Review

Glymphatic stasis at the site of the lamina cribrosa as a potential mechanism underlying open-angle glaucoma

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ABSTRACT
The underlying pathophysiology of primary open-angle glaucoma remains unclear, but the lamina cribrosa seems to be the primary site of injury, and raised intraocular pressure is a major risk factor. In recent years, a decreased intracranial pressure, leading to an abnormally high trans-lamina cribrosa pressure difference, has gained interest as a new risk factor for glaucoma. New research now lends support to the hypothesis that a paravascular transport system is present in the eye analogous to the recently discovered 'glymphatic system' in the brain, which is a functional waste clearance pathway that promotes elimination of interstitial solutes, including β-amyloid, from the brain along paravascular channels. Given that β-amyloid has been reported to increase by chronic elevation of intraocular pressure in glaucomatous animal models and to cause retinal ganglion cell death, the discovery of a paravascular clearance system in the eye may provide powerful new insights into the pathophysiology of primary open-angle glaucoma. In this review, we provide a new conceptual framework for understanding the pathogenesis of primary open-angle glaucoma, present supporting preliminary data from our own post-mortem study and hypothesize that the disease may result from restriction of normal glymphatic flow at the level of the lamina cribrosa owing to a low intracranial pressure and/or a high trans-lamina cribrosa pressure gradient. If confirmed, this viewpoint could offer new perspectives for the development of novel diagnostic and therapeutic strategies for this devastating disorder.

Key words: glaucoma, intracranial pressure, intraocular pressure, lamina cribrosa, trans-lamina cribrosa pressure difference.

INTRODUCTION
Glaucoma is one of the leading causes of irreversible blindness worldwide.1–3 Primary open-angle glaucoma (POAG), the most common type, is a progressive optic neuropathy characterized by slow progressive degeneration of retinal ganglion cells (RGCs) and their axons in the optic nerve, resulting in structural changes in the optic nerve head and corresponding visual field defects.4 The underlying pathophysiology of glaucomatous optic neuropathy remains elusive. The optic nerve head, especially the lamina cribrosa, seems to be the primary site of injury and raised intraocular pressure (IOP) is considered the most important modifiable risk factor for the development of POAG.5 IOP is determined by the balance between the secretion of aqueous humour in the ciliary body and its draining through conventional trabecular meshwork and unconventional uveoscleral outflow pathways.6–8 Recent evidence indicates the presence of distinct lymphatic channels in the human ciliary body and suggests that this novel ‘uveolymphatic’
DISCUSSION

The trans-lamina cribrosa pressure difference and gradient

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 (SAS). The SAS of the optic nerve is in communication with the SAS of the brain in a normal population. Therefore, in addition to IOP, the optic nerve is exposed to the ICP. Normally, the IOP ranges from 11 to 21 mmHg with a mean of 16 mmHg, whereas ICP in healthy supine adults varies between 5 and 15 mmHg with a mean of 12 mmHg. The lamina cribrosa, forming the anatomic floor of the optic nerve head, separates the intraocular space from the orbital SAS. The pressure drop that occurs across the lamina cribrosa (IOP – ICP) is known as the TLCPD. On average, there is a small, posteriorly directed pressure difference (mean 4 mmHg) across the lamina cribrosa in normal eyes. The TLCPD increases with elevation of IOP or reduction of ICP.

Additionally, the distance through which the TLCPD is exerted may be a critical factor. The distance separating the intraocular space from the orbital SAS markedly depends on the thickness of the lamina cribrosa, and the trans-lamina cribrosa pressure gradient is defined as IOP – ICP/thickness of the lamina cribrosa. Normal eyes have a lamina cribrosa thickness of about 450 μm. This results in a pressure gradient of approximately 1 mmHg per 100 μm, making it one of the largest pressure gradients to which any nerve in the body is constantly exposed. As the lamina cribrosa becomes thinner, the trans-lamina cribrosa pressure gradient increases.

CSF pressure and TLCPD in glaucoma and OHT

Recent research findings suggest the potential pathogenic role of an abnormally low CSF pressure, that is, ICP, in the development of POAG and NTG.

In a retrospective case–control study, Berdahl et al. found that mean CSF pressure as measured by lumbar puncture was 33% lower in a group of 28 patients with POAG than in a control group of 49 nonglaucomatous patients (9.2 ± 2.9 vs. 13.0 ± 4.2 mmHg; P < 0.00005).

In another study with a similar design, Berdahl et al. compared lumbar CSF pressure measurements in 57 subjects with POAG, 11 subjects with NTG and 27 subjects with OHT with those of 105 age-matched nonglaucomatous controls. The CSF pressure was significantly lower in patients with POAG than age-matched control subjects without glaucoma (9.10 ± 0.77 vs. 11.80 ± 0.71 mmHg; P < 0.0001). The subjects with NTG also had a lower CSF pressure...
TLCPD was significantly lower (11.80 ± 0.71 mmHg; P < 0.01). Furthermore, the CSF pressure was higher in OHT than in age-matched control subjects (12.60 ± 0.85 vs. 10.60 ± 0.81 mmHg; P < 0.05). The mean TLCPD was 6.1 ± 5.6 mmHg in POAG and 5.0 ± 4.4 mmHg in the NTG subset compared with 1.9 ± 4.4 mmHg in age-matched controls (P < 0.05). In the OHT group, the mean TLCPD was 8.4 ± 5.5 mmHg compared with 4.4 ± 3.5 mmHg in age-matched controls (P < 0.05).

The findings of Berdahl et al\textsuperscript{10,11} were confirmed by more recent prospective studies by Ren et al\textsuperscript{12,13} A first study compared lumbar CSF pressure in OAG patients and nonglaucomatous control subjects. The study included 43 patients with OAG differentiated into 14 patients with normal-pressure glaucoma and 29 patients with high-pressure glaucoma, and 71 control subjects.\textsuperscript{12} The CSF pressure was significantly lower (P = 0.013) in the normal-pressure glaucoma group (9.5 ± 2.2 mmHg) than in the high-pressure glaucoma group (11.7 ± 2.7 mmHg), in which it was significantly (P < 0.001) lower than in the control group (12.9 ± 1.9 mmHg). The TLCPD was significantly (P < 0.001) higher in the high-pressure glaucoma group (12.5 ± 4.1 mmHg) than in the normal-pressure glaucoma group (6.6 ± 3.6 mmHg), in which it was significantly (P < 0.001) higher than in the control group (1.4 ± 1.7 mmHg). By using multivariate analysis, the amount of glaucomatous visual field loss was mainly associated with the TLCPD (P = 0.005).\textsuperscript{12} However, when IOP and CSF pressure were used as single parameters in the multivariate analysis, there was no significant (P > 0.50) correlation between these individual parameters and the perimetric visual field loss.\textsuperscript{12}

In a parallel prospective study, Ren et al.\textsuperscript{13} found that the CSF pressure as measured by lumbar puncture was significantly (P < 0.001) higher in an ocular hypertensive group of 17 patients (16.0 ± 2.5 mmHg) than in the control group (12.9 ± 1.9 mmHg). The TLCPD was significantly (P < 0.001) higher in the ocular hypertensive group (6.7 ± 1.9 mmHg) than in the control group (1.4 ± 1.7 mmHg).\textsuperscript{13}

The lamina cribrosa thickness in glaucoma and OHT

As noted earlier, the trans-lamina cribrosa pressure gradient depends on the pressure difference (IOP – ICP) and the thickness of the lamina cribrosa. Previous findings demonstrated that the lamina cribrosa thickens at the earliest detectable stage of experimental glaucoma in monkeys.\textsuperscript{23} It was suggested that the increase in lamina cribrosa thickness could be the result of several factors that include axonal swelling that is secondary to axonal transport blockage within the laminar trabeculae, oedema of the neural and/or connective tissues, and remodelling and/or synthesis of laminar connective tissue in response to IOP-related damage.\textsuperscript{23} In addition, the lamina cribrosa is significantly thinner in highly myopic eyes than in non-highly myopic eyes, contributing to a steeper trans-lamina cribrosa pressure gradient, which may explain the increased susceptibility to glaucomatous damage in highly myopic eyes.\textsuperscript{24} Investigations have also shown that in an advanced stage of glaucoma, the lamina cribrosa becomes markedly thinner.\textsuperscript{25} The consequence is that the TLCPD occurs over a shorter distance, resulting in a steeper gradient.\textsuperscript{25} Assuming that the steepness of this pressure gradient is of importance for the susceptibility of the optic nerve to glaucomatous damage, this glaucoma-related thinning of the lamina cribrosa may explain why the risk for further glaucoma progression in eyes with advanced glaucoma is increased.\textsuperscript{25} Conversely, recent data indicate that OHT patients have a thicker lamina cribrosa than control subjects, especially in OHT patients with definite high IOP.\textsuperscript{15}

IOP-induced A\textsubscript{β} generation may be involved in RGC death in glaucoma

Considerable evidence indicates that A\textsubscript{β} may be implicated in the development of RGC apoptosis in glaucoma,\textsuperscript{17–20} suggesting a possible link with AD. Previous findings showed that there is IOP-sensitive increase in A\textsubscript{β} in glaucoma.\textsuperscript{17–20} McKinnon et al.\textsuperscript{17} reported that rat RGCs subjected to chronic elevation of IOP exhibit caspase-3-mediated abnormal processing of β-amyloid precursor protein (APP) with increased expression of A\textsubscript{β}. This suggested a new hypothesis for RGC death in glaucoma involving chronic A\textsubscript{β} neurotoxicity, mimicking AD at the molecular level.\textsuperscript{18} Activation of caspases and abnormal APP processing, which includes production of A\textsubscript{β}, are also important events in AD.\textsuperscript{17} Guo et al.\textsuperscript{19} provided further evidence that A\textsubscript{β} is a likely mediator of pressure-induced RGC death. In a rat model mimicking chronic OHT, the authors found that A\textsubscript{β} colocalized with apoptotic RGCs.\textsuperscript{19} They also demonstrated \textit{in vivo} that A\textsubscript{β} induced significant RGC apoptosis.\textsuperscript{19} The authors further provided evidence that targeting A\textsubscript{β} and blocking its effects with combination therapy may represent an effective treatment strategy in glaucoma.\textsuperscript{19} By manipulating the A\textsubscript{β} pathway, the authors investigated three different approaches to targeting A\textsubscript{β} in experimental glaucoma and their combination effects: (i) reduction of A\textsubscript{β} formation by a β-secretase inhibitor; (ii) clearance of A\textsubscript{β} deposition by an anti-A\textsubscript{β} antibody; and (iii) inhibition of A\textsubscript{β} aggregation and neurotoxic effects with Congo red.\textsuperscript{19}
The authors showed that combined treatment (triple therapy) was more effective than either single-agent or dual-agent therapy. Recently, in a study using monkeys with experimental glaucoma, Ito et al. found time-dependent expressions and localization of Aβ in the retina as well as in the optic nerve head after chronic IOP elevation. It is interesting to note that a number of studies have similarly reported increased retinal Aβ in both AD transgenic mice and in human post-mortem retinas of AD patients.

The glymphatic system in the brain

Recently, the ‘glymphatic system’ was discovered for the first time in mice by Iliff et al. Their findings suggested a brain-wide network of paravascular pathways along which a large proportion of subarachnoid CSF recirculates through the brain parenchyma, facilitating the clearance of interstitial solutes, including Aβ, from the brain. CSF, driven in part by arterial pulsatility, enters the brain along para-arterial channels to exchange with interstitial fluid (ISF), which in turn is cleared from the brain along para-venous pathways. As ISF exits the brain through the para-venous route, it travels to the lymphatic vessels in the neck and eventually returns its contents to the systemic circulation. This brain-wide pathway has been called the ‘glymphatic system’, based upon its similarity in function to the peripheral lymphatic system, and its dependence upon astroglial water transport through the water channel aquaporin-4 (AQP4), which is localized to perivascular astrocytic endfeet ensheathing the cerebral vasculature. One implication of these findings is that glymphatic pathway dysfunction may contribute to the deficient Aβ clearance in AD.

In our 2015 paper, we reviewed several lines of evidence suggesting that the glymphatic system may also have potential clinical relevance for the understanding of the pathophysiology of glaucoma. Extrapolating from the brain, the question is whether there is also evidence for a glymphatic clearance pathway in the optic nerve. In light of the key role that the glymphatic pathway may play in the clearance of interstitial solutes from the brain, the observation of such an anatomically distinct clearing system in the optic nerve could be of great importance for our understanding of how solutes are cleared from the ISF in the optic nerve and could 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 optic nerve leading to Aβ accumulation and subsequent glaucomatous optic neuropathy.

In a post-mortem study to investigate the possibility of a paravascular fluid circulation, or at least paravascular spaces, in the human optic nerve, we are currently examining cross sections of human optic nerves by light microscopy after administering India ink by bolus injection into the SAS of the optic nerve (work in progress). Prior to commencement of a formal study, we retrospectively reviewed the light microscopic observations of human cadaver optic nerves harvested from two subjects without known ocular disease. Here, we present our findings in these two subjects. All samples were obtained no later than 6 h after death, following qualified consent for autopsy. All optic nerves including the globe were removed after removal of the orbital roof. The optic nerves were ligated with a 6.0 silk suture proximal to the optic chiasm. The fixative (neutral buffered 4% formalin) was then slowly injected into the SAS with a 19-gauge needle. Care was taken to avoid high-injection pressure in order not to create artefacts. India ink dissolved in 8% formalin (vol:vol = 1:1) was injected slowly under low pressure into the SAS of the optic nerve. The samples were fixed in 4% formalin by immersion for 5 days before further work-up. From each optic nerve, a piece including the midorbital portion and bulbar segment (adjacent to the globe) was processed for paraffin blocks and cut in sections of 5–8 µm thick. The stains used included haematoxylin and eosin, van Gieson elastin, Masson trichrome and Holmes-Luxol. Intriguingly, all two cases showed a very striking accumulation of India ink in paravascular spaces around blood vessel walls, whereas the lumens of these vessels remained unlabelled (Figs 1, 2a, 3). At higher magnification, the deposits were located between collagen fibre bundles lining a slit-like space (Figs 2b, 3). Optimal interpretation of the images was difficult because images taken at lower magnification were no longer available. Such images might have provided a clearer
context of the surrounding tissue, allowing better identification of the blood vessels. However, the blood vessels surrounded by ink were highly suggestive of the central retinal artery and vein. There was uncertainty whether such paravascular spaces also surrounded arterioles and venules in the optic nerve. However, even if the ink is not detectable around arterioles and venules, there is no proof that paravascular spaces are absent around these vessels. Indeed, at least theoretically, the absence of ink around the arterioles and venules in the optic nerve may be because the ink was administered by slow bolus injection under low pressure into the SAS of the optic nerve. Longer periods of ink administration and higher pressures might have resulted in more complete outlining of the microvasculature. Another reason could be that pulsatile vascular movements influence ink dispersion within the paravascular spaces. 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.\(^{28}\) Obviously, vascular pulsations were totally absent in the present post-mortem study. However, independent of the question whether or not there is distribution of ink around the entire vascular system of the optic nerve, our results clearly demonstrate the existence of paravascular spaces in the human optic nerve. Although further studies are needed to substantiate the functional significance of such paravascular spaces, and to determine whether a complete glymphatic transport system is present in the optic nerve, their existence at least suggests possible significance and is of particular interest in the context of the recently discovered paravascular clearance system in the brain. Obviously, the preliminary data presented cannot provide a scientifically acceptable level of evidence, with only two cases, and additional research is needed to confirm our findings.

With regard to the hypothesis presented here, considerable caution is warranted in extrapolating...
observations from brain research to optic nerve disease, and vice versa. Indeed, morphologically and physiologically, the brain and optic nerve are not identical in nature, the former having a large amount of grey and white matter, and the latter has only a very small amount of white matter. Although the precise function of the paravascular spaces in the optic nerve remains to be elucidated, it is intriguing to note that in a report presented at this year’s ARVO Annual Meeting, Hu and colleagues (Hu P, et al. IOVS 2016;57: ARVO E-Abstract 996) provided support for the existence of a glymphatic system in human, non-human primate, rat and mouse retinas. 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.

In addition, in yet another report presented at this year’s ARVO Annual Meeting, Löffler and colleagues (Löfler J, et al. IOVS 2016;57: ARVO E-Abstract 2270) provided support for lymphatic structures in AD mice retinas similar to the glymphatic system in the brain. The authors investigated possible clearance pathways for Aβ in an AD mouse model (SwAPP/Psen1d9). AD mice retinas exhibited enhanced APP production with increased amyloid processing and Aβ accumulation versus wild-type mice. Retinal Aβ plaques were much smaller than in brain. Aβ was located around and in blood vessels, suggesting a cerebral amyloid angiopathy in this model. The authors concluded that Aβ clearance from the retina may occur via lymphatic structures analogous to the described glymphatic system of the brain. These structures appear enhanced in AD.

It is interesting to note that recent studies also suggest a relationship between CSF drainage and aqueous humour outflow. As noted earlier, a novel ‘uveolymphatic’ pathway in the human eye, which may play a role in aqueous humour outflow, has recently been identified.8,9 Using in vivo hyperspectral imaging, Tam et al.32,33 demonstrated that quantum dot tracers injected into the anterior chamber of the eye in mouse drain into the submandibular lymph node. Similarly, after injection into the CSF of the cisterna magna in mice, quantum dot signal was detected using in vivo hyperspectral imaging in submandibular lymph nodes.34 Taken together, these data provide evidence of both ocular and CSF lymphatic drainage.

**Is open-angle glaucoma caused by glymphatic stasis at the site of the lamina cribrosa?**

Given that the aforementioned findings at least suggest the existence of a glymphatic system in human retina, and given that our post-mortem study demonstrated paravascular spaces in the human optic nerve, most likely around the central retinal artery and vein, it would be interesting to further investigate whether a ‘paravascular communication’ exists between the surroundings of the retinal vascular system and the surroundings of the central retinal vessels in the optic nerve.

The central retinal artery is a branch of the ophthalmic artery, which is the first branch of the internal carotid artery.35 It enters the optic nerve approximately 10 to 12 mm posterior to the globe and runs forward within a narrow canal to the optic nerve head in company with the central retinal vein, where it passes through the lamina cribrosa.36 At this level, it divides into two main branches (superior and inferior), each of which further bifurcates into temporal and nasal branches, which supply blood to the nerve fibre layer and the inner layers of the retina, including the ganglion cells.35

On the basis of magnetic resonance imaging findings of Terson’s syndrome (the occurrence of a vitreous haemorrhage in association with subarachnoid haemorrhage) and their review of the literature, Sakamoto et al.36 speculated 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 they may serve as drainage channels from the SAS around the optic nerve to beneath the internal limiting membrane forming the boundary of the retina with the vitreous body. As noted earlier, Aβ is a prominent finding in retinas of glaucomatous animal models and has been suggested to play a role in the development of RGC apoptosis in glaucoma.17–20 At least theoretically, such a paravascular ‘retino-orbital’ continuity, which includes a para-arterial CSF influx route around the central retinal artery to enter the retina, followed by a para-venous clearance efflux route around the central retinal vein, could facilitate elimination of neurotoxins, such as Aβ, induced by high IOP (Fig. 4). Demonstration of such a clearance system would support our hypothesis that glaucoma, just like AD, may occur when there is an imbalance between production and clearance of neurotoxins.5,37

In NTG, reduced clearance of Aβ might predominate as a result of glymphatic pathway dysfunction.5 In high-tension glaucoma, IOP-induced Aβ generation might predominate and even mild impairment of glymphatic pathway function might result in glaucomatous optic nerve damage.5

As noted earlier, there is increasing evidence in the literature that ICP is lower in patients with POAG than in nonglaucomatous control subjects.10–12 In addition, ICP was reported to be lower in the normal-tension form than in high-tension form of POAG.10,12 Several potential mechanisms for
Glaucomatous damage related to decreased ICP have been proposed. Low ICP could play a role in the pathogenesis of glaucoma through a higher pressure difference across the lamina cribrosa influencing the physiology and pathophysiology of the optic nerve head. The optic nerve head is of biomechanical interest because it is a weak spot within an otherwise strong corneo-scleral envelope. The lamina cribrosa, a thin area of scleral tissue that separates two differentially pressurized compartments, has a three-dimensional meshwork structure consisting of astrocyte-covered, capillary-containing, connective tissue beams with pores through which the RGC axon bundles pass. It provides structural and functional support to the RGC axons as they pass from the relatively high-pressure environment in the eye to a low-pressure region in the retrobulbar cerebrospinal space. The forces experienced at the level of the optic nerve head are influenced by both IOP and ICP. Pressure changes in either compartment, the intraocular space or the orbital SAS, alter the pressure distribution across the disc and hence the axial forces and transverse tension acting across optic disc tissue. The effects on the blood vessels, astrocytes and RGC axons may be substantial. Over time, a higher TLCPD may lead to abnormal function and nerve damage due to deformation of the lamina cribrosa, changes in axonal transport with reduced transfer of nutrients to the RGC axons, altered blood flow or other factors. It should be noted that, although the TLCPD is an interesting mechanical concept, Killer and Pircher recently stipulated that more sophisticated methods need to be developed to fulfil the physical requirements for this concept.

Here, we present an additional viewpoint. We believe that restriction of normal glymphatic flow at the level of the lamina cribrosa may be a new potential mechanism of action for low ICP in glaucoma. If the existence of a ‘paravascular communication’ between the retina and the optic nerve were further demonstrated, then failure of this circulation may be a contributing factor for the development of POAG and NTG. Indeed, 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. 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 suppression of glymphatic fluid transport leading to Aβ accumulation and subsequent glaucomatous optic neuropathy. This glymphatic stasis at the site of the lamina cribrosa could be one of the reasons why the lamina cribrosa thickens at the earliest stage of the disease.

CONCLUSIONS

The glymphatic system is a recently discovered brain-wide pathway for waste clearance that utilizes a unique network of paravascular channels to promote efficient elimination of interstitial solutes, including Aβ, from the brain. New research suggests that a similar system is present in the eye. If evidence further confirms the existence of an ocular glymphatic system, this may lead to significant advances in our understanding of pathophysiological mechanisms underlying POAG. In this paper, we have presented a new conceptual framework for understanding the pathogenesis of POAG. Further, we hypothesize that the disease may result from restriction of normal glymphatic flow at the level of the lamina cribrosa owing to a low ICP and/or a high trans-lamina cribrosa pressure gradient. It should be stressed that the few research data currently available, although encouraging, cannot be considered as proof that a glymphatic system exists in the eye. Although much more studies in both the glaucoma and glymphatic fields are required to validate this possibility, further elucidation of the pathophysiology of POAG might offer new perspectives for the development of novel diagnostic and therapeutic strategies for this devastating disorder. We therefore wish to encourage further studies and research in this area.

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