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

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Why We Do What We Do…
Recent SANS Headlines:

- Possible Mars Mission ‘Showstopper’: Vision Risks for Astronauts
- Spaceflight Bad for Astronauts’ Vision, Study Suggests
- The mysterious syndrome impairing astronauts’ sight
- Astronauts Returning to Earth With Vision Problems
- Astronauts’ eyes are at risk after too much time in space
- Too much space travel is hazardous for your eyeballs
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 31Jan17)*
  - Duration: ~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
Background: SANS

- 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)
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- Fundoscopy
- **Optical Coherence Tomography (OCT)**
Clinical Findings
USOS Individuals With Findings: Expeditions 1-48

40 Individuals have one or more of these findings

- Disc Edema: Tested 64, Affected 10
- OCT SD Detachment: Tested 47, Affected 14
- Cotton Wool Spot: Tested 47, Affected 22
- RNFL Thickening: Tested 37, Affected 12
- Retinal Folds: Tested 47, Affected 2
- Scleroma: Tested 64, Affected 1
- Retinal Hemorrhage: Tested 64, Affected 3
- Choroidal Folds: Tested 47, Affected 11
- Choroidal Thickening: Tested 47, Affected 20
- Globe Flattening: Tested 47, Affected 11
- Refractive Error Shift: Tested 47, Affected 12
### USOS Individuals With Findings: Expeditions 1-48

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<table>
<thead>
<tr>
<th>Condition</th>
<th>Tested</th>
<th>Affected</th>
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<tbody>
<tr>
<td>Disc Edema</td>
<td>64</td>
<td>10</td>
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<tr>
<td>ONSD Distention*</td>
<td>47</td>
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<tr>
<td>ON Tortuosity/ Kelting*</td>
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<tr>
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<td>RNFL Thickening*</td>
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<td>Retinal Folds*</td>
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<td>Sclera</td>
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</tr>
<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
USOS Individuals With Findings: Expeditions 1-48

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- Disc Edema: 64 Tested, 10 Affected
- ON Dystrophy/Keeling: 47 Tested, 14 Affected
- Cotton Wool Spot: 64 Tested, 22 Affected
- RML Thickening*: 37 Tested, 7 Affected
- Retinal Folds*: 64 Tested, 12 Affected
- Scleroma: 64 Tested, 2 Affected
- Retinal Hemorrhage: 64 Tested, 1 Affected
- Choroidal Folds: 47 Tested, 11 Affected
- Choroidal Thickening*: 47 Tested, 20 Affected
- Global Flattening: 47 Tested, 11 Affected
- Refractive Error Shift: 47 Tested, 12 Affected
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

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Post Flight OD

- Disc Edema
- ONSD Distention
- ON Tortuosity/Kinking
- Cotton Wool Spot
- RMDL Thickening
- Retinal Folds
- Scleroma
- Retinal Hemorrhage
- Choroidal Folds
- Choroidal Thickening
- Globe Flattening
- Refractive Error Shift

 Tested

 Affected
USOS Individuals With Findings: Expeditions 1-48

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Pre-flight OD:
- Fovea
- Retina
- Choroid

Post-flight OD:
- Fovea
- Retina
- Choroid
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
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- Disc Edema
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- RNFL Thickening**
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- 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/ VO₂ max of 51ml/kg

- *Terrestrially:* Globe flattening associated w/ papilledema
  (i.e., disc edema 2° to increased intracranial pressure); *typically bilateral*
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1 year post-flight

![MRI Image](image_url)
Clinical Findings: *Globe Flattening*

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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 → Cephalad fluid shift → Cerebral venous congestion (i.e., overfilling & distension)
Why is this Happening?

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

- **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
Common Characteristics of the Cases

- Almost all were “long duration” (i.e., >30 day) ISS mission crewmembers
  - One short-duration case w/ subtle disc edema (discovered retrospectively)
  - Severity related to flight duration?? [So...what about a 3-yr Mars mission??]

- **Normal** past medical history:
  - **Negative** for uncontrolled systemic disease
  - None used medications before/during mission that would increase ICP (e.g., vitamin A, tetracycline, corticosteroids, or nalidixic acid)

- ISS cabin
  - Normal pressure & oxygen
  - Elevated CO₂
    - ~0.33-0.5% avg, w/ avg peak ~0.7%; 10x terrestrially: ~0.03-0.04%
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 w/ 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 btwn SANS & CO\(_2\) using HDT (EnviHab)
Source: Mayra Nelma & Simon Clemett, PhD
Lamina Cribrosa Movement

Source: Mayra Nelman & Simon Clemett, PhD

* Indicates Case

* Subject 5

Subject 8
Questions?

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