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LETTER TO THE EDITOR

Age-related macular degeneration, glaucoma and Alzheimer's disease: amyloidogenic diseases with the same glymphatic background?

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Dear Editor,

We read with great interest the paper by Gupta et al. [1] on the "multifaceted involvement of amyloid β (Aβ) in neurodegenerative disorders of the brain and retina". As discussed by the authors, Aβ deposition has been identified in the eye and is linked with distinct age-related diseases including age-related macular degeneration (AMD), glaucoma as well as Alzheimer's disease (AD) [1]. The authors present an integrated view of current understanding of the retinal Aβ deposition and discuss the potential mechanisms for Aβ accumulation in these three disorders [1]. Here, we propose that failure of the so-called 'glymphatic system' may be a novel link underlying increased Aβ accumulation in AMD, glaucoma and AD.

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 Aβ, from the brain [2]. CSF enters the brain along para-arterial channels to exchange with interstitial fluid (ISF), which is, in turn, cleared from the brain along para-venous pathways [2]. Paravascular CSF–ISF exchange in the brain is driven by cerebral arterial pulsation, and is dependent on astroglial water transport via the astrocytic aquaporin-4 (AQP4) water channel [3, 4]. It has been hypothesized that glymphatic pathway dysfunction may contribute to the deficient Aβ clearance in AD [5].

In 2015, Denniston and Keane [6] and our group [7] independently hypothesized the existence of a paravascular transport system in the retina and the optic nerve, respectively, which might be a key player in retinal diseases, such as AMD, and glaucoma. Recent research is now providing more substantial evidence for a glymphatic system in the eye.

The optic nerve, a white matter tract of the central nervous system, is ensheathed in all three meningeal layers and is surrounded by CSF in the subarachnoid space [7]. In a post-mortem study, we examined cross-sections of human optic nerves by light microscopy after injecting India ink into the subarachnoid space of the optic nerve (work in progress). The results demonstrated accumulation of India ink in paravascular spaces around the central

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retinal artery and vein, whereas the lumens of these vessels and the surrounding axons remained unlabeled. In addition, in a report presented at this year's ARVO Annual Meeting, Hu and colleagues (Hu P, et al. 2016 ARVO E-Abstract 996) provided evidence for a glymphatic system in human, non-human primate, rat and mouse retina. Retinas were examined using multimarker immunohistochemistry. An $AQP4^+$ glial network ensheathed the entire retinal vascular system, including between blood vessels, and the authors concluded that this may be the anatomical correlate of a retinal glymphatic system.

Importantly, the above findings may shed light on a new clearance pathway in the eye analogous to the described glymphatic system in the brain. Although it is unknown at present whether or how these systems communicate, these new findings allow to hypothesize that AMD and glaucoma, just like AD, may result from abnormalities in glymphatic fluid transport. Here, we give a personal view of how dysfunction of the glymphatic system may arise in AMD and glaucoma.

AMD is a late-onset, neurodegenerative disease that shares similar risk factors with AD, including aging, hypercholesterolemia, hypertension, obesity, arteriosclerosis, and smoking [8]. While AMD is a retinal disease, AD is reported to affect not only the brain but also the retina. Both diseases are associated with amyloid deposition [8]. Indeed, the Aβ deposited in senile plaques of AD patients is also found in drusen of patients suffering from AMD. Moreover, previous studies showed a possible epidemiological connection between both pathologies [8]. With regard to the viewpoint presented here, it is interesting to note that previous findings showed that glymphatic transport dramatically reduces with age [3], which is the primary risk factor for AMD. Moreover, as noted above, there is evidence demonstrating that cerebrovascular pulsation is critical for paravascular circulation and transport of CSF into the interstitium [4]. Indeed, a recent study demonstrated that cerebral arterial pulsatility is a key driver of paravascular CSF influx and subsequent CSF–ISF exchange in the brain [4]. Loss of elasticity in aging cerebral arteries with progressive arteriosclerosis, or cessation of pulsations, might contribute to failure of the clearance of interstitial waste, including Aβ, from the brain, and might play a role in the pathogenesis of AD [4]. Based on the above considerations, it seems reasonable to speculate that dysfunction of the glymphatic system may be a potential mechanism by which Aβ accumulates within drusen in AMD retinas, given that advanced age and cardiovascular risk factors predispose to the development of the disease, and are associated with a dramatic decline in the efficiency of the glymphatic system.

In glaucoma, impairment of glymphatic clearance could occur due to paravascular communication arrest at the site of the lamina cribrosa. On the basis of magnetic resonance imaging findings of Terson's syndrome (the occurrence of a vitreous hemorrhage in association with subarachnoid hemorrhage), it has been suggested that there may be a continuous network of paravascular channels that surrounds the central retinal vessels in the optic nerve and their branches in the retina, and that may serve as drainage channels from the subarachnoid space around the optic nerve to the retina [9]. Importantly, Aβ has been reported to increase by chronic elevation of intraocular pressure (IOP) in animals with experimentally induced ocular hypertension and to cause retinal ganglion cell (RGC) death [10–13]. McKinnon et al. [10] reported that rat RGCs subjected to chronic elevation of IOP exhibit caspase-3-mediated abnormal processing of β-amyloid precursor protein with increased expression of Aβ. In a rat model mimicking chronic ocular hypertension, Guo et al. [12] found that Aβ colocalized with apoptotic RGCs. They also demonstrated in vivo that Aβ induced significant RGC apoptosis [12]. Recently, in a study using monkeys with experimental glaucoma, Ito et al. [13] found time-dependent expressions and localization of Aβ in the retina as well as in the optic nerve head after chronic IOP elevation. If the existence of a 'paravascular communication' between the retina and the optic nerve were further demonstrated, at least theoretically, such a paravascular 'retino-orbital' continuity could facilitate elimination of neurotoxins, such as Aβ, induced by high IOP. Indeed, Aβ clearance from the retina may occur via paravascular structures similar to the glymphatic system in the brain. Moreover, a growing body of evidence indicates that intracranial pressure (ICP) is lower in patients with primary open-angle glaucoma (POAG) when compared with non-glaucomatous control subjects [14]. Also, ICP was reported to be lower in the normal-tension compared to the high-tension form of POAG [14]. If the ICP is too low, fluid flow from the paravascular spaces in the optic nerve to the paravascular spaces in the retina may decline or stop, given that this paravascular flow must cross the trans-lamina cribrosa pressure barrier. Normally, IOP is higher than ICP [14]. An increase in IOP, a decrease in ICP, or a decrease in the thickness of the lamina cribrosa may increase the pressure barrier against which paravascular flow from the optic nerve to the retina needs to occur. Patients with a low ICP and/or a high trans-lamina cribrosa pressure gradient may, therefore, be more likely to develop glymphatic stasis at the site of the lamina cribrosa leading to Aβ accumulation and subsequent glaucomatous optic neuropathy.

Although much more work is required to substantiate the role of the glymphatic pathway in AMD and glaucoma, further elucidation of common mechanisms linking AMD, glaucoma and AD might offer new perspectives for the development of novel diagnostic and therapeutic strategies

for these disorders. We, therefore, wish to encourage further studies and research in this area.

Sincerely yours,
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Compliance with ethical standards

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