Dilated Prelaminar Paravascular Spaces as a Possible Mechanism for Optic Disc Edema in Astronauts

Peter Wostyn; Frank De Winne; Claudia Stern; Peter Paul De Deyn

INTRODUCTION: A number of ophthalmic abnormalities, including optic disc edema, have been reported in several astronauts involved in long-duration spaceflights. An increased understanding of factors contributing to this syndrome, initially designated visual impairment and intracranial pressure syndrome and recently renamed spaceflight-associated neuro-ocular syndrome, has become a high priority for ESA and NASA, especially in view of future long-duration missions, including trips to Mars. The underlying pathophysiological mechanisms of this syndrome are still not well understood. In the present paper, we propose that optic disc edema in astronauts may occur, at least in part, as a result of retention of interstitial fluid in distended paravascular spaces at the prelaminar region of the optic nerve head. Preflight, in-flight, and postflight analysis of the optic nerve head and surrounding structures by optical coherence tomography in long-duration International Space Station crewmembers could provide important structural information in this respect.

KEYWORDS: glymphatic system, lymphatic system, spaceflight-associated neuro-ocular syndrome, visual impairment and intracranial pressure syndrome.

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It has been reported that a significant proportion of the astronauts who have flown on long-duration missions aboard the International Space Station are experiencing ophthalmic abnormalities, including optic disc edema, optic nerve (ON) sheath distention, globe flattening, choroidal folds, and hyperopic refractive error shifts.[9,12] Understanding this syndrome, initially designated visual impairment and intracranial pressure syndrome, has become a high priority for the European Space Agency and National Aeronautics and Space Administration, especially given that this medical obstacle could impact the visual health of individual astronauts as well as the success of future long-duration interplanetary missions, including trips to Mars.[10]

Currently, the exact mechanisms causing these neuro-ocular findings in astronauts are unknown. Among the several mechanisms proposed to play a role, one initially held hypothesis was that this syndrome is caused by elevated intracranial pressure (ICP) resulting from weightlessness-induced cephalad fluid shifts leading to venous stasis in the head and neck.[9] This stasis could cause impairment of cerebrospinal fluid (CSF) drainage into the venous system and cerebral venous congestion, both of which could lead to a rise in ICP.[9] This elevated ICP could cause ophthalmic changes like optic disc swelling. The ON, a white matter tract of the central nervous system, is ensheathed in all three meningeal layers and surrounded by CSF in the subarachnoid space (SAS).[16] Therefore, in addition to intraocular pressure (IOP), the ON is exposed to the ICP.[16] Based on the results of extensive research, Hayreh[3] concluded that optic disc edema in raised ICP is primarily due to a rise of CSF pressure in the ON sheath, which produces axoplasmic flow stasis in the ON fibers in the surface nerve fiber layer and prelaminar region of the ON head, the latter region situated between the surface nerve fiber layer in front and the lamina cribrosa behind. Axoplasmic flow stasis then results in swelling of the nerve fibers and, consequently, of the optic disc, which, in turn, secondarily compresses the fine, low-pressure venules in that region, resulting in venous stasis and fluid leakage that leads to the accumulation of extracellular fluid.[3]

However, it should be noted that the above syndrome has recently been renamed spaceflight-associated neuro-ocular syndrome (SANS) as the role of high ICP in astronauts is now

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being challenged.[8] Postmission lumbar puncture opening pressures measured thus far were only mildly elevated[8] and recent data from parabolic flights indicated that pathologically elevated ICP may not occur during transient microgravity exposure.[7] Furthermore, although some similarities between SANS and terrestrial idiopathic intracranial hypertension (IIH) were noted, lack of headaches and other findings commonly associated with IIH suggests that increased ICP might not be the sole or even primary cause of optic disc swelling in astronauts and that other mechanisms should be considered.[8]

Compartmentation of CSF in the orbital SAS with locally elevated ON sheath pressures has been proposed as an additional alternate mechanism for explaining optic disc swelling in astronauts.[8,9] Failure of CSF drainage out of the SAS of the ON may lead to such an ON compartment syndrome.[5] Anatomically, the SAS of the ON becomes a cul-de-sac at the back of the eye.[5] The mechanism by which CSF is reabsorbed out of the SAS of the ON is not fully understood.[5] Normally, most of the CSF in the ON sheath accumulates in its bulbous part behind the eyeball.[3] Constant eye movements compress the bulbous segment of the sheath of the ON, creating a pumping action leading to exchange of CSF between the ON sheath and the intracranial space. However, in space in the absence of gravity, bodily fluids, including CSF, shift in the cranial direction. In this case, it is highly unlikely that the CSF once in the orbital CSF space can change its direction of flow from the SAS of the ON toward the intracranial SAS. In addition to arachnoid villi in the meninges of the ON,[13] lymphatics in the dura mater of the human ON have been proposed as a possible outflow pathway for CSF from the ON SAS.[5,6] However, these orbital ON venous and lymphatic drainage systems may be affected by microgravity-induced cephalad fluid shifts, such that CSF outflow from the SAS of the ON may be further impeded.[9]

The end result of either mechanism, increased ICP or sequestration of CSF within the SAS of the ON, is a rise in CSF pressure within the SAS surrounding the ON that may influence the translaminar pressure difference (IOP-ICP). As discussed below, we believe that these two mechanisms, alone or in combination, may result in an imbalance of glymphatic flow at the ON head that may produce varying degrees of optic disc swelling in astronauts.

Recent research has led to the discovery of the 'glymphatic system', a brain-wide network of paravascular channels along which a large proportion of subarachnoid CSF recirculates through the brain parenchyma, facilitating the clearance of interstitial proteins and potentially neurotoxic waste products from the brain.[4] CSF enters the brain along para-arterial channels to exchange with interstitial fluid, which is in turn cleared from the brain along paravenous pathways.[4] Intriguingly, very recent findings provide evidence that a similar system is present in the ON and retina.[11,15,16] The first histological evidence supporting the existence of a paravascular pathway in the human ON came from our postmortem study in which we examined cross-sections of human ONs by light microscopy after injecting India ink into the SAS of the ON.[16] The results demonstrated accumulation of India ink in paravascular spaces most likely around the central retinal artery and vein, whereas the lumens of these vessels remained unlabeled.[16] Further evidence of a glymphatic pathway in the ON in mice has recently been reported by Mathieu et al.[11] Using fluorescent tracer injection into CSF, the authors found CSF entry into the ON along small perforating pial vessels in a size-dependent manner through sleeve-like paravascular spaces between vessel walls and aquaporin 4-positive astrocytic endfeet.[11] Furthermore, new observations also indicate that the ocular glymphatic system may provide an anatomical basis for posterior fluid outflow from the eye to the ON.[15] Indeed, in a Ph.D. thesis defense, Xiaowei Wang[15] demonstrated the existence of an 'ocular glymphatic pathway' by intravitreal injection of fluorescently conjugated human amyloid-β and subsequent confocal and stereofluorescent imaging examination of the retina as well as the ON of the injected eye. The trans-lamina cribrosa pressure difference was identified as the major driving force for the glymphatic ocular outflow to the ON.[15]

We believe that optic disc edema in astronauts may occur, at least in part, as a result of retention of interstitial fluid in distended paravascular spaces at the prelaminar region of the ON head. Indeed, microgravity-induced intracranial hypertension and/or sequestration of CSF within the orbital SAS with locally elevated ON sheath pressures may lead to a translaminar pressure gradient toward the intraocular space, which may block the drainage of the prelaminar paravascular channels to the ON. If the glymphatic ocular outflow is impeded, local paravascular fluid recirculation may be impaired and, consequently, the paravascular spaces may dilate due to fluid retention. It is important to note that previous studies have reported on the presence of a defect in the blood-optic nerve barrier in the region of the optic nerve head, allowing proteins to enter the neural tissue in this location.[2] A blockage of prelaminar paravascular channels leading to local obstruction of glymphatic drainage of proteins may promote protein accumulation within interstitial tissue of the prelaminar region of the ON head, subsequently leading to the accumulation of water driven by osmotic forces. Evidence to support our view was recently presented by Denniston et al.,[1] who reported the presence of perivascular hyporeflective (darkened) areas assessed by systematic spectral-domain optical coherence tomography (SD-OCT) imaging in patients with IIH. This was observed both at the ON head and within the retinal nerve fiber layer scan.[1] The authors hypothesized that this represents dilated ocular perivascular glymphatic channels.[1] Given that SANS bears similarities to terrestrial IIH, it would be interesting to investigate whether eyes from astronauts exhibit changes analogous to the perivascular hyporeflective areas seen on SD-OCT in patients with IIH. Preflight, in-flight, and postflight SD-OCT analysis of the ON head and surrounding structures in long-duration International Space Station crewmembers could provide important structural information in this respect.

The possible role of an insufficiency of lymphatic drainage in microgravity ocular syndrome has recently been nicely discussed by Thornton and Bonato.[14] The authors suggested that swelling of the ON and ON sheath in the case of astronauts may result from a blockage of ON lymphatics, and that pressures

from such tissue expansion may cause higher longitudinal forces on the globe than that postulated from the column of CSF under pressure.[14] This lymphatic dysfunction hypothesis and the glymphatic hypothesis proposed in the present paper might be considered complementary. Indeed, failure of CSF drainage out of the SAS of the ON, due to lymphatic obstruction in microgravity conditions, may result in a higher local pressure in the SAS of the ON, which in turn may impede glymphatic ocular outflow that may produce varying degrees of optic disc swelling, even in the absence of elevated ICP. Further research is needed to determine the possible role of the ocular glymphatic and lymphatic systems in SANS, and offers exciting opportunities to better understand the mechanisms leading to this syndrome and to develop countermeasure strategies.

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