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REVIEW ARTICLE

The escape of retrobulbar cerebrospinal fluid in the astronaut's eye: mission impossible?

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Abstract

Ophthalmic abnormalities including unilateral and bilateral optic disc edema, optic nerve sheath distention, globe flattening, choroidal folds, and hyperopic shifts have been observed in astronauts during and after long-duration spaceflight. An increased understanding of factors contributing to this syndrome, termed spaceflight-associated neuro-ocular syndrome, is currently a top priority for the ESA and NASA, especially since this medical obstacle could impact the visual health of astronauts as well as the success of future missions, including continued trips to the International Space Station, a return to the moon, or a future human mission to Mars. Currently, the exact mechanisms causing this neuro-ocular syndrome are not fully understood. In the present paper, we propose a hypothetical framework by which optic disc edema in astronauts may result, at least partly, from the forcing of perioptic cerebrospinal fluid into the optic nerve and optic disc along perivascular spaces surrounding the central retinal vessels, related to long-standing microgravity fluid shifts and variations in optic nerve sheath anatomy and compliance. Although this hypothesis remains speculative at the present time, future research in this area of investigation could not only provide exciting new insights into the mechanisms underlying microgravity-induced optic disc swelling but also offer opportunities to develop countermeasure strategies.

Introduction

Ophthalmic abnormalities including unilateral and bilateral optic disc edema, optic nerve (ON) sheath distention, globe flattening, choroidal folds, and hyperopic shifts have been observed in astronauts during and after long-duration spaceflight (LDSF) [1, 2]. 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 (SANS), is currently a top priority for the European Space Agency and National Aeronautics and Space Administration, especially since this medical obstacle could impact the visual health of astronauts and could interfere with plans for future missions, including continued trips to the International Space Station, a return to the moon, or a future human mission to Mars [2]. Over the last years, millions of dollars have been allocated for research aimed at clarifying the pathogenesis of SANS. Unfortunately, the exact mechanisms causing SANS have not been fully elucidated [2]. 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 microgravity-induced cephalad fluid shifts leading to venous stasis in the head and neck, which, in turn, could cause an impairment of cerebrospinal fluid (CSF) outflow as well as cerebral venous congestion [1]. However, postmission lumbar puncture opening pressures (LPOPs) measured thus far were only mildly elevated and astronauts did not report typical symptoms of increased ICP commonly seen in patients with terrestrial idiopathic intracranial hypertension (IIH), such as chronic headache, pulsatile tinnitus, or diplopia [2]. Data from parabolic flights indicating that ICP decreases during transient microgravity exposure further challenge the role of high ICP in SANS [3]. Here we propose a hypothetical framework by which

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optic disc edema in astronauts may result, at least partly, from the forcing of perioptic CSF into the ON and optic disc along perivascular spaces surrounding the central retinal vessels, related to long-standing microgravity fluid shifts and variations in ON sheath anatomy and compliance.

Methodology

Analysis of selected articles in the peer-reviewed literature with interpretation and perspective.

Discussion

The optic nerve compartment syndrome hypothesis of optic disc edema in astronauts

It has been proposed that the optic disc swelling in astronauts may not be primarily related to increased ICP, but instead may result from localized CSF events occurring at the level of the intracanalicular and intraorbital ON, producing a type of ON compartment syndrome, with or without a rise in CSF pressure in the entire CSF system [1]. The concept of a terrestrial IIH ON compartment syndrome has previously been proposed by Killer et al. [4], and is further supported by evidence from perioptic CSF dynamics studies [4–6]. Computed tomographic cisternography performed in patients with papilledema due to IIH demonstrated variable reductions of contrast-loaded CSF inflow into the subarachnoid space (SAS) surrounding the ON, suggesting sequestration of CSF in the SAS of the ON [5, 6]. The concept of an ON compartment syndrome in the setting of IIH is further supported by the description of a higher concentration of lipocalin-like prostaglandin D-synthase, also known as beta-trace protein, in the SAS of the ON compared with the lumbar CSF in such patients [4].

The SAS surrounding the ON is a septated, tightly confined, trabeculated, blind-ending (cul-de-sac) space, which is in communication with the intracranial SAS in a normal terrestrial population [4, 7]. The arachnoid and the pia mater, as well as the arachnoid trabeculae and septa traversing the SAS, are lined with meningothelial cells (MECs) [8]. 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 ON sheath pressures [7]. Normally, on Earth, most of the CSF in the ON sheath accumulates in its anterior bulbous portion behind the eyeball [9]. Measurements of the ON sheath diameter 3 mm behind the globe showed that the diameter can change during movements of the eyeball [10]. It is therefore highly plausible that eye movements may cause CSF volume shifts within this location. It has been proposed that constant eye movements may compress the bulbous segment of the ON sheath, creating a pumping action leading to exchange of CSF between the ON sheath and the intracranial space [11]. In space, in the absence of gravity, bodily fluids shift in the cranial direction [12]. In a recent study using magnetic resonance (MR) imaging, Alperin and Bagci [13] found that the magnitude of SANS-associated ocular changes, namely globe flattening and ON protrusion, correlated significantly with increases in the orbital and ventricular CSF volumes. The authors proposed that redistribution of CSF volume from the spinal canal to the cranium, in the absence of gravity, is the primary contribution to the increase in intracranial and orbital CSF volumes. As further proposed by the authors [13], unlike on Earth, where changing from supine to an upright posture reduces intracranial CSF volume due to a shift of CSF from the cranium to the spinal canal, in space, there is no force that intermittently reduces the cranial CSF volume and, thereby, allows reversed movement of CSF from the orbit back into the cranium. Therefore, during LDSF, 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 [1]. In addition, the arrangement of trabeculae and septa in the SAS of the ON offers the possibility that a one-way valve-like mechanism may also cause local CSF entrapment within the SAS of the ON [14]. Furthermore, it is possible that MECs may also play a role in further narrowing the SAS of the ON. Indeed, MECs have been shown to react with swelling and cellular proliferation to biological and mechanical stimuli such as elevated pressure [8, 15]. A marked swelling of MECs of the arachnoid resulting in thickening of the arachnoid membrane has been documented following experimental compartmentalization in sheep [15]. Such swelling and proliferation of MECs may further narrow the SAS surrounding the ON, potentially allowing unidirectional CSF inflow while preventing the backward CSF flow through a one-way valve-like mechanism, before finally also obstructing the CSF inflow. A CSF outflow pathway from the SAS of the ON is therefore of critical importance to prevent CSF accumulation and pressure build-up in this small anatomical compartment that ends blindly behind the globe [14]. The mechanism by which CSF is reabsorbed out of the SAS of the ON is not fully understood [16]. In addition to arachnoid villi in the meninges of the ON [17], lymphatics in the dura mater of the human ON have been proposed as another possible outflow pathway for CSF from the ON SAS [16, 18]. However, these orbital ON venous and lymphatic drainage systems may also be affected by microgravity-induced cephalad fluid shifts, further

impeding CSF outflow and producing increased ON sheath pressures [1]. Thus, it is possible that the optic disc edema observed in astronauts is the result of localized events occurring at the level of the intracanalicular and intraorbital ON that are independent of ICP.

It has also been suggested that asymmetric anatomy in the narrow, septated connections between the intracranial SAS and orbital SAS, although insignificant on Earth, may create differences in flow equilibrium that may lead to asymmetric pressure levels in the perioptic SAS [7]. In support of this notion, asymmetric disc edema has been documented to persist in some astronauts following LDSF even in the presence of normal ICPs. Specifically, in one astronaut, asymmetric disc edema in conjunction with a normal LPOP was observed 1 week after spaceflight [19]. Asymmetric disc edema in another astronaut was documented for over 180 days postflight, in association with asymmetric optic disc morphologic changes which persisted for 630 days postflight in the presence of LPOPs of 22 and 16 cm H20 obtained at 7 and 365 days postflight, respectively [7]. The above findings strongly suggest that asymmetric pressures within the ON sheaths may exist in some astronauts both during and after LDSF.

The potential role of the optic nerve sheath compliance

Wostyn and De Deyn [20, 21] recently hypothesized that astronauts with less compliant ON sheaths may be more likely to develop optic disc swelling, and that the ON sheath response to changing CSF pressure, measured by intrathecal infusion tests, may be a potential predictive biomarker for optic disc edema in astronauts. Hansen and Helmke [22] demonstrated that the human ON sheath expands rapidly in vivo after small CSF pressure changes during intrathecal infusion tests until a saturation point is reached at which no further dilatation occurs. From this point of view, a greater degree of ON sheath rigidity that prevents further ON sheath expansion may result in increased SAS pressure, given that smaller increases in CSF volume will produce significant increases in CSF pressure in the ON sheath [20, 21]. Thus, variations in elasticity within the structure of the ON sheath may produce varying degrees of optic disc swelling between astronauts and even asymmetric disc edema in the same astronaut [20, 21].

Microgravity-induced optic disc swelling due to the forcing of cerebrospinal fluid into the optic nerve along perivascular spaces surrounding the central retinal vessels

Thus, the unique cul-de-sac-like anatomic connection between the intracranial SAS and the SAS of the ON, in conjunction with microgravity-induced cephalad redistribution of CSF along with venous and lymphatic stasis, may produce a type of ON compartment syndrome with locally elevated ON sheath pressures [1, 7, 13, 19]. As noted above, at higher CSF pressure levels, the ON sheath loses its ability to further dilate [22]. When ON sheath expansion and potentially other compensatory decompression mechanisms reach their limit, we hypothesize that CSF may be forced into the ON and optic disc through perivascular spaces, which have been shown to surround the central retinal artery in human ONs [23, 24]. With regard to the present hypothesis, it is essential that the SAS of the ON sheath communicates with the perivascular space of the central retinal artery. However, in an earlier post-mortem study, after injecting dye into the SAS of 80 human ONs, Hayreh [24] reported no continuity between the SAS of the ON sheath and the perivascular space around the central retinal vessels. In humans, a tube of arachnoid surrounds the central retinal artery in the SAS up to its entry into the ON, thus separating the perivascular space from the SAS [24]. In contradiction to these findings, our recent post-mortem study, in which we examined cross-sections of human ONs by light microscopy after injecting India ink into the SAS of the ON, demonstrated a very striking accumulation of India ink in perivascular spaces most likely around the central retinal artery and vein, whereas the lumens of these vessels remained unlabelled [25]. At higher magnification, the deposits were located between collagen fiber bundles lining a slit-like space. Optimal interpretation of the images was difficult because images taken at lower magnification were no longer available due to the retrospective nature of the study. Such images might have allowed better identification of the blood vessels. However, the blood vessels surrounded by ink were highly suggestive of the central retinal artery and vein. There was uncertainty whether such perivascular spaces also surrounded arterioles and venules in the optic nerve. We acknowledge that our findings should be interpreted cautiously, given the inherent limitations of a post-mortem study and the fact that we could not rule out artifacts due to changes in ON sheath pressure resulting from injecting India ink into the SAS of the ON. Nor could we rule out diffusion of ink particles during fixation as an alternate explanation for our findings. Furthermore, our observations were based upon a small sample size, with only two cases, and thus relied upon anecdotal evidence. However, it should be noted that it was also a matter of debate whether the Virchow-Robin space (VRS) in the brain is connected to the SAS, allowing for fluid communication [26]. Although ultrastructural electron microscopic studies agree that pial membranes separate the VRS from the cortical SAS, there is strong evidence indicating that fluid circulates along the VRS [26]. Following the injection of horseradish peroxidase (HRP) into the SAS or lateral

ventricles of cats and dogs, some groups found spread of HRP from the SAS into the VRS, while others were not able to reproduce these findings [26]. Since there is at least some circulation of CSF into and out of the VRS, it has been questioned how fluid and tracers could cross the pial membranes separating the VRS from the SAS [26]. In humans, it was found that the pial barrier was composed of a delicate but apparently continuous layer of cells joined by desmosomes and gap junctions but no tight junctions [26]. According to such morphological studies, it was recognized that the pia is not impermeable to fluids [26]. Further, it was suggested that hydrostatic forces may drive fluids and solutes across the pial membranes [26]. In addition, it was shown that pial membranes between the perivascular space and the SAS could prevent the exchange of larger molecules [26]. With regard to the present hypothesis, the question is whether, in a similar fashion, the arachnoid tube enclosing the central retinal artery may also be permeable to fluids. The cellular architecture of the arachnoid mater, which is composed of several layers of overlapping cells, and the presence of tight junctions between arachnoid cells are believed to contribute to the blood-brain/CSF barrier [27]. This barrier system prevents escape of CSF from the SAS. However, in a previous post-mortem study by Killer et al. [18], India ink injected into the SAS of the human ON subsequently appeared in dural lymphatics. For any dural CSF absorption to occur, presumably CSF would have to pass through the supposed barrier provided by the arachnoid membrane to enter dural tissues [27]. Killer et al. [18] were able to demonstrate that India ink enters into lymphatic capillaries in the dura, possibly via slit-like pores in the neurothelial layer of the arachnoid membrane, suggesting a functional drainage system for CSF from the SAS of the ON into the dura. Here, we present the observation from a previous post-mortem study by Killer et al. [28] in which the authors examined cross-sections of the SAS in human ONs by scanning electron microscopy (SEM). In order to preserve tissue integrity and to avoid artifacts, tissue samples were collected very carefully and handled with great delicacy. At high magnification, the presence of multiple pores in the arachnoid layer and pia mater overlying the ON were clearly seen (Fig. 1). Elucidation of the origin of these openings and determining whether CSF can indeed pass through these pores is currently the subject of further investigation. It is interesting to note that a recent study using SEM revealed that the SAS trabeculae in the brain show permeable characteristics similar to the pores described in the ON SAS [29]. Also of particular interest, here is a recent immunohistochemical study of MECs within human ON sections which demonstrated expression of tight junctions, gap junctions, and the aquaporin 4 (AQP4) water channel in the arachnoid and in subarachnoidal locations along the ON [30]. While tight junctions form a tight barrier

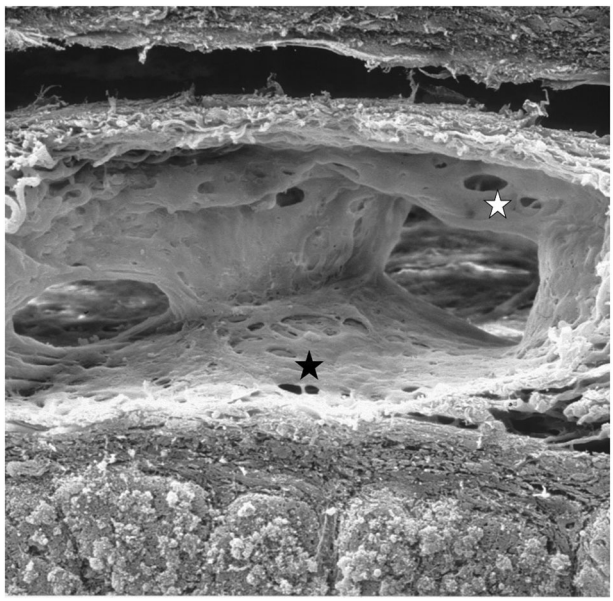

Fig. 1 Scanning electron microscopy appearance of the subarachnoid space in the mid-orbital segment of the human optic nerve (cross-section). High magnification image showing multiple pores in the arachnoid layer (white asterisk) and pia mater (black asterisk) overlying the optic nerve (Figure reproduced from [28])

and selectively prevent the free passage of solutes and molecules between cells, gap junctions allow for the passage of water, small molecules (< 1 kDa), and ions between adjacent cells [30]. AQP4 plays a pivotal role in the function of the 'glymphatic system', a recently discovered brain-wide waste clearance system that utilizes a unique system of perivascular channels, formed by astroglial cells, to promote efficient elimination of soluble proteins and metabolites from the brain [31]. Iliff et al. [32] showed that perivascular AQP4 facilitates the influx of subarachnoid CSF from periarterial spaces into the brain interstitium, as well as the subsequent clearance of interstitial fluid. One could speculate that under prolonged microgravity conditions, MECs could be involved in hydrostatically driven CSF flux across the arachnoid, and in particular across the arachnoid tube enclosing the central retinal artery, by means of cell-cell junctions and AQP4 water channels.

With regard to the contradictory post-mortem human ON findings discussed above [24, 25], it is also important to note that perivascular flow should ideally be studied in the living ON, given that CSF from the SAS has been shown to be driven into the brain perivascular spaces by a combination of arterial pulsatility, respiration, and CSF pressure gradients [31]. In a post-mortem study, the duration, the pressure and the method by which the tracer is injected into the SAS becomes very important. For example, in the post-mortem study by Hayreh [24], the investigation was carried out in dissection room cadavers where the skull was opened and the brain was removed, leaving a long stem of the ON

intracranially. Dye was injected into the space of the sheath of the ON, and the dye distended the sheath of the ON in the orbit and flowed out into the cranial cavity through the optic canal. In our post-mortem study, the ONs including the globe were removed and the ONs were ligated proximal to the optic chiasm before India ink was injected into the SAS of the ON [25].

Although no free communication between the ON SAS and the perivascular space around the central retinal vessels has been observed to date in humans, perhaps, under prolonged microgravity conditions and when compensatory attempts to stabilize the CSF pressure at eye level reach their limit, CSF may be forced across the arachnoid tube enclosing the central retinal artery into the ON. With regard to this viewpoint, it is interesting to note that previous studies of MR imaging in astronauts seem to support this possibility. In a retrospective MR analysis of 27 astronauts previously exposed to microgravity, Kramer et al. [33] identified posterior globe flattening in seven of the 27 astronauts (26%), optic nerve protrusion (indicative of edema) in four (15%), and ON kinking in four (15%). Furthermore, the authors found a central area of T2 hyperintensity in the ON in 26 of the 27 astronauts (96%). In cases characterized by an ON sheath kink, there was a significant increase in the diameter of the central area of T2 hyperintensity at the mid ON [33]. A kink was associated with increased ON sheath diameter, indicating elevated CSF pressure. The authors hypothesized that a kink with distortion of the complex system of arachnoid trabeculae, pillars, and septa in the ON sheath may restrict anterograde CSF flow in the perineural SAS, creating a pressure gradient [33]. They postulated that this phenomenon could result in congestion of the proximal ON perivascular space via communication with the perineural SAS [33]. This is in line with the present hypothesis. Unfortunately, the study by Kramer et al. [33] did not specifically mention whether the four astronauts who exhibited ON kinking and ON protrusion were the same four crewmembers. In another retrospective MR analysis of 21 astronauts, Riascos et al. [34] reported a new finding seen in all study participants: a central T2 hypointensity in the epicenter of the previously described T2 hyperintensity in the ON. The two astronauts not yet exposed to microgravity also showed the central T2 hypointensity in bilateral ONs [34]. The authors speculated that this T2 hypointensity may represent flow voids caused by the central retinal artery [34].

Conclusions

It must be emphasized that our proposed hypothesis remains speculative at the present time, and additional studies are needed to determine whether the forcing of CSF into the ON from the perivascular CSF spaces around the central retinal artery may play a role in the development of both symmetric and asymmetric optic disc edema in astronauts. In the absence of any documented communication between the ON SAS and the perivascular space around the central retinal vessels, our hypothesis may at first sight appear to be less plausible. However, such forcing of CSF into the ON, although insignificant under Earth-gravity conditions, could become important when astronauts are exposed to the very unique environment of prolonged microgravity due to the cephalad redistribution of bodily fluids and CSF. Future research in this area of investigation could not only provide exciting new insights into the mechanisms underlying microgravity-induced optic disc swelling but also offer opportunities to develop countermeasure strategies.

Compliance with ethical standards

Conflict of interest PW is the inventor of a pending patent application pertaining biomarkers for spaceflight-associated neuro-ocular syndrome. The other authors declare that they have no conflict of interest.

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