COMMENTARY

Anemia and Spaceflight Associated Neuro-Ocular Syndrome (SANS)

Ethan Waisberg, MB, BCh, BAO;[1] Joshua Ong, MD;[2] Mouayad Masalkhi;[1] Andrew G. Lee, MD[3,4,5,6,7,8,9,10]

1. University College Dublin School of Medicine, Belfield, Dublin, Ireland
2. Michigan Medicine, University of Michigan, Ann Arbor, Michigan USA
3. Center for Space Medicine, Baylor College of Medicine, Houston, Texas USA
4. Department of Ophthalmology, Blanton Eye Institute, Houston Methodist Hospital, Houston, Texas USA
5. Houston Methodist Research Institute, Houston Methodist Hospital, Houston, Texas USA
6. Departments of Ophthalmology, Neurology, and Neurosurgery, Weill Cornell Medicine, New York, New York USA
7. Department of Ophthalmology, University of Texas Medical Branch, Galveston, Texas USA
8. University of Texas MD Anderson Cancer Center, Houston, Texas USA
9. Texas A&M College of Medicine, Bryan, Texas USA
10. Department of Ophthalmology, University of Iowa Hospitals and Clinics, Iowa City, Iowa USA

Correspondence:
Ethan Waisberg
University College Dublin
School of Medicine
Belfield, Dublin 4, Ireland
E-mail: ethan.waisberg@ucdconnect.ie

Conflicts of interest: The other authors declare no conflicts of interest.

Keywords: anemia; IIH; long-duration spaceflight; SANS

Abbreviations:
CBC: complete blood count
ICP: intracranial pressure
IIH: idiopathic intracranial hypertension
SANS: spaceflight associated neuro-ocular syndrome

Received: June 9, 2023
Accepted: June 16, 2023

Abstract
Spaceflight associated neuro-ocular syndrome (SANS) is a collection of distinct findings seen in some astronauts following prolonged spaceflight and is characterized by: optic disc edema, globe flattening, and choroidal folds. In this manuscript, we describe the potential mechanisms linking anemia and SANS. Future research aimed at understanding the relationship between these conditions may help to develop countermeasures and mitigation efforts for SANS.

Waisberg E, Ong J, Masalkhi M, Lee AG. Anemia and spaceflight associated neuro-ocular syndrome (SANS). *Prehosp Disaster Med.* 2023;38(5):680–682.

Introduction

Anemia has recently been observed in astronauts, the process being termed "Space Anemia."[1] Analyzing blood levels in 14 astronauts after six months during spaceflight, Trudel, et al observed a unique phenomenon that observed that the mechanism of space anemia is contributed by a hemolytic process.[1] Astronauts that undergo long-duration spaceflight can develop a set of distinct findings characterized as spaceflight associated neuro-ocular syndrome (SANS).[2] Currently, SANS serves as one of the largest physiological barriers to future spaceflight, however, the pathophysiology behind this neuro-ophthalmic phenomenon is not well-defined.[3] It was once thought to be due solely to elevated intracranial hypertension, previously named "Vision Impairment and Intracranial Hypertension" (VIIP). Further research has suggested that elevated intracranial pressure (ICP) may not be the sole reason for SANS, however, its role in SANS is still being investigated. In this manuscript, we describe the potential mechanisms linking anemia and SANS. While much is still unknown, the role of anemia/space anemia may be critical in further understanding of these severe diseases.

Space anemia is a phenomenon characterized by a decrease in the number of circulating red blood cells and plasma volume that astronauts encounter while in space.[4] Neocytolysis is a form of selective hemolysis, the process that causes the decrease in red blood cell mass.[5] The investigation of anemia in space is constrained by the scarcity of participants and the harsh environmental circumstances.[1,6] In one investigation, 17,336 measures of hemoglobin concentration were collected from 721 space missions and controls to examine the acute and long-term consequences of space exposure on hemoglobin decrement. The study revealed that space anemia is marked by a gradual decrease in hemoglobin concentration over time.[7]

The inclusion of space anemia in the screening and surveillance protocols of astronauts is crucial, given its potential to negatively impact physical performance and overall health outcomes during and post-space missions.[7] Nevertheless, further investigation is required to comprehensively comprehend the mechanisms that underlie this phenomenon and to develop efficacious interventions that minimize its impact.

The SANS phenomenon is something some astronauts have experienced after spending extended durations in microgravity conditions.[8] Optic disc edema, globe flattening, choroidal folds, and hyperopic shifts are some of the main clinical signs of the disease.[2,9] Although the underlying causes of SANS are not fully understood, it is thought that they are

doi:10.1017/S1049023X23006131

associated with the redistribution of blood flow and bodily fluids that occurs in microgravity, which affects ICP.[8] Whereas the etiology of idiopathic intracranial hypertension (IIH) is believed to be linked to decreased absorption of cerebrospinal fluid.[10] Increased ICP in an alert and oriented patient without a recognized origin is a hallmark of IIH.[10] Headache, visual loss, and pulsatile tinnitus are some of its main symptoms.[11] Impaired cerebrospinal fluid absorption syndrome is assumed to be the condition's underlying cause.[10]

Increased ICP is another theory that has been put out to explain the emergence of SANS. It has been hypothesized that some of these ocular alterations may be significantly influenced by the considerable displacement of bodily fluid toward the head that occurs in microgravity through biomechanical processes.[12] Increased posterior globe flattening has been a SANS finding that has been replicated in head-down tilt bed-rest studies.[13,14]

In recent research, Ferguson, et al compared results in patients with increased ICP from IIH with observations in astronauts following long-duration spaceflight to determine the frequency and location of choroidal and retinal folds. The scientists concluded that there are parallels between the choroidal and retinal fold patterns in SANS and IIH, indicating that elevated ICP might play a role in the onset of SANS.[15]

Idiopathic intracranial hypertension is an elevation of ICP without an identifiable cause (negative neuroimaging and normal cerebrospinal fluid contents); IIH generally affects obese, young women. If left untreated, IIH can cause significant morbidity. The pathophysiology of IIH is not yet fully elucidated, but possible theories include increased cerebrospinal outflow resistance and cerebral venous outflow abnormalities.[16] The relationship between anemia and IIH remains particularly controversial because in young women of childbearing age, iron deficiency anemia is also very common. Many of the factors that have been implicated in the development of IIH are closely related, and it is difficult to isolate a particular risk factor to determine a causal relationship. The rarity of IIH further exacerbates this issue by decreasing the size of available patient cohorts that can be analyzed.

The mechanisms linking anemia and IIH remain ill-defined. The elevated ICP could be related to anemia inducing a hypercoagulable state and increased venous pressure.[17] Another competing hypothesis suggests that decreased hemoglobin levels may cause hypoxia in the brain, resulting in increased ICP because of edema and increased permeability of capillaries.[18] A third theory suggests that a lower hemoglobin level increases the circulating blood volume in the cerebrum, resulting in an increased ICP.[17]

Many cross-sectional studies and case reports suggest a possible causal role of anemia in IIH. Case reports are useful while describing rare relationships, however it is important to acknowledge the potential risks of reporting bias. In this section, we discuss key studies, case reports, and systematic reviews that analyze the relationship of anemia and IIH.

Mollan, et al[19] reported that an association of iron-deficiency anemia and IIH in a neuro-ophthalmology unit with an incidence of 10.3%. This study also included a case series of eight patients with anemia and IIH, with seven of these patients having complete reversal of signs and symptoms after the treatment of anemia alone. Based on these findings, a recommendation for a complete blood count (CBC) was made for patients with signs of raised ICP.[19]

Lin, et al[20] however performed a matched case-control study that found no significant association between anemia and IIH when comparing standardized CBC values, and suggested that the increased prevalence of anemia was due to the demographic overlap with younger women.

Ardissino, et al[21] used multivariate analysis with adjustment of confounders on the records of 231,399 patients, with 667 having a clinical diagnosis of IIH, in the retrospective Clinical Practice Research Datalink which showed that anemia ($P = .033$) was independently associated with IIH.

Waisberg, et al[22] reported on five consecutive cases of fulminant IIH and new onset severe anemia (Hb<80g/L). This case series concluded that a CBC should be performed on all new cases of papilledema since severe anemia is temporally associated with fulminant IIH cases and that the treatment of anemia can be enough to normalize the ICP.

Yu, et al[23] performed a systematic review of the literature on anemia and IIH and found 74 cases of IIH associated with anemia, and of these, only 16 of these patients were obese (body mass index>30kg/m^2). Iron deficiency anemia was the most common cause of anemia. In over 50% of cases with anemia and IIH, the treatment of the anemia alone was sufficient to resolve symptoms, without additional medications or surgery. Future comparative studies are needed to fully elucidate the relationship between anemia and IIH.

Conclusion

There is still much to investigate between anemia, IIH, and SANS. However, this manuscript seeks to review the current literature and understanding of these diseases and the potential connection between these pathologies. As IIH and SANS serve as severe diseases for their respective demographics, understanding the role of anemia is critically important. Future research aimed at understanding the relationship between these diseases may help to develop countermeasures and mitigation efforts.

References

1. Trudel G, Shahin N, Ramsay T, Laneuville O, Louati H. Hemolysis contributes to anemia during long-duration space flight. *Nat Med.* 2022;28(1):59–62.
2. Lee AG, Mader TH, Gibson CR, et al. Spaceflight associated neuro-ocular syndrome (SANS) and the neuro-ophthalmologic effects of microgravity: a review and an update. *NPJ Microgravity.* 2020;6(1):7.
3. Waisberg E, Ong J, Masalkhi M, Lee AG. Optic neuropathy in spaceflight-associated neuro-ocular syndrome (SANS). *Ir J Med Sci.* 2023. Epub ahead of print.
4. Smith SM. Red blood cell and iron metabolism during space flight. *Nutrition.* 2002;18(10):864–866.
5. Santo NGD, Cirillo M, Kirsch KA, et al. Anemia and erythropoietin in space flights. *Seminars in Nephrology.* 2005;25(6):379–387.
6. Waisberg E, Ong J, Zaman N, Kamran SA, Lee AG, Tavakkoli A. A non-invasive approach to monitor anemia during long-duration spaceflight with retinal fundus images and deep learning. *Life Sciences in Space Research.* 2022;33:69–71.
7. Trudel G, Shahin N, Ramsay T, Laneuville O, Louati H. Hemolysis contributes to anemia during long-duration space flight. *Nat Med.* 2022;28(1):59–62.
8. Lee AG, Mader TH, Gibson CR, Brunstetter TJ, Tarver WJ. Space flight-associated neuro-ocular syndrome (SANS). *Eye (Lond).* 2018;32(7):1164–1167.
9. Waisberg E, Ong J, Lee AG. Factors associated with optic disc edema development during spaceflight. *JAMA Ophthalmol.* 2023;141(4):409.
10. Wall M. Idiopathic intracranial hypertension. *Neurol Clin.* 2010;28(3):593–617.

https://doi.org/10.1017/S1049023X23006131 Published online by Cambridge University Press

11. Wang MTM, Bhatti MT, Danesh-Meyer HV. Idiopathic intracranial hypertension: pathophysiology, diagnosis, and management. *J Clin Neurosci.* 2022;95:172–179.
12. Spaceflight Associated Neuro-ocular Syndrome. Glenn Research Center - NASA. https://www1.grc.nasa.gov/space/human-research-program/computational-modeling/spaceflight-associated-neuro-ocular-syndrome/. Accessed May 2, 2023.
13. Sater SH, Conley Natividad G, Seiner AJ, et al. MRI-based quantification of posterior ocular globe flattening during 60 days of strict 6° head-down tilt bed rest with and without daily centrifugation. *J Appl Physiol.* 2022;133(6):1349–1355.
14. Waisberg E, Ong J, Kamran SA, et al. Further characterizing the physiological process of posterior globe flattening in spaceflight associated neuro-ocular syndrome with generative adversarial networks. *J Appl Physiol.* 2023;134(1):150–151.
15. Ferguson CR, Pardon LP, Laurie SS, et al. Incidence and progression of chorioretinal folds during long-duration spaceflight. *JAMA Ophthalmology.* 2023;141(2): 168–175.
16. Mollan SP, Ali F, Hassan-Smith G, Botfield H, Friedman DI, Sinclair AJ. Evolving evidence in adult idiopathic intracranial hypertension: pathophysiology and management. *J Neurol Neurosurg Psychiatry.* 2016;87(9):982–992.
17. Biousse V, Rucker JC, Vignal C, Crassard I, Katz BJ, Newman NJ. Anemia and papilledema. *Am J Ophthalmology.* 2003;135(4):437–446.
18. Reid HA, Harris W. Reversible papilledema in pernicious anemia. *BMJ.* 1951; 1(4696):20–20.
19. Mollan SP, Ball AK, Sinclair AJ, et al. Idiopathic intracranial hypertension associated with iron deficiency anemia: a lesson for management. *Eur Neurol.* 2009;62(2):105–108.
20. Lin WV, Berry S, Nakawah MO, Sadaka A, Lee AG. Idiopathic intracranial hypertension and anemia: a matched case–control study. *J Neuro-Ophthalmology.* 2020;40(2):163–168.
21. Ardissino M, Moussa O, Tang A, Muttoni E, Ziprin P, Purkayastha S. Idiopathic intracranial hypertension in the British population with obesity. *Acta Neurochir.* 2019;161(2):239–246.
22. Waisberg E, Yu CW, Sverdlichenko I, Micieli JA. New onset severe anemia and fulminant idiopathic intracranial hypertension. *Can J Neurol Sci.* 2021;1–3.
23. Yu CW, Waisberg E, Kwok JM, Micieli JA. Anemia and idiopathic intracranial hypertension: a systematic review and meta-analysis. *J Neuro-Ophthalmology.* 2022; 42(1):e78–e86.