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Exploring the interplay between Alzheimer's disease and COVID-19: Insights into cognitive impairment and drug interactions

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Abstract. Alzheimer's disease (AD) is a severe well-known cognitive disease, and it is also the most worldwide cause of dementia. Studies have shown that AD may have some interactions with the coronavirus disease 2019 (COVID-19) in some particular areas. This paper aims to figure out the potential associations how one causes the interplay of another, whether directly or indirectly. In addition, the paper provides a comprehensive mechanism underlying cognitive impairment also known as "brain fog" of COVID-19, including the effects on neurons and glial cells by persistent elevation of the chemokine CCL11. Then the paper provides drug-drug interaction with metabolized by same cytochrome enzymes lead to major changes in the pharmacology of treatments. Finally, the paper concludes the points mentioned about the associations between COVID-19 and AD then suggests the direction of the future studies.

Keywords: Alzheimer's disease, Cognitive Impairment, Drug Interactions, COVID-19

1. Introduction

It's been recorded that a series of pneumonia cases of unfamiliar etiology (December, 2019) , occurred in China with a very similar clinical manifestations to viral pneumonia [1] was named as SARS-CoV-2 (the disease named as COVID-19). SARS-CoV-2 predominately assault on human's respiratory system and cause the following symptoms such like fever, coughs, colds, throat pains, dyspnea, etc. And the elder group is shown to be more vulnerable to the virus [1]. What's more, AD is one of the most familiar kinds of central nervous system comorbidities of COVID-19 [2]. The SARS-COV-2 can cause various neurological symptoms. One hypothesis for the COVID-19 aggravate the symptoms of AD patients is that the virus invades the central nervous system, which is associated with AD infection. Meanwhile, AD patients are more susceptible to COVID-19. This is because they may not have properly remembered or understood the recommended public health precautions [3]. And since COVID-19 management requires self-isolation and quarantine, AD management is not compatible with that of COVID-19 [4]. Among the COVID patients, elder people with dementia are more negatively affected by COVID-19 and take longer to recover [5]. Therefore, the process may worsen the severity of infection and cause greater cognitive impairments. So it's very important to get aware of the association between COVID-19 and AD, the study may raise the attention for better treatments to the present and potential patients.

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2. AD overview

There are more than 25 million people living with dementia in the world nowadays, most of whom have Alzheimer's disease [6]. Alzheimer's disease (AD), a clinical syndrome of cognitive impairment first described more than a hundred years ago, named by German psychiatrist Alois Alzheimer, is the widest cause of dementia, accounting for 75% of dementia cases. The World Health Organization's 2018 report on Alzheimer's disease pointed out that dementia has become a global crisis, with 1 new case of dementia every 3 seconds, about 50 million patients worldwide in 2018, and the number will be unceasing. Until 2030, there will be 82 million and 152 million infections by 2050. Alzheimer's disease (AD) accounts for more than half of people with dementia [8]. AD is a progressive neurodegenerative disease [7]. There were a couple of research suggested that AD is the main onset factor of dementia. Nearly 50% to 75% of patients have dementia caused by Alzheimer's disease. And the situation doubles approximately every 5 years after they get 65 [8]. The prevalence is not a normal part of growing old. The greatest challenge for the AD patients, especially those elder people mainly above 65 is that the illness will deteriorate by aging. The progress is slow or insidious for the onset of the disease. The patients themselves and their family members often cannot recognize when it started. It is more common in the elder group above 70 years old (average 73 years old for men and 75 years old for women), and the symptoms become apparent in a minority of patients after exposure to physical illness, bone fractures, or mental stimulation. It is mainly manifested as a sign of cognitive decline, mental symptoms and behavioral disorders, and a gradual decline in the ability of daily living. In the early stages, memory loss is mild, but the situation will be worsened by time. People will progressively lose the ability to speak and respond to their environment. Typically, the people infected AD can only live four to eight years after diagnosis, but some can live up to 20 years (depending on other factors). For the resent years, AD diagnosis has several breakthroughs. However, the scientists don't yet fully understand the cause of AD. This is likely to be a heterogeneous group of disorders that occur under the influence of multiple factors like psychosocial and biological ones. According to research, there are more than 30 possible factors and hypotheses for the disease, including but not limited to family history, head trauma, female sex, thyroid disease, viral infection, low education level, abnormal childbearing age, etc.

The two main hypotheses are the accumulation of β-amyloid proteins and hyperphosphorylated tau protein aggregation.

Accumulation of β-amyloid (APP)-generated Aβ40-42 contributes to senile plaque formation. Amyloid plaques are extracellular accumulations consists mainly of 40 abnormally folded Aβ with 40 or 42 amino acids (Aβ40 and Aβ42), two by-products APP metabolism. Since it has a high fibrillation rate and Insolubility, Aβ42 shows more in amount than Aβ40 [9].

NFTs, which consist mainly of hyperphosphorylated tau, are another hallmark of AD. At the same time as the NFT is formed, neuronal and synaptic losses occur [10].

3. COVID-19 overview

Coronaviruses are an umbrella term for a large family of viruses that can cause plenty of illnesses, including the common cold, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS). A novel coronavirus was discovered in 2019, which was named severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). The virus can cause the disease named as coronavirus disease 2019 (COVID-19). The World Health Organization (WHO) declared the COVID-19 a pandemic in March 2020. Signs and symptoms of coronavirus disease 2019 (COVID-19) may appear 2 to 14 days after exposure to the virus. Fever, cough, tiredness, etc., can be the common signs and symptoms. Loss of taste or smell may be included as the early symptoms of COVID-19. What's more, the symptoms including shortness of breath or difficulty breathing, muscle pain, sore throat, etc., can be diagnosed as the other symptoms. Most cases related to COVID-19 were lower respiratory tract infections, leading to high rates of virus transmission among hospitals and densely populated areas. 59 is the median age of COVID-19 (range 15–89). Meanwhile, the data showed that men accounted for more than half [11]. Immunocompromised individuals including those with renal and hepatic impairment, especially the elderly, are more susceptible to be infected [11]. The study indicates that

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among COVID-19 patients, nearly 20% of them requiring ICU admission were suffering from neurological problems, including stress, depression, and cognitive impairment, etc. [12]. Most importantly, animal studies have shown significant amyloid plaque formation and tau phosphorylation in mice stimulating long-term hospitalization and delirium in AD mice [13,14]. A set of observations has indicated that individuals who have been in the ICU and subsequently require extended hospital stays or are in the process of recovering from COVID-19 may face an elevated risk of experiencing persistent neurocognitive issues in the long term. These issues could potentially contribute significantly to the development of Alzheimer's disease in those who have been affected by COVID-related health challenges.

4. Brain Fog

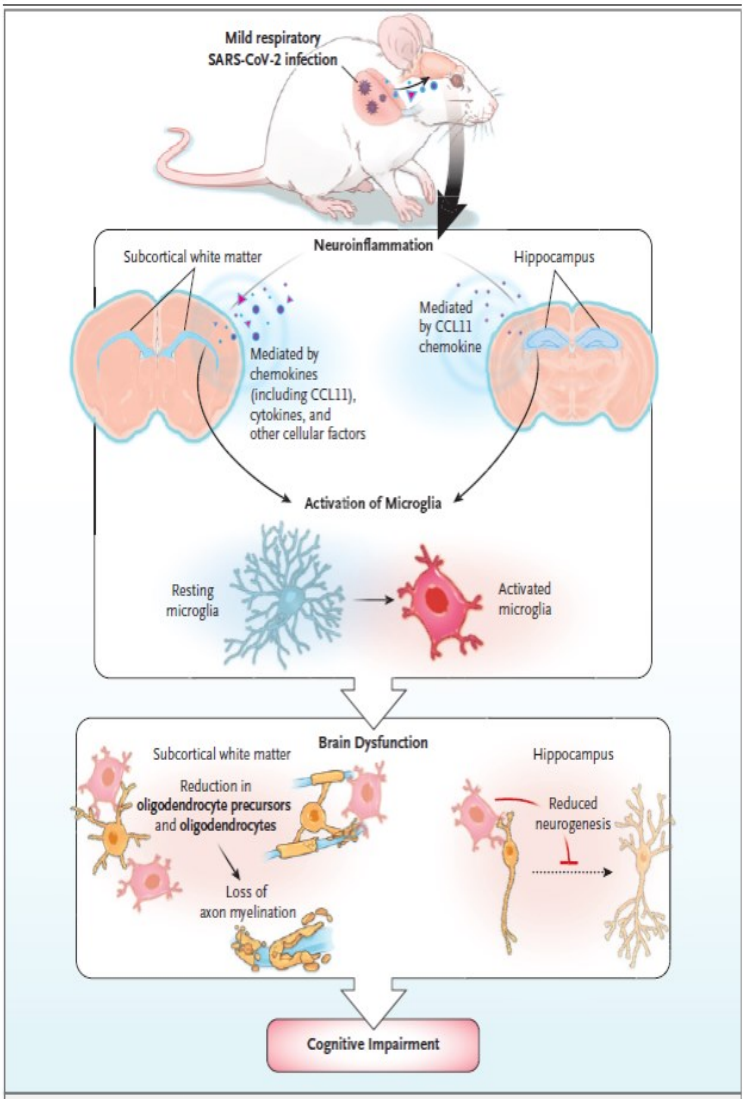

Figure 1. 'How the SARS-COV-2 infection effect on Neural cells.' [15]

Many people who have recovered from COVID-19, including mild cases, report some impairment in attention, execution, language, processing speed and memory. These cognitive impairment symptoms are also known as "brain fog." Along with symptoms such as anxiety, depression, sleep disturbances and fatigue, the emergence of cognitive impairment greatly increases the occurrence of COVID-19 sequelae (also known as long-term COVID-19). After recovery from bacterial or other viral infections, some

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people also develop transient or even persistent cognitive impairment. Due to the lack of long-term follow-up data on patients' neurocognitive aspects, it is difficult to distinguish "brain fog" caused by COVID-19 from similar symptoms caused by other causes, so it is difficult to give a clear diagnosis clinically. The recent study 'Cognitive Deficits in Long COVID-19' indicates that the absence of myelin and axons covered with myelin sheaths remains evident for a duration of at least seven weeks following SARS-CoV-2 infection [16]. Myelin's primary role is to provide insulation for neuronal axons, which is crucial for the speed of electrical conduction in neurons and the metabolic processes of axons. Consequently, the depletion of myelinated axons negatively affects the organization and operation of neural networks. Another study shows that 20% to 70% of patients (even young people) developed neuropsychiatric symptoms (NPs) after COVID-19 and persisted for several months after the disappearance of respiratory symptoms, indicating persistent brain involvement. SARS-CoV-2 enters the ACE2 receptor and can damage endothelial cells, which leading to inflammation, blood clots, and brain damage. In addition, systemic inflammation leads to a decrease in monoamine and trophic factors and microglial activation, leading to increased glutamate and N-methyl-d-aspartic acid (NMDA) and cytotoxicity [17]. A paper published in July 2022 in the top academic journal Cell, Mild respiratory COVID can cause multi-lineage neural cells and myelin dysregulation, elaborated on the effects of COVID-19 infection on neurons. The paper states that mild SARS-CoV-2 infection causes persistent damage to the hippocampus, oligodendrocytes, and significant myelin loss, as well as elevated CSF cytokines/chemokines (including CCL11) (figure 1) [15]. These investigators examined plasma levels of circulating CCL11 cytokine in long-term COVID patients with and without cognitive symptoms. The majority of these individuals underwent a comparatively benign SARS-CoV-2 infection, with over 90% of participants avoiding hospitalization. They found that people experiencing long-term COVID-19 who exhibited cognitive deficits or "brain fog" (n = 48 subjects, 16 men/32 women, mean age 46.1±14.6 years) had elevated levels of CCL11 in plasma compared to those lacking long-term COVID [15].

The research conducted by Fernández-Castañeda et al. offers an explanation for the cognitive dysfunction and brain impairment resulting from SARS-CoV-2 infection. They identified variations in the levels of neuroinflammatory cytokines and chemokines, including CCL11, in the cerebrospinal fluid and serum of mice. Furthermore, significant alterations were also noted in the subcortical white matter region of the mouse brain, primarily involving the activation of microglia and the depletion of oligodendrocytes, precursor cells of oligodendrocytes, and myelin sheaths. Administering CCL11 to mice through intraperitoneal injection activates microglia and hinders the process of neurogenesis [15].

5. Drug Interactions

Certain clinical aspects of COVID-19 can result in potential interactions with Alzheimer's disease (AD) medications, necessitating careful consideration of drug-drug interactions when AD patients are undergoing COVID-19 treatment. Cholinesterase inhibitors (ChEIs), such as donepezil, rivastigmine, and galantamine, are commonly employed in AD therapy [18]. ChEIs may be influenced by the activity of cytochrome P450 (CYP450) enzymes like CYP2D6. Given that some COVID-related drugs, such as chloroquine (CQ) and hydroxychloroquine (HCQ), can undergo metabolism via CYP2D6, there is potential for these medications to significantly impact the pharmacological effects of ChEIs. Recently approved medications like Lopinavir and Ritonavir also pose certain risks in terms of drug-drug interactions. Lopinavir primarily undergoes metabolism through CYP3A enzymes, while ritonavir is a potent inhibitor of both CYP3A and CYP2D6. Additionally, lopinavir-ritonavir acts as an inhibitor of drug transporters such as p-glycoprotein and breast cancer resistance protein, and it functions as an inducer of CYP1A2, CYP2C9, CYP2B6, CYP2C19, and glucanosyltransferase. Consequently, lopinavir-ritonavir has the potential to elevate the plasma concentrations of galantamine and donepezil [19].

6. Conclusion

SARS-CoV-2 infection was first reported in Wuhan (China) in December 2019, and then quickly disseminated across the globe. It was suggested that COVID-19 have direct impact on CNS, which lead

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to neurological problems including cognitive impairment. Furthermore, AD has been identified as one of the most prevalent comorbidities of COVID-19 within the central nervous system. This paper mainly focuses on the present view of COVID-19 and Alzheimer's disease, cognitive impairment and drug-drug interaction. Although the deadly threat of COVID has passed, people should consider COVID-19 as a key catalyst of AD. Future research on the association between COVID-19 and AD could take the following form: (1) In addition to microglia, the role of other cell types (such as astrocytes) in cognitive impairment caused by COVID-19. (2) Verify whether CCL11 can be used as a candidate biomarker for the diagnosis of new crown-related cognitive impairment. (3) A deeper insight into COVID-19 and Alzheimer's drug-drug interactions. (4) Figure out a condition to eliminate long-term cognitive impairment suffering in AD patients with COVID-19.

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