Glaucoma Considered as an Imbalance Between Production and Clearance of Neurotoxins

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Glaucoma Considered as an Imbalance Between Production and Clearance of Neurotoxins

We read with great interest the paper by Yang et al. titled “Optic Neuropathy Induced by Experimentally Reduced Cerebrospinal Fluid Pressure in Monkeys” published recently in Investigative Ophthalmology & Visual Science. We are grateful to the authors for sharing their findings with the scientific community, and we appreciate the opportunity to comment on an issue raised by the authors.

To examine the influence of experimentally reduced cerebrospinal fluid (CSF) pressure on retinal nerve fiber layer (RNFL) thickness and neuroretinal rim area of the optic nerve head, Yang et al. conducted a study on monkeys subjected to an implantation of a lumbar-peritoneal CSF shunt. In the study group ($n=4$ monkeys), the shunt was opened to achieve a CSF pressure of approximately 40 mm H$_2$O, while the shunt remained closed in the control group ($n=5$ monkeys). During a follow-up of 1 year, two out of the four monkeys of the active intervention group showed a progressive reduction in RNFL thickness in both of their eyes, accompanied by a significant increase in the area and volume of the neuroretinal rim and a significant increase in the cup-to-disc area ratio. Two monkeys with artificially low CSF pressure did not develop the optic neuropathy observed in the other two monkeys, nor did any monkey of the control group. The authors emphasized that they did not examine any morphological changes in the lamina cribrosa of the monkeys, and therefore concluded that their study did not present any evidence that low CSF pressure caused glaucoma at normal levels of intraocular pressure (IOP). Their study, however, supported the concept that low CSF pressure alone may cause retinal ganglion cell injury and loss and thus that a low CSF pressure may be a risk factor in all forms of optic neuropathy including glaucoma.

The hypothesis of low CSF pressure, that is, intracranial pressure (ICP), as pathogenically important for glaucoma has attracted much attention in recent years. A growing body of evidence indicates that ICP is lower in patients with primary open-angle glaucoma and normal-tension glaucoma when compared with nonglaucomatous control subjects. These findings support the notion that the relationship between IOP and ICP is complex and thus that a low CSF pressure may be a risk factor in all forms of optic neuropathy including glaucoma.

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With regard to the potential pathogenic role of an abnormally low CSF pressure in the development of optic nerve damage, a remaining question is why two monkeys with artificially low CSF pressure from the study by Yang et al. did not develop an optic neuropathy. According to the authors, one explanation could be that the absence of optic neuropathy in these animals was similar to the clinical observation of OHT, in which despite elevated IOP an optic nerve damage does not develop. In other words, some of the protective factors for OHT may also operate in these two monkeys. This is completely in line with the viewpoint presented in a paper by our group that is being prepared for publication (Wostyn P. et al., manuscript in preparation, 2014).

In this opinion article, based on current literature, we postulate that enhanced CSF turnover and clearance may protect against elevated IOP. Previous findings at least suggest that high IOP may generate neurotoxins that could then be cleared via the CSF. Of particular interest, the accumulation of beta-amyloid (Aβ) in the brain has been postulated to be a neurotoxin that could then be cleared via the CSF. This view seems to be supported by the findings from the study by Yang et al. Indeed, a possible explanation for the absence of optic neuropathy in two monkeys with artificially low CSF pressure could be altered CSF dynamics related to shunt placement, that is, increased CSF flow from the ventricles, leading to enhanced removal of potentially neurotoxic waste products that accumulate in the optic nerve. Although the reduction in CSF pressure by the lumbar-peritoneal CSF shunt may increase the risk of developing optic neuropathy, shunt placement may also have a protective effect due to increased CSF turnover and clearance. We believe that this may explain why two monkeys with artificially low CSF pressure did not develop an optic neuropathy.

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