Author Response: The First Histologic Evidence of a Paravascular Pathway Within the Optic Nerve

We thank Wostyn and colleagues\(^1\) for their supportive comments regarding our recent publication “Evidence for Cerebrospinal Fluid Entry into the Optic Nerve via a Glymphatic Pathway” in Investigative Ophthalmology & Visual Science.\(^2\) Our work provides the first evidence that cerebrospinal fluid (CSF) flows into the optic nerve through paravascular spaces that surround small perforating pial vessels as they enter into the optic nerve.\(^2\) Paravascular flow is dependent on tracer size, and tracers smaller than 70 kDa entered these spaces.\(^2\) This glymphatic pathway is comprised of centripedal spaces bordered by blood vessel walls on one side and aquaporin-4-positive astrocytic endfeet on the other.\(^2\)

The authors refer to their work in which an ink-fixative mixture was injected into the subarachnoid space of 2 postmortem human optic nerve specimens. They saw ink particles around central retinal vessels in the optic nerve, and the published figure from this work appears in both their Letter to the Editor\(^3\) and review article.\(^3\) The authors interpreted this as evidence of “The first histologic evidence of a paravascular pathway within the optic nerve.”\(^3\) The same figure reveals ink in the interfascicular fibrous septa of the optic nerve. Ink particles 0.1 to 1 \(\mu\)m in diameter\(^4\) would be expected to diffuse and move along natural lines of collagen fibril sheath in fibrous septa and around large optic nerve blood vessels,\(^5\) particularly where they are unidirectional.\(^7,8\) Thus, we propose diffusion of ink particles during fixation as an alternate explanation for the authors’ findings. We do not have information about either of the optic nerves used in their study, such as donor age,\(^9\) eye disease,\(^10\) postmortem time to fixation, or conditions of fixative penetration into the tissue, such as temperature, pH, and osmolarity.\(^8\) These issues call for cautious interpretation of the postmortem human tissue findings, and we agree with the authors when they state that “Obviously, the preliminary data presented cannot provide a scientifically acceptable level of evidence, with only two cases, and additional research is needed to confirm our findings.”\(^4\)

In contradiction to the authors’ finding, in an earlier study, after injecting dye into the subarachnoid space of 80 human optic nerves, Hayreh reported no continuity with the space observed around the large central retinal vessels in the optic nerve.\(^11,12\) The lack of communication between these two spaces was confirmed in 20 monkeys in which dye was injected into the CSF.\(^12\)

The optic nerve has a rich supply of small perforating pial vessels arising from the subarachnoid space. We show that CSF flows into the optic nerve through spaces surrounding these small vessels and this paravascular pathway does not extend anteriorly past the glia lamina.\(^2\) Systematic studies are needed to understand the complex emerging fluid pathways of the eye, and we look forward to new insights into the glymphatic pathway and its relevance to eye health and disease.

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