



# Glaucoma as a dangerous interplay between ocular fluid and cerebrospinal fluid

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## ABSTRACT

Glaucoma is a leading cause of irreversible blindness worldwide. Primary open-angle glaucoma, the most common type, is characterized by progressive degeneration of retinal ganglion cells and their axons in the optic nerve, resulting in progressive deterioration of visual fields. The optic nerve head is generally considered to be the primary site of axonal injury in glaucoma. Although the pathophysiology of glaucomatous optic neuropathy is not well understood, elevated intraocular pressure is considered the most important modifiable risk factor. However, in normal-tension glaucoma, intraocular pressure is not elevated and thus other risk factors must also be involved in the optic neuropathy of primary open-angle glaucoma. Several studies reported significantly lower intracranial pressure in patients with glaucoma compared with healthy subjects, suggesting that low intracranial pressure may result in a high pressure difference across the lamina cribrosa, influencing the physiology and pathophysiology of the optic nerve head by the effect of a mechanical force. Moreover, a rapidly evolving literature suggests the existence of an 'ocular lymphatic system'. This opens up new ways to understand the mechanisms underlying a range of ocular diseases such as glaucoma. In the present paper, I hypothesize that an imbalance between intraocular pressure and intracranial pressure, apart from generating mechanical forces at the lamina cribrosa, may lead to a dangerous interplay between ocular fluid and cerebrospinal fluid resulting in impaired cerebrospinal fluid entry into the optic nerve subarachnoid space and optic nerve perivascular spaces, and the perivascular space surrounding the central retinal artery in particular, thereby inhibiting glymphatic clearance of waste products from the retrobulbar or retrolaminar portion of the optic nerve. Should further research demonstrate that the proposed viewpoint is largely correct, it would hold great potential for our understanding of glaucomatous optic nerve damage and would have important implications for diagnosis and therapy of this devastating disorder.

## Introduction

Glaucoma is a leading cause of irreversible blindness worldwide [1,2]. Primary open-angle glaucoma (POAG), the most common type, is characterized by progressive degeneration of retinal ganglion cells (RGCs) and their axons in the optic nerve, resulting in progressive deterioration of visual fields [2]. The optic nerve head is generally considered to be the primary site of axonal injury in glaucoma [3]. From front to back, the optic nerve head consists of: (i) a surface nerve fibre layer, (ii) prelaminar region, (iii) lamina cribrosa, and (iv) retrolaminar region [4]. The lamina cribrosa is a multilayered, collagenous, sieve-like structure that 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 [5,6]. The pressure drop that occurs across the lamina cribrosa is known as the trans-lamina cribrosa pressure difference (TLCPD), that is, the difference of intraocular pressure (IOP) minus intracranial pressure (ICP) [7]. Whether RGC bodies in the retina are damaged first in POAG, or whether some cases of POAG are caused by direct damage to the optic nerve axons, with the RGCs being affected via retrograde optic atrophy later in the course of the disease, remains unclear [8]. Although the pathophysiology of glaucomatous optic neuropathy is not well

understood, elevated IOP is considered the most important modifiable risk factor [7]. However, elevated IOP is not present in all forms of POAG [7,9]. Indeed, in normal-tension glaucoma (NTG), IOP is not elevated and thus other risk factors must also be involved in the optic neuropathy of POAG [7,9]. An intriguing finding of clinical retrospective and prospective studies is that ICP as measured by lumbar puncture is lower in patients with POAG when compared with non-glaucomatous control subjects and additionally, is lower in the normal-tension versus the high-tension form of POAG [10–12]. It has been postulated that 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 by the effect of a mechanical force [7].

Refining our understanding of the interplay between IOP and ICP is essential both for extending our knowledge of the complex pathophysiology of POAG and for developing novel therapeutic strategies for this devastating disorder. In the present paper, I hypothesize that an imbalance between IOP and ICP, apart from generating mechanical forces at the lamina cribrosa, may lead to a dangerous interplay between ocular fluid and cerebrospinal fluid (CSF) resulting in impaired CSF entry into the optic nerve subarachnoid space (SAS) and optic nerve perivascular spaces, and the perivascular space surrounding the central

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retinal artery in particular, thereby inhibiting glymphatic clearance of waste products from the retrobulbar or retrolaminar portion of the optic nerve.

## Discussion

### *Evidence for cerebrospinal fluid entry into the optic nerve via a glymphatic pathway*

The optic nerve is a white matter tract of the central nervous system that extends into the orbit where it is surrounded by CSF in the SAS [13]. It is ensheathed in the meninges throughout its intraorbital and intracanalicular course [13]. The meningeal sheath of the optic nerve has the same lamellar structure as the meninges of the brain [13]. It consists of the pia mater, the arachnoid mater and the dura mater [13]. According to the traditional understanding of CSF physiology, CSF is mainly produced by choroid plexuses within the brain ventricles, from where it flows into interconnecting chambers, namely, the cisterns and the SASS, including the SAS of the optic nerve [14]. The SAS surrounding the optic nerve is in communication with the intracranial SAS in a normal population [15]. Anatomically, the blind end of the SAS in the bulbar segment of the optic nerve resembles a *cul de sac* at the level of the lamina cribrosa [16].

The mechanism by which CSF is reabsorbed out of the SAS of the optic nerve is not fully understood but lymphatics in the dura of the human optic nerve may offer an outflow pathway [15,16]. Lymphatics in the dura of the human optic nerve sheath were first described in 1999 by Gausas et al. [17] and Killer et al. [18]. As an extension of the brain, the optic nerve displays remarkable similarities to the brain in terms of anatomy and functionality [19]. Knowledge obtained from brain research could therefore lead to new insights into the optic nerve, and *vice versa*. Intriguingly, in 2015, two independent studies by Aspelund et al. [20] and Louveau et al. [21] identified a dural lymphatic system in the brain. These two studies further suggested a connection between the newly identified meningeal lymphatic vessels and the recently discovered glymphatic system [20–22]. The glymphatic system was first described by Liff et al. [23] in 2012. The authors defined for the first time a brain-wide network of perivascular channels, which they termed the ‘glymphatic pathway’, along which a large proportion of subarachnoid CSF recirculates through the brain parenchyma, facilitating the clearance of interstitial solutes, including amyloid- $\beta$ , from the brain [23]. This glymphatic pathway consists of 3 serial elements: a peri-arterial CSF influx route, a peri-venous interstitial fluid clearance route, and a trans-parenchymal pathway that is dependent upon astroglial water transport via the astrocytic aquaporin-4 (AQP4) water channel [24]. Extrapolating from the brain, the question arose whether there is also evidence for the existence of a perivascular transport system in the optic nerve analogous to the described glymphatic system of the brain. The presence of a glymphatic pathway in the optic nerve was first proposed in my hypothesis paper published in 2015 [9]. To investigate the possibility of a perivascular circulation in the human optic nerve, we examined cross-sections of human optic nerves by light microscopy after postmortem administration of India ink into the SAS of the optic nerve [25,26]. The study demonstrated a very striking accumulation of India ink in perivascular spaces around the central retinal artery and vein, whereas the lumens of these vessels remained unlabelled [25,26]. At higher magnification, the deposits were located between collagen fiber bundles lining a slit-like space [25,26]. More recently, Mathieu et al. [27] provided the first evidence to support the existence of a glymphatic pathway in the optic nerve following tracer injection into the CSF of live mice. The authors found CSF entry into the optic nerve via spaces surrounding blood vessels, bordered by AQP4-positive astrocytic endfeet [27].

### *The ocular glymphatic system: Is it all about cerebrospinal fluid?*

Importantly, apart from the reported CSF entry into the optic nerve, there also seems to be a flow of ocular fluid from the eye along the optic nerve [28]. Indeed, new observations indicate that the ocular glymphatic system may also provide an anatomical basis for posterior fluid outflow from the eye to the optic nerve that is TLCPD-dependent [28]. In a PhD thesis defense, Xiaowei Wang [28] demonstrated the existence of an ‘ocular glymphatic pathway’ in mice by intravitreal injection of fluorescently conjugated human amyloid- $\beta$  (FITC-hA $\beta$ ) and subsequent confocal and stereofluorescent imaging examination of the retina as well as the optic nerve of the injected eye. The TLCPD was identified as the major driving force for the outflow of ocular FITC-hA $\beta$  to the optic nerve [28]. In a chronic glaucoma mouse model (DBA/2J), aberrantly increased ocular outflow of FITC-hA $\beta$  into the optic nerve was observed only in a stage after IOP increase, not before IOP increase [28].

### *Glaucoma as a result of a dangerous interplay between ocular fluid and cerebrospinal fluid*

In their most recent article, Mathieu et al. [29] provided the first evidence that CSF entry into the optic nerve SAS and optic nerve perivascular spaces is impeded following tracer injection into the CSF in a DBA/2J mouse model of glaucoma. Within the 10-month-old DBA/2J glaucoma group, tracer was absent in the SAS and in the optic nerve in five of eight mice. Remaining mice showed minimal tracer (two of eight), and no difference compared with controls (one of eight). CSF tracer was absent in the laminar optic nerve in all 10-month-old DBA/2J females ( $n = 4/4$ ) and in one of four males [29]. It is interesting to note that there are known sex differences in DBA/2J glaucoma mice, with females displaying earlier onset and a more severe disease phenotype than males [30]. The results of the study by Mathieu et al. [29] seem to support the glymphatic hypothesis of glaucoma [9,26,31]. The theoretical part of this hypothesis was first developed and introduced in my paper published in 2015 [9]. Mathieu et al. [29] noted that the impaired CSF inflow to the optic nerve perivascular spaces in this DBA/2J mouse model of glaucoma appears to be secondary to blocked flow of CSF to the optic nerve SAS, as opposed to localized obstruction of perivascular inflow into the optic nerve. Indeed, the authors did not find any instances in which CSF tracer was present in the optic nerve SAS, but absent in optic nerve perivascular spaces of the same nerve [29]. This finding suggests that localized perivascular inflow obstruction is likely not responsible for impaired CSF inflow into the optic nerve. According to the authors, one explanation for blocked peri-optic CSF flow could be a reduced pressure gradient between the intracranial CSF space and the termination of the optic nerve SAS. Given that lymphatic vessels of the dura mater or orbit have been proposed as a possible outflow pathway for CSF from the optic nerve SAS termination, the authors proposed that if this draining lymphatic system is compromised in glaucoma, the resulting failure of CSF drainage out of the optic nerve SAS will tend to block CSF inflow to the orbital SAS since the pressure gradient no longer favors CSF flow from the intracranial space to the optic nerve and orbit [29].

The question then arises why lymphatic insufficiency should occur in this mouse model of high-tension glaucoma. The aforementioned brain and eye research is of particular interest here, which I believe may shed light on this question. In the brain, it appears that the drainage of interstitial solutes along the peri-venous spaces defined as part of the glymphatic pathway provides these solutes access to the sinus-associated lymphatics, either directly as these large veins merge to form the dural sinuses, or indirectly via the cisternal CSF compartments associated with these structures [22]. As noted above, lymphatic structures have also been described in the dura mater of human optic nerve sheaths [17,18]. I hypothesize that in high-tension glaucoma, the aberrantly increased flow of fluid from the eye to the optic nerve [28] may overload the lymphatics in the dura mater of the optic nerve, in

which the volume load becomes greater than the transport capability. This, in turn, may compromise CSF outflow from the optic nerve SAS, which consequently may decrease the CSF pressure gradient from the intracranial SAS towards the SAS of the optic nerve that normally supports flow of CSF to the optic nerve SAS. In the human optic nerve, the blocked flow of CSF to the optic nerve SAS could impair CSF entry into the perivascular space surrounding the central retinal artery, among other peri-arterial spaces of the optic nerve, thereby inhibiting glymphatic clearance of waste products from the retrobulbar or retrolaminar portion of the optic nerve. In a similar fashion, the lower ICP reported in NTG patients could lead to impaired CSF entry into perivascular spaces of the optic nerve, given that the pressure generated through a constant production of CSF by the choroid plexus, among other factors, drives glymphatic fluid transport [32]. Therefore, I believe that infusion of artificial CSF into the intrathecal space surrounding the spinal cord could offer potential to treat glaucoma by facilitating glymphatic flow in the optic nerve [33].

## Conclusions

To date, it is not clear what the relative contributions of the lymphatic and glymphatic pathways are to the development of glaucoma. The above data highlight the need to further elucidate whether at least some glaucoma cases may result from the toxicity of uncleared protein wastes and whether optic nerve lymphatic insufficiency and/or ocular glymphatic dysfunction may play a contributory role in the pathogenesis of glaucomatous damage. Should further research demonstrate that the proposed viewpoint is largely correct, it would hold great potential for our understanding of glaucomatous optic nerve damage and would have important implications for diagnosis and therapy of this devastating disorder.

## Conflict of interest statement

Dr. Peter Wostyn is the inventor of a pending patent application pertaining to glaucoma treatment using an intrathecal cerebrospinal fluid pump system, filed by P&X Medical NV.

## Statement on the welfare of animals

The article does not contain any studies with animals performed by the author.

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