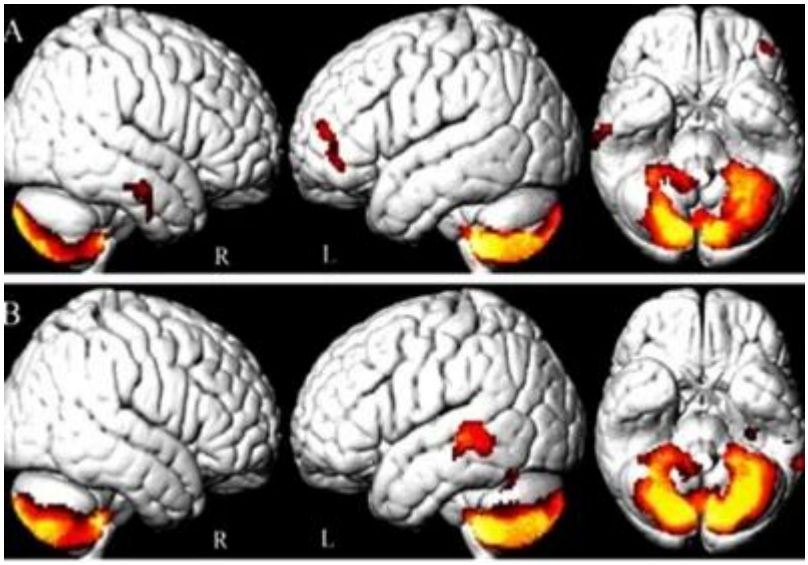
More than two years after the global COVID-19 pandemic, it is clear that infection with severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2) can lead to a new syndrome called long-COVID-19 or post-acute COVID-19 syndrome (PACS). PASC is an umbrella term used to describe a heterogeneous group of patients. This disease is more common in hospitalization survivors, but, even those who have experienced mild acute COVID-19 have a wide range of organ dysfunction. The neurologic sequelae affect the central nervous system (CNS) and peripheral nervous system (PNS) and include cognitive and memory disorders, headaches, stroke, extrapyramidal and movement disorders, mental disorders, encephalitis or encephalopathy, insomnia, peripheral neuropathy, acute inflammatory polyradiculoneuropathy, orthostatic intolerance, and syncope. In this study, the authors from the United States used integrated [11C]PBR28 PET/MR brain imaging and analysis of peripheral blood samples to investigate the association between neuroinflammation and parameters of vascular health in individuals diagnosed with PASC.



About the study

This cross-sectional study enrolled 12 individuals diagnosed with PASC and 43 control individuals not exposed to SARS-CoV-2. Two participants with PASC were hospitalized during the acute COVID-19, and one of them was vaccinated before the acute infection with SARS-CoV-2. Participants with PASC completed questionnaires related to their symptoms and history. All participants completed the Brief Pain Inventory (BPI) and the Beck

Depression Inventory (BDI). None of the PASC participants reported a history of depression before COVID-19.

Neuroinflammation was studied using integrated [11C]PBR28 PET/MR neuroimaging at least ten months after a diagnosis of COVID-19 (mean=20.50 months). The parameters of vascular health, inflammation, and angiogenesis were analyzed in peripheral blood samples taken immediately before the PET/MRI scan. Most control individuals (34/43) were scanned before the pandemic.

The parameters of vascular health, inflammation, and angiogenesis were analyzed in peripheral blood samples taken immediately before the [11C]PBR28 PET/MR brain imaging. Analyzed parameters of vascular health included α2-macroglobulin, orosomucoid, C-reactive protein, fetuin A, fibrinogen, haptoglobin, sL-selectin (soluble leukocyte selectin, or sCD62L), platelet factor 4 (PF4) and pentraxin-2.

Researchers also analyzed levels of cytokines: interleukin (IL)-1β, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12(p40), IL-12(p70), IL-13, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ, monocyte chemotactic protein 1 (MCP-1), and tumor necrosis factor (TNF)-α, and indicators of angiogenesis: angiopoietin-2, bone morphogenic factor (BMP)-9, epidermal growth factor (EGF), endoglin, endothelin- 1, fibroblast growth factor (FGF)-1 and -2, follistatin, granulocyte colony-stimulating factor (G-CSF), heparin-binding EGF-like growth factor (HB-EGF), hepatocyte growth factor (HGF), IL-8, leptin, placental growth factor (PLGF), and vascular endothelial growth factor (VEGF)-A, -C, and-D.

Results

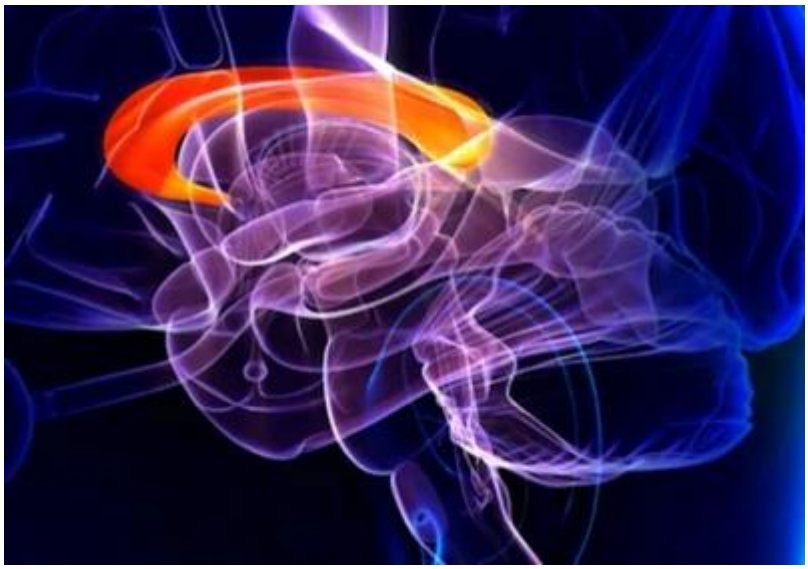
Only two of the 12 individuals diagnosed with PASC met the threshold for moderate depression, and the average depression score was mild. Depression was either denied as a problem (50%), reported as a new (~42%), or seriously new (~8%) problem after COVID-19.

In individuals with PASC, [11C]PBR28 PET/MR showed elevations in binding, as an indicator of neuroinflammation, in a wide range of brain regions, including the midcingulate cortex, corpus callosum, thalamus, basal ganglia/striatum, subfornical organ, anterior cingulate cortex, medial frontal gyrus, and precentral gyrus, compared to controls.

The intensity of the whole-brain PET signal correlated positively with the majority of parameters of vascular health, including fibrinogen, α2-macroglobulin, orosomucoid, fetuin A, sL-selectin, pentraxin-2, and haptoglobin. Interestingly, the PET signal did not correlate

with concentrations of cytokines and indicators of angiogenesis.

Of note, a recent study performed in individuals who had COVID-19 at least four months before enrollment also found alterations in the corpus callosum, including a negative correlation between visuoconstructive testing results and the increased white matter volume in the left and right genu of the corpus callosum.
https://discovermednews.com/visuospatial-deficit-immune-markers-neuroimaging-after-covid-19/



Corpus callosum

Conclusion

These results provide indirect evidence that differences in [11C]PBR28 PET/MR brain binding across a wide range of brain regions, as an indicator of neuroinflammation, could partially reflect variations in vascular anatomy and perivascular immune infiltration. Since the integrity of the blood-brain barrier can be compromised in neuroinflammation, vascular factors may penetrate the brain parenchyma. These results do not establish a causal relationship between neuroinflammation and vascular health, but, they indicate that interaction between neuroinflammation and vascular health could contribute to symptoms of

PASC.

This study has been published on a preprint server and is currently being peer-reviewed.

Journal Reference

VanElzakker MB, Bues HF, Brusaferri L, et al. Neuroinflammation in post-acute sequelae of COVID-19 1 (PASC) as assessed by [11C]PBR28 PET correlates with vascular disease measures. bioRxiv preprint, October 20, 2023. https://doi.org/10.1101/2023.10.19.563117