Examining the Link between SARS-CoV-2 Exposure and Neurodegeneration: Findings from a Study on Hamsters

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Received date: 07-June-2023, Manuscript No: JMSO-23-104782; **Editor assigned:** 10-June-2023, PreQC No. JMSO-23-104782 (PQ); **Reviewed:** 24-June-2023, QC No. JMSO-23-104782 (Q); **Revised date**: 26-June-2023, Manuscript No: JMSO-23- 104782 (R); **Published date:** 29-June-2023, DOI: 10.35248/2376-0389.23.10.6.504

Introduction

The extent of brain infection caused by SARS-CoV-2 and the specific routes of invasion are still uncertain. However, an increasing number of reports indicate that even individuals with mild cases of COVID-19 may experience long-term mental health and neurological consequences. In a recent study mentioned as an example, Kaufer et al. conducted research on a Golden Syrian hamster model of COVID-19. Their findings, published in this issue of eBioMedicine [1-3], demonstrate that while SARS-CoV-2 infection predominantly spares the brain, it does lead to an increase in micro gliosis (activation of brain immune cells) and the accumulation of hyper phosphorylated Tau and alpha-synuclein proteins in remote brain regions. These changes persist after the infection has resolved. The study is notable for two reasons:

- It utilizes an animal model that naturally expresses the ACE2 protein, which is the receptor for most SARS-CoV-2 strains, unlike mice, and exhibits various aspects of COVID-19 pathogenesis seen in humans, including sub-lethal infection and recovery.
- It suggests that even without direct invasion of the brain by SARS-CoV-2, viral infection in the nasal cavity can trigger neuro-inflammation and neurodegenerative alterations in the brain that persist for a considerable period, potentially contributing to a higher long-term incidence of conditions like Alzheimer's or Parkinson's disease.

The evidence for SARS-CoV-2 infecting brain cells, including neurons, in deceased human patients is well-established through post-mortem studies. However, it should be noted that these patients had severe infections, which may have facilitated the virus's access to the brain or compromised protective barriers. Determining whether the virus also infects brain cells in COVID-19 patients who survive mild or moderate disease can only be inferred from their symptoms and clinical signs, as well as from sub lethal infections observed in preclinical models. The entry of the virus into the brain through the olfactory route, given its abundance in the upper respiratory tract, may seem plausible. However, studies present conflicting findings regarding whether the virus infects olfactory sensory neurons, giving rise to alternative hypothetical pathways for viral entry into the brain, such as through the nervus terminalis or the hypothalamus [4].

Furthermore, the extensive destruction of brain endothelial cells by the SARS-CoV-2 main protease, observed in both patients and animal models, including hamsters, suggests that the brain could potentially be exposed to circulating virus particles in the bloodstream. Additionally, contrary to the findings of the current article, other studies have demonstrated infection of neurons in the olfactory bulb of hamsters following nasal administration of SARS-CoV-2, indicating their contribution to viral pathogenesis [5,6].

In this context, it is unfortunate that the current article lacks images of viral protein immune-labeling in the olfactory bulb and other brain regions. Furthermore, the study only utilized one antibody and examined viral presence or absence at a single acute time point, and the methods section does not specify how or in which brain regions viral titers were measured using plaque forming assays.

Whether neuro invasion was truly absent or simply undetectable, the fact that SARS-CoV-2 infection induced neuro-inflammation in the olfactory bulb and led to elevated levels of hyper-phosphorylated Tau and alpha-syncline in the supra-hippocampal cortex, distant from the site of viral administration, with these changes persisting beyond the infection period, is intriguing. These findings bear similarities to a nearly simultaneous study conducted on rhesus and cynomolgus macaques, which demonstrated the persistence of micro gliosis and aggregation of alpha-syncline several weeks after SARS-CoV-2 infection [7].

The connection between viral infections, inflammation, and the risk of developing neurodegenerative disorders has been hypothesized for many years and has been a significant concern since the onset of the pandemic [8]. Indeed, observations from both living COVID-19 patients and post-mortem tissues confirm the presence of changes resembling an acceleration of neurodegenerative processes that typically take years to manifest. However, it remains to be determined whether these changes represent an acute response to infection and/or death, or if they signify the initiation of a long-term breakdown in the brain's ability to sequester or clear pathogenic molecules.

Moreover, SARS-CoV-2 infection appears to activate various molecular pathways implicated in neurodegenerative processes [9,10]. Further mechanistic investigations, including studies utilizing other animal and cellular models, are necessary to gain a deeper understanding of these pathways and their interplay. Additionally, prospective studies conducted on cohorts of human COVID-19 patients are essential to validate the significance of specific pathways in the development of neurodegenerative disorders and long-term functional impairments.

In conclusion, although SARS-CoV-2 infection may be temporary, the concerning prevalence of long-term neurological and mental health effects among a considerable number of patients is alarming. The study conducted by Kaufer et al. sheds light on the presence of persistent neuro-inflammatory and neurodegenerative alterations in the hamster brain beyond the infectious period [2]. This finding contributes another important component to the overall understanding of how SARS-CoV-2 affects the brain, which is crucial for assessing the potential risk of a secondary pandemic characterized by accelerated neurodegeneration and cognitive impairments.

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Cite this article: Fu, X. and Chen W. Examining the Link between SARS-CoV-2 Exposure and Neurodegeneration: Findings from a Study on Hamsters. J Mult Scler 2023, 10(6), 504