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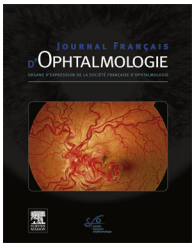

ORIGINAL ARTICLE

Cystic maculopathy of the internal nuclear layer in glaucoma patients

Dégénérescence kystique maculaire de la couche nucléaire interne chez des patients atteint de glaucome

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KEYWORDS
Glaucoma;
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Scotoma;
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Macula

Summary
Purpose. — The study aimed to detect and describe glaucoma-related pseudocystic abnormalities at the internal nuclear layer (INL) of the macula using OCT, in relation with visual field defects and other clinical data.
Patients and methods. — Primary open-angle glaucoma patients presenting for a follow-up visit were consecutively included over 5 months and underwent clinical examination, OCT imaging, and central 10-2 visual field testing. OCT measures included the thickness of the peripapillary retinal nerve fiber layer (RNFL) and macular ganglion cell complex (GCC), together with an analysis of B-Scans and en-face images. All data provided by OCT were analyzed and compared with the visual field testing.
Results. — Fourteen patients out of 216 showed pseudocysts in the INL of the macula. These cysts were hyporeflective, fusiform, and of variable size (15 to 25 μm) and were always associated with a thinning of both the RNFL and GCC. En-face OCT showed evidence of a distribution of cysts in the macular region, based on the appearance of numerous, dense hyporeflective pits whose localization matched precisely with the vision loss as assessed by central 10-2 visual field testing. No other correlations were found.

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Discussion. — Pseudocysts of the internal nuclear layer of the macular region are found in some cases of chronic glaucoma. Their presence is always associated with a scotoma in the visual field and appear to constitute a marker for glaucoma progression. Glaucoma-related central pseudocysts could result from Müller cell changes, excitotoxicity, and/or trans-synaptic retrograde degeneration. The presence of pseudocysts could be a marker of a particular subpopulation whose features remain to be determined.

MOTS CLÉS
Glaucome ;
Pseudokystes ;
Kyste ;
Cellules de Müller ;
Macule

Résumé
Objectif. — Nous rapportons la présence d'anomalies pseudokystiques de la couche nucléaire interne de la rétine détectées en OCT chez des patients glaucomateux, et analysons les conséquences fonctionnelles de celles-ci.
Patients et méthodes. — Dans le cadre d'une consultation spécialisée en glaucome, l'ensemble des patients présentant un glaucome primitif à angle ouvert a bénéficié d'un OCT pour la mesure de l'épaisseur de la couche des fibres optiques peripapillaires (RNFL) et du complexe ganglionnaire maculaire (GCC). L'analyse a été effectuée en B-scan, en OCT « en-face », puis corrélée à un champ visuel automatisé 10-2.
Résultats. — Deux cent seize patients glaucomateux ont été consécutivement examinés. Quatorze présentaient des pseudokystes situés dans la couche nucléaire interne maculaire. Les kystes étaient hyporéflectifs, fusiformes et de taille variable (15 à 25 μm). La présence de pseudokystes était corrélée à un amincissement du GCC et du RNFL. La localisation « en-face » des pseudokystes correspondait spatialement au déficit de sensibilité évalué au champ visuel central.
Conclusion. — Certains patients atteints de glaucome primitif à angle ouvert présentent des formations pseudokystiques détectables en OCT dans la couche nucléaire interne de la région maculaire. Les cellules de Müller pourraient être impliquées dans ce processus pathologique. La présence de kyste correspond toujours à un déficit du champ visuel, et pourrait constituer un marqueur péjoratif d'évolution de la neuropathie glaucomateuse. Ces altérations rétiniennes spécifiques doivent ainsi être distinguées des autres pathologies maculaires.

Glaucomatous optic neuropathy is a chronic and progressive disease that can lead to blindness. Considering these stakes, the insidious, asymptomatic, and irreversible nature of this condition makes detection at the earliest stage of the disease necessary. OCT imaging allows to measure the thickness of the peripapillary nerve fibers (RNFL), but beyond quantifying the thickness of the macular ganglion cell complex (GCC) and detecting incipient thinning that occurs at pre-perimetric stage. In fact, the glaucomatous optic neuropathy preferentially affects the layer of ganglion cells and the internal plexiform [1]. We also report modifications of the internal nuclear layer with the presence of pseudocysts with significant correlations of structure to function. Thus, it would seem that the entire internal retina is involved in the glaucomatous neuro-retinal degeneration [2].

The purpose of this study was to detect, describe, and better understand the presence of pseudocysts in the macular region, localized at the level of the internal nuclear layer, in patients presenting open angle glaucoma.

Patients and methods

From January 2017 to June 2017, in the context of our follow-up visits for glaucoma, all the patients had an OCT examination to measure the thickness of the RNFL as well as the thickness of the macular GCC using XR Avanti™ OCT (Optovue, Fremont, USA). A precise analysis of the B-Scan images with manual measurement of the thickness of INL at the level of the zone of the cysts, as well as the neighboring area, a 6 × 6-mm ''en-face'' OCT examination, with a segmentation (SLAB) of a thickness of 25 microns focused on the internal nuclear layer (which allows to obtain a precise topography of this layer and of the distribution of the pseudocysts), and a central 10-2 visual field (Humphrey™, Zeiss Meditec, Dublin) were carried out. The density of the pseudocysts was measured from ''en-face'' OCT images by using the image J™ software (National Institute of Health, Bethesda, USA) and compared to the average sensitivity by quadrant of the central visual field.

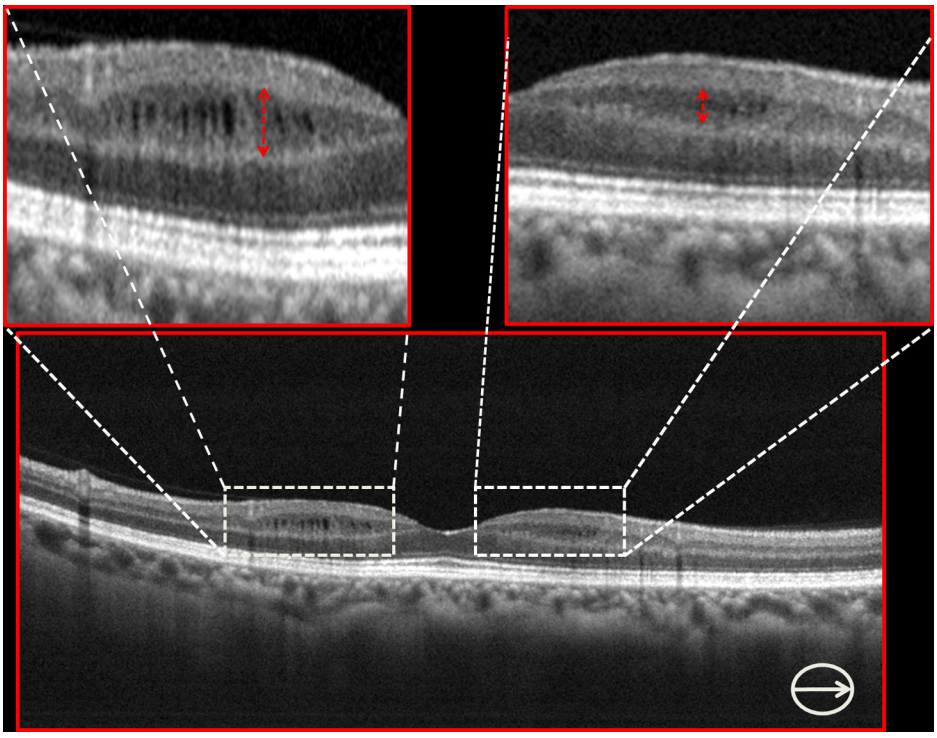

Figure 1. B-scan OCT (XR AVANTI, Optovue, Inc, Fremont CA) of a patient with glaucoma and inner nuclear layer cysts. The thickness of the INL seems proportional to the size of the cysts.

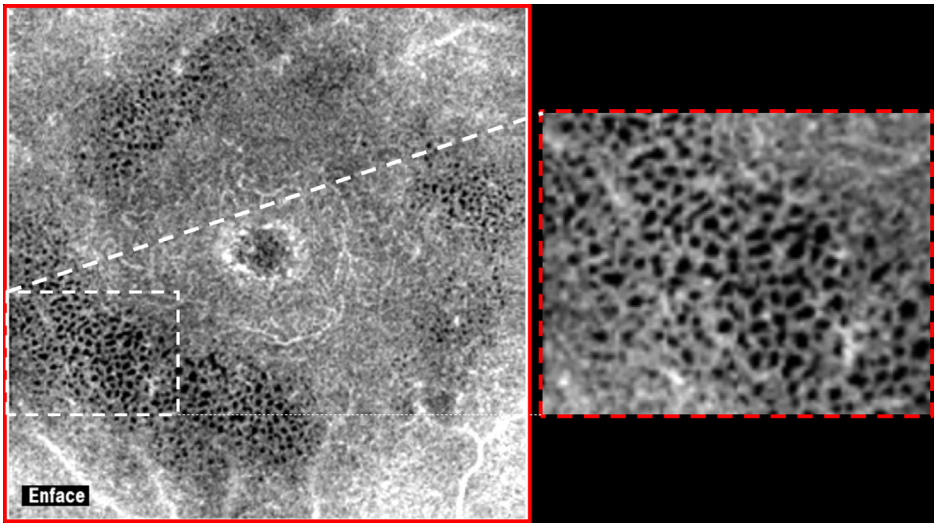

Figure 2. INL cysts seen on C-scan OCT imaging with a 25 μm slab. Highly typical appearance, with small, sharply demarcated hyporeflective vacuoles in the macular region.

Results

We isolated 14 patients out of 216 glaucoma patients presenting pseudocysts at the level of the internal nuclear layer, eight women and six men, with an average age of 58.3 years (range 41—76 years). Thirteen patients were followed and treated for primary open-angle glaucoma (POAG) and one patient had not had any treatment at all.

In all the patients, these cysts presented a hyporeflective, fusiform appearance, perpendicular to the retinal surface (Figs. 1 and 2), and whose size varied from 15 to 25 microns in relation to the thickening of the internal nuclear membrane. The localization of these cysts was always in the central retina, with a greater predominance in the inferior regions (44% and 24% in inferior temporal and nasal regions, respectively, versus 16% in both superior temporal and nasal regions). A localized thickening of the internal nuclear layer was always detected in the region of the pseudocysts as compared with the neighboring internal nuclear layer (Fig. 3).

The cysts of the internal nuclear membrane were associated with a thinning of the GCC and of the RNFL with a

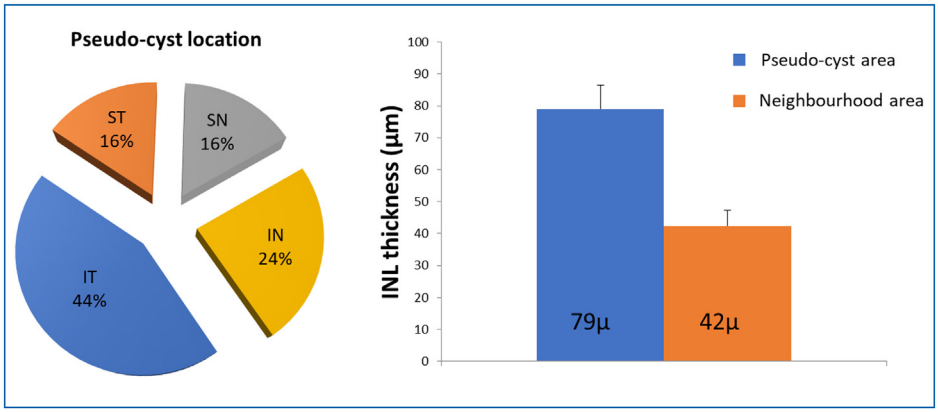

Figure 3. Location of macular cysts, which are predominantly localized in the lower temporal quadrant, and INL thickening observed in the area of the cysts.

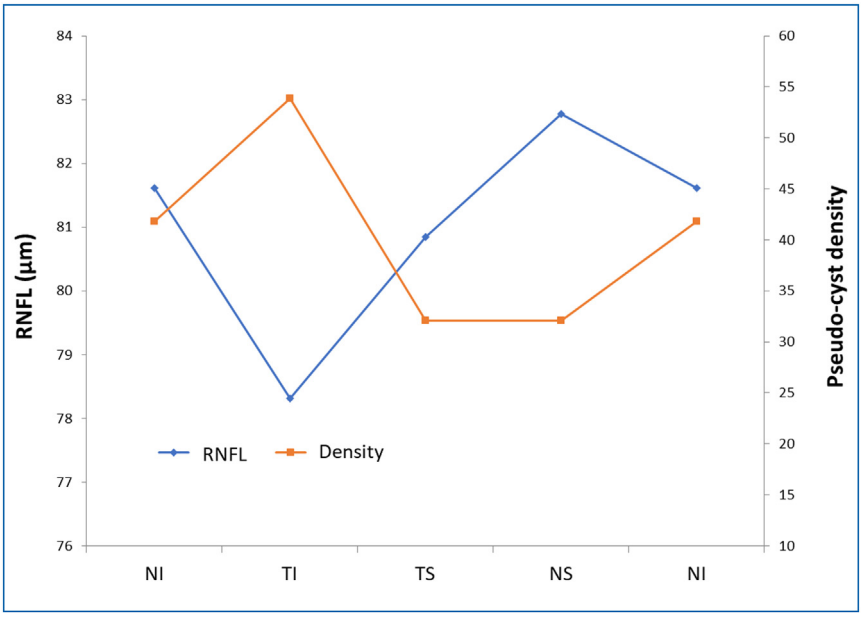

Figure 4. Mirror-image correlation between retinal nerve fiber layer (RNFL) thickness and cyst density measured on C-scan OCT.

trend, but not significant of correlation between the RNFL by quadrant and the cyst density ($P = 0.06$) (Fig. 4).

The ''en-face'' OCT made it possible to show these cysts and their distribution in the macular region. They assumed the appearance of dense, hypo-reflective pits whose localization corresponded precisely with the functional deficit recorded in the central 10-2 visual field (Fig. 5) with a statistically significant correlation between the density of the cysts and the sensitivity of the central visual field ($P = 0.04$) (Fig. 6).

Discussion

The presence of pseudocysts of the internal nuclear layer of the macular retina could be the clinical expression of a retrograde trans-synaptic degeneration in association with the thinning of the GCC in some glaucoma optical neuropathies [2]. Electron microscope studies on ex-vivo retinas from glaucomatous patients have shown neuronal losses at the level of the internal nuclear layer (INL) and the outer nuclear layer (ONL) correlated with changes in the layers of the retinal ganglion cells [3]. In parallel, Müller cells, with their transverse position in the sensorial retina, could play a role as vector in the degeneration of the most superficial layers of the retina up to the internal nuclear layer, the site of the nuclei of the Müller cells (Fig. 7). More precisely, animal models allowed to demonstrate the role of Müller cells as regulators of the neuron death related to excitotoxicity, one of the pathophysiological mechanisms involved in glaucoma [4]. The dysfunction/death of retinal ganglion cells could cause an excess of glutamate, of calcium, and of ATP in the neighborhood, leading to apoptosis in the nearby cellular microenvironment. Thus, the pathological stimulation of the glutamate receptors may induce apoptosis of the neighboring retinal ganglion cells. Glial dysfunction, in particular Müller cells, one may participate in the impairment of glutamate clearance, thus contributing to the excitotoxic

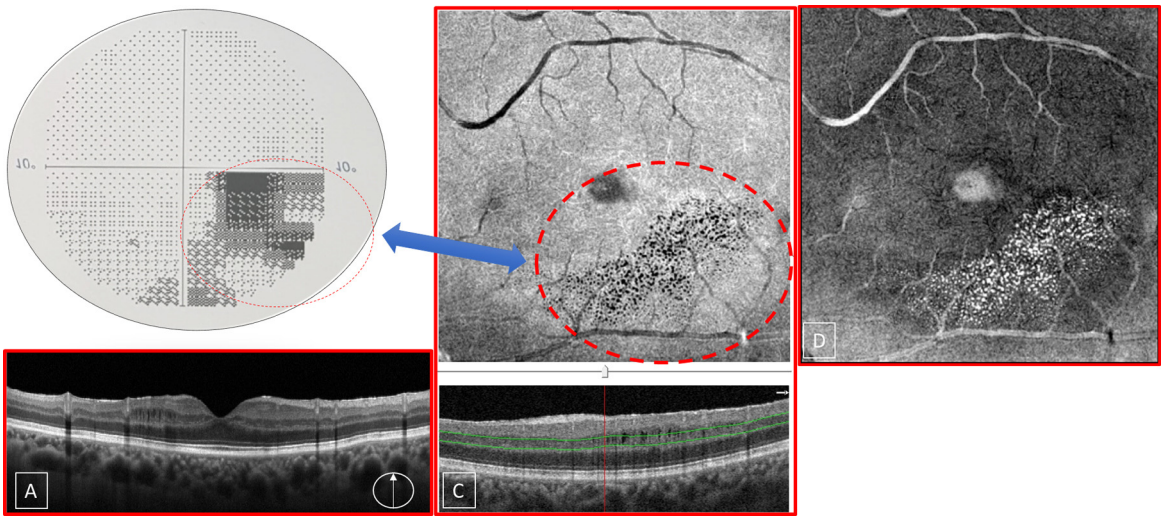

Figure 5. The presence of these cysts on B- and C-scan OCT always implies central scotoma on 10-2 visual field (VF) testing (Humphrey, Carl Zeiss Meditec, Dublin): A. Pseudocysts associated with INL thickening in the inferior fovea region on B-scan OCT (XR Avanti, Optovue, Fremont, USA). B. Central superior visual field deficit on 10-2, Humphrey (Carl Zeiss Meditec, Dublin). The campimetry reading was reversed for better correlation with the C-scan OCT. C. C-scan OCT projection (6 × 6 mm cube) of the pseudocysts which are predominantly localized in the lower temporal quadrant. D. C-scan OCT projection (6 × 6 mm cube) of the pseudocysts with color inversion image processing for better visualization of the pseudocysts.

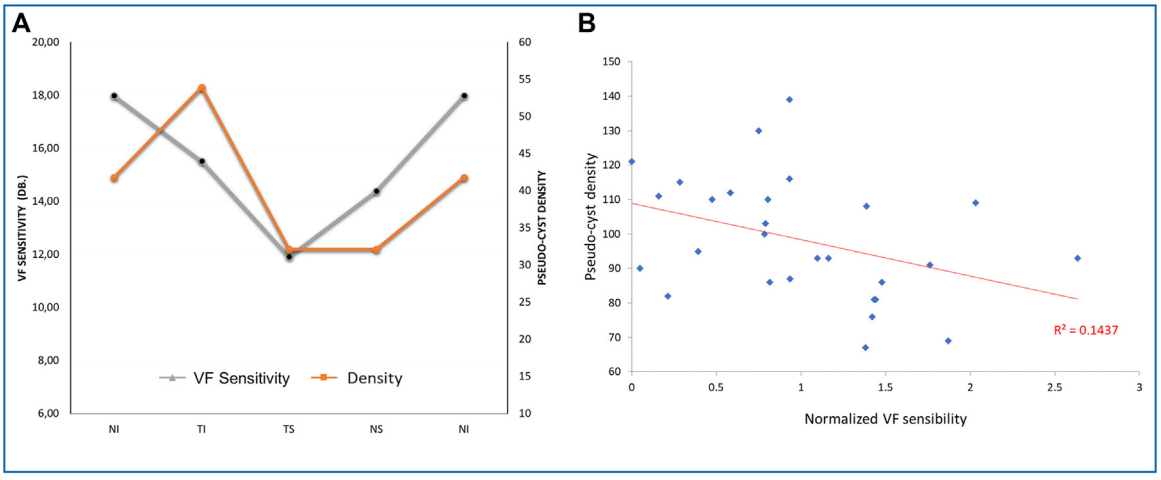

Figure 6. Spatial (A) and overall (B) correlation between cyst density on C-scan OCT expressed as a percentage, and visual field sensitivity expressed in dB.

deleterious consequences [5]. The mechanisms involved in such glial dysfunction, as well as the putative direct role of Müller cells in glaucoma-related retinal degeneration are still to be better understood. This could constitute, however, new therapeutic targets in the field of glaucoma.

The prevalence of pseudocysts in glaucoma patients is probably very underestimated because of the processing of images by summation of different B-scans, which is known to improve the visualization of the interfaces but may blur fine details, and precisely the presence of pseudocysts. Thus, the ''en-face'' OCT is shown to be an effective and complementary tool for detecting these cysts in the work-up of glaucomatous patients. As a result, this imaging procedure, which can be done routinely today, should be systematically proposed in the work-up and follow-up of patients presenting with OAG.

Pseudocysts of the internal nuclear layer are also found in some sequelae of optic neuritis in multiple sclerosis, non-glaucomatous optic atrophies, or in cases of compressive optic neuropathies related to calcified colloid bodies of the optic nerve head [6]. In other neuropathies, Wolff et al. [7] also reported cystic modifications of the internal nuclear membrane, including, among others, glaucomatous neuropathies. On the other hand, all the glaucomatous patients do not present pseudocysts. The fact that they are associated with other acute neuropathies may suggest that pseudocysts indicate some neuronal suffering in glaucoma also. In addition, it should be noticed that we herein reported a clear match between the presence of pseudocysts and paracentral scotoma as assessed by central visual field, further suggesting that pseudocysts may be linked to more severe glaucoma.

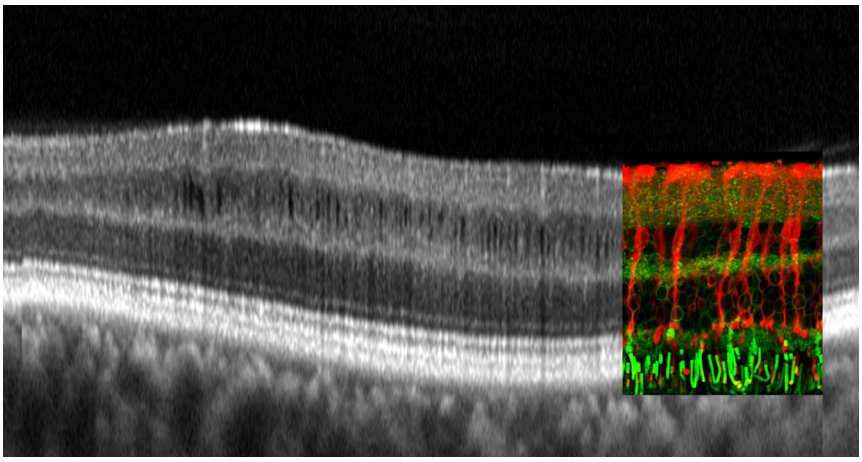

Figure 7. Pseudocysts in the INL seen on B-scan OCT (XR AVANTI, Optovue, Fremont, USA) in a patient with open-angle glaucoma compared with a retinal immunohistochemistry image showing Müller cells and their transverse position in the retina and its nuclei located in the inner nuclear layer. Coll. A Denoyer.

Recent evolutions of OCT, from en-face OCT to OCT-A, which now provide both morphological and functional data, must now find their place in the diagnosis and follow-up of glaucomatous patients. The display of the peripapillary capillaries inside the optic fibers has not yet demonstrated specific interest as compared with the gold standards. In the continuity of this work, it seems pertinent to study the evolution of the density of the superficial capillary plexus situated in the layer of the ganglion cells, but also of the deep vascular plexus situated in the internal nuclear layer by always associating it with the structural analysis of OCT. Prospective and observational clinical studies with large cohorts of patients are necessary to better precise the pathophysiological meaning of these retinal pseudocysts, as well as the place of these recent OCT evolutions in the whole therapeutic management of glaucomatous patients.

The presence of pseudocysts of the internal nuclear layer detected by sectional and ''en-face'' OCT in the macular area can be found, or even reveal, glaucomatous optic neuropathy, and always corresponds to parafoveal scotomas. This new entity must be recognized and differentiated from all other ocular diseases implying liquid cavities in the neurosensorial retina. The pathogenic mechanisms leading to this phenomenon have still to be better studied, in order to understand whether or not these cysts means a particular/severe form of OAG, on the one hand, and also to identify new therapeutic targets, on the other hand. Since ischemia could also participate to neuron and Müller cell suffering, the analysis of the vascular density of the superficial and deep plexus would complete this work in a pertinent way.

Disclosure of interest

The authors declare that they have no competing interest.

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