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Formation of Macular Inner Nuclear Layer Cysts in Optic Atrophy

Multiple studies have reported the presence of inner nuclear layer (INL) cysts in the macula in association with optic atrophy caused by a wide variety of optic neuropathies. These INL cysts are distinguishable from cysts characteristic of macular edema by their lack of leakage on fluorescein angiography. Gelfand et al. first described INL changes of the retina using optical coherence tomography (OCT) in a subset of multiple sclerosis (MS) patients and used the term “microcysts.” They hypothesized that the microcysts were the product of breakdown of the blood-retinal barrier and inflammation resulting in formation of cystic changes in the retina. Subsequent reports noted similar cysts in other types of inflammatory optic neuropathies. Balk et al. and Sotirchos et al. hypothesized that INL cysts were the product of an immune response against aquaporin-4 channel found on Müller cells. Their theory was supported by animal models in which deletion of aquaporin-4 led to induction of retinal inflammation and decreased capacity of Müller cells to regulate osmotic stress. Since these initial reports of INL cysts in inflammatory optic neuropathies, INL cysts have been identified in non-inflammatory optic neuropathies, including Kjer dominant optic atrophy, optic pathway glioma, glaucoma, and Leber hereditary optic neuropathy, suggesting that the etiology of the cysts is non-inflammatory especially given the lack of leakage on intravenous fluorescein angiography.

Histopathologically, INL cysts have been observed in optic nerve degeneration thought to be due to transsynaptic degeneration. Van Buren and Gills and Wadsworth described “cystic degeneration,” resembling INL cysts seen on OCT, following lesions of the optic nerve or chiasm. Histopathologically, INL cysts have been observed in optic nerve degeneration thought to be due to transsynaptic degeneration. Van Buren and Gills and Wadsworth described “cystic degeneration,” resembling INL cysts seen on OCT, following lesions of the optic nerve or chiasm.2,3,13 Histological analysis of the INL has shown the cysts to be filled with fluid, which is consistent with the fluid seen on OCT. The cysts are typically seen in the parafoveal area where the GCL normally is the thinnest. Although the RNFL and GCL thin, vitreous traction on the Müller footplates prevents the retina from collapsing and, therefore, the INL, where Müller cell bodies are located, expands and cystic spaces form (medical illustrator: Rob Flewell, CMI).

However, these cysts are not seen in all patients with optic atrophy, and they seem to be more prevalent in younger patients with intact vitreous base, suggesting that vitreous traction may have a role in their formation. The most direct evidence of traction having a role in the formation of cysts came from Sigler et al. who observed INL cysts in a minority of patients following removal of an epiretinal membrane leading to damage of the retinal nerve fiber and ganglion cell layers. Therefore, Barboni et al.2 offered a hypothesis based on vitreous traction rather than transsynaptic degeneration, since transsynaptic degeneration would be expected to occur in all eyes over a sufficient period of time, and yet these cysts are not seen in all eyes. They highlighted the importance of an attached posterior hyaloid membrane preventing the collapse of the INL and proposed that the spaces that previously were occupied by the now degenerated cells became fluid filled spaces. Their theory was supported by Wen et al.,4 who found INL cysts exclusively in relatively young patients with severe glaucoma. In all of these reports, the cysts were confined mostly to the papillomacular bundle area.

We hereby propose a purely mechanical mechanism for the formation of INL microcysts that would explain why these cysts are seen more commonly in nonglaucomatous optic atrophy of younger patients with intact vitreous and are confined mostly to the papillomacular bundle area. Observational case series of OCT in children with glaucoma and nonglaucomatous optic atrophy support our hypothesis.5 The anatomical configuration of the INL predisposes it to cyst formation for several reasons (Fig. 1):

The INL contains the cell bodies of the majority of neuronal cells of the retina (horizontal cells, amacrine, and bipolar cells). These cells form the short vertical
synapses with the photoreceptors that sandwich the INL.

Lateral connections within the INL are facilitated by the horizontal and amacrine cells.

The INL contains the cell bodies of the Müller cells, which are important vertical glia that span the entire retina from the internal limiting membrane (footplates of the Müller cells are tightly attached to the vitreous) to the external limiting membrane (junction between Müller cells and photoreceptors).

The ganglion cell layer (GCL) in the papillomacular bundle is more than one cell layer in thickness, compared to the remaining retina in which it is only one cell layer thick. Therefore, in optic atrophy involving the papillomacular bundle, injury to the GCL results in a relatively large loss of cellular volume. Combined with vitreous traction on the footplates of the Müller cells, the mechanical vertical and horizontal stresses within the INL result in the formation of cystic spaces.

We examined the retina of a postmortem eye from a 63-year-old woman with bilateral (left greater than right) optic nerve atrophy since the age of 12 years secondary to a pituitary adenoma. Histopathological sectioning revealed that the INL cysts were more frequent and larger in the left compared to the right macula, in addition to the INL being thicker in the left than the right eye even though the number of cells was similar (Fig. 2). Despite the interval of 41 years between the time of optic nerve injury and death, there was no decrease in the number of cells in the INL to confirm transsynaptic degeneration.

Therefore, we believe that INL microcysts are not indicative of retrograde transsynaptic degeneration but rather the product of localized ganglion cell loss and vitreous traction on the Müller cell footplates combined with vertical and horizontal stress on the INL. In keeping this hypothesis, cysts in the INL often were more described in optic neuropathies affecting central vision because the GCL in the papillomacular bundle is a multi-cell rather than single-cell layer in thickness.

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Acknowledgments

Supported by the Heed Foundation and the Knights Templar Grant. The sponsor or funding organization had no role in the design or conduct of this editorial. The authors alone are responsible for the content and writing of this paper.

Disclosures: K. Jiramongkolchai, None; M.T. Bhatti, Novartis (C); A. Proia, None; S.F. Freedman, Pfizer Pharmaceuticals (C); M.A. El-Dairi, Prana pharmaceuticals (C)

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Citation: Invest Ophthalmol Vis Sci. 2016;57:989–991. doi:10.1167/iovs.15-18814