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Relationship between COVID-19 and Alzheimer's Disease

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Abstract

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a life-threatening disease, especially in elderly individuals and those with comorbidities. The predominant clinical manifestation of COVID-19 is respiratory dysfunction, while neurological presentations are increasingly being recognized. SARS-CoV-2 invades host cells primarily via attachment of the spike protein to the angiotensin-converting enzyme 2 (ACE2) receptor expressed on cell membranes. Patients with Alzheimer's disease (AD) are more susceptible to SARS-CoV-2 infection and prone to severe clinical outcomes. Recent studies have revealed some common risk factors for AD and COVID-19. An understanding of the association between COVID-19 and AD and the potential related mechanisms may lead to the development of novel approaches to treating both diseases. It is important to understand the mechanisms by which SARS-CoV-2 invades the central nervous system (CNS) and the associations and potential shared factors between COVID-19 and AD.

Keywords: COVID-19; Alzheimer's disease; correlation; mechanism of action

Introduction

From the beginning of the COVID-19 outbreak, simultaneously with treatment measures, health and preventive measures such as strict quarantine, social distancing, hand washing, disinfection of various surfaces, and wearing a mask among others, as health protocols to reduce and cut off the transmission chain were on the agenda of governments and health organizations [1, 2]. SARS-CoV-2 infects target cells primarily via interaction of the receptor-binding domain of the S protein with the cellular angiotensin-converting enzyme 2 (ACE2) receptor after activation of the S protein by transmembrane serine protease 2 (TMPRSS2) [3]. The S protein is composed of two functional subunits, S1 and S2; S1 is responsible for receptor binding, whereas S2 (the C-terminal domain) is specifically responsible for viral-cellular membrane fusion [4, 5]. Although SARS-CoV-2 primarily targets the respiratory tract, causing fever, dry cough, sore throat, fatigue, and dyspnoea [6], the virus also results in dysfunction of multiple organ systems outside the lung, including the kidneys, liver, brain, heart, gastrointestinal tract and other organ, as ACE2 and other candidate receptors are also expressed in these tissues [7].

In fact, the central nervous system (CNS) complications have been observed in more than 30% of individuals with COVID-19 presenting with a higher infection severity. Emerging studies have revealed the neuroinvasive potential of SARS-CoV-2, with neurological manifestations ranging from lethargy, headache, loss of smell and taste, delirium, insomnia, brain inflammation, stroke, brain haemorrhage to cognitive impairment [8].

Various studies using cultured cells, animal models, and brain tissues from patients who died of COVID-19, have independently revealed the capacity of SARS-CoV-2 to invade the CNS [9]. Supporting evidence from a postmortem study indicated the presence of viral RNA and proteins in the brains of more than half (21 of 40) of German patients who died of COVID-19 [10]. In addition, the presence of SARS-CoV-2 in the cerebrospinal fluid (CSF) of infected individuals also confirms CNS infection. Notably, by employing well-characterized human brain organoids, researchers have visualized widespread infectivity of SARS-CoV-2 and extensive death of virus-infected and nearby neuronal cells, and found that the viral infection can be abrogated by pretreatment with an ACE2 antibody or administration of CSF obtained from patients with COVID-19 [11]. Moreover, brain imaging studies have revealed the presence of multiple haemorrhagic lesions and changes in the brain structure of patients infected with SARS-CoV-2, even in milder cases [12]. Together, this evidence implies that SARS-CoV-2 has the ability to enter the CNS and cause neurological conditions.

In a recent study, diffuse neural inflammatory markers were found in >80% of COVID-19 patient brains, processes which could contribute to the observed neurological symptoms [13]. Furthermore, another pair of frequent symptoms of infection by SARS-CoV-2 are hyposmia and hypogeusia, the loss of the ability to smell and taste, respectively. Interestingly, hyposmia has been reported in early-stage Alzheimer's disease (AD), and AD type II astrocytosis has been observed in neuropathology studies of COVID-19 patients [14].

ACE2 correlation to TGF-β

Recent studies have reported an inverse relationship between ACE2 and transforming growth factor-β (TGF-β). In cancer models, decreased levels of ACE2 correlated with increased levels of TGF-β. In the context of SARS-CoV-2 infection, downregulation of ACE2 has been observed, leading to increased fibrosis formation, as well as upregulation of TGF-β and other inflammatory pathways. Moreover, patients with severe COVID-19 symptoms had higher blood serum TGF-β concentrations than those with mild symptoms, thus further implicating the role of TGF-β and warranting further investigation. Interestingly, reduced angiotensin/ACE2 activity has been associated with tau hyperphosphorylation and increased amyloid beta (Aβ) pathology in animal models of AD [15, 16].

Neuroinflammation is recognized as another characteristic pathophysiology of AD. Microglia and astrocytes are major sources of cytokines in individuals with AD. Dysfunction of the immune system may promote the release of proinflammatory cytokines and result in synaptic damage, neuronal death, and inhibition of neurogenesis, which are related to the pathogenesis of AD [17].

Although accumulating evidence indicates that SARS-CoV-2 can enter the CNS, the presence of the virus in the brain may not critically correlate with the neurological conditions, as postmortem studies have noted occurrence of pronounced neuropathological changes even in patients with COVID-19 in whom the virus was not detected in the CNS. Instead, extensive research on CSF and postmortem brain tissues has indicated that immune dysfunction and pronounced neuroinflammation within the CNS are the main driver of CNS damage and neurological symptoms in infected individuals. Neuroinflammation might result directly from coronavirus infection or from excessive peripheral inflammation. Both SARS-CoV-2 and proinflammatory mediators may promote BBB disruption, allowing the virus to cross the BBB, enter the CNS, and activate microglia and astrocytes, triggering a neuroinflammatory cascade that may contribute to the onset and progression of neurodegeneration [18].

Pathogen-associated molecular pattern (PAMP)

Several previous studies have suggested that the S protein of SARS-CoV-2 might function as a pathogen-associated molecular pattern (PAMP) to drive neuroinflammatory responses through activation of TLRs, which are widely expressed on macrophages and microglia and may function as pattern recognition receptors (PRRs) to recognize molecular sequences common to bacterial and viral pathogens. Microglia have been shown to express a wide range of PRRs, including TLRs, NOD-like receptors, RAGE and scavenger receptors. SARS-

CoV-2 activates these receptors, possibly eliciting neuroinflammatory responses and contributing to disease progression and severity [19].

Astrocytes are also important components of the intrinsic immune response in the CNS following viral infection. An increased plasma concentration of glial fibrillary acidic protein (GFAP), a hallmark of astrocyte activation, is commonly detected in patients with moderate and severe COVID-19. As components of the BBB, astrocytes are highly sensitive to peripheral inflammation. In addition to responding to signals from microglia, astrocytes also rapidly respond to proinflammatory cytokines secreted by endothelial cells. Astrocytes express inflammatory molecules that contribute to neuroinflammation and neurodegeneration upon exposure to activated proinflammatory microglia, including proinflammatory cytokines such as IL-6, IL-1β and TNF-α; PAMPs; and danger-associated molecular patterns. These data clearly indicate that microglia and astrocytes participate in neuroinflammatory responses to viral infection of the CNS [20].

Conclusions

The mechanism by which the virus gains access to the CNS and why patients with AD are at higher risk of virus infection are not well understood. Although people infected with SARS-CoV-2 frequently display neurological symptoms, multiple manifestations remain unrecognized. First, neurological symptoms are often ignored because the first goal is to combat respiratory symptoms. In addition, clarifying the mechanisms by which SARS-CoV-2 invades and spreads throughout the CNS is important for preventing and ameliorating neurological symptoms. Studies are imperatively needed to clarify the potential mechanisms underlying the elevated susceptibility and mortality rate of AD patients to COVID-19 and discover preventive strategies to minimize the risk of viral infection among patients with AD.

References

1. Hashemi Fallah., et al. "A Comprehensive Health Effects Assessment of the Use of Sanitizers and Disinfectants during COVID-19 Pandemic: A Global Survey (preprint)". (2022).
2. Harfouch RM. "Antiviral Effects of Propolis against SARS-COV 2". Int J Clin Med Imaging (2022).
3. Harfouch RM., et al. "Therapeutic approaches for covid 19: Challenges and successes". Annals of Clinical and Analytical Medicine (2021): 228-233.
4. Alhouri Ali., et al. "Possible side effects of using detergents during the Covid19 pandemic in Syria". Ann. Clin. Cases 1.4 (2020): 1023.
5. Harfouch Rim M. "Cytokine Storm syndrome in COVID-19 patients: Characteristics And diagnosis". Journal of Clinical Epidemiology & Toxicology 2.4 (2021): 1-3.
6. Harfouch RM., et al. "Epidemiology of COVID-19 in the most pandemic Countries: A review article". Acad. J. Biotechnol 9.1 (2021): 021-027.
7. Harfouch Rim. "Multiple organs failure in COVID-19 patients". Authorea Preprints (2022).
8. Desforges M., et al. "Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system?" Viruses 12.1 (2019).
9. Harfouch Rim. "Effect of SARS-COV2 virus on nervous system and mental health". Authorea Preprints (2022).
10. Matschke J., et al. "Neuropathology of patients with COVID-19 in Germany: a post-mortem case series". Lancet Neurol 19.11 (2020): 919-29.
11. Jarius S., et al. "Cerebrospinal fluid findings in COVID-19: a multicenter study of 150 lumbar punctures in 127 patients". J Neuroinflammation 19.1 (2022): 19.
12. Coolen T., et al. "Early postmortem brain MRI findings in COVID-19 non-survivors". Neurology 95.14 (2020): e2016-27.
13. Thakur KT., et al. "COVID-19 neuropathology at Columbia University Irving Medical Center/New York Presbyterian Hospital". Brain 144 (2021): 2696-2708.
14. Lou JJ., et al. "Neuropathology of COVID-19 (neuro-COVID): clinicopathological update". Free Neuropathol 2 (2021): 2.

15. Jiang T., et al. "Angiotensin-(1-7) is reduced and inversely correlates with tau hyperphosphorylation in animal models of Alzheimer's disease". Mol Neurobiol 53 (2016): 2489-2497.
16. Kehoe PG., et al. "Angiotensin-converting enzyme 2 is reduced in Alzheimer's disease in association with increasing amyloid-beta and tau pathology". Alzheimers Res Ther 8 (2016): 50.
17. Leng F and Edison P. "Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here?". Nat Rev Neurol 17.3 (2021): 157-72.
18. Abate G, Memo M and Uberti D. "Impact of COVID-19 on Alzheimer's disease risk: viewpoint for research action". Healthcare (2020).
19. Wang WY., et al. "Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease". Ann Transl Med 3.10 (2015): 136.
20. Chen F., et al. "The COVID-19 pandemic and Alzheimer's disease: mutual risks and mechanisms". Transl Neurodegener (2022).