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
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)</th>
<th>Opening pressure (mmHg)</th>
<th>Time after flight (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal range 10-20 cm H₂O</td>
<td>Normal range 5-15 mm H₂O</td>
<td></td>
</tr>
<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>
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<tr>
<td>A</td>
<td>22</td>
<td>16.2</td>
<td>66</td>
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<tr>
<td>F</td>
<td>21.5</td>
<td>15.9</td>
<td>6</td>
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<tr>
<td>B</td>
<td>21</td>
<td>15.4</td>
<td>19</td>
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<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
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2. CO₂ induced VIIP
A Possible Role for CO₂ in 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:

1. Genetic VIIP predisposition to the spaceflight environment
2. CO\textsubscript{2} induced VIIP
3. Ocular structural changes
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4. Brain structural changes
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Probably a combination or other causes as well!
Research Approach
The VIIP Research Plan

Zero VIIP Incidence

Current Incidence of VIIP Findings = 66.7%

Human Research Program
NSBRI
Medical Operations
LSAH
The VIIP Research Plan

Zero VIIP Incidence

VIIP 1 - Knowledge Acquisition

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The VIIP Research Plan

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- VIIP 1: Knowledge Acquisition
- VIIP 2: Technology Development
- VIIP 12: Analogs
- VIIP 13: Countermeasures
The VIIP Research Plan

Human Research Program
NSBRI
Medical Operations
LSAH

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

- 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

- 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

- VIIP Data Mining
  - Venous/Arterial Compliance

- Ongoing
  - Planned
- Completed
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 (D₂O)
- 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

Day 1
supine, upright sitting, 15° HDT baseline

Day 2
supine, 15° HDT with LBNP

Day 3
Chibis LBNP - part 1

Day 4
Chibis LBNP - part 2

FD45

Day 1
dilution measures

R-45

MRI concurrent with Med Ops schedule

R+1/3

R+10

R+30

R+180

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

N=31
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

- HHC
- NSBRI
- SD

- Completed
- Ongoing
- 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 CO\textsubscript{2} & HDT (1 hr)
- Pilot CO\textsubscript{2} & HDT (1 day)
- Short-Term CO\textsubscript{2} & HDT (1 week)
- Chronic CO\textsubscript{2} & 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
NSBRI
SD

- Completed
- Ongoing
- Planned
Thank you!