DOI: 10.1002/alz.056418

BASIC SCIENCE AND PATHOGENESIS

POSTER PRESENTATION

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

COVID-19 and Alzheimer's disease: Meninges-mediated neuropathology

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Abstract

Background: SARS-CoV-2 the causative agent of COVID-19 displays a broad range of pathophysiology. Cytokine storms associated with COVID-19 damage the blood-brain barrier (BBB) and allow pro-inflammatory factors to invade the brain, further promoting neurodegeneration. While SARS-CoV-2 viral RNA and proteins have been detected in brain tissues, the mechanisms of neuroinvasion remain unknown. COVID-19 has had a disproportionate impact on those suffering from neurodegenerative disorders such as Alzheimer's disease (AD). Understanding the mechanisms of SARS-CoV-2 neuroinvasion is crucial to study the long-term neurocognitive effects of COVID-19 on AD pathology. Viruses can infiltrate the brain through the meninges via infected immune cells. The meninges regulate the immune surveillance of the brain and play a key role in the efflux of pathogens from the brain. Meningeal dysfunction has been demonstrated to exacerbate amyloid-beta pathogenesis. In this study, we explore the neuroinvasion pathway of SARS-CoV-2 through the meninges and its effect on AD pathology.

Method: 5x FAD x hACE2 mice were inoculated intranasally with a sublethal dose of SARS-CoV-2. The mice were maintained for 2 weeks. Mouse brains and meninges were harvested. The tissue was stained and immunofluorescence imaging was conducted to study viral proliferation and immune responses. Histo-cytometry was conducted for quantitative imaging analysis. Gene expression studies were done using Nanostring assays. All experiments involving the SARS-Cov-2 virus were carried out in a BSL3 facility.

Result: This ongoing study demonstrates the proliferation of the SARS-CoV-2 virus in the brain via meningeal lymphatics. SARS-CoV-2 infection resulted in increased neuroinflammation. Additionally, inflammatory responses induced meningeal dysfunction resulting in increased amyloid-beta pathology and cerebrospinal fluid drainage.

Conclusion: Given the increasing evidence for a viral hypothesis of Alzheimer's Disease it is extremely important to study the neurodegenerative effects of COVID-19 which has affected millions worldwide. We demonstrate that SARS-CoV-2 infiltrates the brain via the meninges promoting neuroinflammation. Furthermore, amyloid-beta pathologies are exacerbated by COVID-19 in animal models providing preclinical evidence of the long-term neurodegenerative effects of COVID-19.