



A significant increase in brain PET signal, an indicator of neuroinflammation, correlated with blood indicators of vascular health in individuals with post-acute sequelae of COVID-19 | 1

The authors from the United States conducted a case-control observational study using [11C]PBR28 PET neuroimaging and blood analyzes to investigate the association between neuroinflammation and vascular health in individuals with symptoms of post-acute sequelae of COVID-19 (PASC). They also examined whether the parameters of neuroinflammation were elevated in individuals with PASC compared to healthy controls. The results provide indirect evidence that differences in PET signal across brain regions, as an indicator of neuroinflammation, could partially reflect variations in vascular health and perivascular immune infiltration in individuals with PASC.

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. Neurological symptoms in patients with long COVID are the most frequent, persistent and disabling. These symptoms include headaches, visual and olfactory dysfunction, gait disturbances, paresthesia, coordination problems, depression, anxiety, disrupted sleep, and cognitive impairments, such as concentration and memory problems. The underlying mechanisms of PASC are still being investigated, but evidence shows that vascular issues seen in acute COVID-19 illness may persist in some people with PASC.

About the study

In this cross-sectional study, 12 individuals with PASC were compared to 43 control individuals who had no prior exposure to SARS-CoV-2. The inclusion criteria for PASC were based on the International consensus criteria for modified myalgic encephalomyelitis/chronic fatigue syndrome, which required at least one symptom from the following: neurological, immune, gastrointestinal, genito-urinary, and autonomic. All participants diagnosed with PASC had COVID-19 before August 2021, and at least 10 months before the scan date (mean=20.50 months), which indicates pre-Omicron strains. Two participants with PASC were hospitalized during the acute COVID-19 infection, and one of them was vaccinated prior to acute COVID-19 infection. The majority of the controls (34 of the 43) were scanned before the pandemic, whereas all post-pandemic controls had a



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negative plasma antibody test.

Participants with PASC completed questionnaires related to their PASC symptoms and history. In addition, all 12 participants with PASC and 43 control subjects completed the Brief Pain Inventory (BPI) and the Beck Depression Inventory (BDI). None of the PASC participants reported a history of depression prior to COVID-19.

Neuroinflammation was studied using dual PET-MRI neuroimaging. The parameters of vascular health, inflammation, and angiogenesis were analyzed in peripheral blood collected from participants with PASC immediately before their PET scan.

Vascular health indicators tested included α 2-macroglobulin, orosomucoid, C-reactive protein, fetuin A, fibrinogen, haptoglobin, sL-selectin (soluble leukocyte selectin, or sCD62L), platelet factor 4 (PF4) and pentraxin-2.

The cytokines tested included interleukin (IL)-1 β , 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 .

The indicators of angiogenesis tested included 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.

The Results

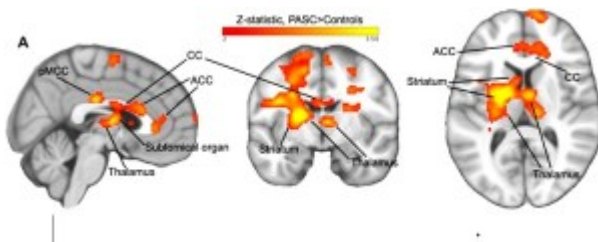
Only two of 12 individuals diagnosed with PASC met the threshold for moderate depression, and the average depression score was mild. Depression was either denied as a problem (50%) or reported as a new (~42%) or serious new (~8%) problem after COVID-19.

In contrast to the healthy controls, the individuals with PASC showed a significant increase in [11C]PBR28 PET signaling, 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

D

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precentral gyrus.



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The intensity of the whole-brain PET signal correlated positively with the majority of indicators of vascular health, including fibrinogen, α 2-macroglobulin, orosomucoid, fetuin A, sL-selectin, pentraxin-2, and haptoglobin.

According to the authors, these results provide indirect evidence that differences in PET signal across brain regions, as an indicator of neuroinflammation, could partially reflect variations in vascular anatomy and perivascular immune infiltration. The integrity of the blood-brain barrier is compromised during neuroinflammation, and, therefore, these vascular factors may penetrate into the brain parenchyma. For example, sL-selectin, an adhesion molecule responsible for the initial attachment of leukocytes to inflamed vascular endothelium, was one of the analytes from the vascular health panel that showed significant correlation with PET signal related to neuroinflammation.

Cytokine concentrations correlated with one another, but, they did not show a correlation with PET signal. Similarly, the indicators of angiogenesis were not correlated with the PET signal.

Although these results do not establish a causal relationship between neuroinflammation and vascular health, they may suggest that an interaction between neuroinflammation and vascular health could contribute to the common symptoms of PASC.

The results of the study have been published on a preprint server and are currently being peer-reviewed.



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Journal Reference

VanElzakker MB, Bues HF, Brusafferri 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>