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>
</tbody>
</table>
Alternative Hypotheses:

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

Smith & Zwart et al. 2015
Alternative Hypotheses:

1. Genetic VIIP predisposition to the spaceflight environment

2. CO$_2$ induced VIIP
A Possible Role for CO\textsubscript{2} in VLP?

- CO\textsubscript{2} 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 CO\textsubscript{2} and symptoms.

A statistically significant association was found between the probability of headaches and average CO\textsubscript{2}, 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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3. Ocular structural changes
4. Brain structural changes
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2. CO$_2$ induced VIIP
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4. Brain structural changes

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

Current Incidence of VIIP Findings = 66.7%

Zero VIIP Incidence

Human Research Program
NSBRI
Medical Operations
LSAH

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The VIIP Research Plan

Zero VIIP Incidence

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VIIP 1 - Knowledge Acquisition
The VIIP Research Plan

Zero VIIP Incidence

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VIIP 12 - Analogs

VIIP 3 - Technology Development

VIIP 1 - Knowledge Acquisition

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The VIIP Research Plan

Zero VIIP Incidence

- VIIP 13 – Countermeasures
- VIIP 12 - Analogs
- VIIP 3 - Technology Development
- VIIP 1 - Knowledge Acquisition

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

### In-Flight Monitoring

- **HHC**
  - Completed
- **NSBRI**
  - Ongoing
- **SD**
  - Planned
Example:

The Ocular Health Study on ISS

(PI: Christian Otto)
<table>
<thead>
<tr>
<th>Preflight Exams</th>
<th>In-flight Exams</th>
<th>Postflight Exams</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-21/18 mo</td>
<td>FD10 FD30</td>
<td>R+1/3 R+30</td>
</tr>
<tr>
<td>L-6/9 mo</td>
<td>FD60 FD90 FD120</td>
<td>R+90 R+180</td>
</tr>
<tr>
<td>Flight Med Clinic • Ocular Ultrasound • Vision Testing • Fundoscopy • Refraction • Pupil Reflexes • Extra-Ocular Muscle Balance • IOP (Tonometry) • OCT/A-scan</td>
<td>R-30</td>
<td>R+360</td>
</tr>
<tr>
<td>Victory Lakes • MRI</td>
<td>• Vision Testing • IOP (Tonometry)</td>
<td>Flight Med Clinic • Ocular Ultrasound • Vision Testing • Fundoscopy • Refraction • Pupil Reflexes • Extra-Ocular Muscle Balance • IOP (Tonometry) • OCT/A-scan</td>
</tr>
<tr>
<td>Flt Med Clinic • Vision Testing • Fundoscopy • Refraction • Pupil Reflexes • Extra-Ocular Muscle Balance • IOP (Tonometry) • OCT/A-scan</td>
<td>• Blood Pressure</td>
<td>Coastal Eye Assoc • Cardiac Ultrasound • Blood Pressure • TCD</td>
</tr>
<tr>
<td>Coastal Eye Assoc • Biomicroscopy/Hi Res Photography</td>
<td>• Fundoscopy</td>
<td>Coastal Eye Assoc • OCT Anterior Segment • Blood pressure</td>
</tr>
<tr>
<td>Coastal Eye Assoc • OCT Anterior Segment</td>
<td>• OCT Anterior Segment</td>
<td>Coastal Eye Assoc • OCT Anterior Segment • Blood pressure</td>
</tr>
<tr>
<td>Bldg. 261 • Cardiac Ultrasound • Blood Pressure • TCD</td>
<td>• OCT Anterior Segment</td>
<td>Bldg. 261 • Cardiac Ultrasound • Blood Pressure • TCD</td>
</tr>
</tbody>
</table>

Medical Activity | Research Additional Activity | Medical Session | Research Additional Session
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$_2$O)
• 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
  - **Day 2** supine, 15° HDT with LBNP

- **FD45**
  - **Day 1** dilution measures

- **R-45**
  - **Day 2** all other baseline measures

- **R+1/3**
  - **MRI** concurrent with Med Ops schedule
  - **Day 3** Chibis LBNP - part 1
  - **Day 4** Chibis LBNP - part 2

- **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 = 0.96, Min 0.86, P<0.001

N=31
VIIP 3: Diagnostic Tools

- Pilot Study: Non-Invasive CVP Device
- Vittamed ICP Device Evaluation
  - ICP Tech Search
  - CCFP Data Mining
  - Cerebtech
    - 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

- HHC: Completed
- NSBRI: Ongoing
- SD: Planned
VIIP 12: Ground-based Analogs & Models

- 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

HHC: Completed
NSBRI: Ongoing
SD: Planned
Thank you!