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Perspective

Intracranial pressure-induced optic nerve sheath response as a predictive biomarker for optic disc edema in astronauts

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A significant proportion of the astronauts who spend extended periods in microgravity develop ophthalmic abnormalities. Understanding this syndrome, called visual impairment and intracranial pressure (VIIP), has become a high priority for National Aeronautics and Space Administration, especially in view of future long-duration missions (e.g., Mars missions). Moreover, to ensure selection of astronaut candidates who will be able to complete long-duration missions with low risk of the VIIP syndrome, it is imperative to identify biomarkers for VIIP risk prediction. Here, we hypothesize that the optic nerve sheath response to alterations in intracranial pressure may be a potential predictive biomarker for optic disc edema in astronauts. If confirmed, this biomarker could be used for preflight identification of astronauts at risk for developing VIIP-associated optic disc edema.

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It has been reported that a significant proportion of the astronauts who have participated in long-duration spaceflights are experiencing ophthalmic abnormalities including optic disc swelling, optic nerve sheath (ONS) distention, globe flattening, choroidal folds and hyperopic shifts [1]. An increased understanding of factors contributing to this syndrome, designated as visual impairment and intracranial pressure (VIIP), has become a high priority for the National Aeronautics and Space Administration (NASA), especially in view of future long-duration missions, including trips to Mars [2]. Currently, the exact mechanisms causing the VIIP syndrome are unknown. Among the several mechanisms proposed to play a role, a leading hypothesis is that the VIIP syndrome is caused by elevated intracranial pressure (ICP) [1].

Although it is assumed that all astronauts exposed to microgravity have some degree of ICP elevation in-flight, not all crewmembers have manifested overt signs or symptoms of the VIIP syndrome [3]. It is believed that some crewmembers are more susceptible than others due to interindividual variations in factors such as genetics, anatomical features or physical fitness [4]. Therefore, to ensure selection of astronaut candidates who will be able to complete long-duration missions with low risk of the VIIP syndrome, it is imperative to identify biomarkers for VIIP risk prediction. At this purpose, we believe that it may be interesting to evaluate the ONS response to alterations in cerebrospinal fluid (CSF) pressure as a predictive biomarker for optic disc edema in astronauts.
Discussion
Two main potential mechanisms underlying the VIIP syndrome

A leading hypothesis is that the VIIP syndrome is caused by elevated ICP resulting from microgravity-induced cephalad fluid shifts leading to venous stasis in the head and neck [5]. This stasis could cause impairment of CSF drainage into the venous system and cerebral venous congestion, both of which could lead to a rise in ICP [5]. Alternatively, the microgravity environment might cause interstitial venous stasis at the level of low pressure CSF venules with subsequent increase in the interstitial fluid content in the brain tissues, resulting in increased ICP [1]. It is interesting to note that a recent study provided evidence for the primary role of CSF and a lesser role of intracranial cephalad vascular fluid shift in the formation of VIIP [6]. Other possible factors contributing to ICP elevation during long-duration spaceflight include defects in the folate- and vitamin B12-dependent one-carbon transfer pathways [7], elevated levels of carbon dioxide on-board the International Space Station (ISS) [8], high sodium ISS diets [9] and regimen of resistance exercise performed to prevent musculoskeletal degradation [9]. Although in-flight ICPs have never been measured, support for this ICP hypothesis of VIIP includes lumbar puncture opening pressures of 28 cm H2O and 28.5 cm H2O documented in astronauts at 12 and 57 days, respectively, after long-duration spaceflight [1]. Although these opening pressures were only mildly elevated, they may have been higher during the mission [1]. After spaceflight, MRI changes in other astronauts suggestive of increased ICP include concavity of the pituitary dome, empty sella and changes in pituitary stalk configuration [5,10].

The optic nerve, a white matter tract of the CNS, is sheathed in all three meningeal layers and surrounded by CSF in the subarachnoid space (SAS) [11]. The CSF in the intracranial SAS is connected to the CSF in the SAS around the optic nerve [11,12]. Because CSF is incompressible, the increased subarachnoid pressure resulting from intracranial hypertension is thought to be directly transmitted from the intracranial compartment to the intraorbital compartment through the perioptic SAS [1,12]. This elevated CSF pressure at eye level results in ONS distention and anteriorly directed forces that indent the posterior sclera resulting in posterior globe flattening, redundancy and folding of the choroid and axial shortening [1]. In addition, as ICP rises, it exceeds intraocular pressure (IOP), and this reversal of the normal trans-lamina cribrosa pressure difference (TLCPD), that is, the difference of IOP minus ICP, may cause arrest of orthograde axonal transport from the ganglion cell bodies in the retina toward the brain and the lateral geniculate ganglion, resulting in accumulation of axonal transport materials, ultimately causing optic disc swelling [13]. NASA's clinical practice guidelines (CPG) classify severity of VIIP by using a four-class ordinal scale based on a refractive change greater than 0.5 diopter and subjective assessment of a presence of orbital and ocular changes [6]. VIIP CPG class 1 and 2 are used when there is no evidence for optic disc edema and VIIP CPG class 3 and 4 are used when there is low-grade and high-grade optic disc edema, respectively [6].

A second main potential mechanism of ophthalmic findings in astronauts is compartmentation of CSF in the orbital SAS [1,5]. The SAS surrounding the optic nerve is a septated, trabeculated blind-ending (cul-de-sac) space [5]. This anatomy, coupled with the cephalad fluid shifts of prolonged microgravity, may inhibit CSF absorption within the orbit through venous and lymphatic mechanisms [5]. Consequently, CSF in the SAS of the optic nerve may gradually become partially or completely sequestered, producing a type of optic nerve compartment syndrome [1]. This sequestration may produce locally elevated ONS pressures and the accumulation of toxic substances that could result in varying degrees of optic disc swelling and/or associated findings (e.g., globe flattening, choroidal folds), even in the absence of elevated ICP [1,5].

The optic nerve sheath response to changing cerebrospinal fluid pressure

A previous study by Hansen et al. [14] performed serial ultrasound measurements of the ONS diameter in 12 patients undergoing neurological testing who were exposed to CSF pressure changes during CSF infusion tests. All patients had been referred to the Neurological Department because of suspected CSF absorption disorder (communicating hydrocephalus or optic disc elevation of unknown origin, six patients each). This study showed that the ONS response operates within a limited CSF pressure interval. At the low pressure end, a certain threshold CSF pressure needs to be exceeded before changes in ONS diameter occur. Above this threshold, the ONS diameter is directly related to the CSF pressure. The authors suggested that elastic structures determine the sheath's pressure response. At higher CSF pressure levels, the ONS may lose its ability for further dilation, which corresponds to a depleted capacity for further expansion. The authors proposed that the ONS saturation effect may relate to radially oriented trabecular fibers that traverse the SAS and connect pia mater of the optic nerve with the innermost arachnoid layer of the sheath. Importantly, comparison of the pressure response in 12 patients showed that changes in ONS diameter were predictable within the same patient but varied interindividually with respect to the relative change...
in ONS diameter per pressure unit and the range of operation (threshold and saturation) [14]. The threshold effect at the lower CSF pressure end was present in all patients, but it commenced at different levels in each individual (between 18 and 30 mmHg). The relative change in ONS diameter per pressure unit (ONS diameter/CSF pressure ratio) varied considerably among patients (range between 0.019 and 0.071 mm/mmHg). In three patients, the ONS diameter remained constant while the CSF pressure rose at maximum infusion to peak levels which resembled a saturation effect. Saturation of the response occurred between 30 and 40 mmHg. In the remaining cases, however, the authors were not able to detect this phenomenon within the pressure range studied. It is important to note that the changes in the ONS diameter occur before changes in the optic nerve are visible on funduscopic examination [15]. Elevated CSF pressure results in an increase in the local ONS diameter before papilledema appears [16].

The CSF pressure-induced ONS response & the risk of VIIP-associated optic disc swelling

Once the ONS reaches its maximum capacity to distend due to saturation of the response, small changes in CSF volume may elicit high increases in CSF pressure in the ONS. Therefore, it seems reasonable to assume that the saturation of the ONS response (constant ONS diameter) will activate the recruitment of compensating routes for CSF drainage in an attempt to stabilize the CSF pressure at eye level. However, such alternative compensatory mechanisms may be limited. It is highly unlikely that the CSF once in the orbital CSF space can change its direction of flow from the SAS of the optic nerve toward the intracranial SAS [17], given the microgravity-induced redistribution of CSF volume from the spinal canal to the cranium [6]. Lymphatics in the dura of the human optic nerve have been proposed as a possible outflow pathway for CSF from the SAS of the optic nerve [17,18]. However, these orbital optic nerve lymphatic drainage systems may be affected by microgravity-induced cephalad fluid shifts, which could lead to lymph stasis [1].

Interestingly, a paravascular transport system within the optic nerve [11] and retina [19], analogous and likely continuous with the recently discovered ‘glymphatic system’ in the brain [20], has recently been identified, and may form a ‘CSF outflow route’. The ‘cerebral glymphatic system’ is a brain-wide network of paravascular pathways along which a large proportion of CSF recirculates through the brain parenchyma, facilitating the clearance of interstitial solutes, including amyloid-β, from the brain [20]. Our group recently suggested the existence of a communication between the glymphatics in the optic nerve and retina [21], and we speculate that in case of microgravity-induced intracranial hypertension, reduction or reversal of the normal TLCPD may result in a one-way directional glymphatic flow to the eye. Normally, IOP exceeds ICP, and on average there is a small force (mean 4 mmHg) directed posteriorly across the lamina cribrosa [22]. This TLCPD may ensure effective posterior paravascular fluid outflow from the eye. However, in case of spaceflight-induced increased ICP, fluid outflow may fail to match ocular paravascular inflow due to the reduction of the normal TLCPD. Ocular paravascular outflow may even be completely impeded if there is reversal of the TLCPD. This may result in glymphatic stasis predominantly within the prelaminar region of the optic nerve head, and we believe that this could contribute to the optic disc edema observed in astronauts. The accumulation of toxic metabolites due to glymphatic stasis then may cause further disc swelling. Evidence to support this view was recently presented by Denniston et al. [23] who reported the potential relevance of the ‘ocular glymphatic system’ to idiopathic intracranial hypertension. Obviously, the saturation-related rise of CSF pressure in the ONS may also produce axoplasmic flow stasis in the optic nerve head with subsequent axonal swelling and optic disc edema.

From the above point of view, astronauts with lower relative CSF pressures at saturation of the ONS response may be more likely to develop optic disc swelling. Indeed, in these subjects, ONS expansion will reach a maximum capacity more rapidly (at lower CSF pressure) and as this compensatory mechanism reaches its limit, CSF may be pushed from the SAS of the optic nerve to the paravascular channels that surround the central retinal vessels in the optic nerve and then to the surroundings of the retinal vascular system. Optic disc edema may occur more quickly in these subjects at least in part as a result of the postulated imbalance between ocular glymphatic inflow and outflow. Moreover, once the maximum buffer capacity of the ONS has been reached, progressively smaller increases in CSF volume are associated with significant increases in CSF pressure in the ONS, which may also produce axoplasmic flow stasis. This would mean that the three patients in the study by Hansen et al. [14] who reached their saturation point at a lower relative CSF pressure would be at highest risk of VIIP-associated optic disc swelling. Interestingly, these three patients also had the lowest ONS diameter/CSF pressure ratio. Therefore, this ratio might serve as another predictive biomarker for optic disc edema in astronauts.

Obviously, mechanisms of optic disc swelling other than increased ICP must also be considered. Furthermore, it should be mentioned that for the moment at least, the role of the ‘ocular glymphatic system’ in the development of
optic disc edema in astronauts remains unproven. The few research data currently available cannot be considered as proof of the existence of an ‘ocular glymphatic system’ and more studies are needed to validate this possibility. However, even though nothing conclusive can yet be said, the recent reports suggesting a paravascular transport system in the eye and optic nerve are encouraging and, if confirmed, could be of great importance for our understanding of the pathogenesis of VIIP-associated optic disc swelling. Moreover, even in the absence of an underlying ‘glymphatic factor’, saturation of the CSF pressure-induced ONS response may facilitate axoplasmic flow stasis in the optic nerve head as small changes in CSF volume will be associated with high increases in CSF pressure in the ONS. Thus, regardless of the specific mechanism, perhaps in some anatomically predisposed astronauts, optic disc swelling may occur more quickly as a result of a lower relative CSF pressure at which the ONS loses its capacity to distend.

It is also important to note that the time in space may be another important factor influencing whether or not astronauts will develop optic disc edema. VIIP was not described on short-term spaceflights, such as the shuttle missions [13]. Maybe the duration was not long enough to develop the VIIP syndrome [13]. However, longer duration spaceflights, such as the 6–12-month time periods that are spent onboard the ISS, allowed enough time for this syndrome to be observed [13]. Living in space for an extended period of time may mainly affect astronauts who reach their ONS saturation point at a lower relative ICP (below the in-flight ICP value), because their maximum capacity to compensate is exceeded for a long time. On the other hand, astronauts with higher relative ICPs at saturation of the ONS response may stay in space for long periods of time without developing optic disc edema because their ONS maintains its ability to further dilate.

Preflight identification of astronauts at risk for developing VIIP-associated optic disc edema

It seems worthwhile to make every effort to identify biomarkers for prediction of VIIP-associated optic disc swelling, especially given that this medical obstacle could impact the visual health of astronauts both during long-duration spaceflight, potentially causing an impact to the mission and after flight, causing significant morbidity. As such, it would be interesting to investigate the predictive value of the CSF pressure-induced ONS response for the development of optic disc edema in astronauts. If confirmed, identifying the individual ONS diameter/CSF pressure ratio and/or the saturation level in astronauts would be extremely important for predicting the risk of VIIP-associated optic disc swelling and for decision making regarding participation in proposed missions. Measurements of the ONS diameter could be done during intrathecal infusion tests for preflight assessment of optic disc edema risk. However, an intrathecal infusion test is a relatively invasive examination procedure and therefore, the benefits that may be derived from the information obtained by the procedure should be carefully balanced against the disadvantages and possible risks for the astronaut. It would be unacceptable to perform a potentially risky procedure if the information gained would not offer significant potential individual and/or societal benefits. Obviously, the availability of a less invasive alternative would be extremely useful. It should also be stressed that microgravity-induced intracranial hypertension, if left untreated, could not only lead to vision alterations, but also to potentially other deleterious health effects. Therefore, astronaut candidates with a negative intrathecal infusion test may still develop health problems related to increased ICP other than ophthalmic abnormalities.

Conclusion & future perspective

Ophthalmic abnormalities including optic disc swelling, ONS distention, globe flattening, choroidal folds and hyperopic shifts have been reported in astronauts following long-duration spaceflight. Understanding factors contributing to this VIIP syndrome has become a high priority for NASA, particularly because this medical obstacle could impact the success of future missions, including trips to Mars. Moreover, in order to better characterize the individual susceptibility to develop the VIIP syndrome, identifying biomarkers for VIIP risk prediction is highly desirable. In the present paper, we have hypothesized that the ONS response to alterations in CSF pressure may be a potential predictive biomarker for optic disc edema in astronauts. If confirmed, this biomarker could be used for preflight assessment of VIIP-associated optic disc swelling risk.

Author contributions

P Wostyn developed the theoretical part of the hypothesis. P Wostyn drafted and wrote the manuscript. PP De Deyn commented and revised the intellectual content of the manuscript. P Wostyn and PP De Deyn have read and approved the final version of the manuscript.
Optic disc edema in astronauts

Perspective

Executive summary

- A significant proportion of the astronauts who spend extended periods in microgravity develop the visual impairment and intracranial pressure (VIIP) syndrome.
- The exact mechanisms causing the observed ocular changes in astronauts are yet to be fully elucidated.

Two main potential mechanisms underlying the VIIP syndrome

- Elevated intracranial pressure resulting from microgravity-induced cephalad fluid shifts is hypothesized to play an important role in VIIP.
- A second main potential mechanism of ophthalmic findings in astronauts is compartmentation of cerebrospinal fluid (CSF) in the orbital subarachnoid space.

The optic nerve sheath response to changing CSF pressure

- A previous study among patients undergoing intrathecal infusion testing showed that the optic nerve sheath (ONS) response was directly correlated with CSF pressure above an individual patient's threshold until a saturation point was reached when no further dilation occurred.

The CSF pressure-induced ONS response and the risk of VIIP-associated optic disc swelling

- We hypothesize that the CSF pressure-induced ONS response may be a potential predictive biomarker for optic disc edema in astronauts.

Future perspective

- If confirmed, this biomarker could be used for preflight identification of astronauts at risk for developing spaceflight-induced optic disc edema.

Financial & competing interests disclosure

P Wostyn is the inventor of a pending patent application pertaining biomarkers for VIIP-associated optic disc edema in astronauts, filed by P&X Medical NV. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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Papers of special note have been highlighted as: • of interest; •• of considerable interest


- The first published report documenting ophthalmic anomalies in astronauts or cosmonauts during or after spaceflight.


- Provides evidence for the primary role of cerebrospinal fluid in the formation of the visual impairment and intracranial pressure syndrome.


- The first published report documenting ophthalmic anomalies in astronauts or cosmonauts during or after spaceflight.


- Provides evidence for the primary role of cerebrospinal fluid in the formation of the visual impairment and intracranial pressure syndrome.


- A recent paper presenting a novel hypothesis for glaucoma pathology based on ocular glymphatic dysregulation.


**An interesting study describing the optic nerve sheath response to alterations in cerebrospinal fluid pressure.**


**The first paper that described the concept of the ‘glymphatic system’.**


**An interesting study reporting the potential relevance of the ‘ocular glymphatic system’ to idiopathic intracranial hypertension.**