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Cerebrospinal Fluid Pressure and Glaucoma

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Abstract
Purpose of Review Glaucoma is the second leading cause of blindness worldwide and remains a disease with a complex underlying pathophysiology. Primary open-angle glaucoma (POAG) is glaucoma in the absence of known causes and often is associated with elevated intraocular pressure (IOP).
Recent Findings Recent studies have focused on the role of cerebrospinal fluid pressure (CSFp) in the development of glaucoma based on the theory that the pressure difference between the intraocular pressure and the intracranial pressure, also known as the translaminar pressure difference (TLPD), is another important risk factor for developing glaucoma. The precise mechanisms by which optic nerve damage occurs remain to be discovered, but the authors believe it is due to impaired axonal transport secondary to an increased pressure difference between the IOP and the CSFp, which are separated by the lamina cribrosa.
Summary This publication will review the current literature available regarding CSFp and glaucoma.

Keywords Cerebrospinal fluid pressure · Glaucoma · Axonal transport · Translaminar pressure difference

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Introduction

Glaucoma is the second leading cause of blindness worldwide and remains a disease with a complex pathophysiology. Although various types of glaucoma exist, they all share the common definition of an optic neuropathy with characteristic optic nerve head changes and characteristic visual field loss. Primary open-angle glaucoma (POAG) is glaucoma in the absence of known causes and often is associated with elevated intraocular pressure (IOP). Recent studies have focused on the role of cerebrospinal fluid pressure (CSFp) in the development of glaucoma based on the theory that the pressure difference between the intraocular pressure and the intracranial pressure, also known as the translaminar pressure difference (TLPD), is another important risk factor for developing glaucoma. It is thought that the cerebrospinal fluid (CSF) can act as a shock absorber to dampen the effects of elevated intraocular pressure (IOP). This review will focus on the TLPD and how it can lead to vision loss if the difference is too great. The precise mechanisms by which optic nerve damage occurs remain to be discovered, but studies have suggested that it is due to impaired axonal transport secondary to an increased pressure difference between the IOP and the CSFp, which are separated by the lamina cribrosa (LC). A deeper understanding of the forces that act upon the axons making up the optic nerve as they traverse through the lamina cribrosa can aid in this discovery.

Cerebrospinal Fluid Production and Dynamics

Cerebrospinal fluid surrounds and fills cavities of the central nervous system, including the optic nerve. The normal volume of CSF is around 150 mL, and this entire

volume is replaced several times per day [1]. Cerebrospinal fluid is produced by the choroid plexus, which is found in the ventricles. The choroid plexus shares common features with the ciliary processes in the eye. Both comprise an epithelia-lined vascular core and are dependent on carbonic anhydrase; and thus, both CSFp and IOP can be lowered by carbonic anhydrase inhibitors. After being produced in the ventricles, CSF passes to the third ventricle and then through the aqueduct of Sylvius into the fourth ventricle. From there, it enters the subarachnoid space and spinal column via the middle foramen of Magendie and the two lateral foramina of Luschka. After circulation, the CSF is reabsorbed into the venous system into the venous sinuses by the arachnoid villi, which are outpouchings of the arachnoid membrane that penetrate gaps in the dura mater.

The craniospinal compartment is composed of neural tissue, blood, and CSF, where the neural tissue makes up 80 % and the blood and CSF compose the remaining 20 %. Since it is a closed system, any change in volume of either of these components could lead to changes in CSFp. Under normal conditions, CSF production will equal CSF resorption. A blockage in CSF outflow will result in an elevation of CSFp, and in an opposite manner any leakage of CSF, such as leak following a lumbar puncture, will cause decreased CSFp. Normal adult CSFp is considered to be between 5 and 15 mmHg [2] and is most commonly measured using a lumbar puncture (LP). Long-term measurement is possible by placing a catheter inside one of the lateral ventricles. These measurements are invasive and taken far from the CSF surrounding the optic nerve, and it is unlikely that the CSFp near the lumbar spine corresponds to that surrounding the optic nerve. Based on current knowledge, the CSFp surrounding the optic nerve is at least equal to or greater than the orbital tissue pressure, otherwise this space would collapse. Orbital tissue pressure has been found to be between 2.6 and 4.4 mmHg in the supine position [3, 4]. There are also controversial anatomical factors that may play a role in the CSFp in this space. Experimental studies in animals showed that CSFp surrounding the optic nerve was equivalent to intracranial pressure [5]. However, Killer et al. noted large trabeculae in the subarachnoid space surrounding the optic nerve, and that the CSF in this area was static rather than flowing freely [6, 7]. Recent efforts by Fleischman et al. found that there is a gravitational dependence on CSF flow within the optic nerve sheath, and that intracranial CSF flow is not separate from flow within the optic nerve [8•].

Thus, a precise and non-invasive measurement technique would provide useful clinical information. There have been numerous attempts, but the results have been underwhelming with questions regarding the accuracy of such methods. Techniques include transcranial Doppler, tympanic membrane reflectivity, and optic nerve sheath diameter using ultrasound or MRI [9, 10]. Two other techniques include refinement of ophthalmodynamometric measures of venous pulsations pressures, and balancing intracranial/orbital ophthalmic artery flow velocities [11–13].

Physiologic Variations of Cerebrospinal Fluid Pressure

Cerebrospinal fluid pressure, like IOP, has normal physiologic variances. Cerebrospinal fluid pressure declines with advancing age. In a review by Fleischman et al. [14•], in adults from age 20–49, the mean CSFp was 11.6 mmHg, and it began to decline in the 50–54-year-old age group to 11.2 mmHg. The trend continued into older ages. This parallels the trend for glaucoma, which is more prevalent with increasing age, hinting that decreased CSFp may play a role in the development of glaucoma [15].

Cerebrospinal fluid pressure is also positively correlated to blood pressure (BP). Ren et al. found that in non-glaucomatous patients, the systolic blood pressure was significantly associated with the CSFp, and also highly associated with IOP. Given that it was associated to both CSFp and IOP, there was no significant association between blood pressure and TLPD [16].

Body mass index (BMI) has also been shown to impact CSFp. Asrani et al. have demonstrated that a low BMI places patients at risk for normal-tension glaucoma (NTG) [17]. A prospective study has confirmed that increased BMI can lead to an increased CSFp [18].

Venous pressure can also affect the CSFp, as elevated venous pressure will reduce the rate of CSF resorption and an increased CSFp. Lastly, the CSFp, like IOP, is pulsatile having a small phase difference with peak IOP lagging behind peak CSFp, but their trough pressures coincide [19].

The Lamina Cribrosa and the Role of Pressure Differences

The lamina cribrosa is a continuation of the posterior sclera that forms the sieve-like perforation, which separates the intraocular space anteriorly and the intracranial space posteriorly. This is the structure through which the retinal ganglion cell (RGC) axons and the central retinal vein exit, and the central retinal artery enters. It is composed of collagen and is usually around 500 μm thick. The sieve-like structure is composed of many pores with the larger pores located at the superior and inferior poles of the optic disc. It has been found to be thinner and will bow posteriorly in patients with glaucoma [20–22]. Anterior to the LC is the choroid, retina, and nerve fiber layer made up of

the ganglion cell axons. Posterior to the LC is the optic nerve subarachnoid space, which surrounds the optic nerve, and is filled with CSF. The optic nerve itself is covered by the pia mater, and the CSF in the subarachnoid space is surrounded by the dura mater and intraconal orbital tissues. The intricacies of the CSF flow in the space posterior to the optic nerve is controversial and will be discussed below.

The ganglion cell axons that make up the optic nerve are exposed to two independent pressurized regions located on either side of the lamina cribrosa: the intraocular space anteriorly and the subarachnoid space that surrounds the optic nerve posteriorly. Both regions have large pressure ranges, with the IOP ranging from 10 to 21 mmHg, and the pressure within the subarachnoid space ranging from 5 to 15 mmHg [2].

The pressure difference between these two regions is known as the translaminar pressure difference (TLPD). Changes to the optic disc can occur if the pressure difference between them becomes too great. For example, optic nerve head swelling can occur if the CSFp is greater than IOP, and optic nerve cupping can occur if the IOP is greater than CSFp, as in glaucoma. Similarly, a translaminar pressure difference may be induced by a reduction in CSF pressure. This condition mimics glaucoma in that the IOP is disproportionately greater than CSFp.

Epidemiological studies have demonstrated this. In a study by Berdahl et al., it was found that patients with POAG had lower mean CSFp (9.2 mmHg ± 0.77) when compared with normals (11.8 mmHg ± 0.71) across different age groups. They also found that patients with "normal-tension glaucoma" had a significantly lower CSFp (8.7 mmHg ± 1.16) when compared to the patients with POAG. They also noted that elevated CSFp may be protective in patients who had elevated IOP, as they had a CSFp of 12.6 mmHg ± 0.85. (Figure 1) [23, 24].

Ren et al. also studied CSFp in patients with POAG, NTG, and controls and their results have supported the findings by Berdahl. Their findings showed that CSFp was lowest in the NTG group (9.5 ± 2.2 mmHg), followed by the POAG group (11.7 ± 2.7 mmHg), and highest in the control group (12.9 ± 1.9 mmHg). They also evaluated the TLPD and found that it was highest in the POAG group (12.5 ± 4.1 mmHg), next highest in the NTG group (6.6 ± 3.6 mmHg), and lowest in the controls (1.4 ± 1.7 mmHg) [16].

Siaudvytyte et al. [25] also looked at the relationship of TLPD in patients with POAG, NTG, and controls. They found lower CSFp in patients with NTG and POAG compared to those in the control group. This study used 2-depth transcranial Doppler to measure CSFp, a technique with an accuracy that has been questioned. The same group then looked at TLPD and the neuroretinal rim area in patients with POAG and NTG. They found that the TLPD was higher in glaucoma patients, and that in the NTG group there was a greater reduction in neuroretinal rim area in patients with higher TLPD. This study used the same technique to measure CSFp [11].

Experimental models have shown that movement of the LC occurs with an increase in IOP [26–28], and also with a reduction of IOP. Lee et al. used enhanced depth spectral-domain-optical coherence tomography (SD-OCT) to assess patients before and after trabeculectomy. Mean IOP decreased from 27.2 ± 8.9 mmHg to 10.5 ± 3.4 mmHg, and they also found that the mean anterior movement of the LC decreased from 614.58 ± 179.57 to 503.90 ± 14.67 μm relative to Bruch membrane opening. In a separate experiment, they measured LC position in patients with POAG before and after the reduction in IOP from 21.2 ± 9.1 mmHg to 10.5 ± 2.6 mmHg, and reported a reduction in mean LC depth from 584.73 ± 160.52 to 529 ± 137.18 μm [29, 30].

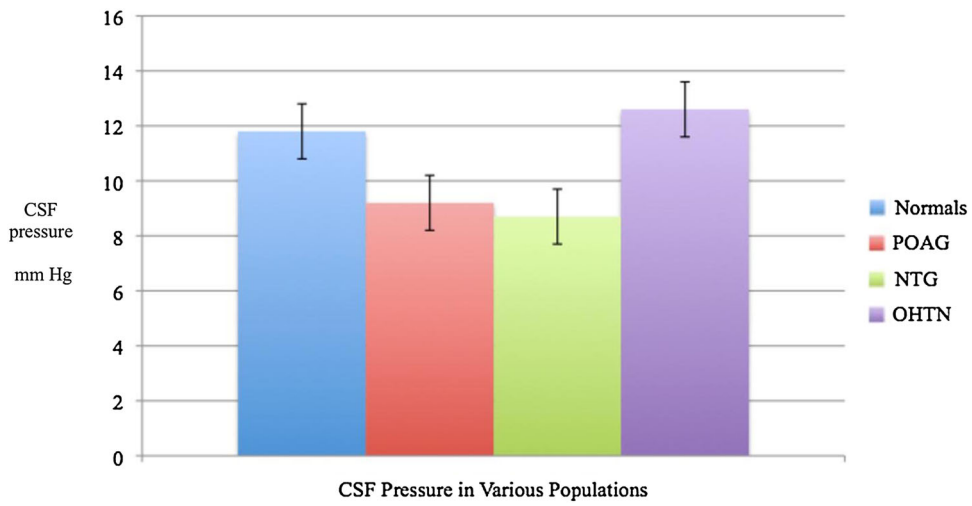

Fig. 1 Depiction of CSF pressure in various populations as discovered by Berdahl et al. [23, 24]. *CSF* cerebrospinal fluid, *POAG* primary open-angle glaucoma, *NTG* normal-tension glaucoma, and *OHTN* ocular hypertension

Much like increasing or decreasing the IOP can cause alteration in the position of the LC, alterations in the CSFp can also affect the position of the LC. The expectation is that decreasing the CSFp will lead to a posterior shift in the LC, and an increase in CSFp will result in the opposite. In a recent case study, enhanced depth SD-OCT showed posterior movement of the LC with reduction of the CSFp via optic nerve sheath fenestration. The prelaminar tissues were displaced 143 μm posteriorly, and the anterior surface of the LC was displaced 137 μm posteriorly [31].

Unlike IOP, the CSFp is markedly altered by postural changes, with the normal range of CSFp in the lateral decubitus position being 5–15 mmHg and in the sitting position being −10 to 0 mmHg at eye level [32]. Although IOP does not change as much as CSFP with respect to postural change, it does increase by 2–4 mmHg when lying down from sitting, possibly from an increase in episcleral venous pressure [33].

As noted above, the subarachnoid space behind the optic nerve does contain septae, which does not allow the CSF to flow freely in this area. It is still believed that the shifting of CSF does occur when one goes from supine to standing, producing a shift in CSFp in various areas of the CSF space. It is presumed that moving from supine to standing would decrease the CSFp in the post-laminar space, given this fluid shift, and would allow for posterior displacement of the lamina cribrosa (LC). One must also acknowledge that the opposite is true, and that moving from standing to supine would cause the LC and other associated optic nerve structures to be anteriorly displaced with movement of the CSF more cephalad. In a report by Fleischman et al., it was noted that the CSF posterior to the lamina cribrosa was consistently larger in the prone position compared to the supine position [8•]. The effects of microgravity have also demonstrated the importance of positioning of the CSF. Prolonged space flight by astronauts for more than 6 months can lead to a clinical syndrome of papilledema, choroidal folds, globe flattening, and a hyperopic shift. This condition is called Vision Impairment and Intracranial Pressure (VIIP). Although the exact cause is not known at this time, it is suspected that microgravity-induced cephalad fluid shift and comparable physiological changes play a significant role in these changes [34].

Axonal Transport

Axonal transport is crucial for cell survival and to maintain overall metabolic balance. Anterograde axonal transport is responsible for delivery of proteins and lipids to the distal synapse, and movement of mitochondria for local energy requirements. Retrograde transport is involved in the clearance of misfolded and aggregated proteins from the axon and intracellular transport of distal trophic signals to the soma [35, 36]. Molecular motors are the drivers of axonal transport. Kinesin is the motor responsible for anterograde transport, and dynein is responsible for retrograde transport [37]. These motors are specialized enzymes and use energy generated from ATP hydrolysis to produce movement along the cytoskeleton, which has three main components: microtubules, actin, and intermediate filaments [38]. When axonal transport is impaired, it is likely the result of dysfunction of the molecular motors or a component of the cytoskeleton. Axonal transport consists of both fast and slow transport. Fast transport is mostly responsible for movement of vesicular cargo, while slow axonal transport is mainly concerned with transport of cytoskeletal proteins, microtubules, neurofilaments, and actin, along with many additional cytosolic proteins. Fast transport moves at rates of 100–400 mm/day (1–5 μm/second), and slow transport at rates of 0.2–0.5 mm/day (0.0002–0.05 μm/second) [39].

Previous studies have shown that an experimentally elevated IOP is capable of an impediment of both the orthograde and the retrograde axoplasmic flow in animals [40–46]. The location of this impediment in the orthograde and retrograde axoplasmic flow appears to be the lamina cribrosa, where the translaminar pressure difference between the IOP and the CSFp occurs. As the RGC axons pass through the optic nerve head (ONH) and lamina cribrosa, they turn 90°, a course that may increase susceptibility to impaired axonal transport. As they pass through the pores in the lamina cribrosa, they are subject to further biomechanical stress.

The RGCs carry out highly energy-dependent activity, which requires constant distribution of mitochondria. The ONH and LC have been shown to be an area where mitochondria can accumulate under normal conditions [47, 48]. This accumulation increases under glaucomatous conditions [49–51]. Martin et al. found that acute and chronic IOP elevation causes accumulation of the retrograde transport of dynein at the optic nerve head [52]. Although this may just represent increased energy demand under high-IOP conditions at the ONH, it is likely that the transport of mitochondria may be impaired at this level secondary to an increased TLPD. It is also thought that damage to microtubules and neurofilaments secondary to the TLPD can affect axonal transport. Although the mechanism is not clear at this time, it is thought to be related to reduced ATP availability [53, 54].

More recently, studies have looked at the role of the TLPD and its effect on axonal transport. A study on monkeys with an experimental chronic lowering of the CSFp by implanting a lumboperitoneal shunt revealed that the monkeys with low CSFp showed a loss of the retinal nerve fiber layer thickness and width of the neuroretinal rim. In the above-mentioned study, it had remained unclear

whether the CSFp reduction-associated damage to the optic nerve was glaucomatous or whether it was an unspecific optic nerve damage, but it was believed to be from impaired axonal transport [55••]. In a study by Zhang et al., that looked at both elevated IOP or lowered CSFp in animals, it was revealed that in both conditions, both the orthograde axoplasmic flow and the retrograde axonal transport in the retinal ganglion cell axons were impeded. They also discovered that the recovery of the retrograde axonal transport after the short-term CSFp reduction was slower than the recovery of the retrograde axonal transport after the acute IOP elevation, although the translaminar pressure difference was higher in the high-IOP group compared to the low-CSFp group. They suggested that some aspects in the mechanism of optic nerve damage might be shared in animals with short-term elevations in IOP, and animals with short-term lowering of CSFp [56••].

Conclusion

As the population ages, it is estimated that the number of people with glaucoma worldwide will increase to 111.8 million in 2040 [57]. These estimates are important in guiding the designs of glaucoma screening, treatment, and related public health strategies. A deeper understanding of the mechanisms responsible for glaucomatous nerve damage is therefore needed.

Recent findings have implicated the role of CSFp in the development of glaucoma. The pressure difference between the intraocular pressure and the intracranial pressure, also known as TLPD, is another important risk factor for the development of glaucoma.

Epidemiologic studies have shown that both decreased CSFp and an elevated TLPD are significant risk factors for developing glaucoma. It is believed that there is an impairment of axonal transport caused by the elevated TLPD, with the site of impairment being the lamina cribrosa. Experimental studies have shown that increased IOP, decreased CSFp, and an increased TLPD can all lead to impaired axonal transport and in turn, glaucomatous damage. As we continue to learn more about glaucoma, it is important to understand that glaucoma is a two-pressure disease, where knowledge about the CSFp could be just as important as the IOP.

Compliance with Ethical Guidelines

Conflict of Interest Michael Greenwood declares no conflict of interest. John Berdahl reports personal fees from Vittamed, outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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