DOI: 10.1002/alz.056183

BASIC SCIENCE AND PATHOGENESIS

POSTER PRESENTATION

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

Role of SARS-CoV-2 in causing blood-brain barrier leakage and microglial activation as a risk factor of cognitive deterioration in subjects at risk of Alzheimer's disease

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Abstract

Background: The recent pandemic provides evidence of altered central nervous system (CNS) function in response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-COV-2 invades the CNS by binding angiotensin-converting enzyme 2 (ACE2) expressed on neurons and glia. SARS-COV-2 may have effects on increased permeability of endothelial cells within the blood-brain barrier (BBB) as studies have shown that the S1 protein can transverse the BBB. This is interesting because leakage of the BBB is implicated in Alzheimer's disease (AD) pathogenesis. We hypothesized that SARS-CoV-2 infection leads to innate stimulated inflammation, ultimately activating microglial cells and an influx of pro-inflammatory cytokines and leukocytes in the meninges, contributing to increased permeability of the BBB. This BBB permeability increases AD susceptibility in subjects at risk by causing irreversible damage to the BBB and microglial cell activation.

Method: We developed a double transgenic mouse model using mice expressing human ACE2 receptor and 5xFAD mice that exhibit increased neuropathology seen in human AD allowing modeling of AD in SARS-CoV-2 pathogenesis. The hACE2/5xFAD double transgenic mice were intranasally inoculated with a sub-lethal dose of SARS-CoV-2 to test the hypothesis that SARS-COV-2 potentiates AD pathology and cognitive deterioration through impairment of the BBB. Leukocyte and cytokine populations were measured by flow cytometry and single-nuclei RNA sequencing of the meninges for characterization of microglial populations.

Result: SARS-CoV-2 creates a cytotoxic environment in the brain immediately following infection in hACE2/5xFAD mice leading to leakage of the BBB in the meninges. Activation of microglial innate cells by SARS-COV-2 invasion of the CNS will cause neural deterioration having long term implications on cognitive function. The hACE2/5xFAD mouse model allows us to uncover implications for SARS-COV-2 on AD cognitive deterioration.

Conclusion: The hACE2/5xFAD mouse allows modeling of SARS-CoV-2 in developing AD cases and allowed us to determine the immune environment generated in the meninges in response to SARS-CoV-2 infections. This mouse model provides a platform to proactively determine the effects of SARS-CoV-2 in developing AD cases, a methodology to be exploited for future mouse models determining the relationship of other viruses on AD pathology, and the opportunity to address phenotypes with therapeutics for preventative initiatives.