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
- 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)
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

**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
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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

40 Individuals have one or more of these findings

- Disc Edema
- ON Distortion
- Cotton Wool Spot
- RNFL Thickening
- Retinal Folds
- Scleroma
- Retinal Hemorrhage
- Choroidal Folds
- Choroidal Thickening
- Globe Flatness
- Refractive Error Shift
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
- ONSD Distention
- ON Tortuosity/Keeling
- Cotton Wool Spot
- RNFL Thickening
- Retinal Folds
- Scleroma
- Retinal Hemorrhage
- Choroidal Folds
- Choroidal Thickening
- Globe Flattening
- Refractive Error Shift
USOS Individuals With Findings: Expeditions 1-48

40 Individuals have one or more of these findings

- Fovea
- Retina
- Choroid

Pre-flight OD

Post-flight OD

- ONSD Distention*
- ON Torsion/Kinking*
- Cotton wool spot
- RNFL Thickening*,**
- Retinal folds*
- Scleroma
- Retinal hemorrhage
- Choroidal folds
- Choroidal Thickening*
- Globe flattening
- Refractive error shift
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 with observed optic disc edema OU
USOS Individuals With Findings:
Expeditions 1-48

40 Individuals have one or more of these findings
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

MRI

Pre-flight
Clinical Findings: *Globe Flattening*

- **Case Example:**
  - Male, mid 40s at time of flight
  - No significant PMH/PSH/PFH
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- **Terrestrially:** Globe flattening associated w/ papilledema (i.e., disc edema ² to increased intracranial pressure); typically bilateral

  6 days 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/ VO₂ max of 51ml/kg

- *Terrestrially:* Globe flattening associated w/ papilledema (i.e., disc edema 2° 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
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 $\rightarrow$ Fluid is pulled downward by gravity (i.e., hydrostatic pressure)
- Microgravity $\rightarrow$ 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)
Why is this Happening?

Microgravity $\rightarrow$ Cephalad fluid shift $\rightarrow$ 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 CO$_2$
  - ~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%
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*
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 & CO₂ using HDT (EnviHab)
ONH Surface Topography

* Subject 1

Subject 2

* Subject 3

* Subject 4

* Subject 5

* Subject 6

* Subject 7

Subject 8

Subject 9

Subject 10

Subject 11

Subject 12

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

* Indicates Case

Source: Mayra Nelman & Simon Clemett, PhD

Subject 5

Subject 8
Questions?

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