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REVIEW ARTICLE

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Spaceflight associated neuro-ocular syndrome (SANS): an update on potential microgravity-based pathophysiology and mitigation development

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Long-duration spaceflight is associated with neurologic and ophthalmic clinical and imaging findings in astronauts termed spaceflight associated neuro-ocular syndrome (SANS). These microgravity-induced findings have been well documented by the National Aeronautics and Space Administration (NASA) and are clearly a potential risk for future human space exploration. The underlying pathogenesis of SANS is not well understood, although multiple hypotheses have emerged. Terrestrial analogues and potential countermeasures have also been studied to further understand and potentially mitigate SANS. In this manuscript, we review the current understanding of SANS, discuss the prevailing hypotheses for pathogenesis, and describe current developments in terrestrial analogues and potential countermeasures for SANS.

Eye (2023) 37:2409–2415; https://doi.org/10.1038/s41433-023-02522-y

INTRODUCTION

Prolonged exposure to microgravity during long-duration spaceflight (LDSF) produces variable physiologic and pathologic cardiovascular, haematologic, skeletomuscular, and neuro-ocular changes in the human body [1–3]. The neuro-ocular clinical and imaging findings have been termed spaceflight associated neuro-ocular syndrome (SANS). These findings observed in astronauts during and after LDSF include unilateral or bilateral optic disc oedema, chorioretinal folds, retinal nerve fibre layer (RNFL) thickening, hyperopic refractive shifts, and posterior globe flattening [2, 4, 5]. The findings of SANS are being monitored longitudinally by the National Aeronautics and Space Administration (NASA) [2, 4]. The underlying pathogenesis behind SANS remains ill-defined and the aetiology is likely multi-factorial. However, several hypotheses have been proposed to explain the pathophysiology of SANS. In this paper, we will review these SANS hypotheses, discuss terrestrial analogues for further understanding SANS on Earth, and elaborate upon technology developments to mitigate or assess SANS for future spaceflight.

SANS FINDINGS AND HYPOTHESES

The initial description of SANS findings was reported by Mader et al. in a cohort of 7 astronauts following LDSF on the International Space Station (ISS) [6]. Ophthalmic pre- and post-flight testing included eye examinations, fundus photography, optical coherence tomography (OCT), post-flight orbital magnetic resonance imaging (MRI), and lumbar punctures [7]. Following LDSF, 5 of these astronauts had optic disc oedema, 5 had choroidal folds, 3 had cotton wool spots, 6 had RNFL thickening, and 6 had diminished near vision [6]. MRI findings also demonstrated optic nerve sheath distension and tortuous optic nerves [6]. Subsequent reports found that SANS optic disc oedema may persist for months after returning to Earth [8]. Hyperopic refractive errors, posterior globe flattening, and choroidal folds have been observed to persist for years post-LDSF [4, 9]. An astronaut who had unilateral choroidal folds and a single cotton wool spot after LDSF developed new SANS findings in repeat LDSF several years later with the new onset of optic disc oedema and more widespread choroidal folds in the same eye [10]. In this section, we discuss various hypotheses that have been offered that may help to explain SANS pathogenesis including elevated intracranial pressure, compartmentalization of the orbital nerve sheath, the ocular glymphatic system, choroidal expansion, upward brain shift, cerebral blood volume pulsatility, and nutritional/metabolic/genetic factors (Table 1).

ELEVATED INTRACRANIAL PRESSURE AND ORBITAL OPTIC NERVE SHEATH COMPARTMENTATION

The initial hypothesis to explain SANS was based on the notion that cephalad fluid shifts in microgravity may lead to increased intracranial pressure (ICP) [6]. Thus, the initial term for the syndrome was "Visual Impairment and Intracranial Pressure (VIIP)"

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Received: 20 September 2022 Revised: 21 March 2023 Accepted: 4 April 2023
Published online: 18 April 2023

Table 1. Proposed contributory aetiologies in spaceflight associated neuro-ocular syndrome (SANS).

Hypothesis	Summary
Elevated intracranial pressure and/or compartmentation of the orbital optic nerve sheath	Possible elevated intracranial pressure leading to optic disc oedema is seen similarly in idiopathic intracranial hypertension (IIH). Cephalad fluid shifts during long-duration spaceflight may impact the tightly confined cul-de-sac-like anatomic connection between the intracranial and optic nerve subarachnoid space, potentially leading to unequal changes in optic nerve sheath cerebral spinal fluid outflow with an asymmetric increase in CSF pressure surrounding the orbital optic nerve.
Ocular glymphatic system	Microgravity-induced flow imbalance of the ocular glymphatic system may lead to prelaminar optic disc oedema. Perioptic cerebrospinal fluid may be forced into the optic nerve and optic disc along the perivascular spaces of the central retinal vasculature.
Choroidal expansion	An abrupt increase in choroidal volume from microgravity-induced cephalad shifts which may affect the development of optic disc oedema.
Mechanical brain shift	The upward brain shift observed in astronauts following long-duration spaceflight may pull of the optic nerve which may cause the dura of the optic nerve sheath to produce an anterior counterforce forward to produce posterior globe flattening.
Cerebral blood volume pulsatility	An increase in cerebral blood volume pulsatility may generate remodelling in posterior ocular structures over prolonged periods of microgravity in long-duration spaceflight.
Venous stasis and cytotoxic oedema	Venous stasis from cephalad fluid shifts in microgravity may lead to a reduction of nutrient delivery and metabolite activity, as well as an increase in free radicals. Downstream consequences, including reduced Na^+/K^+ ATPase activity and upregulation of matrix metalloprotease-9 (MMP-9), may contribute towards optic disc oedema.
Nutritional, metabolic, and genetic factors	Various nutritional, metabolic, and genetic factors may play a role in SANS development, including elevations in serum homocysteine, cystathionine, methylmalonic acid, and 2-methylcitric acid. Astronauts with an elevated number of G alleles in methionine synthase reductase (MTRR) 66 and C alleles of serine hydroxymethyltransferase 1 (SHMT1) 1420 also had increased odds of visual disturbances. More ophthalmic changes were also observed in astronauts with lower concentrations of B-vitamins B6 and folate.

[4]. Optic disc oedema and optic nerve sheath expansion are also seen terrestrially with increased ICP in idiopathic intracranial hypertension (IIH) [11]. However, several clinical findings have been noted in astronauts which suggest that the aetiology of SANS may be more complex than simply increased intracranial pressure. In addition to optic disc oedema, individuals with IIH often experience symptoms of increased ICP (e.g., significant headaches, pulse synchronous tinnitus, and diplopia) [11]. However, astronauts with SANS did not experience the same degree of headaches, tinnitus, or diplopia of terrestrial IIH [4]. Post-flight lumbar puncture (LP) data in SANS is limited but astronauts with opening pressure data had only mildly elevated ICP measurements of 28 and 28.5 cm H_2O at 12 and 57 days post-flight, respectively. Additional LP data in other SANS astronauts had levels of 21 and 22 cm H_2O at 19 and 60 days post-flight, respectively [6]. Additionally, three out of the five astronauts that demonstrated optic disc oedema in the first report of SANS presented with either asymmetric or unilateral optic disc oedema, whereas optic disc oedema in IIH is typically symmetrical and bilateral [4]. One report described asymmetric optic disc oedema for 6 months following a LDSF mission with lumbar puncture opening pressures of 22 cm H_2O and 16 cm H_2O performed 7 days and 12 months post-LDSF, respectively [8]. It has been proposed that this asymmetry could be caused by a microgravity-induced asymmetric increase in CSF pressure within the perioptic subarachnoid space. The septated and confined cul-de-sac-like anatomic connection between the intracranial and optic nerve (ON) subarachnoid space (SAS) may create a fragile flow equilibrium that may be impacted by the cephalad fluid shifts during LDSF [8]. Asymmetric optic nerve sheath (ONS) anatomy, that may be clinically insignificant terrestrially, may cause unequal changes in ONS CSF outflow, an asymmetric sequestration of CSF and an asymmetric increase in CSF pressure surrounding the orbital ON with or without elevated ICP [8].

The asymmetry of optic disc oedema in SANS is a large consideration in the discrepancy between SANS and IIH. Lee et al. provides an in-depth analysis of the various clinical differences between IIH and SANS, including the increased prominence of retinal cotton wool spots in SANS compared to IIH, and the difference in risk factors and exposure amongst these two pathologies [5]. It is also possible, as proposed by Lawley et al., that complete removal of gravity might not pathologically elevate ICP by Earth standards but may prevent the normal terrestrial lowering of ICP when the subject is upright [12]. The discrepancies between IIH and VIIP led NASA in 2017 to change the name of the syndrome to “SANS”.

The relationship of ICP to intraocular pressure (IOP) has also been an interest for the development of SANS [4, 13]. With a suspected elevated optic nerve sheath pressure (from elevated ICP) compared to IOP during prolonged microgravity, SANS has been hypothesized to have a negative translaminar pressure gradient (TLPG) mathematically represented as [(Intraocular Pressure – Intracranial Pressure)/(Lamina Cribrosa Thickness)] [4, 14]. Berdahl et al. hypothesized that in microgravity, CSF does not pool in the caudal spinal column but rather diffuses throughout the subarachnoid space, leading to a CSF pressure greater than IOP [13]. The authors also hypothesize that raising orbital pressure/IOP, equilibrating the change in the TLPG during spaceflight, may protect astronauts from SANS [13]. Counter-measure research surrounding the modulation of the TLPG has been conducted which is further discussed in the countermeasure section.

OCULAR GLYMPHATIC SYSTEM

The glymphatic system is a recently discovered waste clearance system consisting of perivascular channels in the central nervous system [15]. Tracer-based research studies have demonstrated the

presence of the glymphatic system within optic nerve structures [16]. This glymphatic system may impact optic disc oedema in astronauts through two mechanisms. First, Wostyn et al. hypothesizes that increased ICP during microgravity exposure may reduce or reverse the normal trans-lamina cribrosa pressure difference (TLCPD). This pressure difference is thought to be a primary driving force for ocular glymphatic outflow [17]. This pressure reversal may produce a one-way valve-like process between the glymphatics in the optic nerve and the retina, leading to a partial, or potentially total blockage of the posterior fluid outflow from the ocular system. This obstruction may cause glymphatic stasis at the optic nerve head, particularly the prelaminar region, which may contribute to the optic disc oedema documented in SANS [17]. Second, Wostyn et al. also proposes that optic disc oedema in SANS may be partly contributed from perioptic CSF being forced into the optic disc and nerve along glymphatic perivascular spaces of the central retinal vasculature. The magnitude of this process is likely related to variations in optic nerve sheath compliance and the degree of microgravity-induced fluid shifts [18, 19].

CHOROIDAL EXPANSION

It has been proposed that microgravity-induced cephalad fluid shifts may cause venous congestion in the neck and head leading to a sudden increase in vortex vein pressure. Since the choroid drains into the vortex vein system and lacks autoregulation, an acute increase in choroidal volume and a concomitant sudden spike in IOP may occur. Early head-down tilt, parabolic flight, and Space Shuttle studies all documented sudden increases in IOP [20–22]. A 2020 study by Macias et al. documented peripapillary choroidal expansion in conjunction with optic disc oedema during LDSF that persisted for 30 days post-mission [23]. Feola et al. developed and studied geometric ONH models and suggested that peripapillary choroidal expansion may affect the development of optic disc oedema [24]. Wostyn et al. proposed that in addition to the acute pooling of choroidal blood during LDSF, there may be a concomitant circumferential chronic accumulation of choroidal interstitial fluid in the peripapillary region that may also impact the formation of optic disc oedemain astronauts with SANS [25]. As interstitial fluid may take weeks to dissipate through the glymphatic system this may explain the slow recovery of both choroidal expansion and optic disc oedema following space missions.

MECHANICAL BRAIN SHIFT

Another hypothesis focuses on the mechanical shifts of the brain observed post-LDSF [26]. Post-mission MRIs in LDSF astronauts have shown an upward shift of the brain and optic chiasm [27]. Shinojima et al. proposed that this brain upward shift may set the stage for the posterior globe flattening and optic nerve sheath distension in SANS [28]. The authors proposed that this mechanical shift may lead to rearward pull of the optic nerve which causes the dura of the optic nerve sheath, connected to the periosteum of the orbital bone, to produce a counterforce forward onto the posterior globe. The pull of the optic nerve may lead to expansion of the optic nerve sheath [28].

CEREBRAL BLOOD VOLUME PULSATILITY

Strangman et al. hypothesized that SANS may be due to cerebral blood volume pulsatility that leads to a chronic water hammer effect on ocular structures [29]. The authors conducted the Studying the Physiological and Anatomical Cerebral Effects of CO_2 and Tilt (SPACECOT) study which analyzed cerebral blood volume pulsatility during head-down tilt, an analogue for SANS, with near-infra-red spectroscopy. The authors reported an increased cerebral blood volume pulsatility from this terrestrial analogue and hypothesized that chronic arterial pulsatility may generate remodelling in posterior ocular structures over prolonged periods of time [29].

VENOUS STASIS AND CYTOTOXIC OEDEMA

Galdamez et al. applied the pathophysiology of terrestrial cerebral oedema to explain the potential physiological process of optic disc oedema in SANS [30]. During microgravity, cerebral venous stasis secondary to cephalad fluid shifts may lead to interruptions in nutrient delivery and metabolic activity [31]. Adenosine triphosphate (ATP) generation may be impaired as a result, which may lead to a reduction in Na^+/K^+ ATPase activity. With an inability to maintain the physiologic low levels of intracellular Na^+, oedema may occur. Areas that require higher ATP demand, such as the optic nerve head that contains unmyelinated nerve fibres, may be affected more severely from this stasis, thus leading to optic disc oedema in SANS [30]. Inflammatory and oxidative pathways may also impact venous stasis and oedema formation. During these processes, neutrophils and activated microglial may release inflammatory products including free radicals [30, 32]. Free radicals can also inhibit Na^+/K^+ ATPase activity, as well as increase expression for matrix metalloprotease-9 (MMP-9), a proteolytic enzyme noted to degrade basement membrane and tight junctions [30, 33]. The combined oxidative and inflammatory mediators that arise from venous stasis may also play a role in other hypotheses, including the ocular glymphatic system and choroidal expansion, for a multi-factorial impact in the development of SANS.

NUTRITIONAL, METABOLIC, AND GENETIC FACTORS

Nutritional, metabolic, and genetic factors have also been studied as contributory factors in SANS [34–36]. Zwart et al. reported that astronauts who had SANS findings post-flight had elevations in serum homocysteine, cystathionine, methylmalonic acid, and 2-methylcitric acid compared to astronauts without ophthalmic changes post-mission [37]. The concentration differences in these 1-carbon metabolism markers observed in astronauts with and without SANS suggest that polymorphisms in enzymes involved in the 1-carbon metabolism pathway may play a role in the development of SANS [35, 37]. Further studies based on these biochemical findings have been conducted to understand the metabolic and genetic components that may lead to SANS [35, 36]. Zwart et al. reported that an elevated number of G alleles in methionine synthase reductase (MTRR) 66 and C alleles of serine hydroxymethyltransferase 1 (SHMT1) 1420 increased the odds of visual disturbances in astronauts [35]. The authors also reported that astronauts with lower concentrations of B-vitamins B6 and folate had more ophthalmic changes post-flight. The authors also noted a key finding that no subjects with SHMT 1420 TT genotype had any evidence of optic disc oedema post-mission, indicative of a possible protective effect [35]. These findings are consistent with the underlying theory that there may be a genetic component to the development of SANS.

Major strides have been made since the initial report to further the understanding of SANS. It is likely that the underlying pathophysiology of SANS arises from multiple factors. In-flight analysis and monitoring of an astronaut's neuro-ophthalmic system will continue to provide additional information. Current in-flight ophthalmic imaging onboard the ISS includes fundus photography, orbital ultrasound, and OCT. In 2018, additional OCT analytic techniques, including Multicolor Imaging (Fig. 1.) and OCT angiography (OCTA) became available onboard the ISS which are anticipated to provide further insight into SANS such as changes of the choroidal and retinal vasculature during microgravity [4, 38].

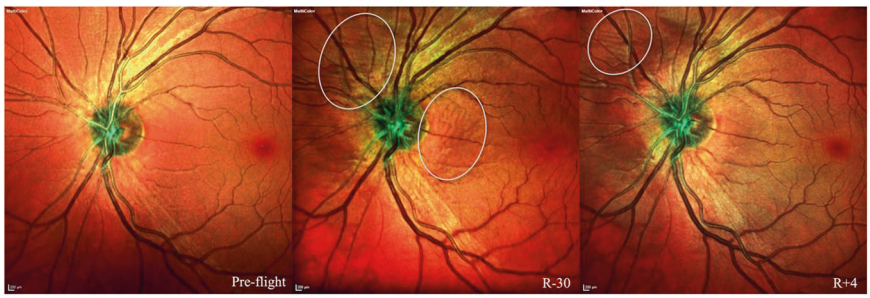

Fig. 1 Pre-flight, in-flight (R-30, 30 days before returning to Earth), and post-flight (R+4, 4 days before returning to Earth) Multicolor Imaging in an astronaut that developed spaceflight associated neuro-ocular syndrome (SANS) during a spaceflight mission. R-30 and R + 4 showcase choroidal folds (circled) as well as potential optic nerve head protrusion from SANS. Courtesy of NASA. Reprinted with permission from Ong et al. [38] under Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license (https://creativecommons.org/licenses/by-nc/4.0/).

TERRESTRIAL ANALOGUES FOR SANS

Understanding SANS using the affected cohort of astronauts after LDSF has been a major limiting factor for research as very few individuals travel to the ISS per year. As with studying the effects of microgravity on other physiologic systems, terrestrial analogues serve as an alternative to studying SANS during spaceflight. Analogues that have been critical for studying spaceflight physiology across various disciplines (e.g., neuro-ophthalmic, cardiovascular, musculoskeletal) on Earth include dry/wet immersion, parabolic flight, head-down tilt bed rest, and unilateral lower limb suspension [39, 40]. In the setting of understanding ICP's role in SANS development, parabolic flight has been an instrumental analogue to further understand ICP changes during microgravity. A study with individuals with Ommaya reservoirs allowing for direct ICP measurements observed that acute removal of gravity in parabolic flight decreases the typical reduction of ICP to levels observed when seated 90° on Earth. The study authors suggested that over a longer course of microgravity, these attenuations in the reduction of ICP may lead to remodelling of the eye [12].

Head-down tilt bed rest (HDTBR) has emerged as a promising terrestrial analogue for SANS [36, 41, 42]. This research platform places supine subjects at a 6° head-down angle and mimics cephalad fluid shifts in microgravity [41]. HDTBR studies have observed optic nerve sheath distension, retinal nerve layer thickening, and choroidal engorgement [41]. Strict HDTBR refers to a setting where subjects refrain from lifting their head/torso or using a standard pillow throughout the study. Strict 6° HDTBR for 30 days was observed to produce optic disc oedema of varying Frisén grades [42]. This study was performed in a mildly hypercapnic environment to mimic CO_2 levels on the ISS. Further HDTBR studies investigated the role of hypercapnia in SANS development. In a subsequent study, optic disc oedema and chorioretinal folds were produced with strict HDTBR in a normocapnic environment, suggesting that strict HDTBR can independently produce signs of SANS without a hypercapnic environment [43].

HDTBR has also been instrumental in studying SANS aetiology. In the hypothesis of chronic cerebral blood volume pulsatility leading to ocular structure changes in SANS, the SPACECOT authors utilized HDTBR to evaluate pulsatility with near-infrared spectroscopy [29]. In the evaluation of single-nucleotide polymorphisms in 1-carbon metabolism pathways as a risk factor for SANS, HDTBR was utilized to stratify the magnitude of optic disc oedema in individuals with variations in risk alleles (MTRR 66G and SHMT1 1420C) [36]. The authors observed that individuals with 3 or 4 risk alleles had a 40 µm greater increase in total retinal thickness than those with 0 to 2 risk alleles after 30 days of HDTBR. The authors concluded that these results may help to explain the variability of SANS findings observed in astronauts [36].

HDTBR continues to be the standard terrestrial analogue for studying SANS. However, the Earth-based platform carries several limitations including small study sizes and long periods in strict tilt. By nature, subjects have their posterior side pressed against the bed throughout the study, which is not experienced during spaceflight. A study analyzing retinal changes in HDTBR as a terrestrial analogue for SANS observed opposite microvascular response in the retinal vasculature when comparing 70 days of HDTBR and six months of spaceflight on the ISS [44]. Utilizing software to analyze fractal dimension and vessel length density in the retina [44, 45], the study authors observed that vascular density decreased in astronauts after LDSF whereas vascular density increased in HDTBR [44]. The study authors stated that HDTBR has advanced the understanding of SANS, however, these differences in retinal vasculature response may be a result of the presence (HDTBR) and absence of gravity (spaceflight) [44]. In a study comparing astronauts following spaceflight and HDTBR, the study authors observed a significant difference in the increase in choroidal thickening in astronauts compared to HDTBR with a mean difference of 27 µm between groups [46]. There was also a greater degree of peripapillary total retinal thickness in HDTBR compared to astronauts, and a greater proportion of individuals in the HDTBR developed optic disc oedema compared to astronauts after similar duration of spaceflight [46]. The authors concluded that HDTBR induces choroidal thickening to a smaller degree and optic disc oedema to a greater degree when compared to spaceflight [46]. While there is no perfect equivalent to studying SANS on Earth, HDTBR serves as a promising platform to screen for risk factors and test countermeasures for future spaceflight.

POTENTIAL COUNTERMEASURES FOR SANS

As a potential risk for LDSF, SANS may require mitigation strategies and possible countermeasures prior to future human exploratory missions [2]. While the aetiology of SANS continues to be investigated, SANS countermeasures have also been explored including lower body negative pressure (LBNP), venoconstrictive thigh cuffs, goggles, artificial gravity, and pre-flight genetic assessments [47–52]. Several of these technologies have been utilized for other physiological systems (e.g., cardiovascular) that are already onboard the ISS [53], while others are being evaluated on Earth [48, 50, 51].

REDUCTION IN CEPHALAD FLUID SHIFTS/ENHANCING VENOUS RETURN

LBNP is a technique that reduces the cephalad fluid shifts in spaceflight, thus serving as a promising countermeasure for SANS [51, 54]. While different variations of this technique have been

explored, the overarching principle is to apply negative pressure in the lower body to attenuate headward fluid shifts. The Chibis (in the Russian section of the ISS) is a LBNP system that is currently onboard the ISS [50]. Its in-flight utilization may give further insight into the effects of LBNP on SANS development. In an Earth-based study in patients with Ommaya reservoirs that allowed for direct ICP measurements, Petersen et al. simulated elevated ICP with 15° head-down tilt and observed that LBNP decreased ICP. The authors concluded that 20 mmHg of LBNP may be the ideal settings to safely counteract SANS without impairing cerebral perfusion pressure [55]. Regarding choroidal vasculature, Hearon et al. observed that 8 hours of nightly 20 mmHg of LBNP mitigated choroidal engorgement in supine bed rest [54]. Traditional LBNP devices are often heavy or require the individual to remain close to a wall-mounted power supply. Current research in LBNP for SANS includes the development of mobile and flexible LBNP gravity suit [50, 51]. It should be noted that a recent study by Pardon et al. documented that acute exposure to 25-mmHg LBNP during spaceflight did not alter optic nerve head or retinal morphology suggesting that longer durations of fluid shift reversal may be needed to mitigate spaceflight-induced changes [56]. Venoconstrictive thigh cuffs and centrifuge artificial gravity have also been explored as countermeasures for SANS, acting in a similar principle of mitigating cephalad fluid shifts during microgravity [49, 52, 57]. Impedance threshold devices, which allow for the generation of negative intrathoracic pressure to increase venous return, have also been studied as a countermeasure for SANS. Hansen et al. conducted a study that observed the effects an impendence threshold device applying −7 cm H_2O for 5 min in individuals with Ommaya reservoirs allowing for direct ICP measurements [58]. It was noted that the application of the impedance threshold device significantly reduced both central venous pressure and intracranial pressure compared to baseline (free breathing). The study authors also compared this method with acute thigh cuff inflation which showed that the impedance threshold device technique had a greater effect in reducing ICP [58].

MODULATION OF THE TRANSLAMINAR PRESSURE GRADIENT

Ocular goggles have also been explored as a tool to modulate cerebro-ocular haemodynamics in SANS [48]. As discussed in the hypothesis section, there is a hypothesized negative translaminar pressure gradient during spaceflight, and attenuation of this negative gradient may protect astronauts from SANS [13]. As such, reducing intracranial pressure, increasing intraocular pressure, or modulating cerebral blood flow have been proposed as countermeasures for reversing this suspected negative TLPG in SANS [48]. In an investigative head-down tilt study for SANS, Scott et al. observed an increase in IOP and TLPG in subjects who wore swimming goggles compared to subjects who did not. The goggles provided a static increase in IOP, which when compared to the subjects who did not wear goggles, was elevated by a mean difference of 2.9 mmHg [48]. The authors concluded that altered cerebro-ocular haemodynamics can be partially mitigated with goggles, and that future research may help to further understand if increasing IOP is an effective countermeasure for SANS [48]. Current research of goggles that can actively change pressure around the orbit is being conducted as a SANS countermeasure [59].

PHARMACOLOGIC COUNTERMEASURE AND GENETIC ANALYSIS

As discussed in the hypothesis section, there are nutritional, metabolic, and genetic components that have been identified in the risk of developing SANS [35]. Genetic identification of risk alleles MTRR 66G and SHMT1 1420C can help determine which individuals will have a lower risk of developing SANS for LDSF [35]. B-vitamin supplementation may help to reduce the risk of SANS [60]. Further research and mitigation of these known risks for SANS will be essential to protect astronaut health and mission performance. The development of effective countermeasures for SANS is an ongoing process. Further understanding the risk factors for SANS can help reduce the risk of SANS development for future spaceflight.

CONCLUSION AND FUTURE DIRECTIONS

Continued research in understanding the pathogenesis of SANS is important for future LDSF and human space exploration. By understanding the underlying mechanisms of SANS, more precise developments in terrestrial analogues and countermeasures may be needed. Further understanding of the physiological risks (e.g., genetic, metabolic, anatomic) that may increase the risk of SANS is critical. As humanity prepares for spaceflight missions that are longer than what is known, it is imperative to anticipate these long-term risks on the neuro-ophthalmic system.

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ACKNOWLEDGEMENTS

We thank Tyson Brunstetter, OD, PhD and William Tarver, MD, MPH for their review and input for this manuscript.

AUTHOR CONTRIBUTIONS

JO drafted the initial manuscript. THM, CRG, SSM, and AGL provided critical edits and feedback for the manuscript. All authors contributed to the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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