Deficient Optic Nerve Sheath Occlusion in NTG Patients: Optic Nerve Damage Due to Translaminar Pressure Imbalance, Glymphatic Failure, or Both?

I read with great interest the article by Kristiansen et al.[1] entitled "Optic Nerve Subarachnoid Space Posture Dependency – An MRI Study in Subjects With Normal Tension Glaucoma and Healthy Controls," published recently in *Investigative Ophthalmology & Visual Science*. I believe the data offered could have great importance for a better understanding of the pathophysiology of normal tension glaucoma (NTG). I would like to congratulate the authors for their valuable study and would appreciate the opportunity to make a comment.

Kristiansen et al.[1] examined the change in optic nerve subarachnoid space (ONSAS) volume between different body positions in patients with NTG and healthy controls. Their hypothesis was that a collapse of the midorbital section of the ONSAS in the upright posture may protect healthy subjects from low intracranial pressures and large translaminar cribrosa pressure differences (TLCPDs), and that dysfunction of such an occlusion mechanism could partly explain NTG pathophysiology in accordance with the TLCPD theory.[2,3] A disrupted ONSAS collapse could result in a small (drained) ONSAS volume with corresponding lower ONSAS pressure and thus abnormally high TLCPD, resulting in glaucomatous optic nerve damage.[2] Kristiansen et al.[1] observed a significant difference in ONSAS volume change between NTG patients and healthy controls when subjected to posture changes, specifically when going from an upright to a head-down posture, as patients with NTG displayed a larger change in volume. This difference was particularly seen in the bulbar ONSAS segment. According to the authors, this might indicate that NTG patients had been exposed to a lower ONSAS pressure in the upright posture, which suggests an increased TLCPD at the lamina cribrosa. The authors concluded that their findings support dysfunction of an occlusion mechanism of the optic nerve sheath as a potential pathophysiological component in NTG patients.

Whereas the mechanistic description of pathophysiology by Kristiansen et al.[1] is focused on the pressure balance over the lamina cribrosa, there are other theories related to altered optic nerve cerebrospinal fluid (CSF) dynamics in NTG. A novel theory proposed by our group for NTG pertains to the glymphatic system concept.[4,5] The presence of a glymphatic pathway in the optic nerve and the theory that a dysfunctional glymphatic system may be involved in the pathogenesis of glaucoma were first proposed by our group in 2015.[6] In 2017, Mathieu et al.[7] found evidence that CSF enters the optic nerve via a glymphatic pathway in mice. The authors found paravascular CSF entry into the optic nerve up to and including the glia lamina, the mouse equivalent of the human lamina cribrosa. They suggested that CSF flow through the optic nerve may play a role in neurotoxin clearance in the laminar and retrolaminar optic nerve, with potential implications for the pathogenesis of glaucoma.[7] In a more recent article, Mathieu et al.[8] provided evidence that CSF entry into the ONSAS and optic nerve paravascular spaces is impeded following tracer injection into the CSF in a DBA/2J mouse model of glaucoma. The authors noted that the impaired CSF inflow to the optic nerve paravascular spaces in this DBA/2J mouse model of glaucoma appears to be secondary to blocked flow of CSF to the ONSAS, as opposed to localized obstruction of paravascular inflow into the optic nerve.[8] Indeed, the authors did not find any instances in which CSF tracer was present in the ONSAS but absent in optic nerve paravascular spaces of the same nerve.[8]

Given that impaired inflow of CSF to the ONSAS may compromise the glymphatic paravascular flow of CSF through the optic nerve, it seems reasonable to assume that a dysfunctional collapse of the ONSAS in the upright posture, resulting in a small (drained) ONSAS volume, may affect paravascular entry of CSF into the optic nerve in addition to the effects in TLCPD changes. Given the above considerations, I believe that a deficient occlusion mechanism of the optic nerve sheath could, at least theoretically, result in both a pressure imbalance over the lamina cribrosa and compromised glymphatic flow in the optic nerve. From this point of view, dysregulation of the glymphatic pathway in the optic nerve might be an additional alternative mechanism to explain how a dysfunctional collapse of the ONSAS may contribute to the development of NTG.

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