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EDITORIAL

Cerebrospinal fluid pressure and glaucomatous optic disc cupping

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In 1925 [1], Szymansky and Wladyczko postulated that low cerebrospinal fluid pressure (CSFP) might play a role in the development of optic disc cupping, and their concept has been resurrected periodically ever since [2–5]. The basic premise is that in raised CSFP, the lamina cribrosa bows forward to cause optic disc edema, while a fall in CSFP would cause the reverse, i.e., a bowing back of the lamina cribrosa and cupping. To assess the scientific rationale behind this notion, one has to consider the following fundamental relevant issues.

Pathogenesis of optic disc edema in raised CSFP

I investigated this experimentally in 67 rhesus monkeys, implanting an intracranial balloon which when gradually inflated over a period of several months, simulated a slow growing intracranial tumor [6–11]. This resulted in development of elevated CSFP and optic disc edema. Several studies were then performed to investigate the pathogenesis of optic disc edema in raised CSFP and these showed that optic disc edema is primarily due to axoplasmic flows stasis caused by the raised CSFP [9, 10]. The axoplasmic flow stasis causes swelling of the axons in the prelaminar region and surface nerve fiber layer of the optic disc, resulting in optic disc edema. Histopathologic studies in these eyes with optic disc edema showed no "bowing forward of the lamina cribrosa" [6–9], contradicting the impression that optic disc swelling in raised CSFP is caused by bowing forward of the lamina cribrosa.

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Morphological properties of the lamina cribrosa

The lamina cribrosa is a firm, dense, horizontal, compact band of connective tissue bridging the scleral canal (Fig. 1) [12, 13]. The band is anchored at the periphery to the surrounding sclera with thick columns of connective tissue, centrally attached to the connective tissue surrounding the central retinal vessels, and shows a slight concavity towards the vitreous side [12]. It has many openings of different sizes for transmission of the nerve-fiber bundles. Longitudinal fibrous septa of the retrolaminar part of the optic nerve are firmly anchored to the posterior surface of the lamina cribrosa (Fig. 1) [12]; this must prevent its bowing forward.

Role of translaminar pressure difference in CSFP and IOP in optic disc cupping

A recent study claimed: "CSF pressure may play an important contributory role in the pathogenesis of POAG (primary open-angle glaucoma)" [5], but in that study, the difference in the means of CSFP between the control and POAG groups was only 3.8 mmHg, with 15 mmHg intraocular pressure (IOP) in both groups. The concept that a translaminar pressure difference of only 3.8 mmHg produced by the low CSFP is strong enough to cause

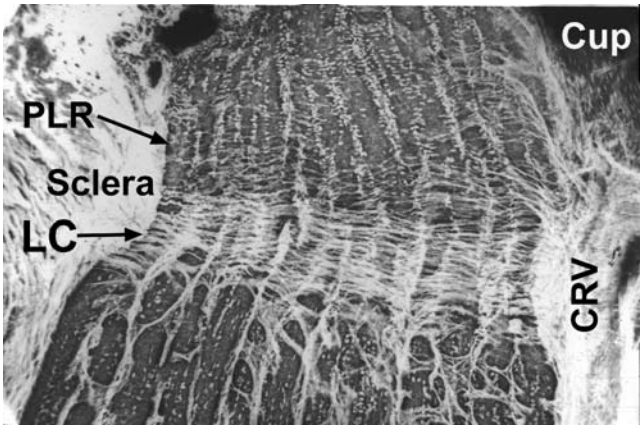

Fig. 1 Longitudinal section of anterior part of the optic nerve of rhesus monkey, showing anchorage of the connective-tissue strands of the lamina cribrosa to the sclera at the periphery and to the connective-tissue sheath of the central retinal vessels centrally (Hortega's stain) (reproduced from Hayreh and Vrabec [12]). Abbreviations: *CRV* Connective tissue sheath of the central retinal vessels. *LC* Lamina cribrosa. *PLR* Prelaminar region

bowing back of the dense, compact band of connective tissue of the lamina cribrosa (Fig. 1) has little scientific credibility. In this connection, one has to consider a basic issue: can the difference between CSFP and IOP alter the position or shape of the lamina cribrosa? Normal CSFP is 4.5–15 mmHg (average of about 9 mmHg). Normal IOP is 11–21 mmHg (average of about 16 mmHg). Taking for the sake of argument, an extreme example: low CSFP of about 5 mmHg and IOP 21 mmHg, that gives a translaminar difference of 16 mmHg. Is this difference capable of causing cupping? The answer is, definitely not. As mentioned above, the lamina cribrosa is a rigid, compact band of connective tissue, anchored firmly to the surrounding sclera and posteriorly to the longitudinal fibrous septa of the optic nerve (Fig. 1), not a free-floating, thin, elastic membrane separating the IOP and CSFP. The following two types of experimental studies give further support.

(i) Acutely elevated CSFP with normal IOP: In 35 rhesus monkeys [6, 8], I acutely raised the CSFP to 40–60 mmHg at the rate of 5 mmHg every 5 min. This failed to produce any ophthalmoscopically detectable bulging forward of the disc surface, in spite of as much as 40-mmHg difference between the CSFP and IOP. Normally seen optic disc edema with raised CSFP is due to axoplasmic flow stasis, which takes several days to develop; such a brief acute rise in CSFP does not result in optic disc edema.

(ii) Acutely elevated IOP with normal CSFP: Conversely, there are several studies that have investigated the effect of acute elevation of IOP on the lamina cribrosa in enucleated human eyes [14, 15] and in primate eyes [16–19].

(a) Enucleated human eyes: The effect of acute elevation of IOP to 50–60 mmHg was investigated by two different techniques [14, 15]. This showed bowing back of the lamina cribrosa by only 35 μm in one study [14] and 79 μm in another [15].

(b) Primate eyes: In these studies, using different techniques, backward displacement of the optic disc surface with raised IOP was evaluated in normal eyes. An increase of IOP to 45 mmHg pushed back the optic disc surface by 17.8 μm in one study (using Humphrey Retinal Analyzer [16]) and by 28 μm in another (using digitized images of Topcon simultaneous stereoscopic photographs [17]). In another study [18], when IOP was elevated to 30 mmHg, confocal scanning laser tomography showed backward displacement of disc surface by 15–86 μm.

All these experimental studies show that even a marked difference between the IOP and CSFP (which is unlikely to occur clinically) caused no ophthalmoscopically detectable change in the lamina cribrosa (or anterior surface of the optic disc). This is also supported by a study [19] where three clinicians (masked) could not detect short-term changes in the surface of the optic disc of monkeys consistently from stereoscopic photographs when the IOP was elevated from 10–45 mmHg. Thus, these experimental studies do not support in any way the speculation that low CSFP causes bowing back of the lamina cribrosa and optic disc cupping. The same holds true for the theory of Jonas et al. [3–4], in normal or highly myopic eyes.

Role of axoplasmic flow stasis in optic disc cupping

There was a flurry of interest in investigating axoplasmic flow obstruction among glaucoma researchers in the mid-1970s, when it was postulated that this was probably the cause of optic disc cupping and visual field defects in glaucomatous optic neuropathy [20]. However, the overwhelming evidence is that axoplasmic flow stasis plays no role in glaucomatous optic neuropathy; for instance:

(a) Axoplasmic flow stasis always causes axonal swelling [9–11] and consequently optic disc edema, but this is never seen at any stage in glaucomatous optic neuropathy.

(b) Axoplasmic flow stasis has been demonstrated in many optic nerve disorders [11], but none of these develop optic disc cupping.

(c) It could be argued that chronic axoplasmic flow stasis may cause axonal damage in the optic nerve and loss of axons alone; however, loss of axons alone (as in ascending and descending optic atrophy) is generally not associated with disc cupping.

(d) Axoplasmic flow stasis per se causes no visual loss, as, for example, in optic disc edema due to raised CSFP and ocular hypotony.
(e) In normal tension glaucoma, the IOP is normal, too low to produce any axoplasmic flow stasis, and yet eyes have optic disc cupping.

The idea that axoplasmic flow stasis has a role in the development of glaucomatous optic neuropathy has been largely abandoned.

Mechanism of optic disc cupping in glaucomatous optic neuropathy

This is discussed at length elsewhere [21, 22]. To understand the mechanism of backward bowing of the lamina cribrosa in optic disc cupping in glaucoma, it is essential to bear in mind the following facts:

(a) The optic nerve head is primarily supplied by the posterior ciliary artery circulation [23]
(b) There is overwhelming evidence now that vascular insufficiency plays an important role in the development of glaucomatous optic neuropathy [24–26]
(c) Identical optic disc cupping develops in arteritic anterior ischemic optic neuropathy associated with giant cell arteritis [22, 27, 28]
(d) Histopathologic study of the optic nerve in experimental glaucomatous optic neuropathy in rhesus monkeys has shown marked thickening and fibrosis of the retrolaminar longitudinal fibrous septa, as well as axonal atrophy and gliosis [29]
(e) Development of Schnabel's cavernous degeneration in retrolaminar optic nerve in glaucomatous optic neuropathy is well known. Histopathologic studies of the optic nerve in arteritic anterior ischemic optic neuropathy [22, 30, 31], as well as in experimental occlusion of the posterior ciliary arteries [32], have shown development of Schnabel's cavernous degeneration, fibrosis of the retrolaminar fibrous septa, axonal atrophy and gliosis, similar to experimental glaucomatous optic neuropathy [29]

Briefly, given these pieces of evidence, the following three factors seem to play major roles in optic disc cupping and backward bowing of the lamina cribrosa in glaucomatous optic neuropathy:

(i) The glial prelaminar region of the optic nerve head is a thick tissue and constitutes the major part of the optic disc volume (Fig. 1) [12, 29]. Loss of this tissue occurs in both glaucomatous optic neuropathy [29] and arteritic anterior ischemic optic neuropathy [22, 30]. Atrophy of the prelaminar region must considerably reduce the volume of the optic disc and increase the size of the cup
(ii) Ischemia of the lamina cribrosa causes degenerative changes and weakness
(iii) As mentioned above, the longitudinal fibrous septa of retrolaminar optic nerve are firmly anchored to the posterior surface of the lamina cribrosa (Fig. 1) [12], and there is marked thickening and fibrosis of these fibrous septa in glaucoma and arteritic anterior ischemic optic neuropathy [29, 30]. We have ample evidence that abnormal fibrotic tissue contracts with time.

Thus, these three factors in combination cause the bowing backward of the lamina cribrosa in optic disc cupping: (a) gradual contraction of fibrotic retrolaminar longitudinal fibrous septa attached to the posterior aspect of the lamina cribrosa (Fig. 1) must pull the latter backward; (b) ischemic degeneration of the lamina cribrosa, by weakening it, further aggravates its bowing backward; and (c) cavernous degeneration and loss of the normal retrolaminar neural tissue collapses the posterior support of the lamina cribrosa.

Thus, evidence indicates that optic disc cupping in glaucomatous optic neuropathy and arteritic anterior ischemic optic neuropathy is due to combined abnormalities in the prelaminar, laminar, and retrolaminar regions of the optic nerve head [29, 30]. Interindividual variations in the blood supply [16], morphological properties of the optic nerve head, and other factors may produce interindividual variations in the development of cupping.

From this brief discussion, it is evident that the optic disc swelling seen in raised CSFP and glaucomatous optic disc cupping are totally unrelated.

Conclusions

The concept that the translaminar imbalance between the IOP and CSFP caused by low CSFP can cause bowing back of the rigid, compact band of lamina cribrosa and play a role in development of glaucomatous optic neuropathy has little scientific validity.

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