Author Response: The “Ocular Glymphatic System”: An Important Missing Piece in the Puzzle of Optic Disc Edema in Astronauts?

We thank Wostyn and De Deyn for their comments regarding the relevance of our work to optic disc edema in astronauts. New findings related to lymphatic and glymphatic pathways of the eye have been exciting subjects of discussion with NASA (National Aeronautics and Space Administration) and the Canadian Space Agency.

Astronauts returning from space flight missions may suffer from transient or persistent impaired vision. The typical cluster of eye findings of papilledema, choroidal folds, and cotton wool spots has recently been coined as “space flight-associated neuro-ocular syndrome” (SANs). Microgravity-associated cephalad fluid shifts are implicated in this condition; however, the exact etiology is unclear. The swollen optic disc appearance of papilledema is typically associated with elevated intracranial pressure (ICP), and until recently, astronauts were believed to develop high ICP. Optical coherence tomography of the optic disc after space flight, however, shows microanatomic changes that are not associated with raised cerebrospinal fluid (CSF) pressure. The finding that CSF pressure did not go up under microgravity conditions further challenges the role of high ICP in astronauts, and the etiology of disc edema in astronauts remains unknown.

We hypothesize that lymphatic drainage plays an important role in removing excess fluid from and around the optic nerve, related to cephalad fluid shifts during long-duration space flight. Impaired lymphatic function may account for some of the ocular findings and vision impairment observed in astronauts.

We found CSF entry into the optic nerve along small perforating pial vessels in a size-dependent manner through sleeve-like paravascular spaces between vessel walls and aquaporin-4-positive astrocytic endfeet. Just how this fluid moves within the optic nerve interstitial tissue, whether by bulk flow or by diffusion, still needs to be worked out. Another remaining challenge is to determine how excess fluid leaves the optic nerve. It is possible that lymphatics in the optic nerve sheath and orbit drain excess optic nerve fluid and periphereal nerve CSF to the same cervical nodes that drain CSF.

Lymphatic drainage may be impeded in microgravity conditions. To test this, ground-based models such as hindlimb unloading in rodents may be useful, given that they mimic bone loss, muscle atrophy, and cardiovascular changes observed in astronauts after space flights. In this head-down position model, the active pump of the cervical lymphatic vessels is inhibited. Passive lymphatic flow is also likely altered because of changes in gravitational forces and central venous pressure.

To understand vision impairment faced by astronauts on long-term missions, an interdisciplinary approach combining noninvasive imaging and body fluid-based biomarkers is needed. Inflight studies of astronauts may validate biomarkers at point of care and lead to new monitoring tools and countermeasures. The lymphatic and glymphatic systems offer exciting opportunities to understand the changes that threaten vision in astronauts, with the potential for new strategies to overcome barriers to human deep space exploration.

References


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