, Sadun AA. Microcystic macular degeneration from optic neuropathy: not inflammatory, not trans-synaptic degeneration. Brain 2013; 136: e239.

Bringmann A, Wiedemann P. Muller glial cells in retinal disease. Ophthalmologica 2012; 227: 1–19.

Fortune B, Wang L, Bui BV, Burgoyne CF, Cioffi GA. Idiopathic bilateral optic atrophy in the rhesus macaque. Invest Ophthalmol Vis Sci 2005; 46: 3943–56.

Gelfand JM, Nolan R, Schwartz DM, Graves J, Green AJ. Microcystic macular oedema in multiple sclerosis is associated with disease severity. Brain 2012; 135: 1786–93.

Gills JP Jr, Wadsworth JA. Degeneration of the inner nuclear layer of the retina following lesions of the optic nerve. Trans Am Ophthalmol Soc 1966; 64: 66–88.

Jindahra P, Petrie A, Plant GT. The time course of retrograde transsynaptic degeneration following occipital lobe damage in humans. Brain 2012; 135: 534–41.

Kaufhold F, Zimmermann H, Schneider E, Ruprecht K, Paul F, Oberwahrenbrock T, et al. Optic neuritis is associated with inner nuclear layer thickening and microcystic macular edema independently of multiple sclerosis. PLoS One 2013; 8: e71145.

Kisimbi J, Shalchi Z, Mahroo OA, Mhina C, Sanyiwa AJ, Mabey D, et al. Macular spectral domain optical coherence tomography findings in tanzanian endemic optic neuropathy. Brain 2013 [Epub ahead of print].

Koo HC, Rhim WI, Lee EK. Morphologic and functional association of retinal layers beneath the epiretinal membrane with spectral-domain optical coherence tomography in eyes without photoreceptor abnormality. Graefes Arch Clin Exp Ophthalmol 2012; 250: 491–8.

Lujan BJ, Horton JC. Microcysts in the inner nuclear layer from optic atrophy are caused by retrograde trans-synaptic degeneration combined with vitreous traction on the retinal surface. Brain 2013 [Epub ahead of print].

Reichenbach A, Wurm A, Pannicke T, Iandiev I, Wiedemann P, Bringmann A. Muller cells as players in retinal degeneration and edema. Graefes Arch Clin Exp Ophthalmol 2007; 245: 627–36.

Saidha S, Sotirchos ES, Ibrahim MA, Crainiceanu CM, Gelfand JM, Sepah YJ, et al. Microcystic macular oedema, thickness of the inner nuclear layer of the retina, and disease characteristics in multiple sclerosis: a retrospective study. Lancet Neurol 2012; 11: 963–72.

Sigler EJ, Randolph JC, Charles S. Delayed onset inner nuclear layer cystic changes following internal limiting membrane removal for epimacular membrane. Graefes Arch Clin Exp Ophthalmol 2013; 251: 1679–85.

Sotirchos ES, Saidha S, Byraiah G, Mealy MA, Ibrahim MA, Sepah YJ, et al. *In vivo* identification of morphologic retinal abnormalities in neuromyelitis optica. Neurology 2013; 80: 1406–14.

Van Buren JM. Trans-synaptic retrograde degeneration in the visual system of primates. J Neurol Neurosurg Psychiatry 1963; 26: 402–9.

Vujosevic S, Midena E. Retinal layers changes in human preclinical and early clinical diabetic retinopathy support early retinal neuronal and muller cells alterations. J Diabetes Res 2013; 2013: 905058.

Wolff B, Basdekidou C, Vasseur V, Mauget-Faysse M, Sahel JA, Vignal C. Retinal Inner Nuclear Layer microcystic changes in optic nerve atrophy: a novel spectral-domain OCT finding. Retina 2013 [Epub ahead of print].