Potential Involvement of the "Ocular Glymphatic System" in Optic Disc Edema in Astronauts

Peter Wostyn; Frank De Winne; Claudia Stern; Thomas H. Mader; Charles Robert Gibson; Peter Paul De Deyn

INTRODUCTION: A significant proportion of the astronauts who spend extended periods in microgravity develop ophthalmic abnormalities, including optic disc edema, optic nerve sheath distention, globe flattening, chorioretinal folds, hyperopic refractive error shifts, and nerve fiber layer infarcts. A constellation of these neuro-ophthalmic findings has been termed "spaceflight-associated neuro-ocular syndrome". An increased understanding of factors contributing to this syndrome is one of the top priorities for ESA and NASA because the length of missions is expected to increase substantially in the future. As discussed in the present article, the very recent discovery of an "ocular glymphatic clearance system" can potentially help to unlock mechanisms underlying microgravity-induced optic disc edema. Observations pertaining to the ocular glymphatic pathway provide supporting evidence for the hypothesis, originally proposed by our group, suggesting that the glymphatic outflow from the eye into the optic nerve may be impeded under prolonged microgravity conditions, leading to optic disc edema.

KEYWORDS: astronaut, intracranial pressure, ocular glymphatic system, optic disc edema, trans-lamina cribrosa pressure difference.

Wostyn P, De Winne F, Stern C, Mader TH, Gibson CR, De Deyn PP. ***Potential involvement of the "ocular glymphatic system" in optic disc edema in astronauts.*** **Aerosp Med Hum Perform. 2020; 91(12):975–977.**

A significant proportion of the astronauts who spend extended periods in microgravity develop ophthalmic abnormalities, including optic disc edema (ODE), optic nerve sheath distention, globe flattening, choroidal and retinal folds, hyperopic refractive error shifts, and nerve fiber layer infarcts (i.e., cotton wool spots).[5] A constellation of these neuro-ophthalmic findings has been termed "spaceflight-associated neuro-ocular syndrome" (SANS)[3] and is currently defined as having one or more of the following new findings during or immediately after spaceflight: clinically significant ODE; chorioretinal folds; globe flattening; and hyperopic refractive error shifts (approved by the NASA JSC Human System Risk Board, Houston, TX). The earliest signs of SANS are detected in roughly 70% of astronauts during or following long-duration spaceflight. Clinically significant ODE, the defining characteristic of SANS, has been diagnosed in approximately 16–19% of astronauts who have been examined using fundoscopy or as determined by optical coherence tomography (OCT) peripapillary total retinal thickness change during and after long-duration spaceflight.[4] Moreover, astronauts with SANS can experience ocular changes that remain unresolved years after flight.[5] Currently, the exact mechanisms causing SANS are unknown. Given that SANS is one of the top priorities for the European Space Agency (ESA) and the National Aeronautics and Space Administration (NASA), and especially in view of future long-duration spaceflight missions, including continued trips to the International Space Station, a return to the Moon, or a future human mission to Mars, there is an urgent need to better understand the mechanisms leading to this neuro-ocular syndrome and to develop countermeasure strategies. As discussed in the present article, the very recent discovery of an "ocular glymphatic clearance system" can potentially help to unlock mechanisms underlying microgravity-induced ODE.

Two basic mechanisms, or perhaps a combination of the two, have been previously hypothesized to account for elevated cerebrospinal fluid (CSF) pressure within the orbital subarachnoid space (SAS) that may be responsible for spaceflight-related ocular changes. The first mechanism is based on the notion that SANS is caused by elevated intracranial pressure (ICP) resulting

From the Department of Psychiatry, PC Sint-Amandus, Beernem, Belgium.

This manuscript was received for review in May 2020. It was accepted for publication in September 2020.

Address correspondence to: Peter Wostyn, Department of Psychiatry, PC Sint-Amandus, Reigerlostraat 10, 8730 Beernem, Belgium; wostyn.peter@skynet.be.

DOI: https://doi.org/10.3357/AMHP.5670.2020

from weightlessness-induced cephalad fluid shifts leading to venous stasis in the head and neck.[5] This stasis could cause cerebral venous congestion and impairment of CSF drainage into the venous system, both of which could lead to a rise in ICP.[5] This increased cerebral subarachnoid CSF pressure could be transmitted directly from the intracranial compartment to the intraorbital compartment through the perioptic SAS.[5] The second mechanism proposes that the ocular changes may result from SANS-related compartmentalization of CSF in the orbital SAS.[5] According to this hypothesis, the cul-de-sac anatomy of the confined perioptic SAS, which is further constricted through numerous trabeculae and septa, coupled with the cephalad fluid shifts of prolonged microgravity, may result in a fragile flow equilibrium that may lead to the sequestration of CSF within the orbital SAS with locally elevated optic nerve sheath pressures.[5] The end result of either mechanism, increased ICP or sequestration of CSF within the SAS of the optic nerve, is a rise in CSF pressure within the SAS surrounding the optic nerve that may influence the trans-lamina cribrosa pressure difference (TLCPD). The TLCPD is defined as the difference between intraocular pressure minus optic nerve SAS pressure.

A more novel mechanism proposed by our group[7–14] for microgravity-induced ODE pertains to the ocular glymphatic system concept. In a recent paper published in *Aerospace Medicine and Human Performance*,[11] we hypothesized that ODE in astronauts may result, at least partly, from glymphatic stasis predominantly within the prelaminar region of the optic nerve head. Under normal physiological conditions, the TLCPD is directed posteriorly across the lamina cribrosa. We speculated that under microgravity conditions, elevation of optic nerve sheath pressure, due to a rise in ICP and/or sequestration of CSF within the orbital SAS, may lead to a reduction or reversal of the normal posteriorly directed TLCPD, which in turn may block the glymphatic efflux of ocular fluid into the optic nerve. As discussed below, new research now provides indirect experimental evidence in support of this glymphatic hypothesis.[6]

In 2012, the "glymphatic system" was first described in mice by a team of researchers headed by Iliff and Nedergaard.[1] Their findings suggested a brain-wide network of perivascular pathways along which a large proportion of subarachnoid CSF recirculates through the brain parenchyma, facilitating the clearance of interstitial solutes, including amyloid-β (Aβ), from the brain.[1] CSF enters the brain along periarterial channels to exchange with interstitial fluid, which is in turn cleared from the brain along perivenous pathways for ultimate clearance via cervical lymphatic vessels.[1] From the SAS, CSF is driven into the Virchow-Robin spaces by a combination of arterial pulsatility, respiration, slow vasomotion, and CSF pressure gradients.[2] The subsequent transport of CSF into the dense and complex brain parenchyma is facilitated by aquaporin-4 (AQP4) water channels which are expressed in a highly polarized manor in astrocytic endfeet ensheathing the cerebral vasculature.[2] Importantly, a new study led by Nedergaard[6] identified a novel ocular glymphatic clearance route for fluid and wastes via the proximal optic nerve in rodents. Aβ was cleared from the retina and vitreous via a pathway dependent on glial water channel AQP4. After traversing the lamina barrier, intra-axonal Aβ was cleared via the perivenous space and subsequently drained to lymphatic vessels. To define the role of the TLCPD in transport of Aβ tracer, the researchers manipulated ICP by either withdrawal or infusion of artificial CSF in the cisterna magna while monitoring ICP. Decreasing ICP was associated with a sharp increase in the total Aβ tracer signal and peak intensity of Aβ tracer transport in the proximal optic nerve 30 min after intravitreal injection. Conversely, increasing ICP significantly decreased Aβ tracer clearance into the optic nerve. These data showed that the TLCPD is a major driver of ocular glymphatic outflow.[6] Very interestingly, these data also suggest that a rise in orbital CSF pressure, assumed to occur in microgravity, would directly inhibit this ocular glymphatic outflow.[6] This lends support to the hypothesis, originally proposed by our group,[7,9–12] suggesting that the glymphatic outflow from the eye into the optic nerve may be impeded under prolonged microgravity conditions, leading to fluid stasis within the prelaminar optic nerve head. Retrograde CSF influx into the prelaminar optic nerve head could then further contribute to the ODE seen in astronauts.[7–10,12–14]

In conclusion, observations pertaining to the ocular glymphatic pathway provide critical new insights into how ICP, and thus orbital CSF pressure, can alter basic fluid transport in the eye. Although these novel findings were reported in rodents, we believe that they can potentially help to unlock mechanisms underlying ODE in astronauts. Future research in this area of investigation could not only provide exciting new insights into the mechanisms responsible for microgravity-induced ODE but also offer opportunities to develop countermeasure strategies.

ACKNOWLEDGMENTS

Financial Disclosure Statement: The authors have no funding to report. The authors have no conflicts of interest to declare.

Authors and affiliations: Peter Wostyn, M.D., Department of Psychiatry, PC Sint-Amandus, Beernem, Belgium; Frank De Winne, Ph.D., European Space Agency, European Astronaut Centre, Cologne, Germany; Claudia Stern, M.D., Ph.D., Institute of Aerospace Medicine, German Aerospace Center (DLR), Cologne, Germany; Thomas H. Mader, M.D., Moab, UT, USA; Charles R. Gibson, O.D., Coastal Eye Associates, Webster, TX, and KBR, Houston, TX, USA; Peter P. De Deyn, M.D., Ph.D., Department of Biomedical Sciences, Laboratory of Neurochemistry and Behavior, Institute Born-Bunge, University of Antwerp, and Department of Neurology and Memory Clinic, Middelheim General Hospital (ZNA), Antwerp, Belgium, and Department of Neurology and Alzheimer Research Center, University of Groningen and University Medical Center Groningen, Groningen, The Netherlands.

REFERENCES

1. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Sci Transl Med. 2012; 4(147): 147ra111.
2. Jessen NA, Munk AS, Lundgaard I, Nedergaard M. The glymphatic system: a beginner's guide. Neurochem Res. 2015; 40(12):2583–2599.
3. Lee AG, Mader TH, Gibson CR, Tarver W. Space flight-associated neuro-ocular syndrome. JAMA Ophthalmol. 2017; 135(9):992–994.

4. Macias BR, Patel NB, Gibson CR, Samuels BC, Laurie SS, et al. Association of long-duration spaceflight with anterior and posterior ocular structure changes in astronauts and their recovery. JAMA Ophthalmol. 2020; 138(5):553–559.
5. Mader TH, Gibson CR, Pass AF, Kramer LA, Lee AG, et al. Optic disc edema, globe flattening, choroidal folds, and hyperopic shifts observed in astronauts after long-duration space flight. Ophthalmology. 2011; 118(10):2058–2069.
6. Wang X, Lou N, Eberhardt A, Yang Y, Kusk P, et al. An ocular glymphatic clearance system removes β-amyloid from the rodent eye. Sci Transl Med. 2020; 12(536):eaaw3210.
7. Wostyn P. Optic disc swelling in astronauts: a manifestation of "glymphedema"? J Glaucoma. 2019; 28(11):e166–e167.
8. Wostyn P. "Houston, we have a problem": "We are losing our eyesight". Exp Eye Res. 2019; 186:107725.
9. Wostyn P, De Deyn PP. Intracranial pressure-induced optic nerve sheath response as a predictive biomarker for optic disc edema in astronauts. Biomark Med. 2017; 11(11):1003–1008.
10. Wostyn P, De Deyn PP. The "ocular glymphatic system": an important missing piece in the puzzle of optic disc edema in astronauts? Invest Ophthalmol Vis Sci. 2018; 59(5):2090–2091.
11. Wostyn P, De Winne F, Stern C, De Deyn PP. Dilated prelaminar paravascular spaces as a possible mechanism for optic disc edema in astronauts. Aerosp Med Hum Perform. 2018; 89(12):1089–1091.
12. Wostyn P, Killer HE, De Deyn PP. Why a one-way ticket to Mars may result in a one-way directional glymphatic flow to the eye. J Neuroophthalmol. 2017; 37(4):462–463.
13. Wostyn P, Mader TH, Gibson CR, Killer HE. The escape of retrobulbar cerebrospinal fluid in the astronaut's eye: mission impossible? Eye (Lond). 2019; 33(10):1519–1524.
14. Wostyn P, Mader TH, Gibson CR, Killer HE. The perivascular space of the central retinal artery as a potential major cerebrospinal fluid inflow route: implications for optic disc edema in astronauts. Eye (Lond). 2020; 34(4): 779–780.