ONE-CARBON METABOLISM AND SANS: 2022 UPDATE

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Spaceflight Associated Neuro-ocular Syndrome, or SANS, affects a subset of astronauts (1, 2), and biochemical evidence has documented differences in those astronauts (3). Specifically, they had higher circulating concentrations of metabolites of the one-carbon metabolic pathway (1C), including homocysteine, and these concentrations were higher *before flight* (3). After ruling out many potential confounding factors in these otherwise healthy individuals (e.g., sex, kidney function, vitamin status, coffee consumption), a study of genetics was warranted. In an initial pilot effort, we documented a genetic predisposition to develop ophthalmic changes after long-duration space flight (4). That is, from a limited study of 5 single-nucleotide polymorphisms (SNPs), we found that the G allele for the MTRR A66G SNP was associated with a greater risk of choroidal folds and cotton-wool spots after flight, and the C allele for SHMT1 C1420T was protective against optic disc edema (4). These data provide a potential pathway for understanding why some individuals develop SANS, while others do not. The initial pilot study of 5 SNPs yielded striking findings, but the 1C pathway is far more complex. An effort was undertaken to examine more than 500 1C SNPs to see if a broader examination could help illuminate this association. That work is ongoing.

The astronaut findings led us to advocate for the inclusion of 1C pathway genetic and biochemistry testing on other SANS-related projects, noting that genetics might help identify responders, non-responders, or outliers. The first such effort yielded evidence of an association of specific forms of the MTRR and SHMT-1 SNPs and vitamin B12 status with end-tidal CO_2 after acute carbon dioxide exposure (5). The second such effort led to the identification that individuals exposed to strict head-down tilt and CO2 for 30-d who developed optic disc edema also had risk alleles for the two SNPs described above (6).

Additionally, we identified a clinical population with many characteristics either attributed or purported to be involved in the ocular changes seen in affected astronauts: women with polycystic ovary syndrome (PCOS). PCOS is a condition of androgen excess and anovulatory menstrual cycles. The shared characteristics and clinical findings between SANS and PCOS generally include higher circulating homocysteine concentrations, increased retinal nerve fiber layer thickness, increased androgen concentrations (or responses), and altered carbohydrate metabolism. To our knowledge, no study has examined whether women with PCOS have asymptomatic ophthalmic anomalies observed in astronauts with SANS. While researchers have evaluated the one-carbon metabolism pathway polymorphisms of PCOS patients, and initial studies show an association with certain one-carbon polymorphisms, none have looked at the set of SNPs identified in our studies that are associated with ophthalmic changes in astronauts. Accordingly, we designed a study to evaluate the association of one-carbon pathway SNPs and ophthalmic findings in patients with PCOS and/or IIH compared to controls. Subjects provided blood samples for vitamin and one carbon biochemistry analyses, an extensive analysis of >500 SNPs associated with one carbon metabolism and had eye examinations and ocular imaging. Data analysis are underway.

The data collected to date have shown associations between one carbon pathway biochemistry and genetics and incidence of SANS. The mechanisms for SANS has yet to be identified, although many hypotheses exist. Based on our data, we have developed (8, 9) and expanded (6) a multi-hit hypothesis for how these seemingly disparate findings could be linked. While intriguing, the hypothesis represents the starting point for further research.

We aim to clarify the relationship between B-vitamin status and genetics with regard to the risk of SANS. Ultimately, understanding the mechanism(s) behind this will provide a means to predict, prevent, or treat these ophthalmologic pathologies in astronauts, and terrestrial populations.

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