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Dilated Virchow-Robin spaces in primary open-angle glaucoma: a biomarker of glymphatic waste clearance dysfunction?

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We read with great interest the article entitled ''Ocular blood flow and cerebrospinal fluid pressure in glaucoma'' by Promelle et al. (1). The authors review the most recent research on alterations in ocular blood flow and/or cerebrospinal fluid (CSF) flow in glaucoma. They state that blood–CSF flow interactions may be involved in glaucoma, and also note that ''the CSF's behavior is supposedly linked to blood pulsatility.'' We fully agree with this notion, as we believe that the vascular system could play a role in the pathogenesis of glaucoma through a mechanical interplay with the CSF circulation.

The subarachnoid space (SAS) of the optic nerve (ON) is contiguous with the SAS of the brain in a normal population. Growing evidence in the literature provides strong support for the concept that CSF pressure and composition in the SAS surrounding the ON may have fundamental significance in the pathogenesis of glaucoma (2,3). As an extension of the brain, the ON displays remarkable similarities to the brain in terms of anatomy and functionality (4). Knowledge obtained from brain research could therefore lead to new insights into the ON and vice versa. Recently, the ''glymphatic system'' of the brain has been discovered in rodents by Iliff et al. (5). The authors argued that this system was critical to the efficient clearance of interstitial solutes, including amyloid-β, from the brain (5). Their findings suggested a brain-wide paravascular pathway in which CSF flows from the SAS along the arteries and arterioles into the paravascular Virchow-Robin spaces (VRSs) to exchange with interstitial fluid (ISF), and ISF is cleared from the brain into the VRSs surrounding the exiting veins. As ISF exits the brain through the paravenous route, it travels to the lymphatic vessels in the neck, and eventually returns its contents to the systemic circulation.

Paravascular CSF recirculation and ISF solute clearance is dependent upon water transport via astroglial aquaporin-4 water channels, which are localized to perivascular astrocytic endfeet ensheathing the cerebral vasculature (5). Importantly, there is also evidence demonstrating that there is a mechanical interplay between the intracranial vascular system and the glymphatic system. 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 (6). Loss of elasticity in aging cerebral arteries with progressive atherosclerosis, or cessation of pulsations, might contribute to failure of the clearance of interstitial waste, including amyloid-β, from the brain, and might play a role in the pathogenesis of Alzheimer's disease (6).

The above findings indicate that the VRSs have an important role in the homeostasis of cerebral fluids in the central nervous system (7), and suggest a possible correlation between VRS enlargement and a disturbance of CSF dynamics. Indeed, if CSF outflow is reduced as a consequence of either CSF flow obstruction or cerebral artery pulsatility inefficiency, or cerebrospinal venous insufficiency and lymphatic disorders, local perivascular CSF recirculation may be impaired and, consequently,

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the VRSs may dilate due to fluid retention (7). Interestingly, dilated VRSs are a known histological feature of cerebral small vessel disease and can be demonstrated on magnetic resonance imaging (8).

Since the ON is a direct extension of the brain, the question is whether there is also evidence for the existence of a paravascular transport system in the ON. The observation of such an anatomically distinct clearing system in the ON could also provide new insights into the pathogenesis of glaucoma. Indeed, if confirmed, one might expect that a dysfunctional glymphatic system could ultimately result in reduced neurotoxin clearance in the ON and lead to glaucomatous neurodegeneration (4).

Many studies have demonstrated vascular-related risk factors for glaucoma. Atherosclerotic cerebrovascular disease is a risk factor for glaucomatous optic neuropathy, and both systemic hypertension and systemic arterial stiffness have been reported to be associated with primary open-angle glaucoma (POAG) (9,10). Given that impairment of the arterial pulsation-driven "perivascular pump" may lead to CSF flux disturbance, and given that distension of the VRSs may be related to the fluid retention in and along the paravascular circulation (7), we postulate that dilated VRSs could occur in POAG in association with arterial stiffening or loss of arterial pulsatility. Interestingly, in accordance with this view, a very recent study showed significantly higher deep white matter lesion load and increased numbers of dilated VRSs in association with POAG suggesting the presence of significant cerebral small vessel disease (8). If dilation of VRSs may result from a disturbed interplay between the vascular and glymphatic system, then preventing arterial stiffness may protect against glaucoma, at least in part, by promoting solute clearance via the CSF.

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