• Review Article •

Spaceflight-associated neuro-ocular syndrome: a review of potential pathogenesis and intervention

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Abstract

● With the continuing progress in space exploration, a new and perplexing condition related to spaceflight ocular syndrome has emerged in the past four decades. National Aeronautics and Space Administration (NASA) has named this condition "spaceflight-associated neuro-ocular syndrome" (SANS). This article gives an overview of the current research about SANS and traditional Chinese medicine (TCM) by analyzing the existing publications on PubMed and CNKI and reports from NASA about SANS, summarizing the potential pathogenesis of SANS and physical interventions for treating SANS, and discussing the feasibility of treating SANS with TCM. Due to the unique characteristics of the space environment, it is infeasible to conduct large-scale human studies of SANS. SANS may be the result of the interaction of multiple factors, including inflammation and fluid displacement in the optic nerve sheath and cerebrospinal fluid. We should pay attention to SANS. Visual function is not only related to the health of astronauts but also closely related to space operations. TCM has antioxidative stress and antiapoptotic effects and is widely used for optic nerve diseases. TCM has great potential to prevent SANS.

● **KEYWORDS:** spaceflight-associated neuro-ocular syndrome; intervention; pathogenesis; microgravity; traditional Chinese medicine
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INTRODUCTION

Over the last 50y, visual anomalies associated with spaceflight have been found through testing and sporadic reports[1-2]. Mader *et al*[3] published the results of seven astronauts' complete eye examinations for the first time in 2011 before and after six months of space flight. Six astronauts underwent postmission optical coherence tomography (OCT) and magnetic resonance imaging (MRI), and 4 underwent lumbar punctures, the ophthalmic findings included disc edema in 5 astronauts, globe flattening in 5, choroidal folds in 5, cotton wool spots in 3, nerve fiber layer thickening in 6, and decreased near vision in 6. The results of ocular testing showed that a subset of crew members experienced visual performance decrements and one or more of the following ocular findings: hyperopic shift, cotton wool spots, choroidal folds, optic disc edema, optic nerve sheath (ONS) distention, and posterior globe flattening with varying degrees of severity and permanence[4]. National Aeronautics and Space Administration (NASA) defined this syndrome, spaceflight-associated neuro-ocular syndrome (SANS), to include optic disc edema, globe flattening, choroidal and retinal folds, hyperopia, and increased intraocular pressure. The term SANS refers to the changes in the physiological structure of the eye and the optic nerve (ON) caused by the redistribution of body fluids to the head in long-term microgravity environment[5].

CLINICAL HISTORY

In the late 1980s, to better study the eye problems during space flights, NASA conducted a questionnaire survey of short-and long-duration spaceflight astronauts about inflight visual changes. This postflight survey of approximately

300 astronauts revealed that 23 percent of short-duration shuttle pilots and 48 percent of astronauts on long-duration International Space Station (ISS) missions occurred varying degrees of near visual acuity decline[6]. According to newer data, the incidence could be as high as 75 percent, with men being more affected than women[7]. Since space flight began, there have been reports of vision changes in astronauts during flight (although there is no statistically significant difference before and after flight)[8]. Limited by early inspection equipment and short flight times, the ophthalmologic changes were relatively minor and brief. Until 2011, changes such as choroidal folds, globe flattening, and optic disc edema were observed in astronauts after long-term flight[3]. These changes may result from a rise in intracranial pressure (ICP) from cephalad fluid shifts during long-duration spaceflight (LDSF), and this condition has been labeled by NASA as visual impairment and intracranial pressure (VIIP) syndrome[9]. Symptoms of astronauts after LDSF include optic disc edema, globe flattening, and other symptoms that were partially similar to those of terrestrial idiopathic intracranial hypertension (IIH), but astronauts did not develop the typical symptoms of IIH, such as headache, structural changes in the olfactory nerve, or pulsatile tinnitus[10]. Thus, over time, the role of elevated ICP as the sole mechanism to explain the onset of these symptoms has been questioned. Over the next few years, the potential risk of permanent ocular changes has been proposed by comparison of pre-and postflight orbital MRIs, axial length measurements, and OCT[3,11-12]. In order to better reflect the uncertainty of pathogenesis and possible multifactorial etiology, the term was changed from VIIP to SANS[5,13-14].

POTENTIAL PATHOGENESIS

Although the specific etiology and exact mechanism of these eye changes in astronauts are not yet clear, related studies have found that after entering a microgravity environment, astronauts experience increased ICP, neurological and biochemical changes, and lymphatic and venous system circulation disorders, which may be involved in the occurrence and development of the disease. Several possible mechanisms have been proposed in recent years. Changes in ocular structural and ON are most likely due to the cephalad fluid shift (including intravascular extravascular shift) during LDSF perhaps combined with additional spaceflight-related factors, including cerebrospinal fluid (CSF) pressure elevation, decreased venous compliance, and alterations in CSF dynamics[5,11,15-18]. In addition, the spaceflight environment may introduce other unique factors that play an additive role in the etiology of SANS, such as the elevated ambient levels of carbon dioxide on the ISS, the use of onboard exercise devices such as the advanced resistive exercise device, the increased radiation exposure, or some combination of these or other factors[19]. Certainly, some crew members are more susceptible due to their genetic/anatomical predisposition or lifestyle related factors[20-21].

The most important and profound physiological response after entering microgravity environment is fluid redistribution, which is regarded as a major mechanism of SANS[11,15]. In the terrestrial environment, CSF is largely produced in the choroid plexus and drains into the lower pressure cervical venous vasculature[22], and drainage of the CSF, lymphatics and vasculature is assisted by the pull of gravity. In the microgravity environment, the increase of venous cross-sectional area and the change of blood flow velocity suggest the possibility of venous congestion[23-24]. The internal jugular veins (IJV) are the primary outflow pathway in prone or supine[25]. Venous congestion may impair cerebral and ocular vein outflow, including those of the vortex veins, through which the majority of the ocular blood leaves the eye. Decreased venous outflow may subsequently lead to decreased CSF outflow, increasing ICP and transmission along the ONS. The choroid is the main blood supply to the ocular tissues[26]. The relevance to ocular function is that a local increase in choroidal thickness at the globe posterior may produce foveal displacement, resulting in a hyperopic shift as well as an increase in intraocular pressure (IOP)[27-28]. Some researchers have proposed that choroidal and vortex vein congestion might also play a role and could cause the observed structural changes described in SANS. Marshall-Goebel *et al*[29] analyzed the change in ultrasound-derived IJV cross-sectional area and noninvasive IJV pressure in ten astronauts by OCT and IOP before flight (seated and supine posture) and ~150d into a 6-month mission on the ISS. These data suggest that altered venous hemodynamics (increased choroidal and retinal thickness) during spaceflight may contribute to SANS. Kramer *et al*[30] conducted a prospective longitudinal MRI study of astronauts with planned LDSF, and high intracranial volumetry and aqueductal CSF hydrodynamics were quantified before spaceflight and at 1, 30, 90, 180, and 360d after landing. The data indicated that LDSF was associated with increased pituitary deformation, altered CSF hydrodynamics, and expansion of summated brain and CSF volumes. The decrease in venous congestion and CSF outflow disorders caused by space flight increases ICP to a certain extent, and pressure is transferred to orbit, resulting in dilation of the ONS and optic disc edema. These changes are similar to those occurring in terrestrial IIH[31]. IIH, also known as pseudotumor cerebri, is characterized by headache, yet imaging evaluation reveals no intracranial space-occupying tumors, more than 90% of IIH patients have significant headaches, but only mild or sporadic headaches have occurred among astronauts aboard the ISS[11]. Likewise, transient visual obscurations lasting seconds at a

time and diplopia are seen in IIH patients but have never been reported in astronauts[32]. And, highly asymmetric or unilateral disc edema has only been recorded in 3%-10% of IIH patients[32]. In an attempt to further evaluate the elevated ICP theory, astronauts underwent postflight lumbar punctures to measure ICP, moderately elevated post LDSF lumbar puncture opening pressures of 28 and 28.5 cm of water were measured in astronauts at 12 and 57d postflight, and may have been higher during the mission[3]. Increased ICP can lead to optic disc swelling (papilledema) caused by high CSF pressure in the distal ONS, elevation of the pressure in the central retinal vein, and impaired perfusion of the neurons as their axons traverse the lamina cribrosa[13].

Recent research has revealed that the connection between the ONS and the CSF is another pathophysiological factor that may produce SANS[11,17]. In all CSF compartments, CSF pressure and composition were assumed to be largely homogeneous within moderate limits[33]. However, it has been demonstrated that the ON subarachnoid spaces (SAS) can become isolated from other CSF compartments in specific ON diseases, resulting in ONS compartment syndrome[5,34]. In the absence of elevated ICP, the interplay of venous congestion, glymphatic stasis, inflammation, and other variables may result in ONS CSF draining, resulting in locally increased pressure inside the ONS.

CSF stasis is caused by a blockage of the veins and lymphatics, which leads to a decrease in the outflow of CSF. As a result, venous and lymphatic stasis might result in ischemia and perfusion damage. SANS is also thought to be associated with inflammatory alterations. In a mouse model of ICP (elevated and sustained for 2wk), Shen *et al*[35] discovered a loss of retinal ganglion cell (RGC) somas in the retina and RGC axons within the ON, as well as impairments in both RGC electrical function and contrast sensitivity. Elevated ICP also increased ganglion cell layer expression of hypoxia-inducible factor-1 alpha. Furthermore, individual genetic variables, as well as greater amounts of CO_2 and radiation, contributed to the occurrence of SANS[14,36].

PHYSICAL INTERVENTION

Entry into weightlessness causes an immediate and sustained fluid shift toward the head, which, compared to those of upright postures on earth, increases central and cranial blood and fluid filling[24,37-38]. Due to the lack of gravitational stress, astronauts are not able to “stand up” and periodically unload cerebral structures, leading to mild but chronic cephalad fluid congestion, which we and others have hypothesized to be an initiating and driving factor in the development of SANS[5]. Considering the drainage disorders of the vascular and lymphatic systems, pressure changes, and changes in brain and eye volume caused by the microgravity environment, fluid displacement, especially head level shift, should be taken as the core of countermeasures to prevent SANS. Based on this, current research is focused on devices to combat the redistribution of body fluids, braslet thigh cuffs, a modified Kaatsu system, an impedance threshold device, artificial gravity, and a lower body negative pressure (LBNP) device are among the devices used[4].

Lower Body Negative Pressure is a Potential Method for SANS Treatment LBNP is a unique approach because it induces a blood transfer from the upper (above the iliac crest) to the lower body compartment. It causes blood to pool in the lower portions of the body, reducing venous return to the heart. Petersen *et al*[39] developed, manufactured, and tested a wearable, mobile, and elastic LBNP device (gravity suit) that included pressurized pants with built-in shoes to sustain ground reaction forces (GRF) and a thoracic vest to distribute load throughout the whole axial length of the body. The cardiovascular response and the footward fluid shift from the internal jugular venous cross-sectional area were assessed by measuring the GRF on the feet and shoulders of eight healthy volunteers using ultrasound. The conclusion was that LBNP is a potential countermeasure to reverse the cranial fluid shift associated with weightlessness. Moreover, to evaluate the potential of LBNP as a countermeasure against ICP variability and to evaluate its potential clinical application, the efficacy and dose response of LBNP in reducing ICP were tested at different pressures. According to the findings, 20 mm Hg LBNP is the ideal level of pressure for diminishing ICP without lowering cerebral perfusion pressure or stroke volume[40]. In addition, nine healthy male individuals took part in a crossover design research with five different head-down tilt (HDT) conditions: -6, -12, and -18° HDT, 12° HDT with -20 mm Hg (low-level) LBNP, and 12° HDT with a 1% CO_2 atmosphere, each for five hours. Based on the MRI data, LBNP reduced the increases in ONS diameter and intracranial CSF during HDT[41]. Moreover, the sudden cessation of LBNP can move blood to the thorax, leading to a transient increase in blood pressure[42].

Thigh Cuffs Arbeille *et al*[43] observed that the use of thigh cuffs in HDT considerably altered the time course of cardiovascular adaptation, resulting in a cardiovascular equilibria that differed from that attained after a few hours in either simulated or real microgravity. The thigh cuff helps reduce venous stasis in the head by mechanically capturing a large amount of blood flow in the veins of the lower limbs, thereby reducing edema of the face and chest cavity. In this study, the new hemodynamic balance, which was close to the cardiovascular level before HDT, was reached at 8h after thigh cuff use[43]. Therefore, astronauts and subjects report comfort in HDT when using thigh cuffs. During a 6-month space flight, the adaptation of an

astronaut's heart, arteries and veins to weightlessness with and without the thigh cuff was monitored, and the results suggested that the properties of the vein wall may have been altered[44]. It is clearly obvious that this simple approach can limit the amount of time that brain tissue is exposed to elevated venous pressure and avoid brain edema during any long-term exposure to actual or simulated microgravity. More complex postflight venous tests, however, will be necessary.

Intermittent Artificial Gravity With the establishment of the head-down position model and the induction of papillary edema, it is possible to examine countermeasures in test subjects to be able to apply them to astronauts in the future. One possible countermeasure is intermittent artificial gravity. This can be generated using a short-arm human centrifuge. The organs (especially the heart and blood vessels) adapt to microgravity because the lack of transmural pressure along the blood vessels can cause remodeling. Daily intermittent artificial gravity can prevent this adaptation of blood vessels and the deterioration associated with cardiovascular diseases[12,45].

Other Countermeasures The difference in IOP and CSF pressure across the lamina cribrosa is known as the translaminar pressure difference[46]. However, spaceflight provokes larger increases in ICP than IOP, resulting in a negative and anteriorly directed translaminar pressure gradient (TLPG)[12]. Hence, countermeasures that prevent or reverse a negative TLPG have been considered. Scott *et al*[47] found that swimming goggles were associated with increased IOP and TLPG in HDTs. Both IOP and TLPG were higher in participants who wore swimming goggles than in those who did not wear goggles.

Taking traditional Chinese herbs antagonized the negative influences of bed rest on visual function; Xu *et al*[48] observed the influence of 21d of bed rest on intraocular pressure, visual field and near vision in humans randomly divided into a control group and a Chinese herb group to study the countermeasure of Chinese herbs against weightlessness. A -6° HDT was used to simulate weightlessness. The IOP and near vision results showed wavelike decreases during bed rest, and there was a clear correlation between the two parameters. It was shown that the day on which the most significant decrease in near vision occurred was also the day on which the most significant drop in IOP occurred.

The high energy requirements of the visual system require a rich supply of oxygen and nutrients, making it sensitive to oxidative stress. Excessive free radicals lead to mitochondrial dysfunction, resulting in retinal metabolic disorders and neurodegeneration[49]. Injury factors such as high IOP, deprivation of neurotrophic factors, excitatory amino acid toxicity, vascular spasm, inadequate perfusion, tissue anemia, and hypoxia can all lead to the death of RGCs[50]. Thus, the retina is one of the most vulnerable targets in the space environment. As a countermeasure to retinal damage onboard the ISS, space agencies launched a project called coenzyme Q10 (CoQ10). The CORM project, financed by the Italian Space Agency (ASI), began in the summer of 2017. Lulli *et al*[51] investigated the impacts of the spaceship environment on ARPE-19 cells as well as the possible protective benefits of CoQ10 by measuring apoptotic rate, telomeric DNA damage, cytoskeletal alteration, and exome and transcriptome modifications. The findings of this study will evaluate whether human retinal pigment epithelial cells are damaged in the ISS's microgravity and cosmic radiation-rich environment and whether CoQ10 may be deemed an effective protective measure[51].

CONCLUSION

Although the current research has not clarified the mechanism of SANS, eye damage in astronauts is undeniable and worthy of our attention. Based on the distinctive characteristics of the space environment, cephalad fluid shift (intravascular and extravascular shift), ONS and CSF are regarded as the main causes of SANS which is the result of the interaction of multiple factors. Some important progress has been made in the existing research on the protection of SANS by physical intervention measures, which plays a positive role in SANS. There have been an increasing number of pharmacological studies on traditional Chinese medicine (TCM) recently. TCM has shown unique advantages in preventing and treating diseases, especially optic neuropathy. We are conducting a study on the mechanism of TCM intervention in rat fundus lesions under simulated weightlessness to observe the effects of TCM. We hope to provide different ideas for this research.

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