The Visual Impairment Intracranial Pressure Syndrome in Long Duration NASA Astronauts: An Integrated Approach

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Background
VIIP Clinical Findings

• To date 22/31 U.S. astronauts have developed some or all of the following findings either during or following a six-month spaceflight:

  • Hyperopic shift
  • Choroidal folds
  • Optic Nerve Sheath Distention
  • Optic nerve kinking
  • Globe flattening
  • Optic disc edema (papilledema) N=7
  • Cotton wool spots N=3
  • ↑ CSF pressure postflight 5/6 subjects: 21.0-28.5 cmH₂O

- Kramer et al. (2012)
Pre to Postflight Disc Edema (First case 2005)

**Pre Flight**
Fundoscopic images of the right and left optic discs.

**Post Flight**
Fundoscopic images of the right and left optic discs showing Grade 3 edema (right) and Grade 1 edema (left).
Prolonged Disc Edema May Lead to Peripheral Visual Field Loss

1. Normal Visual Field with normal blind spot (in black)
2. Early Defect, Enlarged Blind Spot and Inferior Nasal Loss
3. Severe Visual Constriction
Main Hypothesis
Head-ward fluid shift due to microgravity

Increased intracranial pressure (ICP)

Elevated ICP transmitted to the eye and optic nerve
Evidence
NASA Crewmember LPs to Date

- LPs are done in crewmembers only if clinically indicated
- 6 LPs conducted postflight in crewmembers with optic disc edema, no preflight LP as baseline
- Postflight measurements of ICP via LP have demonstrated elevated ICP in 5/6, ranging 15.4-21mmHg. Clinical intervention recommended when ICP>20.0mmHg
  - Does not reflect in-flight ICP (fluid shift + CO₂), suspected to be higher

<table>
<thead>
<tr>
<th>Case</th>
<th>Opening pressure (cm H₂O) Normal range 10-20 cm H₂O</th>
<th>Opening pressure (mmHg) Normal range 5-15 mm H₂O</th>
<th>Time after flight (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>28.5</td>
<td>21.0</td>
<td>57</td>
</tr>
<tr>
<td>C</td>
<td>28</td>
<td>20.6</td>
<td>12</td>
</tr>
<tr>
<td>A</td>
<td>22</td>
<td>16.2</td>
<td>66</td>
</tr>
<tr>
<td>F</td>
<td>21.5</td>
<td>15.9</td>
<td>6</td>
</tr>
<tr>
<td>B</td>
<td>21</td>
<td>15.4</td>
<td>19</td>
</tr>
<tr>
<td>E</td>
<td>18</td>
<td>13.2</td>
<td>8</td>
</tr>
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</table>
Alternative Hypotheses:

1. Genetic VIIP predisposition to the spaceflight environment
One-Carbon Metabolism

- Methylated Acceptors
- SAH
- SAM
- HCY
- CYS
- α-KBT
- PRP-CoA
- 2MCA
- B6
- AA, FA
- THF
- 5-MTHF
- MTHFR
- CC
- MTRR
- B12
- MS
- MTHFR
- SHMT
- 5, 10-MTHF
- SUC-CoA
- Glycine
- Serine
- Dietary Folate
- Dietary Protein
- Muscle Catabolism

Graph showing homocysteine levels (µmol/L) across different conditions.

CPG = 1-4
CPG = 0

AA/AG
GG

Smith & Zwart et al. 2015
Alternative Hypotheses:

1. Genetic VIIP predisposition to the spaceflight environment

2. CO$_2$ induced VIIP
CO₂ is an extremely potent vasodilator, and its levels on ISS are x10 of Earth levels.

A study by a joint NASA team (medical operations, LSAH, toxicology) evaluated in-flight data from expeditions 2-31, looking for a relationship between levels of CO₂ and symptoms.

A statistically significant association was found between the probability of headaches and average CO₂, for both 24-hour and 7-day averages.

Alternative Hypotheses:

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2. CO$_2$ induced VIIP
3. Ocular structural changes
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4. Brain structural changes
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1. Genetic VIIP predisposition to the spaceflight environment
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4. Brain structural changes

Probably a combination or other causes as well!
Research Approach
The VIIP Research Plan

Zero VIIP Incidence

Current Incidence of VIIP Findings = 66.7%
The VIIP Research Plan

Zero VIIP Incidence

Current Incidence of VIIP Findings = 66.7%

VIIP 1 - Knowledge Acquisition

Human Research Program
NSBRI
Medical Operations
LSAH
The VIIP Research Plan

Zero VIIP Incidence

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VIIP 1 - Knowledge Acquisition

VIIP 3 - Technology Development

VIIP 12 - Analogs

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VIIP 13 – Countermeasures

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Current Incidence of VIIP Findings = 66.7%
VIIP 1: Etiology and Risk Factors

- VIIP Data Mining
  - Venous/Arterial Compliance

- CSF Dynamics pre/postflight (MRI)
- Venous Sinus Evaluation
- Diffusion Tensor Imaging (MRI)
- Brain Gene Expression Signatures
- CSF Production & Outflow (rodents)
- Cephalad Fluid Redistribution (MRI)
- VIIP Biomarker
- CO₂ Data Mining Vision
- CO₂ Data Mining headaches

- Mapping by VESGEN
  - Data Mining – Ocular Structure
  - Ocular Structure & Biomechanics
  - Compartment Syndrome
  - SD-OCT Analysis
  - Effects of Gamma Radiation

- 1-Carbon Polymorphism
  - Retinal Gene Expression during μG
  - Retinal Gene Changes in HLS

- ICP in Short & Simulated Microgravity
  - Direct ICP in Microgravity

- Ocular Health Study
- Fluid Shifts
- Occ. Surveillance Data Mining
- SD/Visual Health (MRID)
- Digital Astronaut Modeling

- Eye & Cranio-Venous Modeling
- Contribution of Medications
- Influence of Exercise Modality
- Acute CO₂ & HDT (1 hr)
- Pilot CO₂ & HDT (1 day)
- Short-Term CO₂ & HDT (1 wk)
- Chronic CO₂ & HDT (1 month)
- Long-Term Impacts of VIIP
  - Evidence Report

- Med Ops In-Flight Monitoring

HHC: Completed
NSBRI: Ongoing
SD: Planned
Example:

The Ocular Health Study on ISS

(PI: Christian Otto)
Comprehensive Examinations in Ocular Health

- B-scan Ocular Ultrasound
- Intraocular Pressure
- Optical Coherence Tomography (OCT)
- Fundoscopy
- Computer-based vision testing
- Cardiac and transcranial Doppler for vascular compliance
Example:

The Fluid Shifts Study on ISS

(PI’s: Michael Stenger, Alan Hargens & Scott Dulchavsky)
In-Flight Sessions (FD 45, R-45)

Test Day 1

Fluid compartmentalization measures:
- Total Body Water ($D_2O$)
- Extracellular (NaBr)
- Intracellular (Calculated)

Test Day 2

Ultrasound measures of fluid shifts:
- Vascular measures of head/neck (i.e., carotid, jugular, vertebral, cerebral)
- Cardiovascular, ophthalmic, and portal vein measures
- Tissue thickness forehead and eyelid

Other physiological measures:
- Intracranial Pressure (CCFP/DPOAE)
- Intraocular Pressure (Tonopen/iCare and Ultrasound)
- Ocular Structure (OCT)
- Blood Pressure / Heart Rate / Vascular Resistance

Test Days 3 & 4

- Similar to Day 2 w/ addition of Chibis LBNP
Reversal of Fluid Shift by LBNP (Chibis)
Fluid Shifts Timeline

L-21/18 months

MRI concurrent with Med Ops schedule

L-90

Day 1
supine, upright sitting, 15° HDT baseline

FD45

Day 1
dilution measures

R-45

Day 2
supine, 15° HDT with LBNP

Day 2
all other baseline measures

R+1/3

MRI concurrent with Med Ops schedule

R+10

Single Day Sessions
supine, upright sitting, 15° HDT measures
No LBNP

R+30

R+180
Preliminary Results:

Intracranial pressure during parabolic flight induced zero G
Ommaya Reservoir - Commonly used intraventricular chemotherapeutic delivery device. Allows access to brain’s ventricular system through overlying skin allowing pressure measurement.
Levine & Lawley, personal communication (2015)
Preliminary Results:

Cardiovascular predisposition
Correlation of Preflight Cardiovascular Score and Postflight Eye Outcomes

Best correlation = 0.91, Max = .96, Min .86, P<0.001
VIIP 3: Diagnostic Tools

- Pilot Study: Non-Invasive CVP Device

- Vittamed ICP Device Evaluation
- Non-Invasive ICP Ground Comparison
- ICP Tech Search
- CCFP Data Mining
- Cerebrotech
  - Non-Invasive ICP Flight Hardware Development
  - Validation of Non-Invasive ICP

- Retinal Vascular Remodeling
  - SD/Visual Acuity Software & In-Flight Tonometer Upgrade
  - SD/Flight Fundoscopy Trade Study
  - SD/Flight Fundoscopy Upgrade
  - SD/Diagnostic OCT Trade Study
  - SD/Development In-Flight diagnostic OCT

- Volumetric Ophthalmic Ultrasound & ICP
- VIIP Hardware TechWatch

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Ophthalmic and Optic nerve Sheath Modeling

- HLS Rodent Model for VIIP
- Digital Astronaut: VIIP Modeling
- Cranial Venous Circulation Modeling
- Acute CO₂ & HDT (1 hr)
- Pilot CO₂ & HDT (1 day)
- Short-Term CO₂ & HDT (1 week)
- Chronic CO₂ & HDT (1 month)
- Rodent Retinal Changes with HLS
- Rodent Retinal Changes with Spaceflight
- Rodent Retinal Changes with Radiation

HHC
NSBRI
SD

- Completed
- Ongoing
- Planned
VIIP 13: Countermeasures

- In-Flight CO₂ Reduction
- Fluid Shifts Flight Study (LBNP)
- Influence of Exercise Modality
- Evaluation of an Impedance Threshold Device
- Mechanical Countermeasures - Evaluation of Marketed Devices
- Thigh Cuffs Ground Evaluation
- Pharmacological Countermeasures
- Countermeasure Optimization Ground Study
- Countermeasure Optimization In-Flight

- Completed
- Ongoing
- Planned
Thank you!