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Mini Review

Alzheimer's Disease Susceptibility to Sars-CoV-2 and Impact of Viral Infection on AD Patients

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Alzheimer disease (AD) seriously affects the elderly and causes cognition disabilities leading to morbidity and mortality [1]. Coronavirus 2 or Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), the pathogen of COVID-19, is an enveloped RNA beta-coronavirus that directly invades the central nervous system (CNS). COVID-19 disease impacts the brain and accelerates Alzheimer's related symptoms through damaging the blood-brain barrier (BBB) [2]. SARS-CoV-2 may affect memory even after several months from bearing mild disease conditions, which can have a negative impact on health.

Following invasion of the virus into the CNS, subsequent interaction occurs between SARS-CoV-2 spike protein and the angiotensin-converting enzyme 2 (ACE2) [3,4]. In the brain, ACE-2 is expressed both on neurons and glial cells as well as on endothelial and arterial smooth muscle cells. ACE-2 is also expressed on the temporal lobe and hippocampus, which represent cerebral regions involved in the pathogenesis of Alzheimer's Disease (AD) [3].

In AD, an important neurological disorder affecting brain abilities is related to toxic-metabolic encephalopathy (TME) due to an imbalance in electrolytes, hormones, or other body chemicals. This condition is also observed in advanced cases of COVID-19.

Neuroinflammation is implicated in AD pathology and is also figured out in COVID-19 infection and hence it may be suggested that viral infection may accelerate the progression of brain inflammatory neurodegeneration in AD. In addition, individuals with type 2 diabetes (T2D) are at an increased risk for AD as well as severe outcomes after SARS-CoV-2 infection. Type I interferon response plays an important role in both host response to viral infection, as well as AD pathology and may be an efficient therapeutic target in both AD and COVID-19 [5].

It is an important challenge to investigate metabolic biomarkers relating AD to coronavirus infection. In this concern, it was postulated that APOE4, is a genetic risk factor for AD [6] and may also increase the exposure to coronavirus infection which causes COVID-19. Thus, APOE4 could exert multiple actions for high infection and mortality rates of the patients, or generally, with COVID-19 [7].

It was previously reported that patients with AD disease, once infected by the underlying coronavirus SARS-CoV-2, are 5 times likely to die of this infectious disease [8]. However, reduced expression levels of APOE in both brain and peripheral systems suggest that this variant causes an increased risk not only for AD, but also for systemic susceptibility to coronavirus infection [7,8]. In other words, patients with APOE4-associated AD may carry higher vulnerability in their peripheral organs such as the lung, possibly via enhancing the receptors' activities and facilitating the coronavirus entry. Comparing to two other isoforms, APOE4 is genetically associated with reduced APOE levels for increased coronavirus infection and disease progression risks, and consistently with severe COVID-19 as well. Thus, there is

evidence APOE4 is an important risk marker for the severity of COVID-19 pathology in patients with AD. If further verified, APOE genotyping may help guide evidence-based healthcare of the comorbid patients.

An interesting question is raised whether patients with COVID-19 could develop AD? Overall, Corona viruses can enter the CNS via different routes, including retrograde axonal transport via the olfactory and enteric neurons or infected lymphocytes, which cross the disrupted blood-brain barrier (BBB) [9]. Since aging is characterized by a gradual loss of the BBB integrity [10], therefore, the elderly could be more susceptible to neuroinvasion during SARS-CoV-2 infection. Consequently, the resulting neuroinflammation could become uncontrollable, especially in the aged people, which have a weaker immune system response [11,12]. Neuroinflammation, associated with intense oxidative stress, could induce neurodegeneration, potentially favouring the development of neurodegenerative diseases, such as AD [13,14]. Moreover, endothelial dysfunction, which is a pathognomonic characteristic of COVID-19, and loss of pericytes could impair the clearance of cerebral metabolites, including Aβ peptides. Thus, it may be assumed that the SARS-CoV-2 neuro-invasion could induce Aβ generation, as part of the immune response, and the b-amyloid cascade leading to b-amyloid deposition [15].

In conclusion, COVID-19 may heighten the risk of developing Alzheimer's, and COVID-19 can cause an increase in blood-based molecular biomarkers for Alzheimer's disease.

In addition, the memory disabilities in these patients may impair their understanding to comply with preventive measures for COVID-19 such as social distancing, mask wearing, and frequent hand sanitizing [16].

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