Alzheimer's disease is characterized by senile plaques composed of amyloid-beta peptides and neurofibrillary tangles composed of hyperphosphorylated microtubule-associated tau proteins, which lead to brain atrophy. Long/post-COVID represents a heterogeneous nosological entity, but the most frequent, persistent, and disabling symptoms are neurological. Cognitive impairments, collectively known as "brain fog", have been widely recognized as neurological sequelae of COVID-19. As recent findings have shown an increase in Alzheimer's disease-related plasma biomarkers in post-acute COVID-19, in this study, the Chinese authors investigated Alzheimer's disease-like neuropathological changes in *postmortem* human brain samples from patients who died of acute COVID-19 and COVID-19 convalescents who died within 4-13 months after acute infection.

Investigations of Alzheimer's disease pathogenesis demonstrated the accumulation of amyloid-beta peptides, chronic neuroinflammation, tau pathology, and irreversible neuron loss. The functions of tau, the microtubule-associated protein abundant in neurons, are regulated by site-specific phosphorylation events. Disruption in the normal tau phosphorylation, which plays a key role in the pathogenic processes in Alzheimer's disease and other tauopathies, was detected in axons very early. Conformational changes and polymerization of tau, as well as neuronal dysfunction and death, follow abnormal tau phosphorylation. The levels of total tau and tau phosphorylated at threonine 181 (Thr181), threonine 217 (Thr217) and threonine 231 (Thr231) in plasma and cerebrospinal fluid are diagnostic of Alzheimer's disease during the preclinical period with high accuracy. *Postmortem* histopathological examinations showed that all of these p-tau species are present in pretangles and neurofibrillary tangles in the brains of patients with Alzheimer's disease.

Interestingly, in 2021, Yapici-Eser et al. hypothesized that mimicry between human proteins and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) proteins may have a role in neurobiological pathways that underlie the neuropsychiatric manifestations of COVID-19 and long COVID syndrome. They utilized a computational methodology (Host-Microbe Interaction PREDiction Algorithm) to detect mimicry between human proteins and SARS-CoV-2 proteins and classified these interactions according to the molecular paths of COVID-19-associated neuropsychiatric symptoms. The results showed that SARS-CoV-2 proteins mimic 17 proteins linked with Alzheimer's disease-amyloid secretase pathway and 25 proteins linked with Alzheimer's disease-presenilin pathway, like beta-secretase, presenilin-1, amyloid-beta precursor and gamma-secretase subunit-2. (Yapici-Eser et al. Neuropsychiatric Symptoms of COVID-19 Explained by SARS-CoV-2 Proteins' Mimicry of Human Protein. Front Hum Neurosci 2021 15:656313.)

https://www.frontiersin.org/journals/human-neuroscience/articles/10.3389/fnhum.2021.656313/full

About the study

This pilot study included a small number of *postmortem* brain samples from three cohorts: patients who died from acute COVID-19 (n = 6), convalescents from COVID-19 who died within 4-13 months of acute infection ($n = 7$), and uninfected controls ($n = 6$). The SARS-COV-2 infection and recovery were confirmed or ruled out by nucleic acid amplification test. Only individuals without cognitive impairments before SARS-COV-2 infection were included.

Since the hippocampus and medial entorhinal cortex are prone to phosphorylated tau accumulation and neurodegeneration and play a crucial role in the development of Alzheimer's disease, the researchers investigated the levels and distribution of phosphorylated tau in these regions. They also examined two other Alzheimer's disease-related pathologies, amyloid-beta deposition, and hippocampal neuron loss, as well as a possible SARS-COV-2 invasion into the brain.

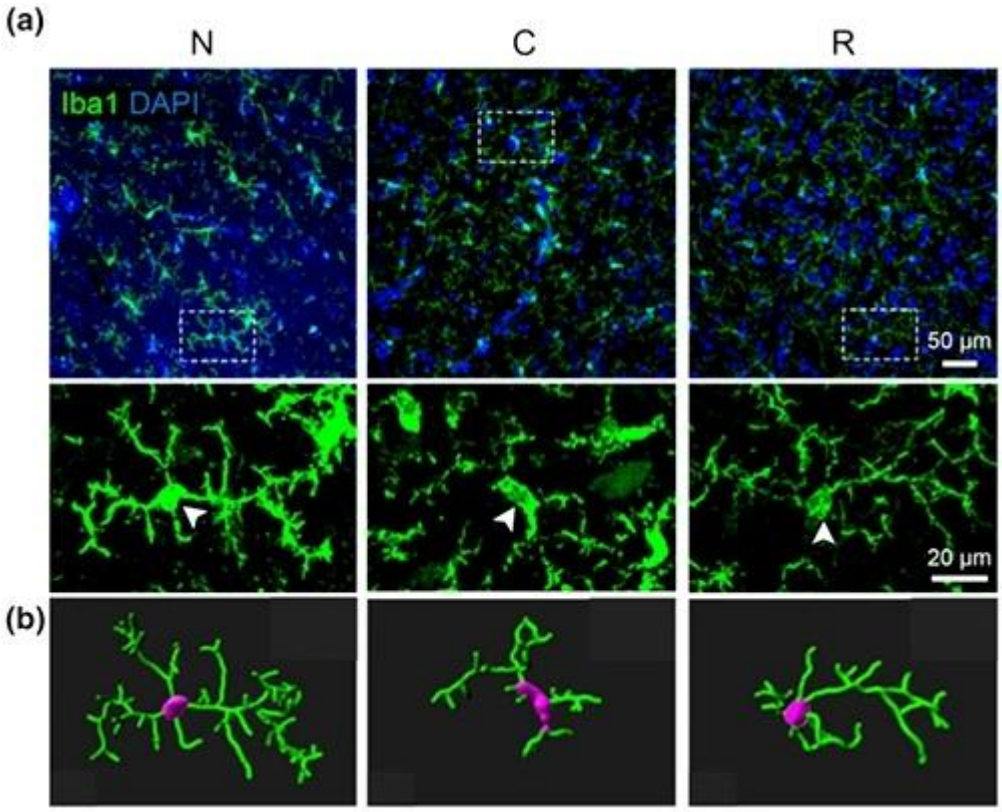
Since abnormal glial activation and neuroinflammation contribute to the increase of phosphorylated tau in Alzheimer's disease, glial dysfunction in the hippocampus and medial entorhinal cortex was also examined.

Results

There was no significant change in phosphorylated tau and total tau in the hippocampus and medial entorhinal cortex from patients who died from acute COVID-19 and uninfected controls. Also, there was no significant change in the size and density of amyloid-beta plaques and hippocampal neuron loss in those who died from acute COVID-19 and COVID-19 convalescents.

Nevertheless, phosphorylated tau, particularly phosphorylated tau Thr181 and Thr217, and hyperphosphorylated tau AT8+, all of which are associated with Alzheimer's disease, were unexpectedly up-regulated in the hippocampus and medial entorhinal cortex of COVID-19 convalescents who died within 4-13 months of acute infection compared to uninfected controls. In contrast, there was no significant change in phosphorylated tau in olfactory areas, including the olfactory bulb, anterior olfactory nucleus, olfactory tubercle, piriform cortex, and lateral entorhinal cortex.

The numbers of microglia and glial fibrillary acidic protein (GFAP)-labeled astrocytes were unchanged in the hippocampus and medial entorhinal cortex of individuals who died of acute COVID-19 and COVID-19 convalescents who died within 4-13 months of acute infection. However, both groups had morphological signs of microglial activation, and up-regulation of ionized calcium-binding adaptor molecule1 (Iba1), trans had membrane glycoprotein CD68, GFAP, and S100 beta.



The original figure from an article by Qi X et al. Prolonged upregulation of glia activation and inflammatory factors expression in the hippocampus of COVID-19 convalescents

The levels of inflammatory cytokines, including tumor necrosis factor-alpha, interleukin(IL)-1β, and IL-6 were up-regulated in deceased COVID-19 convalescents and patients who died of acute COVID-19. Other cytokines like IL-10 and IL-18, and neuroinflammation-related proteins like high mobility group box 1 and plasminogen activator inhibitor-1 were nearly unchanged.

According to the authors, these results demonstrated prolonged glial activation and neuroinflammation, two important drivers of tau hyperphosphorylation in Alzheimer's disease by dysregulation of tau kinases and phosphatases.

Immunohistochemical staining of the SARS-COV-2 nucleocapsid and spike proteins did not detect SARS-CoV-2. Also, real-time quantitative reverse transcription PCR (RT-qPCR) or droplet digital PCR (ddPCR) did not detect SARS-COV-2 ORFab1 and nucleocapsid protein mRNA.

Conclusion

This study showed an abnormal accumulation of hyperphosphorylated tau proteins in *postmortem* samples of the hippocampus and medial entorhinal cortex of COVID-19 convalescents who died within 4-13 months after acute COVID-19. The results also showed prolonged glial activation and neuroinflammation. There was no change in beta-amyloid deposition and hippocampal neuron number. The SARS-COV-2 invasion was not detected in brain regions analyzed.

The authors concluded that these results provided neuropathological evidence that COVID-19 is associated with an increased risk for Alzheimer's disease.

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Journal Reference

Qi X, Yuan S, Ding J et al. Emerging signs of Alzheimer-like tau hyperphosphorylation and neuroinflammation in the brain post recovery from COVID-19. Aging Cell. 2024;00:e14352. https://doi.org/10.1111/acel.14352