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COVID-19 and neurodegenerative diseases

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Abstract. – OBJECTIVE: The pandemic of Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) continues, and SARS-CoV-2 variants continue to emerge. In addition to typical fever and respiratory symptoms, many patients with COVID-19 experience a variety of neurological complications. In this review, we analyzed and reviewed the current status and possible mechanisms between COVID-19 and several typical neurodegenerative diseases, particularly Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, hoping to propose the potential direction of further research and concern.

MATERIALS AND METHODS: Electronic literature search of the databases (Medline/PubMed, Web of Science, and Google Scholar). The keywords used were COVID-19, SARS-CoV-2, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. The retrieved relevant articles were reviewed and critically analyzed.

RESULTS: SARS-CoV-2 is a highly neuroinvasive neurotropic virus that invades cells through angiotensin-converting enzyme 2 (ACE2) receptor-driven pathway. SARS-CoV-2 neuroinvasion, neuroinflammation, and blood-brain barrier (BBB) dysfunction may contribute to the pathogenesis of neurodegenerative diseases.

CONCLUSIONS: Some patients with neurodegenerative diseases have already shown more susceptibility to SARS-CoV-2 infection and significantly higher mortality due to the elderly population with underlying diseases. Moreover, SARS-CoV-2 could cause damage to the central nervous system (CNS) that may substantially increase the incidence of neurodegenerative diseases and accelerate the progression of them.

Key Words:
COVID-19, SARS-CoV-2, Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the pathogenic agent of COVID-19, which deteriorated into a global pandemic in 2020. This pandemic has threatened the lives and health of millions of people around the world with a mortality rate of about 5%-10%[1]. By June 7, 2022, WHO data[2] showed that there were 530,266,292 confirmed cases with 6,299,364 deaths of COVID-19. Coronaviruses (CoVs) are single-stranded RNA viruses with a non-segmental positive-sense chain, with the continuous emergence of SARS-CoV-2 variants, no specific drugs have been officially used to treat or prevent COVID-19 so far[3]. COVID-19 patients have typical signs and symptoms, such as headache, muscle pain or joint pain, shortness of breath, fatigue, fever, etc[4]. Angiotensin-converting enzyme 2 (ACE2) is a main receptor of SARS-CoV-2. SARS-CoV-2 spike protein binds to ACE2 through the receptor-binding domain (RBD) on the surface of the SARS-CoV-2 S protein and utilizes transmembrane protease serine 2 (TMPRSS2) to enter the host cells and spread subsequently[5-7]. ACE2 is highly expressed on both vascular endothelial cells and epithelial cells within the lung, intestine, skin, spleen, as well as brain[8]. Significantly, some scholars[9] have shown that ACE2 is widely expressed in distinct brain areas, such as substantia nigra, middle temporal gyrus, the posterior cingulate cortex, ventricle, and olfactory bulb, which makes SARS-CoV-2 invade the brain tissue easily.

Nearly 3 million people die from neurological diseases worldwide *per* year, including neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclero-

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sis, etc[10]. With global aging and the extension of the human life span, the prevalence of neurodegenerative diseases is also increased remarkedly. Oxidative stress, neuroinflammation, cytokine storm and immune response are the main inducements of neurodegenerative diseases[11-13]. Cao et al[14] showed that accelerated epigenetic aging was associated with the SARS-CoV-2 infection and the development of severe COVID-19. The elderly has a higher mortality rate compared to other kinds of patients infected with SARS-CoV-2, with mortality rates more than five times higher in patients over 80 years old[15]. Figure 1 schematically depicts several possible routes of SARS-CoV-2 invasion into the CNS. SARS-CoV-2 is thought to enter the brain by the following several routes: (1) retrograde entry through neurons of the olfactory system; (2) infection of cerebrovascular endothelial cells to reach the brain with broken BBB; (3) infection of immune cells to transfer the virus into the brain. Nearly 80% of COVID-19 patients were found to present with neurological symptoms[16]. Indeed, it has been reported that COVID-19 can cause various neurological symptoms, including altered mental status, impaired consciousness, encephalopathy, dementia-like disorders, encephalopathy, psychosis, and cerebrovascular events, through the following ways: direct neurological effects of "SARS-CoV-2", co-infection and neurological complications[17]. Douaud et al[18] also reported that SARS-CoV-2 may cause brain atrophy. Of the 785 participants investigated, 401 of them were infected with SARS-CoV-2. Compared to uninfected participants, COVID-19 patients lost about 0.2%-2% additional brain gray matter, with the most loss in volume of the olfactory bulb; Moreover, the whole brain size of COVID-19 patients was also greatly reduced; additionally, COVID-19 patients showed a marked decrease in cognitive ability[18].

Although the neurological and psychiatric complications of COVID-19 are widely reported, it is still unclear how COVID-19 affects the neurodegenerative process. This review highlights the relationship between COVID-19 with several typical neurodegenerative diseases, focusing on the potential mechanisms whereby SARS-CoV-2 infection may contribute to the pathogenesis of neurodegenerative diseases.

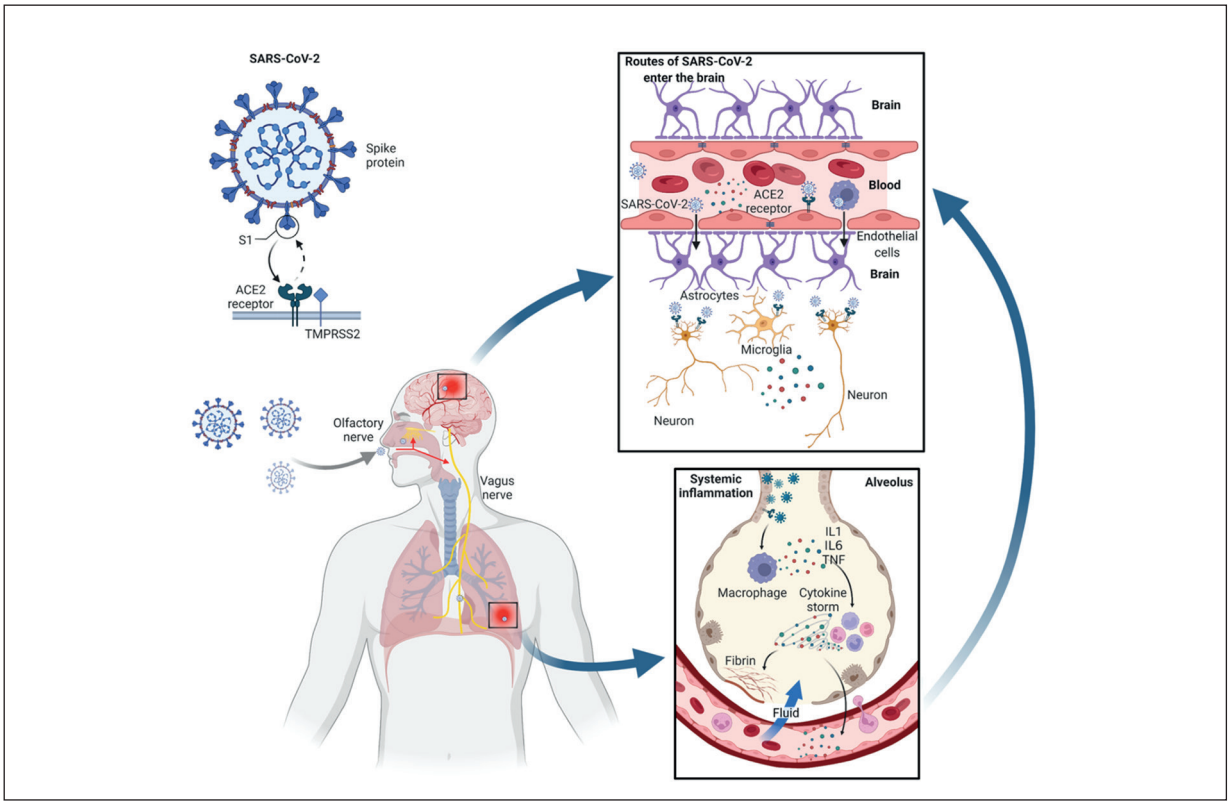

Figure 1. Activation of systemic inflammation and potential routes of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to the central nervous system (CNS).

Materials and Methods

The purpose of this review is to summarize and analyze a series of scientific studies that show the possible effects of SARS-CoV-2 infection on patients with neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis. Electronic literature search was performed by these databases (Medline/PubMed, Web of Science, and Google Scholar). The keywords used were COVID-19, SARS-CoV-2, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. The retrieved relevant articles were systematically reviewed and critically analyzed.

Results

COVID-19 and Alzheimer's Disease

AD is the most general type of neurodegenerative disease, accounting for 60-80% of dementia[19,20]. The main clinical manifestations are progressive memory loss and cognitive impairment, which are more common in the elderly over 65 years old[21]. The prevalence of AD is gradually increasing with the global aging around the world. The prevalence rate of people over 65 years old is about 10% while that of people over 80 years old is about 40%[20]. Two main pathological features of AD are amyloid beta-protein (Aβ) aggregation and neurogenic fiber tangles (NFT)[22]. Tau, a major microtubule-associated protein in the brain, is a core component of NFT[23]. Areas of the brain responsible for memory and learning are impaired by the deposition of Aβ or NFT, resulting in neurological dysfunction in patients[24].

The amyloid cascade hypothesis suggests that mutations in the gene encoding β-amyloid precursor protein (APP) lead to the deposition of Aβ that causes neuronal damage[25]. ACE2 plays a role in the classical renin-angiotensin system (RAS) and has been proved to be positively correlated with oxidative stress within the brain of patients with AD[26]. ACE2 activates the RAS system and then mediates the production of Aβ and phosphorylation of tau protein[27,28]. In addition, activation of inflammatory signaling pathways and the occurrence of oxidative stress also contribute to the pathological mechanisms of AD[29,30]. Due to the complex pathogenesis of ADs, such as age, immune environment, and genetic factors, the therapeutic options are multifaceted, including reducing Aβ deposition, inhibiting tau protein aggregation, and anti-inflammatory strategies[20,31]. AD patients utilize anticholinesterase inhibitors and memantine to reduce neuronal damage[32]. Besides, TNF-α inhibitors can significantly reduce the burden of NFT, APP, and Aβ plaques[33]. Coenzyme Q10, mitoquinone mesylate, MitoQ, and latrepirdine are used to relieve oxidative stress and protect the nervous system[30]. Nonsteroidal anti-inflammatory drugs (NSAIDs) can be applied to regulate neuroinflammation and immunotherapy that stimulates microglia to phagocytize Aβ, etc[34].

Age is the primary risk factor for both COVID-19 and AD, with the prevalence of AD doubling every 5 years at the age of 65[35]. Epidemiological data both from China and Italy[36,37] show that the morbidity and mortality of COVID-19 are positively correlated with ages. Studies[38] also have shown that SARS-CoV-2 infection in patients triggers encephalopathy, apparent agitation, confusion, and executive difficulties syndromes like inattention, disorientation, poorly organized actions in response to commands, etc. A retrospective study[39] showed that 189 of the 7334 COVID-19 patients had AD, and AD was associated with a high risk of mortality (OR 3.09, 95% CI 2.00-4.78, $p < 0.001$). Another observational study[40] showed that COVID-19 was diagnosed in 31 of 204 Alzheimer's disease patients and frontotemporal dementia patients. Among them, 22 were AD patients (70.9%), and 12 of the 22 AD patients (54.5%) died. The possible mechanisms of COVID-19 that cause the deterioration of AD may include systemic inflammation production, cytokine storm, over-activation of the RAS system, activation of innate immunity, oxidative stress production, direct viral infection, or direct cytolytic β-cell damages, etc[41,42]. After binding of SARS-CoV-2 to cellular ACE2, the ACE2 expression can be downregulated which led to increased expression of angiotensin II (Ang-II). Ang-II is not only a potent vasoconstrictor but also a pro-inflammatory factor[43,44]. Its increased expression may lead to activation of the RAS system, which then exacerbates oxidative stress and the inflammatory response of microglia cells[41]. Cytokine storm occurs in elderly patients after infection of SARS-CoV-2, which is caused by dysregulation and overreaction of the immune system to the virus, further accelerating the progression of AD in patients with COVID-19[24]. In addition, SARS-CoV-2 spike S protein can also promote the aggregation of tau protein by

secreting extracellular vesicles (EV) or direct intercellular contacts, which would promote the pathological process of AD[45].

AD and SARS-CoV-2 are mutually reinforcing relationships. On one side, the pathological mechanism of AD would aggravate the infection of SARS-CoV-2 by activating inflammatory cascades, oxidative stress, and immune response disorders. On the other side, SARS-CoV-2 infection may increase the risk of AD in the future by causing neuroinflammation, classic RAS over-activation, BBB injury, etc[46]. It has been reported[47] that the mortality rate of SARS-CoV-2 infected patients with AD is higher than that of non-AD patients, suggesting that AD is a high-risk factor for death in the COVID-19. Therefore, the current global transmission of SARS-CoV-2 has profound implications for AD patients. In addition to monitoring the cognitive function of AD patients closely and carrying out the conventional anti-inflammatory and antioxidant treatment[48], effective prevention of SARS-CoV-2 is also necessary, such as repeatedly teaching AD patients to wear medical surgical masks, wash their hands regularly, and receive timely vaccination, etc. Thus, it can avoid the spread of SARS-CoV-2 among AD patients and prevent COVID-19 from aggravating the pathogenesis of AD at the same time.

COVID-19 and Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide, of which the incidence has increased dramatically with the aging of the population[49]. This disease is mainly caused by a combination of genetic variation and environmental factors. Neuropathological hallmarks of PD normally include degeneration of the substantia nigra pars compacta and accumulation of α-synuclein in Lewy bodies[50]. The etiology of PD is still obscure. In current studies, its underlying molecular pathogenesis includes α-synuclein proteostasis, mitochondrial dysfunction, oxidative stress, neuroinflammation, etc[51-54]. The clinical presentation of PD contains the motor features characterized by tremor and slowness of movements, as well as non-motor symptoms including cognitive decline, depression, and pain[55]. Drug therapy based on dopamine replacement is a preferred treatment against PD that could largely alleviate motor symptoms[56]. As for those patients developing intractable L-DOPA-related motor complications, deep brain stimulation (DBS) is an additional effective treatment strategy[57]. However, currently applied treatments only relieve clinical symptoms to a certain extent while cannot prevent the pathological progression of the disease, thus most of them are only symptomatic[58].

Previous studies[59,60] have found that specific past diseases, advanced age, and male gender seem to be highly related to the susceptibility to suffering from severe COVID-9. Thus, it is proposed that PD may increase the morbidity and mortality risk of COVID-19[59]. A cohort study[60] including 117 community-dwelling PD patients with COVID-19 showed that the frailty caused by advanced PD significantly increased the mortality risk of COVID-19. By comparing COVID-19 case fatality rate (CFR) in 694 PD patients with 78,355 ones without PD *via* the TriNetX COVID-19 research network, a recent study[61] suggested that COVID-19-related CFR was increased in patients with PD (5.5% non-PD *vs.* 21.3% PD; $p < 0.001$, χ^2 test). A systematic review of 16 studies[62] reporting on a total of 11,325 PD patients, 1,061 with a confirmed diagnosis of COVID-19 indicated a higher case fatality in PD patients affected by COVID-19, with an overall mortality rate of 18.9% (n = 201/1061) than the general population. A cross-sectional study[63] using an administrative claim database covering 1468 hospitals and 5,210,432 patient hospitalizations, reported that the COVID-19 infection rate was significantly higher in PD patients than that in non-PD patients (1.1% *vs.* 0.6%, $p < 0.001$); the inpatient mortality rate of COVID-19 was also much higher in PD patients than that in non-PD patients (35.4% *vs.* 20.7%, $p < 0.001$). According to the above studies, it can be concluded that PD patients are more frequently affected by COVID-19 and have increased COVID-19-associated mortality, compared to non-PD patients.

Recent studies[64] reported that PD patients with COVID-19 developed new or worsening motor or nonmotor symptoms. There may be a close potential relationship between SARS-CoV-2 infection and PD. Recent studies[65] have indicated the neurotropic potential of SARS-CoV-2 which may easily invade the brain tissue through the olfactory tracts, resulting in anosmia or ageusia which are two typical precursor features of Parkinson's disease. Consistently, SARS-CoV-2 could invade neurons by binding to the ACE2 receptor which is expressed at high levels by dopamine neurons in the midbrain. Besides, SARS-CoV-2 binds to ACE2 in respiratory epithelial cells and epithelial cells, then triggered a cytokine storm, with significant elevation in levels of IL-1, IL-6, and

tumor necrosis factor that may increase the risk of Parkinson's disease after the induction of a systemic inflammatory state[66-68]. α-Syn is an aggregation-prone protein that is considered to be a key factor in the pathogenesis of PD. Recently, SARS-CoV-2 protein was reported to interact with α-Syn and induces Lewy-like pathology *in vitro*[69]. Moreover, it has also been reported that between the gastrointestinal tract and the central nervous system, the interaction of colonic inflammation, intestinal microbial imbalance, and α-synuclein up-regulation induced by viral infection may lead to PD[70]. SARS-CoV-2 can also trigger neuroinflammation *via* inducing proinflammatory cytokines in microglia, the principal immune cells within the central nervous system. The environment under persistent chronic inflammation and neuronal damages can affect dopaminergic neurons in the substantia nigra pars compacta, effectively leading to neurodegeneration in PD[71].

For patients with PD, COVID-19 posed new challenges. Many reports suggest that unregulated NLRP3 inflammatory body activation is one of the causes of the cytokine storm. Thus, inhibiting the NLRP3 inflammasome can counteract chronic neurodegenerative diseases (including AD and PD) triggered by SARS-CoV-2 infection[72]. In the CNS, microglia act as a central housekeeper to maintain a homeostatic state, and it has been indicated that by effective initiation, microglial responses can coordinate the clearance of SARS-CoV-2 in the CNS[73]. As a common drug with antiviral properties, amantadine is currently available for the treatment of PD patients infected with SARS-CoV-2, by downregulating CTSL and lysosomal pathway disorders and by changing pH to remove viral proteins and anti-parkinsonian properties[74].

COVID-19 and Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive, incurable, and fatal neurodegenerative disease characterized by degeneration of upper and lower motor neurons, leading to muscle weakness and eventual paralysis[75]. Respiratory paralysis is the leading cause of death in patients, usually within three to five years[76]. As a most common neurodegenerative disease during middle age, ALS has an onset often in the middle-to-late 50s[77]. The incidence rate of this disease is about 2.76 *per* 100,000 people, with a prevalence of 9.62 cases in every 100,000 people worldwide[78,79]. The main pathological feature of ALS is the accumulation of neurotoxic misfolded proteins, inclusions, and aggregates within motor neurons. Importantly, 97% of ALS patients have TDP43 protein lesions[75]. SOD1 gene is also regarded as the main risk gene for ALS, encoding SOD1 protein, which is involved in oxidative stress, neuroinflammatory response, immune response disorder, mitochondrial dysfunction, neurotoxic microglia, and astrocyte recruitment[80-83]. The damage of motor neurons always leads to the deterioration of muscle function, which will cause physical weakness, muscle atrophy, and paralysis. Besides, up to 50% of patients have cognitive or behavioral impairments during the disease development, including dysphagia, dysarthria, emotional lability, executive dysfunction, etc[84-86]. The etiology of ALS is complicated and most treatments against it are only palliative and symptomatic. For example, muscle relaxants are used for spasms; both Edaravone and AMX0035 are used to decrease neuronal death, antioxidation and metabolic stress, while immunomodulatory therapy, such as dimethyl fumarate and IL-2, are used to regulate the function of Treg cells, alleviating neuroinflammation and protect neurons. Finally, Masitinib can inhibit the activation of microglia[83,84]. Furthermore, gene therapy is used to modify genetic factors, such as ASOs binding targeted mRNA, RNA interference pathway through siRNAs, gene delivery, etc[87].

COVID-19 has been shown to affect ALS patients significantly. In a recent study[88], two ALS patients experienced a rapid neurological decline after infection with SARS-CoV-2; One month later, the patients had a marked decline in fine motor skills of hands and leg strength. Another study[89] reported that 3 patients without a history of other neurological or autoimmune diseases were later diagnosed with ALS after the onset of COVID-19. Moreover, during the pandemic period, ALS patients are mostly in a state of anxiety, depression, as well as deterioration of motor function. Of note, the faster the disease progresses, its anxiety symptoms will appear more serious[90,91]. In COVID-19, respiratory distress is the most characteristic symptom, while the overwhelming majority of patients with ALS die of respiratory paralysis. Thus, COVID-19 may be fatal for ALS patients[92].

During the COVID-19 pandemic, it is vital to provide help to ALS patients with psychological, physical, emotional, or mental problems, such as supporting online psychological counseling, antidepressants, and anti-anxiety drugs[93,94]. As a

rapidly developing field, telemedicine continues to explore patients' disease care with the support of a variety of ways, including remote video conference, e-mail and mobile applications, which can effectively enable patients to receive professional neurological evaluation and course observation under an isolated state[95]. Compared with the traditional medical environment, telemedicine helps patients to have better access to medical experts, enhances the medical level, and improves the diagnosis and treatment of patients, while it is not affected by the location[96]. It is of far-reaching significance to implement telemedicine services for patients with ALS during the pandemic.

Conclusions

Many recent studies[97-99] have found that patients with neurodegenerative diseases may be more susceptible to SARS-CoV-2 infection, and these patients with COVID-19 deteriorated more rapidly which caused a high mortality rate. Therefore, there may be an interactive relationship between COVID-19 and neurodegenerative diseases. Currently, several pathways have been proposed by which COVID-19 affects the CNS. Converging studies showed evident damages caused by SARS-CoV-2 in the CNS that may substantially increase the incidence of neurodegenerative diseases and accelerate the progression of these diseases[100,101]. So far, there are still no specific drugs against COVID-19. However, for neurodegenerative patients infected with COVID-19, anti-neuroinflammatory drugs with the capability of crossing the BBB are promised to potentially exert therapeutic effects. Moreover, the exact mechanisms underlying COVID-19 that affect neurodegenerative diseases is still unclear that may vary according to different types of neurodegenerative diseases. Thus, comprehensive clinical, laboratory, and neuropathological studies are further needed to be applied to the patients, to elucidate the specific pathophysiological mechanisms of neurodegeneration caused by COVID-19, which will greatly help to explore more effective treatments to reduce the risk of these neurological complications and decrease the mortality of COVID-19 infected patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval

This article does not contain any studies with human participants or animals performed by any of the author.

Authors' Contribution

All authors contributed to the study conception and design. Data collection and analysis were performed by Y.-W. Fu and H.-S. Xu. The manuscript was prepared by Y.-W. Fu, H.-S. Xu, and S.-J. Liu. All authors have read and approved the final manuscript.

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