LEARNING OBJECTIVES

1. Describe the history, clinical findings, and possible pathogenic etiologies of neuro-ophthalmic findings discovered in astronauts after long-duration space flight.
2. Discuss the terrestrial implications of such findings.
3. Describe potential countermeasures to decrease risk to future missions and our astronauts.

CME QUESTIONS

1. Which of the following neuro-ophthalmic findings have been seen after long duration space flight?
   a. Anisocoria
   b. Optic disc edema
   c. Ocular motor cranial neuropathy
   d. Bitemporal hemianopsia

2. Which of the following fundus findings have been documented in astronauts after long duration space flight?
   a. Choroidal folds
   b. Retinal vein occlusion
   c. Angle closure glaucoma
   d. Retinal artery occlusion

3. Which of the following have been seen radiographically in long duration space flyers?
   a. Globe flattening
   b. Venous sinus thrombosis
   c. Suprasellar mass
   d. Intracranial hemorrhages

4. Which of the following is the refractive error shift that has been seen most frequently in long duration space flight astronauts?
   a. Myopic shift
   b. Hyperopic shift
   c. Astigmatic shift
   d. Higher order aberration shift

KEY WORDS

1. Astronaut
2. Optic Disc Edema
3. Choroidal Folds
4. Papilledema
5. Hyperopic Shift
6. Long Duration Space Flight

INTRODUCTION

Physiologic and pathologic systemic responses and novel but dramatic ocular changes are known to occur in the microgravity environment of outer space. The precise effects of the long duration space flight environment on the human eye and brain remain ill-defined but over the last decade, the United States National Aeronautics and Space Administration’s (NASA) Space Medicine Division has documented varying degrees of optic disc edema, globe flattening, choroidal folds, cotton wool spots (CWS), and hyperopic refractive error shifts in astronauts during and after long-duration space flight. In addition, neuroradiographic and ultrasonographic findings have demonstrated structural correlates to the clinical findings experienced by our long duration space flyers including flattening of the posterior globe and increased cerebrospinal fluid signal in the optic nerve sheaths. Although there have been some similarities of these radiographic and neuro-ophthalmic clinical findings with terrestrial idiopathic intracranial hypertension (IIH), there have also been clear differences. The clinical features of this unique patient cohort during space travel suggest specific neuro-ophthalmologic responses that might be inherent to long duration exposure to the microgravity space environment. We described our clinical experiences in a prior report and we proposed at that time that these neuro-ophthalmic findings may represent pathologic processes related to intraocular, intra-optic nerve, intraorbital, intravascular, or intracranial changes. There is also a cephalad fluid shift experienced by our astronauts during microgravity exposure that might be the key to the underlying pathogenesis. Alternatively, increased intracranial pressure (ICP), translaminar pressure differences between intraocular pressure (IOP) and ICP, or
alterations in the cardiovascular or cerebrovascular systems have also been proposed as potential alternative but not necessarily mutually exclusive pathogenic mechanisms.

The objectives of this presentation include: 1) To describe the neuro-ophtalmic changes seen in astronauts after long duration space flight; 2) To detail the possible hypotheses for an etiologic mechanism including intravascular, intracranial, intraorbital, intrasheath, and intraocular changes related to long duration space flight and microgravity; 3) To compare and contrast terrestrial IIH and postoperative ischemic optic neuropathy (ION) with the findings in long duration space flyers and to discuss the possible implications of our space flight findings for these terrestrial neuro-ophthalmic disorders.

In 2013, Mader et al. described the history, clinical findings, and possible etiologies of ophthalmic findings discovered in astronauts after long-duration space flight on the International Space Station (ISS). This retrospective, observational report described the neuro-ophthalmic findings in 7 astronauts as well as an analysis of post-flight questionnaires about in-flight vision changes in approximately 300 additional astronauts. All 7 subjects underwent complete eye examinations before and after their ISS mission, including cycloplegic and/or manifest refraction and fundus photography. Six underwent post-mission optical coherence tomography (OCT) and magnetic resonance imaging (MRI); 4 had lumbar punctures (LP). After 6 months of space flight, 7 astronauts had ophthalmic findings, consisting of optic disc edema in 5, globe flattening in 5, choroidal folds in 5, CWS in 3, nerve fiber layer thickening by OCT in 6, and decreased near vision in 6 astronauts. Five of 7 astronauts with near vision complaints had a hyperopic shift of +0.50 diopters (D) between pre/post-mission spherical equivalent refraction in 1 or both eyes (range: +0.50 to +1.75 D). These 5 cases also showed a structural correlate of globe flattening (axial hyperopic shortening) on orbital MR and ultrasound imaging. Lumbar punctures (LP) performed in the 4 cases with optic disc edema documented opening pressures (OP) of 22, 21, 28, and 28.5 cm H2O performed 60, 19, 12, and 57 days post-mission, respectively. The 300 post-flight questionnaires documented that approximately 29% of short (space shuttle) duration and 60% of long-duration mission flyers on ISS had experienced a degradation in distant and near visual acuity. Although most of the visual changes were reversible or correctible to 20/20, some refractive error changes remained persistent even years after flight.

Table 1 (see next page) (reprinted with permission from) summarizes the neuro-ophthalmic findings in 7 ISS crew members. In addition, NASA follows longitudinally the health of the astronaut corps in the Lifetime Surveillance of Astronaut Health (LSAH) program. Table 2 (see next page) demonstrates the in-flight and post flight refractive changes from shuttle and ISS flyers in the LSAH. Figure 1 (see below) shows an example of fundus photography documentation of preflight and post-flight development of optic disc edema in one long duration space flyer. Figure 2 (see below) demonstrates the orbital MRI (T2 weighted) findings of flattening of the posterior globe, CSF fluid in the optic nerve sheath, and an elevated optic disc. Figure 3 (see next page) shows choroidal folds OU in a long duration flyer post flight which were not present on fundus photographs preflight.
DISCUSSION

Although optic disc edema, globe flattening, choroidal folds, and hyperopic shifts have been reported in terrestrial IIH, the neuro-ophthalmic findings in our long duration space flyers at NASA seem to have unique and somewhat perplexing clinical and radiographic differences when compared with IIH.1-12 First, our affected space flyers do not report the typical and classic symptoms of increased ICP seen in terrestrial IIH (e.g., headache, pulse synchronous tinnitus, or diplopia).1 Second, although choroidal folds and hyperopic shifts are sometimes seen in terrestrial IIH, these findings seem to be a more common finding in our returning astronauts. Third, distal retinal CWS are also not a typical component of IIH and yet they are present in our cohort. Finally, although several reports have described the ultrasonography, OCT, MRI and CT scan findings in IIH that include flattening of the posterior globe and CSF enlargement of the subarachnoid space (SAS) around the ON sheath these structural findings seem more

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Table 1. Neuroophthalmic Changes in Astronauts

<table>
<thead>
<tr>
<th>ISS Crew Member</th>
<th>Mission Duration (mos)</th>
<th>Preflight Refractive Change</th>
<th>Postflight Refractive Change</th>
<th>Intracocular Pressure (mmHg)</th>
<th>Funduscopic Examination Postflight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>OD: -1.50 sph VS -1.25 - 0.25 x 105</td>
<td>OS: -2.25 - 0.25 VS -2.50 - 0.50 x 105</td>
<td>15 OU</td>
<td>Choroidal folds OD</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>OD: +0.75 sph VS +2.00 sph</td>
<td>OS: +0.75 to 0.25 x 105 VS +2.00 - 0.50 x 140</td>
<td>14 OU</td>
<td>Bilateral disc edema OD &gt; OS</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>OD: -0.50 sph VS -0.25 sph</td>
<td>OS: plano to 0.50 x 090 VS -0.75 - 0.75 x 090</td>
<td>10 OU</td>
<td>Choroidal folds VS Cotton wool spot OS</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>OD: -0.75 to 0.50 x 100 VS Plano</td>
<td>OS: OD: +0.75 - 0.50 x 105 VS Plano</td>
<td>15/13</td>
<td>Bilateral disc edema OD &gt; OS</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>OD: -5.75 to 1.25 x 010 VS -5.50 - 1.50 x 015</td>
<td>OS: -5.00 - 1.50 x 180 VS -4.75 - 1.75 x 100</td>
<td>14/12</td>
<td>Small hemorrhage OD</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>OD: +0.25 sph VS +2.00 - 0.50 x 028</td>
<td>OS: OD: +1.00 sph VS +2.00 x 010</td>
<td>14 OU</td>
<td>Disc edema OD</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>OD: +1.25 sph VS +2.75 sph</td>
<td>OS: OD: +1.25 sph VS +2.50 x 010</td>
<td>16 OU</td>
<td>Choroidal folds OD &gt; OS</td>
</tr>
</tbody>
</table>

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Table 2. Reported In-Flight Subjective Visual Changes and Postflight Refraction Changes of National Aeronautics and Space Administration Astronauts (Not Including International Partners) from 1989 to 2009

<table>
<thead>
<tr>
<th>Description</th>
<th>Shuttle % (n)</th>
<th>ISS-Long Duration % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased DVA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (n)</td>
<td>581</td>
<td>44</td>
</tr>
<tr>
<td>None</td>
<td>93.5 (543)</td>
<td>88.1 (39)</td>
</tr>
<tr>
<td>Mild</td>
<td>5.7 (33)</td>
<td>2.4 (1)</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.9 (5)</td>
<td>4.8 (2)</td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0)</td>
<td>4.8 (2)</td>
</tr>
<tr>
<td>Decreased NVA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (n)</td>
<td>581</td>
<td>44</td>
</tr>
<tr>
<td>None</td>
<td>76.7 (448)</td>
<td>52.3 (23)</td>
</tr>
<tr>
<td>Mild</td>
<td>17.6 (103)</td>
<td>13.6 (6)</td>
</tr>
<tr>
<td>Moderate</td>
<td>5.5 (32)</td>
<td>27.3 (12)</td>
</tr>
<tr>
<td>Severe</td>
<td>0.2 (1)</td>
<td>6.8 (3)</td>
</tr>
<tr>
<td>Refraction change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (n)</td>
<td>587</td>
<td>44</td>
</tr>
<tr>
<td>None</td>
<td>88.9 (522)</td>
<td>65.9 (29)</td>
</tr>
<tr>
<td>Mild</td>
<td>9.2 (54)</td>
<td>25.0 (11)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.9 (11)</td>
<td>2.3 (1)</td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0)</td>
<td>6.8 (3)</td>
</tr>
</tbody>
</table>

DVA = distance visual acuity; ISS = International Space Station; NVA = near visual acuity.
Source: Lifetime Surveillance of Astronaut Health (LSAH) Program, NASA Johnson Space Center.
pronounced (especially relative to the lack of symptoms) in our astronauts than in typical IIH. In IIH, the elevated subarachnoid CSF pressure caused by intracranial hypertension is believed to be directly transmitted from the intracranial compartment to the intraorbital compartments through the perioptic SASs. This increased ICP causes a distension of the ON sheaths and secondary stasis of axoplasmic flow leading to axonal swelling and resultant bilateral optic disc edema, which we call papilledema on Earth.

It remains unclear whether the optic disc edema seen in our astronauts after long duration space flight actually represents true papilledema or not. LP OP (admittedly performed days to weeks after return to Earth) have been borderline high but uniformly unimpressive for elevated ICP that we typically see in IIH. Elevated intrasheath CSF pressure is thought to cause the subarachnoid compartment to exert an anterior force that indents the posterior sclera resulting in posterior globe flattening, redundancy and folding of the choroid, and axial shortening with a secondary hyperopic shift. This CSF fluid in the optic nerve sheath may account for the radiographic findings of both terrestrial IIH and the findings in our astronauts.

Since the end of the US space shuttle program, NASA astronauts must now make the return to Earth from the ISS via the Russian Soyuz. This return in Kazakhstan (in the former Union of Soviet Socialist Republics (USSR)) makes the political and operational logistics for measuring OP in our astronauts immediately upon landing or even within a few days more difficult. Thus, when NASA physicians have been able to perform an LP it is often delayed to well beyond the return date. We have reported some elevated OP measurements of 28.5 and 28 cm H2O at 57 days and 12 days, respectively, in some astronauts after returning to Earth. Although these OPs were only mildly elevated, these LP results could represent the downslope of a CSF pressure spike that may have existed during microgravity exposure on ISS. It should be noted that we have no experience with and very limited capability for performing an LP in space.

The possible mechanisms of an IIH-like syndrome in our astronauts may involve a rise in cephalad venous pressure brought about by microgravity fluid shifts. Prior head-down and microgravity studies have documented that cerebral arterial diameter and blood flow velocity are autoregulated and do not change significantly during space flight but microgravity fluid shifts have been documented to cause jugular vein distension, possibly implicating cerebral venous congestion as a mechanism. The traditional understanding of ICP regulation on Earth assumes that CSF is largely produced in the choroid plexus and drainage depends on the pressure difference between the CSF and the venous system. Perhaps venous stasis in the head and neck (valveless veins as opposed to valves in the lower extremity veins preventing flow against gravity), produced by cephalad fluid shifts during space flight, might be a cause of impairment of CSF outflow, lymphatic outflow, or cerebral venous outflow reduction or congestion which could increase ICP.

Another alternate hypothesis is that the rate of CSF formation and absorption (outflow) is a balance between hyperosmolar plasma in high pressure capillaries, and the subsequent absorption of the formed hypo-osmolar interstitial fluid by the low-pressure venules that are in anatomic proximity to the high-pressure capillaries. Thus, in a microgravity environment venous stasis at the level of low pressure CSF venules and a subsequent decrease in the osmotic drive toward absorption may occur.

Yet, another possible explanation of these findings is that the ON head edema may not be ICP related papilledema. Instead it may be that the intraocular and intraorbital findings are the result of localized CSF events occurring at the level of the intraorbital ON with or without a rise in CSF pressure in the entire CSF system. This might explain the lack of significantly higher ICP on the LPs that have been performed to date and also the lack of typical symptoms of increased ICP in our astronauts as compared with terrestrial IIH. The OP is assumed to be equal throughout the CSF system but this may not necessarily be the case. In addition, impaired exchange of fluid between the intracranial CSF and that in the SAS of the ON has been proposed as a possible mechanism to explain persistent papilledema and visual loss in patients with terrestrial IIH despite a functioning lumboperitoneal shunt (LPS) and also might be the explanation for “normal or near normal” OP in some patients who clearly have clinical IIH on Earth.

The role of CSF stasis rather than elevation of ICP is also an intriguing hypothesis. It has been suggested that CSF is constantly produced and absorbed in the entire CSF system as a consequence of filtration and reabsorption of water volume through the capillary walls into the surrounding brain tissue. This implies that the CSF exchange between each portion of the CSF system and the surrounding tissue may depend on pathophysiologic conditions that predominate locally within those compartments. Animal studies have also documented a potential role of lymphatic drainage of CSF via the ethmoidal lymphatic system and there may be analogous lymphatic drainage pathway in the dura of the CSF outflow pathway of the optic nerve in the orbit. We have also seen impaired olfactory function in terrestrial IIH and in the head down tilt position (perhaps analogous to the cephalad fluid shift seen in our astronauts) and this might support the hypothesis.
of a role for lymphatic drainage outflow abnormalities at the level of the olfactory system and cribiform plate. Thus, these orbital ON lymphatic drainage systems may be affected by initial cephalad directed flow and then persistent microgravity exposure could lead to secondary lymph stasis, which could produce increase in ON sheath pressures within the unique cul de sac–like anatomically closed system. Our neuro-ophthalmology colleagues, Dr. Killer et al have proposed such a theory of a terrestrial IIH compartment syndrome with a bottleneck in CSF passage between the orbit and optic canal and we believe this to be a compelling hypothesis for the findings that we see in our astronaut cohort.

Although theoretically ocular hypotony (i.e., low IOP) could produce similar findings to our cases (e.g., choroidal folds and optic disc edema) we do not believe that hypotony is at play in our astronauts. Although there is an initial spike in IOP on exposure to microgravity this is followed by a decrease in IOP over a period of days. No long-term studies of IOP have been performed in microgravity to document specific trends but we have not found any evidence of low or high IOP in our astronauts. Head-down bed rest studies suggest that the initial spike in IOP is followed by a leveling or lowering of IOP over a period of days. The initial spike in IOP supports the hypothesis that there is choroidal expansion brought about by cephalad fluid shifts. The subsequent decrease in IOP after the initial IOP spike may be the result of a compensatory decrease in aqueous volume. However, we have not seen any support for IOP as the causative factor in microgravity/spaceflight related optic disc edema.

Likewise, the etiology of the hyperopic shift supports the cephalad fluid shift hypothesis. The phenomenon of hyperopic shift is so common that NASA astronauts over the age of 40 years are routinely offered the use of plus lens “Space Anticipation Glasses” preflight should they experience a hyperopic shift during the mission. The hyperopic shift usually occurs after weeks or months in space, has a gradual onset, is variable in magnitude, and strangely may persist for months to years after return to the 1-G Earth environment. Although one long-duration, head-down study documented a decrease in near visual acuity after 4 to 5 days of head-down tilt, another similar study noted no visual changes. As postulated previously, choroidal expansion on top of the normal aging related presbyopia process in those flyers over age 40 years may lead to a progressive shortening of the axial length that could theoretically cause a hyperopic shift. Although changes in corneal refractive power after exposure to changes in atmospheric pressure and oxygen partial pressure could be a possible mechanism considerable prior work has shown that normal, non-post-refractive surgery corneas are not subject to refractive changes during exposure to changing environmental conditions of spaceflight. Likewise, we do not believe that intraocular fluid shifts are producing any lenticular changes as the etiology for the hyperopic shift.

Instead, we hypothesize that choroidal expansion at least partially accounts for the hyperopic shift. The spongy, highly vascular choroid is normally approximately 0.3 mm in thickness; is drained by the vortex veins; and is likely sensitive to impeded outflow produced by microgravity and cephalad fluid shifts. Choroidal volume changes in microgravity may also be responsible for the abrupt increase in IOP (within 30 seconds) in orbital and KC-135 parabolic flights as well as head-down studies. The cephalad fluid shift could also cause venous congestion in the neck and head that might lead to a rise in vortex vein pressure and perhaps decreased choroidal drainage and stagnation or pooling of blood in the choroid. Choroidal vasculature alterations have been reported in highly myopic eyes on Earth. A shortening of the distance between the macula and the lens of 0.33-mm anteriorly at the macula would lead to a 1-D shift toward hyperopia. For patients with permanent refractive error change, this choroidal pooling may gradually expand the delicate collagen lamella of the choroid beyond its normal anatomic structural boundaries such that the choroid becomes permanently distended even on return to the 1-G environment and in the presence of normal venous backpressure. The choroidal folds that we see might be the structural marker of this change. Newell hypothesized that visible choroid folds may occur as a result of a combination of variable anatomic attachments of the choroid to Bruch’s membrane and some factor that causes congestion in the choriocapillaris.

Even more intriguing, unilateral CWS have been noted (n=3 astronauts) after exposure to extended microgravity. CWS are thought to be accumulations of cytoplasmic debris caused by focal obstruction of orthograde and or retrograde axoplasmic transport and they may leave a permanent retinal defect and are thought to reflect precapillary arteriolar closure. Although CWS are nonspecific, they are well known to occur in a number of conditions including diabetes mellitus, HIV retinopathy, Purtscher retinopathy, high-altitude retinopathy, and hypertensive retinopathy. None of these clinical conditions offer insight into why these findings occur in our astronauts but it has been postulated that perhaps local asymmetric microgravity related changes in CSF flow within the intraorbital portion of the ON may lead to a biochemically altered CSF that may cause a metabolic toxicity to the ON and set the stage for focal arteriolar closure in the retina. The role of radiation exposure including cosmic rays in space or during extravehicular activity outside of the ISS remains unknown and the CWS may not be directly related to the other neuro-ophthalmic findings seen in our astronauts.

Recently we described an astronaut with two long-duration (6 months) exposures to microgravity. Before and after his first long-duration space flight, he underwent complete eye examination, including fundus photography. Before and after his second flight, 9 years later, he underwent preflight fundus photography, OCT, ocular ultrasonography, brain
MRI and then in-flight fundus photography and ultrasound. After his first long-duration mission, the astronaut was documented to have eye findings limited to unilateral choroidal folds and a single CWS. During the subsequent 6-month mission, he developed more widespread choroidal folds and new onset of optic disc edema in the same eye. This bothersome finding suggests that the effects of repeated exposure to space flight and microgravity might be cumulative.57

Finally, the findings in our astronauts might also have some bearing on further understanding of the pathogenesis or treatment of terrestrial IIH and another condition with cephalad fluid shift as a risk factor, ischemic optic neuropathy (ION) after spine surgery. Spine surgery in the prone position produces a similar morphologic change in the head, face, and neck (postoperative facial edema) as the cephalad fluid shift experienced by our astronauts. In terrestrial patients who have lost vision due to ION after spine surgery the impaired venous return in the orbit has been hypothesized as a potential risk factor. Likewise in our head tilt down studies similar hypotheses about cephalad fluid shift as a pathogenic mechanism have been suggested.

This raises additional questions about possible pathogenic mechanisms for optic disc edema in terrestrial causes of disc edema without elevated ICP. Further study is necessary to determine the etiology for the findings in our long duration space flyers. It is hoped that we will be able to document a single or predominant mechanism and propose specific countermeasures in preparation for a return to longer duration space flight including the possibility of future missions to ISS or to asteroids, a return trip to the moon, or perhaps a future manned mission to the planet Mars.

CME ANSWERS
1. b
2. a
3. a
4. b

DISCLOSURES
* Although Dr. Lee has served as a neuro-ophthalmology consultant for NASA and the contents of this specific manuscript were vetted and reviewed by NASA, the views and opinions represented here are those of the author as well as content already within the public domain and thus do not necessarily represent the views of the space agency (NASA) or the United States government.

REFERENCES


AUTHOR REFERENCES

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