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Intracranial pressure and glaucoma: Is there a new therapeutic perspective on the horizon?

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ABSTRACT

Primary open-angle glaucoma is one of the leading causes of irreversible blindness worldwide. Raised intraocular pressure is the most important modifiable risk factor and lowering it remains the mainstay therapeutic approach for slowing optic nerve damage and visual field progression in glaucoma patients. An intriguing finding of clinical retrospective and prospective studies is that intracranial pressure is lower in patients with glaucoma. Furthermore, in a recent study on monkeys subjected to an implantation of a lumboperitoneal cerebrospinal fluid shunt to lower intracranial pressure, chronic reduction in intracranial pressure was associated with the development of glaucoma-like pathology in half of the monkeys. In addition, a very recent study demonstrated that patients whose intracranial pressure has been lowered following ventriculoperitoneal shunt placement, as treatment for normal pressure hydrocephalus, have a significantly increased risk of developing normal-tension glaucoma. These findings suggest that a reduced intracranial pressure may play an important role in the pathogenesis of glaucoma. This may be due to an abnormally high pressure difference across the lamina cribrosa resulting in biomechanical changes of the optic nerve head and/or to a deficient clearance of toxic substances, particularly in the subarachnoid space of the optic nerve and/or in the 'ocular glymphatic system'. The search for drugs or medical devices useful to ameliorate glaucoma by lowering the trans-lamina cribrosa pressure difference and/or by facilitating cerebrospinal fluid circulation may therefore be an important area for future research. In this article, we propose that infusion of artificial cerebrospinal fluid through an implantable pump into the intrathecal space surrounding the spinal cord could be a new promising strategy for the treatment of glaucoma. Although the implantation of such a cerebrospinal fluid pump is a relatively invasive intervention, it seems worthwhile to make every effort to identify new therapies for patients who suffer from this devastating disease, especially given the significant number of patients for whom non-invasive treatment options are ineffective.

Introduction

Glaucoma is one of the leading causes of irreversible blindness worldwide [1–3]. 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 structural changes in the optic nerve head and corresponding visual field defects [4]. The lamina cribrosa, a sieve-like structure in the posterior part of the sclera that allows passage of the RGC axons and central retinal vessels, seems to be the primary site of axonal injury in glaucoma [5]. Raised intraocular pressure (IOP) is considered the most important modifiable risk factor for the development of POAG, but elevated IOP is not present in all forms of glaucoma [6]. Indeed, in a significant proportion of patients designated as normal-tension glaucoma (NTG) subjects, the disease occurs in spite of normal IOP [6]. In addition, many patients with POAG are still undergoing progressive visual field loss and/or optic disc cupping despite normalization of IOP with pressure-lowering treatment strategies [7,8]. Clearly, factors other than IOP are likely to be involved in the optic neuropathy of POAG [8]. Other risk factors associated with POAG include age, family history, gender, ethnicity, central corneal thickness, high myopia, and systemic factors [9,10]. In addition, recent reports have emphasized that low intracranial pressure (ICP) may play an important role in glaucoma development [6]. In the present paper, we briefly review studies

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dealing with possible ICP involvement in glaucoma, discuss potential mechanisms by which low ICP may contribute to glaucomatous optic nerve damage, and offer a possible new approach to treat glaucoma.

Discussion

Low intracranial pressure may be a risk factor for the development of glaucoma

A growing body of evidence indicates that glaucoma is a condition that develops from a mismatch in pressures across the lamina cribrosa [6]. The optic nerve, a white matter tract of the central nervous system, is ensheathed in all three meningeal layers and surrounded by cerebrospinal fluid (CSF) in the subarachnoid space (SAS) [11]. Therefore, in addition to IOP, the optic nerve is exposed to the ICP [6]. The lamina cribrosa separates these two pressurized regions [6]. The difference between the posteriorly directed IOP and anteriorly directed ICP across the lamina cribrosa is known as the trans-lamina cribrosa pressure difference (TLCPD) [6]. Normally, the IOP ranges from 11 to 21 mmHg with a mean of 16 mmHg [6]. Normal ICP in healthy supine adults varies between 5 and 15 mmHg with a mean of 12 mmHg [6]. This results in a small, posteriorly directed pressure difference (mean 4 mmHg) across the lamina cribrosa [6]. The pressure drop that occurs across the lamina cribrosa (IOP-ICP) increases with elevation of IOP or reduction of ICP [6].

An intriguing finding of clinical retrospective and prospective studies is that ICP is lower in patients with POAG when compared with nonglaucomatous control subjects and additionally, is lower in the normal-tension versus the high-tension form of POAG [12–14]. These studies of CSF pressure in patients with glaucoma took the lumbar puncture CSF pressure measurement as surrogate for pressure in the orbital CSF space [12–14]. When ICP was measured noninvasively using a specialized transcranial Doppler device, it was found that ICP was 2–3 mmHg lower in patients with OAG, especially in NTG, compared with healthy subjects [15]. It should be noted that two recent studies did not confirm lower ICP in NTG patients [16,17]. However, Siaudvytyte et al. [18] reported that in patients with NTG with differing ICP values, as measured by transcranial Doppler ultrasonography, lower ICP was associated with significantly lower neuroretinal rim area.

About 40 years ago, Yablonski et al. [19] observed glaucoma-like changes in normotensive eyes of cats in which the ICP was reduced below atmospheric pressure. However, the authors never published their findings formally (except in abstract form) and therefore it is difficult to evaluate the merits of their research. Interestingly, in a recent study on monkeys subjected to an implantation of a lumboperitoneal (LP) CSF shunt to lower ICP, chronic reduction in ICP was associated with the development of glaucoma-like pathology in half of the monkeys [20]. These monkeys showed a statistically significant decrease in the area and volume of the neuroretinal rim, an increase in the volume of the optic cup, and a reduced thickness of the retinal nerve fiber layer [20]. In addition, a very recent study demonstrated that patients whose ICP has been lowered following ventriculoperitoneal (VP) shunt placement, as treatment for normal pressure hydrocephalus, are almost 40 times more likely to suffer from NTG than elderly Italian patients without hydrocephalus [21].

The above findings support the notion that the relationship between IOP and ICP may play a fundamental role in the development of glaucoma [6]. Given that a decrease in ICP may be a risk factor for developing glaucoma, perhaps in the future, the disease might be treated from the intracranial compartment side of the lamina cribrosa in addition to lowering IOP [22]. In the present article, we propose that infusion of artificial CSF through an implantable pump into the intrathecal space surrounding the spinal cord could be a new treatment option for glaucoma.

Potential mechanisms through which low intracranial pressure may cause glaucomatous optic nerve damage

At least three major mechanisms have been proposed to explain how low ICP may contribute to glaucomatous optic neuropathy: (i) a barotraumatic pathomechanism; (ii) failure of CSF dynamics; and (iii) ocular glymphatic system dysfunction. While some of the proposed mechanisms may yet prove to be non-factors in glaucoma, they seem at least plausible given the current state of knowledge in the published literature.

Barotraumatic pathomechanism

First, 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 [6]. As noted above, strong evidence suggests that the principal site of RGC axonal insult in glaucoma is at the level of the lamina cribrosa within the optic nerve head [5]. The optic nerve head is of biomechanical interest because it is a weak spot within an otherwise strong corneoscleral envelope [23]. The lamina cribrosa has a three-dimensional meshwork structure consisting of astrocyte-covered, capillary-containing, connective tissue beams with pores through which the RGC axon bundles pass [23–26]. 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 [23]. The forces experienced at the level of the optic nerve head are influenced by both IOP and ICP [27]. Pressure changes in either compartment, the intraocular space and/or the orbital SAS, alter the pressure distribution across the disc and hence the axial forces and transverse tension acting across optic disc tissue [27]. 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, altered blood flow, or other factors [6].

However, it is critical to separate the biomechanical effects of ICP that acts only on the optic nerve head and IOP that acts both directly on the anterior surface of the optic nerve head and through scleral canal expansion at the laminar insertion [23]. Indeed, the forces of ICP act only on the retrolaminar optic nerve, and thereby affect laminar and optic nerve head biomechanics only through the TLCPD. This is different than IOP, which acts on the entire interior of the globe, and therefore involves peripapillary traction on the lamina cribrosa at its insertion into the neural canal wall.

Failure of cerebrospinal fluid dynamics

The second mechanism, proposed by our group, suggests that low ICP could be linked to glaucoma through its association with deficient clearance of toxic substances due to disruption of normal optic nerve CSF circulation [28]. A decreased ICP can be the consequence of reduced CSF production. Indeed, the ICP is built up by the equilibrium between the production and outflow of CSF [28]. According to the classic model of CSF hydrodynamics, CSF is actively produced mainly within the brain ventricles by choroid plexuses and reabsorbed into the venous blood system by the arachnoid villi [29]. The CSF turnover rate is directly proportional to the CSF formation rate and inversely related to the volume of the CSF space [30,31]. In a young adult with normal CSF production (0.4 mL/min) and a total CSF space volume of 150–160 mL, CSF turnover is about 4.0 volumes per day [31]. A decrease of CSF production rate thus reduces the CSF turnover rate [28]. This decrease in CSF flow rate may result in the accumulation of biologically highly active substances in the CSF leading to neurotoxicity. Indeed, CSF circulation and turnover are considered to play a key role in the elimination of toxic metabolites from the brain interstitium [31]. Disruption of normal CSF flow, resulting in reduced CSF clearance and accumulation of amyloid-β (Aβ) in the brain, is believed to contribute to the development of Alzheimer's disease (AD) [31].