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Alzheimer's disease and glaucoma : look-alike neurodegenerative diseases

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Alzheimer's disease and glaucoma: look-alike neurodegenerative diseases.

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Dr. Peter Wostyn is the inventor of pending patent applications pertaining to glaucoma and Alzheimer's disease treatment using an intrathecal cerebrospinal fluid pump system, filed by P&X Medical NV. The other authors declare no conflicts of interest.

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Dear Editor,

We read with great interest the paper by Lee et al. [1] entitled “Associations between recent and established ophthalmic conditions and risk of Alzheimer’s disease” published recently in *Alzheimer’s & Dementia*. We are grateful to the authors for sharing their valuable data with the scientific community, and we appreciate their efforts to investigate associations of ocular diseases with Alzheimer’s disease (AD) risk. The authors reported a 46% higher AD risk in participants with recent glaucoma compared with those without. They further concluded that “subsequent studies of ophthalmic diseases in relation to AD may provide important insights in their shared pathological pathways, thus enabling better techniques to prevent and treat”. For the reasons discussed below, we fully agree with this notion.

Considerable evidence indicates that amyloid- β ($A\beta$), one of the key histopathological findings in AD, may be implicated in the development of retinal ganglion cell apoptosis in glaucoma, suggesting a possible link with AD [2,3]. Guo et al. [3] further provided evidence that targeting $A\beta$ and blocking its effects with combination therapy may represent an effective treatment strategy in glaucoma. Our group hypothesized that glaucoma, just like AD, may occur when there is an imbalance between production and clearance of neurotoxins, including $A\beta$ [4]. We further postulated that a dysfunction of the glymphatic pathway may play an important role in the pathogenesis of glaucoma [5]. Very recent research now lends support to this new hypothesis.

The ‘glymphatic system’ is a recently defined brain-wide paravascular pathway along which a large proportion of subarachnoid cerebrospinal fluid (CSF) recirculates through the brain parenchyma, facilitating the clearance of interstitial solutes, including $A\beta$, from the brain [6]. From the subarachnoid space, CSF is driven into the Virchow-Robin spaces by a combination

of arterial pulsatility, respiration, and CSF pressure gradients [7]. The subsequent transport of CSF into the dense and complex brain parenchyma is facilitated by aquaporin-4 (AQP4) water channels which are expressed in a highly polarized manner in astrocytic endfeet ensheathing the cerebral vasculature [7]. Glymphatic activity decreases sharply during aging, perhaps partly due to the decline in CSF production and CSF pressure, among other factors [7]. Furthermore, impairment of the glymphatic system has been shown in animal models of AD and in AD patients [8].

Similar to the glymphatic flow in the brain parenchyma, a glymphatic system in the optic nerve has recently been proposed by our group [5]. The optic nerve, a white matter tract of the central nervous system, is ensheathed in all three meningeal layers and surrounded by CSF in the subarachnoid space [5]. Evidence of a glymphatic pathway in the optic nerve in mice has very recently been reported by Mathieu et al. [9]. Using fluorescent tracer injection into CSF, the authors found CSF entry into the optic nerve along small perforating pial vessels in a size-dependent manner through sleeve-like paravascular spaces between vessel walls and AQP4-positive astrocytic endfeet [9]. The authors concluded that this finding may be highly relevant to a fundamental understanding of optic nerve function in health and diseases, including glaucoma [9]. Further studies are needed to elucidate whether at least some glaucoma cases may result from the toxicity of uncleared protein wastes, including A β , and whether glymphatic dysfunction may play a contributory role in the pathogenesis of glaucomatous damage. As the pressure generated through a constant production of CSF by the choroid plexus, among other factors, drives glymphatic fluid transport [7], it is interesting to note that clinical retrospective and prospective studies found that CSF pressure is lower in patients with primary open-angle glaucoma (POAG) when compared with nonglaucomatous control subjects and additionally, is lower in the normal-tension versus the high-tension form of POAG [10]. Therefore, we believe that infusion of artificial CSF into the intrathecal space surrounding the spinal cord could offer

potential to treat glaucoma by facilitating CSF circulation and glymphatic flow in the optic nerve. If intrathecal CSF infusion were proven to be effective in treating glaucoma, this new treatment could also protect against the subsequent risk of developing AD, given that this therapeutic approach may increase the rate of CSF turnover and glymphatic clearance with enhanced removal of toxic solutes, such as A β , from the brain.

Sincerely yours,

Peter Wostyn, MD

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