RE-EVALUATION OF IIH AS THE IDEAL TERRESTRIAL ANALOG FOR SANS: IS THERE A BETTER MODEL TO CONSIDER?

Shehzad Batliwala, DO[1]; Tyson J. Brunstetter, OD, PhD[2]; Bill J. Tarver, MD[2,]; Simon J. Clemett[2]; Mayra A. Nelman[2]; Sara S. Mason[3]; Clarence Sams, PhD[2]

[1]Dean McGee Eye Institute, Oklahoma City, OK; [2]Nasa Johnson Space Center, Houston, TX; [3]KBRWyle, Houston, TX

Introduction

While astronauts are returning from long duration spaceflight with multiple ocular signs that mimic those seen in terrestrial patients with elevated intracranial pressure (ICP), evidence has yet to prove a clinically significant increase in ICP during space.[1] Preliminary research evidence may even suggest that ICP decreases in microgravity. Idiopathic intracranial hypertension (IIH) has long been considered the ideal terrestrial analogue to Spaceflight Associated Neuro-ocular Syndrome (SANS).[1] However, there are several critical features of SANS that do not complement any reported case of IIH on Earth. These findings mandate a closer look at the accuracy of IIH as a terrestrial SANS analog.

Diagnosis of SANS[1]

SANS can be associated with several ocular findings with varying degrees of severity. These include cotton-wool spots, retinal hemorrhages, choroidal and retinal folds, optic disc and retinal edema, optic nerve sheath distention, posterior globe flattening, and hyperopic shifts. Since optic disc edema is the SANS sign most threatening to crewmember health and mission effectiveness, it is the basis for diagnosing SANS. *Currently, the SANS case definition is: optic disc edema of Frisen Grade ≥1, based on fundoscopic imagery*.

Methods

A retrospective literature review was conducted to discover any reported ocular IIH findings that bear resemblance to the unique findings observed in SANS. Data were analyzed to compare and contrast SANS with IIH cases. Some parameters addressed included globe flattening, choroidal and retinal folds, choroidal vascular engorgement, and disc edema findings.

Is ICP the culprit?

Condition	IIH	SANS
Female/Male Sex Ratio	9/1	0/10
BMI	Obese (>90%)	Athletic to Normal
Symptoms (HA, TVL, etc.)	HA (94%), TVO (68%), VL (30%)	HA (0%), TVO (0%), VL (0%)
Asymmetric Papilledema	< 4% side predominance	Right always worse than left
Anatomic Changes (GF, CF, ONSD)	Yes	Yes, but different
LPOP	>25 cm H_2O (normal to ~50cm)	16cm – 28.5cm H_2O

Table 1: A comparison of demographics, symptoms, and objective ocular and diagnostic findings in IIH and SANS. Bidot et al: J Neuro-Ophthalmol 2015; 35: 31-36

HA: headache; TVO: transient visual obscuration; VL: visual loss; GF: globe flattening; CF: choroidal folds; ONSD: optic nerve sheath diameter; LPOP: lumbar puncture opening pressure

Results

Comparison of Globe Flattening in SANS vs IIH

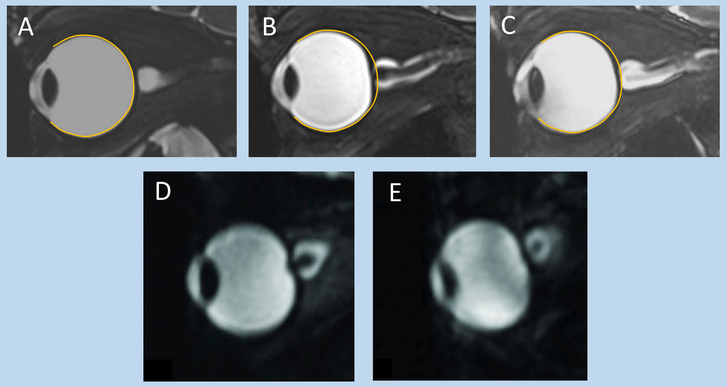

Figure 1: A SANS case[1] with globe flattening is illustrated: A) Pre-flight MRI; B) 6 days post-flight; and C) 1 year post-flight. While two IIH cases[2] are illustrated in: D) minimal globe flattening and extensive optic nerve protrusion; and E) flat globe with minimal nerve protrusion.

	SANS	IIH
Choroidal Folds	11 (23%)	14 (6%)
Retinal Folds	2 (4%)	87* (39%)
Subjects Tested	47	225

Table 2: Relative prevalence of choroidal and retinal folds in SANS vs IIH populations. SANS data obtained from 47 USOS astronauts tested during Exp 1-48.[1] IIH data obtained from 125 eyes studied in the IIH Treatment Trial. [3] * In the latter, the majority (79%) of eyes with RF did not have choroid involvement. [3]

Retinal Pigment Epithelium / Basement Membrane Angles

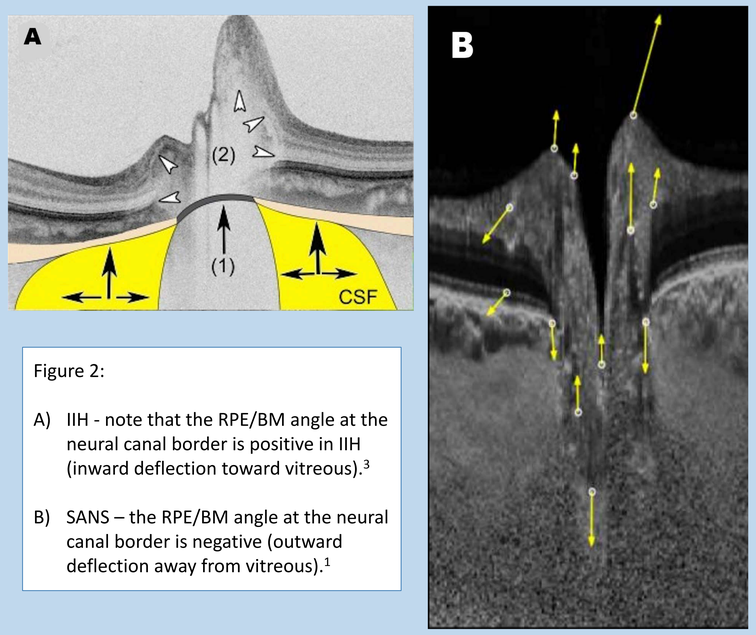

Figure 2:

A) IIH - note that the RPE/BM angle at the neural canal border is positive in IIH (inward deflection toward vitreous).[3]

B) SANS – the RPE/BM angle at the neural canal border is negative (outward deflection away from vitreous).[1]

Table 1 illustrates that astronauts with SANS do not have the typical risk factors for IIH, nor do they report the classic symptoms of IIH.[1] Figure 1 illustrates that while there are variations in the degree of nerve protrusion and globe flattening seen in IIH, these changes are usually much more pronounced in SANS cases.[3-5] Table 2 shows that the prevalence of choroidal folds is much higher in SANS, while the prevalence of retinal folds is higher in the IIH population.[3] The IIH Treatment Trial also reported that 79% of enrolled eyes did not have any choroid involvement.[3] Figure 2 illustrates one of the more notable differences between SANS and IIH in that the RPE/BM angle is oftentimes deflected inwards towards the vitreous in IIH and outwards away from the vitreous in SANS.[4,6,7] For two diseases in which disc edema is thought to occur from an increased ICP, this finding is particularly contradictory.

Discussion

	SANS	IIH	POAG	Ocular HTN	Hypotony Maculopathy
ONH	Edema	Edema	Cupping	Normal	Edema
ICP	???	↑	Dec	↑	Normal
IOP	Normal, after initial increase	Normal	↑	↑	Dec
GF	Flat	Some	No	No	Flat
CF	Yes	Some	No	No	Yes
Ref. Shift	Hyperopic	Rare	No	No	Hyperopic
Time course	Long	Various	Long	Long	Short

Table 3: Overlap Between SANS and Other Terrestrial Analogues[4]

Although similarities in ocular signs exist between SANS and IIH, there are noticeable differences between the two syndromes that behoove the need to look beyond a pathologically elevated intracranial pressure. Table 3 lists several characteristics of ocular conditions that overlap with SANS, all of which are consolidated into what is known as the unified pressure theory (UPT).[4] The dynamic changes occurring at the optic nerve head (ONH) due to the translaminar pressure difference (TLPD) is at the crux of this theory. For example, the changes occurring at the ONH in POAG may be opposite of SANS. Ocular HTN is a model that speculates a higher CSF pressure may be protective and counters the impact of an elevated IOP to avoid optic disc cupping.[4] Hypotony maculopathy is a condition with very low IOP that leads to many of the signs seen in SANS such as GF, CF, and hyperopic shift. Treatment is done via raising IOP, which reverses disc edema, GF, CF, and the hyperopic refractive error.[4] A very similar treatment could potentially be the strategy for a SANS countermeasure. A potential limitation of the TLPD model is that its supportive literature uses retrospective data where postural differences between ICP and IOP measurements were not taken into account.[10] Data from the Fluid Shifts Study where hydrostatic forces are eliminated when obtaining these measurements will give a more accurate representation of the TLPD in 0g. A vascular model is equally important in characterizing SANS. Choroid expansion in particular may suggest a vascular origin of the choroid folds, since the spongy, malleable choroid tissue lacks autoregulation and thus is more susceptible to mechanical folding due to 0g-induced obstruction of venous outflow, which could lead to venous congestion in the eye.[1,6] Choroid expansion is not a documented finding in IIH, although there is a paucity of information in the literature regarding measurement of this parameter in IIH patients.[1,9] Furthermore, in some cases of IIH, choroidal folds precede the development of optic disc edema and in others they have been the only presenting sign of raised ICP.[1] On the contrary, 60% of astronauts that have disc edema also have choroidal folds, and there are no cases that have choroidal folds without the presence of disc edema.[1,4,5] If choroid expansion can help explain the presence of choroidal folds in SANS, and if disc edema and choroidal folds are relatively tightly correlated, then a vascular etiology may play a role in the development of disc edema. Furthermore, recent studies have found that impairment in functional cerebrovascular hemodynamics and a resulting ocular hypoperfusion may be the underlying cause of demyelinating diseases like optic neuritis.[8] Specifically, the study reported that choroidal hypoperfusion is positively correlated with the severity of swelling of rNFL. If 0g-induced choroidal engorgement leads to any level of venous stasis and congestion, this can contribute to choroidal and papillary vascular hypoperfusion and produce disc swelling similar to what is seen in acute optic neuritis. OCT angiography on orbit might be useful as a future modality to further define these vascular changes. The UPT along with a focus on ocular hemodynamics and perfusion can help researchers gain a broader insight into the complex interplay of multiple variables that comprises SANS.

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Abbreviations Defined

ONH: optic nerve head
CF: choroidal folds
RF: retinal folds
TLPD: translaminar pressure difference
GF: globe flattening
RS: refractive shift
UPT: unified pressure theory
RPE/BM: retinal pigment epithelium / bruch's membrane
POAG: primary open angle glaucoma