Letters

COMMENT & RESPONSE

Blood Biomarkers May Have Found a New Frontier in Spaceflight

To the Editor We congratulate zu Eulenburg et al[1] for their longitudinal study of postspaceflight changes in blood-based biomarkers in 5 cosmonauts. Unlike a previous study, which used magnetic resonance imaging to evaluate the neurologic changes after spaceflight in cosmonauts,[2] blood-based biomarkers may present a practical breakthrough in monitoring neurologic health in real time in space on successful validation of the current findings. Their findings are remarkable in that several biomarkers (eg, neurofilament light chain [NfL], glial fibrillary acidic protein [GFAP], amyloid-β proteins 42 and 40) showed elevations postspaceflight compared with prespaceflight. However, there are several key limitations that we thought were worth highlighting to the *JAMA Neurology* readership.

The sample size was small (n = 5), and results need to be replicated in a larger sample. However, the time-course patterns of select biomarkers showed an interesting quadratic trend, where most biomarkers peaked at 1 week postspaceflight and began returning to baseline level at 3 weeks postspaceflight. This pattern poses a question as to whether it is the long stay in space (average of 6 months) or the sudden change from microgravity in space to gravity on earth that triggers the elevations of blood biomarkers. If the former is correct, degenerative cellular responses to microgravity would have been progressive during the 6-month space mission, and biomarker levels at 1 day postspaceflight would have shown more remarkable changes from prespaceflight, instead of gradually increasing upon their return. The latter is also plausible because returning from space is a very stressful experience on the body,[3] possibly triggering an inflammatory response, and microstructural components of the brain must readapt to gravity on earth. Given that NfL and GFAP are sensitive to very mild subconcussive head impacts (eg, soccer heading),[4,5] their elevations may be due to the crossing effect of nongravity to gravity. Blood sampling during the space mission would have addressed this issue.

It would also be paramount to understand why the biomarker time series of some individuals showed minimal from spaceflight whereas others exhibited continued elevation up to 3 weeks postspaceflight. A larger-scale multinational study in cosmonauts will allow stratification of additional factors, such as sex, age, genetic variance, years of spaceflight training, number of space missions, and any preexisting comorbidities. With plans for longer-duration spaceflights and recent developments in civilian access to space, delineating the neurologic consequences of spaceflight is critical, and we look forward to continued investigations of the effects of spaceflight on neurologic health using blood-based biomarkers.

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In Reply I thank Zuidema and colleagues for their interest in our study on changes of blood-based biomarkers in long-duration space flyers after return to Earth from a 6-month mission aboard the International Space Station (ISS).[1] I agree that the methods used in our longitudinal study could open the door to accessible and precise health surveillance of astronauts' neurological health in future space missions. I concur with the need to replicate the findings from our pilot study in another sample. Small sample sizes are an intrinsic challenge for all spaceflight-associated research, and such studies are only powered to detect large effect sizes as observed in our study. Repeated within-participant measures can help overcome some of the constraints related to small samples. Our study was hypothesis driven because several neuroimaging studies from our group had identified detrimental effects on brain structure in long-duration cosmonauts,[2-4] increasing the plausibility of our findings.

Because biomarker data were collected only at baseline and at 3 time points postflight, the apparent nonlinearity of the postflight biomarker curves should be interpreted with caution as long as we do not have in-flight data available. In my understanding of our data and the literature, our findings do not reflect the stress stemming from the return trip to Earth as suggested in the letter. We interpret them to mainly result from the long-duration alteration of cranial circulation in microgravity.

Head decelerations experienced during a descent in the Soyuz capsule from the ISS are below 4*g* and do not represent minor concussions (concussion threshold, 85-90*g*). These minor head decelerations during the return together with the established short half-life of our examined biomarkers (<48 hours for all presented proteins except neurofilament light chains) do not explain a parameter elevation for 3 weeks. During the return, ISS cosmonauts experienced the forces of only one long half-parabola. A parabolic flight study in 6 individuals found a slight (10%) elevation of 1 parameter, the glial fibrillary acidic protein, within an hour after exposing this group to the gravitational transitions of 31 full parabolas from hypergravity to microgravity and back to hypergravity (1.8*g*).[5] Nevertheless, a minor contribution from the effects of return to Earth on the first postflight data point cannot yet be ruled out.

We found changes in brain proteins representing the glia, the axons, and the neuronal tissue up to 3 weeks after a mission. This argues for a long and systemic reparatory process, a process of which we have neither fully captured the onset nor the tail. Only then will we be able to comprehensively assess and grade the implicated brain injury after long-duration exposure to microgravity.

The final points raised by Zuidema and colleagues have my full support: To understand the interindividual variance and associated risk factors of the brain-structural response to prolonged space travel will require joint larger studies coordinated across space agencies. Such studies will provide further insights into the mechanisms by which space travel affects the brain and potentially identify mitigating measures that can be undertaken to protect the brain during deep space exploration.

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Large Collaborative Registries and Real-world Data to Manage Amyloid-Related Imaging Abnormalities

To the Editor Hall et al[1] describe a patient with prodromal Alzheimer disease who developed 6 relapsing episodes of amyloid-related imaging abnormality edema (ARIA-E) over 44 months of treatment within the aducanumab long-term extension period. Together with the recently reported 41.3% risk of ARIA in the Phase 3 Study of Aducanumab in Early Alzheimer's Disease (EMERGE and ENGAGE) trials,[2] we believe this work is of particular interest as it points out ARIA as a timely research and clinical priority, prompting the urgent need to define standardized guidelines for the treatment and follow-up monitoring of such side events.

Notably, this patient was cared for with dose suspension until ARIA-E resolution and patient-centered discussion with consideration of testing after each ARIA-E episode. Nevertheless, this did not prevent the occurrence of multiple recurrences after the reintroduction of each treatment, even at a reduced dose, culminating with ARIA hemorrhage concomitant with the sixth ARIA-E episode before the trial was halted.

Recent findings from natural history and posttreatment outcomes of spontaneous ARIA in the large longitudinal registry, the Inflammatory Cerebral Amyloid Angiopathy and Alzheimer's Disease Biomarkers International Network (iCAβ), anticipate the transient and potentially relapsing inflammatory nature of ARIA-E and suggest the effectiveness of intravenous corticosteroid pulse therapy and slow oral taper for preventing recurrences.[3]According to this, the here-reported patient[1] might have benefited from such a therapy to avoid or at least reduce the number of ARIA-E episodes. Given the controversial approval of aducanumab by the US Food and Drug Administration and other monoclonal antiamyloid antibodies expected to follow in the next years, ARIA will represent a clinical challenge. This prompts the need for large collaborative registries, such as the iCAβ International Network, which gather data on the real-world course and effects of both spontaneous and treatment-related ARIA, in order to fill current knowledge gaps and establish recommendation updates based on evaluation of all lessons learned.[3]

In this regard, we propose the following 4 main research queries: (1) Is ARIA-E representing an exaggerated neuroinflammatory adverse effect that should benefit from corticosteroid treatment?[3,4] (2) Do we need to treat with corticosteroids independently of ARIA-E overt symptoms?[3,4] (3) How long should the taper be?[3] (4) Which biomarkers are suited to overcome the current interpretative issues and lack of specificity in monitoring the effective response to therapy and prediction of recurrences?[3-5]As leaders of the iCAβ,[3] the European Alzheimer Disease Consortium, and as clinicians and researchers in the cerebral amyloid angiopathy–related inflammation and Alzheimer disease immunotherapy fields, we strongly believe that a uniform strategy is needed in order to manage ARIA and to limit recurrences.

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