Fast circulation of cerebrospinal fluid : an alternative perspective on the protective role of high intracranial pressure in ocular hypertension

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REVIEW

Fast circulation of cerebrospinal fluid: an alternative perspective on the protective role of high intracranial pressure in ocular hypertension

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As ocular hypertension refers to a condition in which the intraocular pressure is consistently elevated but without development of glaucoma, study of it may provide important clues to factors that may play a protective role in glaucoma. β-amyloid, one of the key histopathological findings in Alzheimer's disease, has been reported to increase by chronic elevation of intraocular pressure in animals with experimentally induced ocular hypertension and to cause retinal ganglion cell death, pointing to similarities in molecular cell death mechanisms between glaucoma and Alzheimer's disease. On the other hand, recent studies have reported that intracranial pressure is higher in patients with ocular hypertension compared with controls, giving rise to the idea that elevated intracranial pressure may provide a protective effect for the optic nerve by decreasing the trans-lamina cribrosa pressure difference. The speculation that the higher intracranial pressure reported in ocular hypertension patients may protect against glaucoma mainly through a lower trans-lamina cribrosa pressure difference remains at least questionable. Here, we present an alternative viewpoint, according to which the protective effect of higher intracranial pressure could be due, at least in part, to a pressure-independent mechanism, namely faster cerebrospinal fluid production leading to increased cerebrospinal fluid turnover with enhanced removal of potentially neurotoxic waste products that accumulate in the optic nerve. This suggests a new hypothesis for glaucoma, which, just like Alzheimer's disease, may be considered then as an imbalance between production and clearance of neurotoxins, including β-amyloid. If confirmed, then strategies to improve cerebrospinal fluid flow are reasonable and could provide a new therapeutic approach for stopping the neurotoxic β-amyloid pathway in glaucoma.

Key words: Alzheimer's disease, cerebrospinal fluid clearance, glaucoma, intracranial pressure, ocular hypertension

Glaucoma is one of the leading causes of irreversible blindness.[1] Primary open-angle glaucoma (POAG), the most prevalent type, is a progressive optic neuropathy with characteristic structural changes in the optic nerve head and corresponding visual field defects.[2,3]

Raised intraocular pressure (IOP) remains one of the most important risk factors for POAG.[1,3] The precise mechanisms by which elevated IOP may lead to optic nerve damage are still unknown. Simple mechanical damage is unlikely. Moreover, a significant proportion of patients with POAG has normal IOP measurements, a condition known as normal tension glaucoma (NTG).[4–9] Why glaucoma occurs with normal IOP has been the subject of debate for decades. Furthermore, not all subjects with raised IOP develop glaucoma. Patients in whom the optic nerve and visual field show no signs of glaucomatous damage but the IOP is above the normal range are classified as having ocular hypertension (OHT). Only a small percentage of such patients may convert to POAG.[10]

A possible explanation suggested for the enigma of normal tension glaucoma and ocular hypertension is the trans-lamina cribrosa pressure difference (TLCPD). The optic nerve, a white matter tract of the central nervous system (CNS), is ensheathed in all three meningeal layers and surrounded by cerebrospinal fluid (CSF) in the subarachnoid space (SAS).[3] Therefore, in addition to IOP, the optic nerve is exposed to the intracranial pressure (ICP).[11] The lamina cribrosa, forming the anatomic floor of the optic nerve head, separates these two pressurised regions.[11,12] The difference between the posteriorly directed IOP and anteriorly directed intracranial pressure across the lamina cribrosa is known as the trans-lamina cribrosa pressure difference.[13] Normally, the IOP ranges from 11 to 21 mmHg with a mean of 16 mmHg.[11] The normal range of intracranial pressure is 5 to 15 mmHg with a mean of 12 mmHg, when measured by lumbar puncture in the lateral decubitus position.[11] This results in a small, posteriorly directed pressure difference (mean 4 mmHg) across the lamina cribrosa.[11] From a mechanical perspective, a similar posteriorly directed force is caused by either a lower pressure on the cerebrospinal fluid side of the lamina or a higher pressure on the intraocular side.[1]

A growing body of evidence indicates that cerebrospinal fluid pressure, that is, intracranial pressure, is lower in patients with POAG and normal tension glaucoma, when compared with non-glaucomatous control subjects.[1,13,14] These findings support the notion that the relationship between IOP and intracranial pressure may play a fundamental role in the development of glaucoma.[11] A decreased intracranial pressure, leading to an abnormally high trans-lamina cribrosa pressure difference, could result in baro-traumatically induced optic nerve damage at the site of the lamina cribrosa. Conversely, recent studies have reported that intracranial pressure is higher in patients with ocular hypertension compared with controls, giving rise to the idea that this elevated intracranial pressure may provide a protective effect for the optic nerve by decreasing the trans-lamina cribrosa pressure difference.[13,15]

The hypothesis of low intracranial pressure as pathogenically important for glaucoma has attracted a lot of attention in recent years; however, a number of objections has been raised against the speculation that the trans-laminar imbalance between the IOP and intracranial pressure caused by low intracranial pressure can cause bowing back of the rigid, compact band of lamina cribrosa, and consequently cause glaucomatous optic disc cupping.[16,17] A lower trans-lamina cribrosa pressure difference as explanation for the protective effect of high intracranial pressure in ocular hypertension also remains questionable. Indeed, in this opinion article, we discuss arguments against the hypothesis that the higher intracranial pressure reported in patients with ocular hypertension could protect against glaucomatous optic nerve damage mainly through a lower pressure difference acting across the optic nerve head. Within this context, we provide an alternative perspective on the protective role of high intracranial pressure in ocular hypertension. Based on current literature, we postulate that the protective effect of higher intracranial pressure can be due, at least in part, to a pressure-independent mechanism, namely faster cerebrospinal fluid production leading to increased cerebrospinal fluid turnover with enhanced removal of potentially neurotoxic waste products that accumulate in the optic nerve. This alternative viewpoint raises the possibility of explaining and integrating multiple previous research findings on both ocular hypertension and glaucoma, and may shed light on a new clearance pathway in the optic nerve.

CEREBROSPINAL FLUID PRESSURE AND TRANS-LAMINA CRIBROSA PRESSURE DIFFERENCE IN GLAUCOMA AND OCULAR HYPERTENSION: THE DATA

Recent research findings suggest the potentially pathogenic role of an abnormally low cerebrospinal fluid pressure in the development of POAG and normal tension glaucoma. In a retrospective case-control study, Berdahl, Allingham and Johnson[1] found that mean cerebrospinal fluid pressure as measured by lumbar puncture was 33 per cent lower in a group of 28 patients with POAG than in a control group of 49 non-glaucomatous patients (9.2 ± 2.9 mmHg versus 13.0 ± 4.2 mmHg or 124 ± 39 mmH_2O versus 177 ± 57 mmH_2O; $p < 0.00005$).

In another study with a similar design, Berdahl and colleagues[13] compared lumbar cerebrospinal fluid pressure measurements in 57 subjects with POAG, 11 subjects with normal tension glaucoma (a subset of POAG), and 27 subjects with ocular hypertension with 105 age-matched control subjects without glaucoma (66 in the age-matched control group for comparison with POAG and the subset of normal tension glaucoma and 39 in the age-matched control group for comparison with the ocular hypertensive group). The average age of POAG (70.5 ± 12.9 years) and subjects with normal tension glaucoma (68.0 ± 17.1 years) was higher than that of ocular hypertensive subjects (55.4 ± 18.6 years).[13] The cerebrospinal fluid pressure was significantly lower in POAG compared with age-matched control subjects without glaucoma (9.1 ± 0.77 mmHg versus 11.8 ± 0.71 mmHg; $p < 0.0001$). The subjects with normal tension glaucoma also had a lower cerebrospinal fluid pressure compared with the control subjects (8.7 ± 1.16 mmHg versus 11.8 ± 0.71 mmHg; $p < 0.01$). Furthermore, the cerebrospinal fluid pressure was higher in ocular hypertension than in age-matched control subjects (12.6 ± 0.85 mmHg versus 10.6 ± 0.81 mmHg; $p < 0.05$). The mean trans-lamina cribrosa pressure difference was 6.1 ± 5.6 mmHg in POAG and 5.0 ± 4.4 mmHg in the subset of normal tension glaucoma compared to 1.9 ± 4.4 mmHg in age-matched controls ($p < 0.05$). In the ocular hypertensive group, the mean trans-lamina cribrosa pressure difference was 8.4 ± 5.5 mmHg compared to 4.4 ± 3.5 mmHg in age-matched controls ($p < 0.05$).

The findings of Berdahl and colleagues[13] were confirmed by more recent prospective studies by Ren and colleagues.[14,15] A first study compared lumbar cerebrospinal fluid pressure in POAG patients and non-glaucomatous control subjects. The study included 43 patients with POAG differentiated into 14 patients with normal pressure glaucoma and 29 patients with high pressure glaucoma and 71 control subjects.[14] The cerebrospinal fluid 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 trans-lamina cribrosa pressure difference 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). Using multivariate analysis, the amount of glaucomatous visual field loss was mainly associated with the trans-lamina cribrosa pressure difference ($p = 0.005$);[14] however, when IOP and cerebrospinal fluid 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.[14]

In a parallel prospective study, Ren and colleagues[15] found that the cerebrospinal fluid 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 trans-lamina cribrosa pressure difference 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).[15]

ARGUMENTS AGAINST AN EXCLUSIVE ROLE OF TRANS-LAMINA CRIBROSA PRESSURE DIFFERENCE IN CASE OF HIGH CEREBROSPINAL FLUID PRESSURE

Despite the strength of the forementioned findings, high cerebrospinal fluid pressure and the resulting decrease in trans-lamina cribrosa pressure difference have not yet been proven to play a role in the prevention of glaucomatous optic nerve damage in eyes with ocular hypertension. Given that it is not possible to measure the retro-laminar pressure clinically, the previously noted retrospective[1,13] and prospective[14,15] studies of cerebrospinal fluid pressure in patients with glaucoma and ocular hypertension took the lumbar cerebrospinal fluid pressure measurement as

surrogate for pressure in the orbital cerebrospinal fluid space; however, this assumption is only true if cerebrospinal fluid pressure is homogenous in all cerebrospinal fluid spaces. In a study of 18 patients with normal tension glaucoma, Killer and colleagues[18] demonstrated that cerebrospinal fluid does not communicate freely between the intracranial subarachnoid space and that of the optic nerve and questioned whether the cerebrospinal fluid pressure is the same in these two cerebrospinal fluid spaces.

Even assuming that the high lumbar cerebrospinal fluid pressure in patients with ocular hypertension results in a decreased trans-lamina cribrosa pressure difference, a curious question remains as to why the subjects of the ocular hypertensive group should be protected against glaucoma, given that the trans-lamina cribrosa pressure difference was significantly higher in this group than in the control group.[15] In the study by Berdahl and colleagues,[13] the trans-lamina cribrosa pressure difference in the ocular hypertensive group was higher even when compared to the older glaucoma groups. Given that a recent study demonstrated that cerebrospinal fluid pressure decreases with older age,[19] this higher trans-lamina cribrosa pressure difference in the younger ocular hypertensive group may even be an underestimation. Berdahl and colleagues[13] suggested that the trans-laminar pressure gradient (the pressure difference across a specific distance) acting across the lamina cribrosa in combination with the inherent structural and physiological properties of the lamina (thickness, rigidity, elasticity and blood flow) may explain why a large percentage of ocular hypertensive patients do not convert to glaucoma, despite a high trans-lamina cribrosa pressure difference. Ren and colleagues[15] also suggested structural and biomechanical differences in the optic nerve head anatomy, as a possible reason why the elevated trans-lamina cribrosa pressure difference in some ocular hypertensive subjects did not lead to glaucomatous optic nerve damage. According to the authors, another reason could be that the correction of the IOP measurements for their dependence on the central corneal thickness was not sufficient, so that in reality the IOP in the ocular hypertensive group was lower than assumed.[15] Yet another reason could be that some of the eyes of the ocular hypertensive group might be pre-glaucomatous, in which detectable changes had not yet developed.[15]

FAST CIRCULATION OF CEREBROSPINAL FLUID AS A POSSIBLE PROTECTIVE FACTOR FOR GLAUCOMA

The potential role of cerebrospinal fluid flow dynamics in ocular hypertension

As noted previously, despite their higher cerebrospinal fluid pressure, subjects with ocular hypertension were found to have an elevated trans-lamina cribrosa pressure difference when compared with control subjects.[13,15] The trans-lamina cribrosa pressure difference in the ocular hypertensive group in the study by Berdahl and colleagues[13] was higher even when compared to the older glaucoma groups. Therefore, assuming that a higher cerebrospinal fluid pressure may be protective against glaucoma, it can hardly be expected that this is mainly due to a lower pressure difference across the lamina cribrosa. Here, we propose an alternative explanation, according to which the normal or high cerebrospinal fluid pressure reported in ocular hypertensive patients (in the study by Berdahl and colleagues[13] still within normal limits but 16 mmHg in the study by Ren and colleagues[15]) could be an indicator of a faster cerebrospinal fluid formation rate leading to increased cerebrospinal fluid turnover and clearance, thereby protecting against glaucomatous optic nerve damage. A higher cerebrospinal fluid pressure can be the consequence of a faster rate of cerebrospinal fluid production. Indeed, the cerebrospinal fluid pressure is the result of the production and outflow of cerebrospinal fluid.[20] According to the classic model of cerebrospinal fluid hydrodynamics, cerebrospinal fluid is actively produced mainly within the brain ventricles by choroid plexuses and reabsorbed into the venous blood system by the arachnoid villi.[20] Cerebrospinal fluid turnover is defined as the volume of cerebrospinal fluid produced in 24 hours divided by the volume of the cerebrospinal fluid space.[21]

There is evidence that circulation and turnover of cerebrospinal fluid helps to clear toxic metabolites, such as β-amyloid (Aβ) that is a hallmark protein in Alzheimer's disease (AD), from the interstitial fluid (ISF) space of the brain to the bloodstream.[21] Cerebrospinal fluid flows from the brain ventricles into interconnecting chambers, namely, the cisterns and the subarachnoid spaces, including the SAS of the optic nerves.[22] The SAS of the optic nerve harbours a distinct lymphatic outflow system in the dura mater[23] and is lined with meningothelial cells (MECs), which were shown to be involved in the clearance of waste products from the cerebrospinal fluid and in maintaining the optic nerve microenvironment.[18,24] Li and colleagues[25] found that meningothelial cells are highly active phagocytes capable of ingesting and digesting large amounts of apoptotic cells and that meningothelial cells can have an anti-inflammatory action following the uptake of apoptotic cells. Phagocytosis of β-amyloid via meningothelial cells has been demonstrated recently (HE Killer, 2014, personal communication). Importantly, a recent study in an experimental animal model provided evidence for a possible toxic effect of stagnant cerebrospinal fluid on the optic nerve.[26] Given the central role of cerebrospinal fluid turnover in the clearance of potentially toxic molecules from the central nervous system[21] and given that an efficient cerebrospinal fluid turnover may be vital for the integrity of the optic nerve, we believe that higher cerebrospinal fluid pressure could be protective against glaucoma through a faster rate of cerebrospinal fluid production and turnover. One might expect that such faster circulation of cerebrospinal fluid could ultimately result in increased neurotoxin clearance from the subarachnoid space surrounding the optic nerve and protect against glaucomatous optic nerve damage. According to this hypothesis, the protective effect of higher cerebrospinal fluid pressure could at least partially be due to faster cerebrospinal fluid circulation, turnover and clearance. Obviously, the lower pressure difference across the lamina cribrosa and other mechanisms might also operate at the same time.

Glaucoma considered as an imbalance between production and clearance of neurotoxins

IOP-INDUCED INCREASE IN β-AMYLOID AND β-AMYLOID -MEDIATED RETINAL GANGLION CELL DEATH

An obvious question is why enhanced optic nerve subarachnoid cerebrospinal fluid turnover and clearance should protect against elevated IOP. In other words, is there evidence that high IOP may generate neurotoxins that could then be cleared via the cerebrospinal fluid? In this context, it is interesting to note that previous findings showed that there is an IOP-sensitive increase in β-amyloid in glaucoma,[27–30] suggesting a

possible link with Alzheimer's disease, which is the most common type of dementia. It is characterised neuropathologically by the presence in the brain of extracellular senile plaques and intracellular neurofibrillary tangles, along with neuronal cell loss.[12] The major component of senile plaques is the small peptide β-amyloid.[12] Neurofibrillary tangles are mainly composed of abnormally phosphorylated tau protein.[12] Evidence exists of build-up of β-amyloid in retinal ganglion cells in experimental rat glaucoma.[27] Activation of caspases and abnormal β-amyloid precursor protein (APP) processing, which includes production of β-amyloid, are important events in Alzheimer's disease.[27] McKinnon and colleagues[27] detected a similar situation in experimental glaucoma. Indeed, in their study using a chronic ocular hypertensive rat glaucoma model, the authors found that caspase-3 is activated in retinal ganglion cells, where it cleaves β-amyloid precursor protein to produce neurotoxic fragments that include β-amyloid.[27] This suggested a new hypothesis for retinal ganglion cell death in glaucoma involving chronic β-amyloid neurotoxicity, mimicking Alzheimer's disease at the molecular level.[28] Guo and colleagues[29] provided further evidence that β-amyloid is a likely mediator of pressure-induced retinal ganglion cell death. In a rat model mimicking chronic ocular hypertension, the authors found that β-amyloid colocalised with apoptotic retinal ganglion cells.[29] They also demonstrated in vivo that β-amyloid induced significant retinal ganglion cell apoptosis.[29] The authors further provided evidence that targeting β-amyloid and blocking its effects with combination therapy may represent an effective treatment strategy in glaucoma.[29] Recently, in a study using monkeys with experimental glaucoma, Ito and colleagues[30] found time-dependent expressions and localisation of β-amyloid in the retina as well as in the optic nerve head after chronic IOP elevation.

DECREASED β-AMYLOID AND INCREASED TAU IN VITREOUS FLUID (GLAUCOMA) AND CEREBROSPINAL FLUID (ALZHEIMER'S DISEASE)

Studies consistently report decreased levels of β-amyloid (1-42) and increased levels of tau in cerebrospinal fluid from patients with Alzheimer's disease in comparison with healthy subjects.[31,32] Among patients with Alzheimer's disease, the consistent finding of low concentrations of β-amyloid (1-42) in cerebrospinal fluid compared with those of age-matched controls is thought to be due to increased aggregation, fibril and plaque formation, with decreased clearance of these peptides from the central nervous system.[33] To test the idea that β-amyloid (1-42) and tau contribute to the development of glaucoma, Yoneda and colleagues[32] measured β-amyloid (1-42) and tau concentrations in vitreous fluid samples from eyes of patients with glaucoma. The authors found significantly decreased vitreous levels of β-amyloid (1-42) and significantly increased vitreous levels of tau in patients with glaucoma in comparison with the levels in control subjects with macular holes.[32] Although the authors did not investigate histopathological changes (such as the formation of β-amyloid plaques or tau-containing intraneuronal neurofibrillary tangles in the retina) in their patients, their findings suggested that the neurodegenerative processes in glaucoma might share, at least in part, a common mechanism with Alzheimer's disease.[32]

OVERLAPPING β-AMYLOID CLEARANCE PATHWAYS IN THE BRAIN AND THE OPTIC NERVE

Knowledge obtained from Alzheimer research could lead to new insights into the pathogenesis of glaucoma. Of major interest for the hypothesis presented here, Alzheimer's disease is thought to be caused by an imbalance between production and clearance of β-amyloid, leading to β-amyloid accumulation in the central nervous system.[34] β-amyloid is cleared from the central nervous system by several pathways:

1. across the blood-brain barrier (BBB) by active transport
2. via solute diffusion and the bulk flow of interstitial fluid into cerebrospinal fluid
3. by active transport across the choroid plexus and
4. by *in situ* enzymatic degradation.[35]

Previous studies have reported β-amyloid clearance pathway alterations in the aged brain.[35] Aging alters the β-amyloid transporter expression at the blood-brain barrier.[36,37] There is a significant decrease in the expression of the blood-brain barrier β-amyloid efflux transporters low-density lipoprotein receptor-related protein 1 (LRP-1) and P-glycoprotein with age, whereas the expression of the receptor for advanced glycation end-products (RAGE), a β-amyloid influx transporter, is increased.[36,37] These changing efflux and influx expression profiles likely diminish β-amyloid clearance from the central nervous system,[37] imparting a greater clearance burden to the cerebrospinal fluid circulation. Aside from the age-related alterations in blood-brain barrier transporter expression, enzymatic degradation of β-amyloid may also be diminished.[35] Therefore, cerebrospinal fluid bulk flow and turnover may become increasingly more important for metabolite clearance in the aging brain.[35] In analogy to the major role attributed to cerebrospinal fluid in clearance of interstitial solutes, including β-amyloid from the brain, one might speculate that cerebrospinal fluid bulk flow might also be one of several clearance pathways that influence accumulation of β-amyloid in the optic nerve. Given the up-regulation of β-amyloid and other putative neurotoxins after IOP elevation, rapid cerebrospinal fluid production and hence faster cerebrospinal fluid circulation could then exert protective effects against glaucoma. This might explain the higher cerebrospinal fluid pressure reported in subjects with ocular hypertension (that is, elevated IOP but without development of glaucoma), given that the cerebrospinal fluid pressure is dependent on a balance between the production and reabsorption of cerebrospinal fluid. Evidence for overlapping β-amyloid clearance pathways in the brain and the optic nerve comes from studies of optic nerves in Alzheimer's disease, suggesting that altered expression of LRP-1 and RAGE in the microvasculature may play an important role in the pathogenesis of optic neuropathy in Alzheimer's disease by reducing the efflux of β-amyloid out of the optic nerve into the systemic circulation, and by increasing the inward flux of β-amyloid into the optic nerves, respectively.[38,39] In optic nerves of patients with Alzheimer's disease, LRP-1 is downregulated, whereas RAGE is upregulated.[38,39] A loss of LRP-1 expression and an overexpression of RAGE have also been shown in human cerebral microvasculature in Alzheimer's disease and appear to be associated with the accumulation of β-amyloid in the brain.[40]

FLOW OF FLUIDS IN THE ANTERIOR PART OF THE OPTIC NERVE

With regard to the hypothesis presented here, considerable caution is warranted in extrapolating observations from Alzheimer and brain research to optic nerve disease. Indeed, the present hypothesis assumes that the optic nerve subarachnoid cerebrospinal fluid exchanges with its interstitial fluid compartment, allowing clearance of interstitial

solutes, including β-amyloid. The question is whether there is some level of exchange between the interstitial fluid of the optic nerve and the surrounding cerebrospinal fluid. Previous studies investigating the flow of fluids in the anterior part of the optic nerve are of particular interest here and seem to confirm this possibility. In these investigations, electronmicroscopic studies and a variety of tracer substances were used.[41] These studies demonstrated that the fluids from the vitreous body and the optic nerve move from opposite directions and converge at the optic nerve head.[41,42] Indeed, several studies[41–43] found that there is a backward bulk flow of fluid from the vitreous into the optic nerve head. In addition, several studies established that there is a flow of fluid from the subarachnoid space of the optic nerve into the optic nerve and optic nerve head.[41,42,44,45]

Supportive evidence for a protective role of fast CSF circulation against elevated IOP

Circumstantial evidence supporting our idea that normal or fast cerebrospinal fluid circulation may be protective against elevated IOP comes from a study evaluating the frequency of glaucoma and ocular hypertension among patients with Alzheimer's disease. In a nursing home-based study in Germany, Bayer, Ferrari and Erb[46] studied 112 patients with Alzheimer's disease and 116 control subjects. The prevalence of glaucoma was reported to be 25.9 per cent in patients with Alzheimer's disease and 5.2 per cent in the control group. Glaucomatous visual field loss and/or optic disc cupping were the criteria for the diagnosis of glaucoma. Intriguingly, the occurrence rate of ocular hypertension with normal visual fields and normal optic nerve heads in patients with Alzheimer's disease was 0 per cent compared to a prevalence of 7.8 per cent in the control subjects.[46] The authors assumed the optic nerve to be less resistant to elevated IOP levels in patients with Alzheimer's disease.[46] We believe there may also be a possibility that elevated IOP without development of glaucoma is absent in Alzheimer's disease due, at least in part, to decreased metabolite clearance via the cerebrospinal fluid. Indeed, defective cerebrospinal fluid turnover with diminished clearance of β-amyloid is suspected to be a contributor to the pathogenesis of Alzheimer's disease.[21] Cerebrospinal fluid turnover rate is directly proportional to cerebrospinal fluid formation rate and inversely related to the volume of the cerebrospinal fluid space.[47] A normal turnover rate in man is about four volumes of cerebrospinal fluid per 24 hours.[47] Although not supported by definite evidence, cerebrospinal fluid production has been reported to be decreased in patients with Alzheimer's disease.[21,48] Even if the cerebrospinal fluid formation rate is not affected in Alzheimer's disease, there might be a diminished cerebrospinal fluid turnover rate caused by the increase in cerebrospinal fluid volume that is associated with cerebral atrophy.[47] Accordingly, in Alzheimer's disease, the cerebrospinal fluid turnover rate can fall to less than 1.5 volumes per day, a threefold decrease, thus compromising the cerebrospinal fluid sink action to clear harmful metabolites from the brain.[47,49] Interestingly, Silverberg and colleagues[50] reported in 2006 on intraventricular cerebrospinal fluid pressure in patients with Alzheimer's disease. This study showed a high occurrence of very low cerebrospinal fluid pressure among patients with Alzheimer's disease.[50,51] In a very recent study, Fleischman and colleagues[52] identified a significant cerebrospinal fluid pressure decrease in middle-age patients with Alzheimer's disease compared with controls. Given that intracranial pressure depends on cerebral tissue volume, cerebrospinal fluid volume and cerebral blood volume, the marked reduction in cerebrospinal fluid production reported in patients with Alzheimer's disease could be the cause of the lower cerebrospinal fluid pressure.[20] Theoretically, cerebral atrophy in Alzheimer's disease might lead to a further reduction of cerebrospinal fluid pressure.[20,51] Considering all of this, the absence of ocular hypertension in patients with Alzheimer's disease [46] is in line with the idea that normal or fast circulation of cerebrospinal fluid may play a role in the prevention of glaucomatous optic nerve damage in eyes with ocular hypertension. In a similar way, coincidence of Alzheimer's disease and glaucoma in many patients is predicted by our hypothesis.

CONCLUSIONS

As ocular hypertension refers to a condition in which IOP is consistently elevated but without development of glaucoma, study of it may provide important clues to possible factors that might play a protective role in glaucoma. Moreover, given that the optic nerve is a white matter tract extending from the brain and given the remarkable similarities between these two parts of the central nervous system, knowledge about mechanisms and processes taking place in the brain may have a wider application to the eye. In this article, we have presented a hypothesis according to which the higher cerebrospinal fluid pressure reported in ocular hypertensive patients could protect against glaucoma through its association with faster cerebrospinal fluid circulation and clearance. From this point of view, the higher intracranial pressure could be an indicator of a higher rate of cerebrospinal fluid formation leading to increased cerebrospinal fluid turnover with enhanced removal of potentially neurotoxic waste products that accumulate in the optic nerve. The protective factor then is not exclusively of a biomechanical nature (lower pressure difference across the lamina cribrosa) but also of a biochemical one (increased neurotoxin clearance). This suggests a new hypothesis for glaucoma, which, just like Alzheimer's disease, may be considered then as an imbalance between production and clearance of neurotoxins, including β-amyloid. If indeed cerebrospinal fluid is involved in the clearance of solutes and wastes from the optic nerve, then strategies to improve cerebrospinal fluid flow could provide a new therapeutic approach in glaucoma. In general, investigating common pathways with the brain may yield valuable clues to aid in the search for new therapeutic targets for ocular diseases, such as glaucoma. Therefore, ophthalmologists and researchers in neuro-medicine should exchange their expertise in order to increase insights that can ultimately lead to improved prevention and treatment of glaucoma.

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