Introduction to Spaceflight Associated Neuro-ocular Syndrome (SANS) and its Risk to NASA Astronauts

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06 October 2017
Why We Do What We Do…
Recent SANS Headlines:

- **Too much space travel is hazardous for your eyeballs**
- **Astronauts’ eyes are at risk after too much time in space**
- **The mysterious syndrome impairing astronauts’ sight**
- **Astronauts Returning to Earth With Vision Problems**
- **Space travel is causing visual impairment for some astronauts. Will this prevent travel to Mars?**
Background: The Space Environment

- Bottom-line: Not human friendly. For example…
  - **Vacuum**: No atmosphere; no air
  - **Gravity**
    - Gravity reduces w/ distance. ISS (@ ~200-250 mi) feels 90% of Earth’s gravity…But…
    - ISS moves at ~17,500 mph, in constant freefall = “Microgravity”
  - **Temperature extremes**
  - **Ionizing (high energy) radiation**: Galactic cosmic rays, solar proton events
  - **Orbiting space junk/debris**: >550K larger than 1cm
  - **Spaceflight Associated Neuro-ocular Syndrome (SANS)**
    - Formerly called Visual Impairment Intracranial Pressure (VIIP)
    - A top risk to Deep Space Journey (e.g., mission to Mars)
Background: **ISS**

- **International Space Station (ISS)**
  - In use since 2000
    - 51 expeditions completed
  - \( n = 58 \) (as of 31 Jan 17)
  - Duration: \( \text{~0.5 to 1y} \)
  - International partners
    - United States
    - Russia
    - European Union
    - Canada
    - Japan
  - Crew: Typically 5-6
  - “Low Earth orbit”

* Person flights; may include multiple-time flyers w/in program
Background: *The Future*…

- NASA to send humans to: An **asteroid** by 2025; **Mars** in the 2030s
Ocular testing has been performed pre- & post-flight

Initial eye/vision testing capability on ISS was…
  • Ophthalmoscope (astro-physicians only)
  • Paper VA chart
  • Amsler grid

Sentinel SANS case discovered in 2005, post-flight
  • Optic disc edema & cotton wool spot

Surveillance/medical data collection has evolved
  • Some SANS-related testing began in 2008 (w/ Exp 18), but inconsistent
  • Feb 2010 (Exp 23): Standardized medical monitoring (i.e., “Eye MED B”) established
Ocular Surveillance
Ocular Surveillance

Terrestrially
- 3T MRI – Special “NASA Astronaut” protocol
- Visual Field (Threshold) Perimetry
- Cycloplegic Refraction

Terrestrially & On-Orbit
- **Vision Exam**
  - Distance visual acuity (ISS: Acuity Pro on laptop)
  - Near visual acuity (ISS: Handheld card)
  - Amsler grid (ISS: Laptop)
- Ocular Ultrasound
- Tonometry (when clinically indicated)
- Fundoscopy
- Optical Coherence Tomography (OCT)
Ocular Surveillance

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Clinical Findings
USOS Individuals With Findings:
Expeditions 1-48

40 Individuals have one or more of these findings
USOS Individuals With Findings: Expeditions 1-48

40 Individuals have one or more of these findings

<table>
<thead>
<tr>
<th>Condition</th>
<th>Tested</th>
<th>Affected</th>
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<tbody>
<tr>
<td>Disc Oedema</td>
<td>64</td>
<td>10</td>
</tr>
<tr>
<td>ONSD Distention</td>
<td>47</td>
<td>14</td>
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<tr>
<td>ON Tortuosity/Kinking</td>
<td>47</td>
<td>22</td>
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<tr>
<td>Cotton Wool Spot</td>
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<td>7</td>
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<td>RPE1 Thickening</td>
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<td>37</td>
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<tr>
<td>Retinal Folds</td>
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<td>12</td>
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<tr>
<td>Sotoma</td>
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<td>Choroidal Folds</td>
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<td>Choroidal Thickening*</td>
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<tr>
<td>Globe Flatting</td>
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<td>12</td>
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<tr>
<td>Refractive Error Shift</td>
<td>47</td>
<td>9</td>
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**Clinical Findings: Optic Disc Edema**

**Pre-flight** fundoscopic images of the optic discs

**Post-flight** images of optic discs, showing *Grade 3 edema OD* & *Grade 1 edema OS*
Clinical Findings: Optic Disc Edema

- **Terrestrially**: Optic disc edema is associated with:
  - **Unilateral**: Optic neuritis, optic neuropathy, retinal artery/vein occlusion
  - **Bilateral**: Increase in ICP…
    - IIH (→ “papilledema”)
    - Intracranial mass
    - Obstructive hydrocephalus
    - Cerebral edema
    - Increased CSF production
    - Decreased CSF absorption
    - Venous outflow obstruction
  - Typically reduces VA, enlarges blind spot, causes relative afferent pupillary defect & color impairment

Fundoscopic image of optic disc OD, 10 days after return to Earth
- Arrows: “C” shaped halo of edema
Clinical Findings: Optic Nerve Sheath Distention

Post-flight ultrasound image of globe, optic nerve (ON; purple), and optic nerve sheath (green). Showing:
- ON Sheath distention
- ON tortuosity

- ON Sheath *terrestrially*:
  - Normal diameter (ONSD) < 5.9 mm
  - Enlargement typically associated w/ increased ICP
USOS Individuals With Findings: Expeditions 1-48

40 Individuals have one or more of these findings

- Disc Edema
- Optic Nerve Sheath Distention
- ON Tortuosity/Kinking
- Cotton Wool Spot
- RNFL Thickening
- Retinal Folds
- Sclerotomia
- Retinal Hemorrhage
- Choroidal Folds
- Choroidal Thickening
- Globe Flattening
- Refractive Error Shift

Post Flight OD
### USOS Individuals With Findings: Expeditions 1-48

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Clinical Findings: *Choroidal Folds*

- Choroidal thickening due to vessel engorgement → induces choroidal (and sometimes retinal) folds
- Usually run horizontally (not concentrically around ONH)
- Can resolve post-flight or can persist (for 5+ yrs)
- So far, no clinically-significant impact on BCVA
- *Terrestrially:* Assoc. w/ choroidal tumors, scleritis, retrobulbar mass, papilledema/IIH
Clinical Findings: *Retinal Nerve Fiber Layer Thickening*

Post-flight OCT “circle scans” showing RNFL thickening consistent w/ observed optic disc edema OU
USOS Individuals With Findings:
Expeditions 1-48

40 Individuals have one or more of these findings

- Disc Edema
- ONSD Distention
- Optic Nerve Torsion
- Cotton Wool Spot
- RNFL Thickening
- Retinal Folds
- Scleroma
- Retinal Hemorrhage
- Choroidal Folds
- Choroidal Thickening
- Globe Flattening
- Refractive Error Shift

Tested

Affected
Clinical Findings: *Globe Flattening*

- **Case Example:**
  - Male, mid 40s at time of flight
  - No significant PMH/PSH/PFH
  - No meds
  - Normal BP (118/64)
  - Normal lipids
  - ECG Stress test normal w/ VO$_2$ max of 51ml/kg

- **Terrestrially:** Globe flattening associated w/ papilledema (i.e., disc edema $2^\circ$ to increased intracranial pressure); typically bilateral

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**Pre-flight MRI**
Clinical Findings: *Globe Flattening*

- **Case Example:**
  - Male, mid 40s at time of flight
  - No significant PMH/PSH/PFH
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![MRI Image](image)  
6 days post-flight
Clinical Findings: Globe Flattening

- Case Example:
  - Male, mid 40s at time of flight
  - No significant PMH/PSH/PFH
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  - ECG Stress test normal
    w/ VO₂ max of 51ml/kg

- *Terrestrially:* Globe flattening associated with papilledema (i.e., disc edema due to increased intracranial pressure); typically bilateral

1 year post-flight
Clinical Findings: *Globe Flattening*

- **Case Example:**
  - Male, mid 40s at time of flight
  - No significant PMH/PSH/PFH
  - No meds
  - Normal BP (118/64)
  - Normal lipids
  - ECG Stress test normal
    w/ VO$_2$ max of 51ml/kg

- **Terrestrially:** Globe flattening associated w/ papilledema
  (i.e., disc edema 2$^\circ$ to increased intracranial pressure); **typically bilateral**
Clinical Findings: *Hyperopic Shift*

- Of the active astronaut population…
  - 80% wear vision correction (32% contact lenses)
  - Mean age = 47 yrs
  - Majority are presbyopic (i.e., a normal, age-related, progressively worsening inability to focus clearly on near objects)

- Post-flight questionnaires (1989 - 2011): 29% of short- & 60% of long-duration mission astronauts report a *subjective degradation in vision*, especially at near
  - Provided “Space Anticipation Glasses”
Why is this Happening?
Why is this Happening?

- Terrestrially → Fluid is pulled downward by gravity (i.e., hydrostatic pressure)
- Microgravity → Fluid is free to uniformly distribute (i.e., hydrostatic pressure is eliminated)

Consider how hydrostatic pressure affects fluid/blood distribution in humans…

And what happens in its absence…
Why is this Happening?

Microgravity $\rightarrow$ Cephalad fluid shift $\rightarrow$ Cerebral venous congestion (i.e., overfilling & distension)
Microgravity → Cephalad fluid shift → Cerebral venous congestion (i.e., overfilling & distension)

Why is this Happening?

- **Hypothesis #1**: *Increased intracranial pressure* (ICP)
  - e.g., Enough to cause an imbalance between ICP & intraocular pressure (i.e., translaminar pressure gradient)
- **Hypothesis #2**: *A local eye problem*
  - e.g., Compartmentalization of perioptic subarchnoid spaces
- **Hypothesis #3**: *Individual anatomical/genetic factors*
  - e.g., Altered folate-dependent 1-carbon metabolism
- **Hypothesis #4**: *Venous congestion* alters local physiology and/or places direct pressure on retinal axons
In-flight Exacerbating Factors??

Resistive Exercise

High Oral Sodium Intake
Prepackaged Foods…
Up to 5000+ mg/day

High CO₂
~10x terrestrial levels

In-flight Pharmaceuticals
Common Characteristics of the Cases
Almost all were “long duration” (i.e., >30 day) \textit{ISS mission crewmembers}

- One short-duration case w/ subtle disc edema (discovered retrospectively)
- \textit{Severity related to flight duration??} [So…what about a 3-yr Mars mission??]

\textbf{Normal} past medical history:

- \textit{Negative} for uncontrolled systemic disease
- None used medications before/during mission that would increase ICP (e.g., vitamin A, tetracycline, corticosteroids, or nalidixic acid)

\textbf{ISS cabin}

- Normal pressure & oxygen
- Elevated CO$_2$
  - \~0.33-0.5\% avg, w/ avg peak \~0.7\%; \textit{10x} terrestrially: \~0.03-0.04\%
Common Characteristics of the Cases

- All had normal pre-flight eye exams
- None experienced loss in BCVA, color vision, or stereopsis
- None complained of severe headaches, transient vision obscurations, double vision, pulsatile tinnitus, or vision changes during eye movements (i.e., classic symptoms of idiopathic intracranial hypertension)

- OD affected more than OS in all cases. If monocular, always OD

- For 14 crewmembers having complete pre-flight & on-orbit OCT data, regardless of SANS diagnosis, ALL show signs of:
  - Choroidal engorgement, Optic disc edema (subclinical or clinical), extending into the retinal nerve fiber layer; Retinal venous engorgement
Clinical & Research Update
Ongoing SANS Efforts: Clinical/Research

**Clinical**

- **“Form & Function”**: Are there any RNFL thickness losses (*via OCT*)? If so, are there correlations with any reduction in visual sensitivity (*via visual field*)?
  - **KEY Concern/Risk**: Potential impact of disc/retinal edema during longer duration missions (>>12 months)

- Deploy *next-generation OCT*:
  - Faster (~60%); better signal-to-noise; MultiColor imaging

- Consider deploying an ISS *visual field device*

- Consider possibility of *venous congestion* as a SANS contributing factor

**Research**

- Ocular Health Study & Fluid Shifts Study
- Clinical relevance of MRI-based findings
- Implementation of direct ICP measures (Lumbar puncture pre- & post-mission)
- Correlation between SANS & CO$_2$ using HDT (EnviHab)
Source: Mayra Nelma & Simon Clemett, PhD
ONH Surface Topography

* Indicates Case

Source: Mayra Nelman & Simon Clemett, PhD
Lamina Cribrosa Movement

Source: Mayra Nelman & Simon Clemett, PhD

* Indicates Case

Subject 5

Subject 8
Questions?

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Acknowledgements

- William J. Tarver, MD, MPH
- C. Robert Gibson, OD
- Julia Wells, RN, BSN
- Clarence Sams, PhD
- Mary Van Baalen, PhD
- Sara Mason
- Russell Derrick
- Simon Clemett, PhD
- Mayra Nelman
- Michael Stenger, PhD
- Steven Laurie, PhD
- Brandon R. Macias

1. NASA Johnson Space Center
   Houston, TX
2. Coastal Eye Associates
   Webster, TX
3. KBRWyle
   Houston, TX
4. Jacobs Technology, Inc.
   Houston, TX