A General Decline in Cerebrospinal Fluid Flow

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A General Decline in Cerebrospinal Fluid Flow: An Overlooked Risk Factor for Glaucoma?

We read with great interest the article by McCulley et al (1) entitled "Intracranial pressure and glaucoma." We are grateful to the authors for sharing their valuable insights with the scientific community, and we would appreciate the opportunity to comment.

In their article, the authors discuss the evolving role of intracranial pressure (ICP) in the pathophysiology of glaucoma and note that it is plausible that local alterations in optic nerve structure, blood supply, or axonal transport could result from changes in ICP. However, the authors do not discuss the potential role of a diminished cerebrospinal fluid (CSF) circulation in the development of glaucoma. We believe that a general decline in CSF flow may be an overlooked factor in the debate on the potential role of low ICP in glaucoma.

The hypothesis of low ICP as pathogenetically important for glaucoma has attracted a lot of attention in recent years. Retrospective studies conducted by Berdahl et al (2,3) have provided intriguing findings in relation to ICP among patients with glaucoma, and they were confirmed by a more recent prospective study by Ren et al (4). The lower ICP reported in primary open-angle glaucoma (POAG) and normal-tension glaucoma (NTG) patients 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 (5).

However, a number of objections have been raised regarding the speculation that the mismatch in pressures across the lamina cribrosa may indeed contribute to glaucomatous optic nerve damage. According to Hayreh (6,7), there is no scientifically valid support for the concept that the translaminar imbalance between the intraocular pressure and ICP caused by low ICP can cause bowing back of the rigid, compact band of lamina cribrosa and consequently cause glaucomatous optic disc cupping. In view of many arguments against a simple biomechanical mechanism, our group recently presented an alternative viewpoint that the harmful effect of lower ICP in patients with NTG could be due, at least in part, to a biochemical mechanism (8). Indeed, given that the lower ICP in patients with NTG may result from decreased CSF production (9), we postulated that this lack of CSF production and the resulting general decline in CSF flow could ultimately result in reduced neurotoxin clearance along the optic nerves and lead to glaucomatous damage. Interestingly, a study in an experimental animal model provided evidence for a possible toxic effect of stagnant CSF on the optic nerve (10). Therefore, we believe that a general decline in CSF flow could be an alternative explanation as to why glaucoma develops in patients with low ICP. Given that ICP is lower in patients with POAG when compared with nonglaucomatous control subjects and, additionally, is lower in the normal-tension vs. the high-tension form of POAG (2–4), the reduction in CSF production and turnover, with diminished clearance of neurotoxins, might be the necessary, if not sufficient, factor in the pathogenesis of glaucoma.

Given the above considerations and given that both the hydrostatic pressure and the dynamics of CSF may be potentially important for the physiological stability of the optic nerve (11), it may be worth discussing and exploring the potential role of a general decline in CSF flow in the pathogenesis of glaucoma.

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A General Decline in Cerebrospinal Fluid Flow: An Overlooked Risk Factor for Glaucoma?: Response

We are grateful for the attention received by our recent article (1). Dr Wostyn et al have suggested an additional potential mechanism by which intracranial pressure (ICP) might relate to the development of glaucoma, specifically that alterations in cerebrospinal fluid (CSF) flow may be a contributing factor. This proposal is based on the lack of conclusive evidence that translaminar pressure gradient (TPG) is a glaucoma risk factor. This notion is supported, in part, by referencing Hayreh, who has stated that the alterations in TPG could not result in deformation of the lamina cribrosa (LC) (2). As outlined in detail in our article, there are several recent studies, most using optical coherence tomography, which demonstrated inward and outward bowing of the LC with alterations in IOP and ICP (3–9). There also are numerous examples where alterations in ICP result in other structural changes, such as bone remodeling (10–12). We agree that TPG-related deformation of the LC remains to be conclusively established to be a glaucoma risk factors, but there is sufficient evidence to warrant further investigation.

We also agree that other factors may contribute to the glaucoma phenotype. Speculation that "stagnant CSF" may occur with reduced CSF production and result in accumulation of "toxins" is thought provoking. This raises several questions; for example, if toxin accumulation occurs, why should injury seemingly be limited to the optic nerve, sparing other neural structures, which also are bathed in CSF? Why would toxic-induced atrophy not manifest with optic disc pallor, as seen with toxic optic neuropathies, as opposed to cupping? Moreover, pressure is determined by a number of factors, with production rate being only one component. Are we certain that reduced production of CSF and not other factors such as increased resorption is responsible for the lower ICP measured in the various glaucoma subtypes linked to ICP? For example, the findings of Chang and Singh (13) suggest an increased prevalence of glaucoma in patients with normal pressure hydrocephalus (NPH). It has been hypothesized that this could be a consequence of the CSF shunting procedures, commonly used to treat NPH. In such patients, therapeutic lowering of ICP increases the TPG, possibly accounting for the increased frequency of glaucoma.