Impact of COVID-19 Pandemic on Patients with Neurodegenerative Diseases

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Abstract

COVID-19 pandemic has produced a devastating effect on global health security and social-economy. The COVID-19 pandemic, caused by the novel SARS-CoV-2 virus, is associated with a broad pathophysiology that has resulted in worldwide mortality and morbidity. While primarily regarded as a respiratory virus, SARS-CoV-2 produces wide-ranging and often unpredictable neurological symptoms, ranging from anosmia to encephalitis to increased stroke risk, that complicate clinical management. Elderly people, particularly those with underlying diseases, have been found most vulnerable from higher mortality rate. Neurodegenerative diseases are a group of incurable neurological disorders that result in loss of neuron and/or myelin sheath, which affect hundreds of millions of elderly populations and usually need long-term care. Elderly population is believed to be one of the most vulnerable communities to COVID-19 pandemic. It has been observed that SARS-CoV-2 infection plays significant role in the pathogenesis and/or the management of neurodegenerative diseases with different mechanisms. Here, we have reviewed the current status of the impact of COVID-19 in the patients with several neurodegenerative diseases, along with potential targets for therapeutic development to reduce neurological severity.

Keywords: COVID-19, Neurodegenerative diseases, Neurological severity, SARS-CoV-2, Therapeutic development

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1. Introduction
Coronavirus disease (COVID-19) is a respiratory infection. It was found to spread swiftly over the entire world after its first case that was discovered in December 2019 (in Wuhan, China). On 30 January of 2020, the World Health Organization (WHO) declared this disease as a global health hazard and subsequently, a pandemic was declared on March 11, 2020. The highly infectious disease was attributed to a novel coronavirus known as SARS-CoV-2. It has a low overall mortality rate in children, but is widely recognized to produce a substantially greater mortality rate in the elderly population across the globe. COVID-19 (SARS-CoV-2) is disseminated easily through respiratory droplets produced by an infected individual when talking, sneezing, or coughing. The incubation period is 5 to 6 days. This respiratory disease begins with modest symptoms such as a cold or cough and progresses to a serious sickness characterised by a blockage of respiratory system as well as high fever [1]. SARS-CoV-2 has capability of attacking and infiltrating brain. According to current studies, neurological symptoms have been reported in more than one third of COVID-19 individuals with severe illness [2].

Research studies have suggested adverse impact of COVID-19 pandemic on patients with various neurodegenerative diseases (Figure 1). Here, we will describe some of the potential adverse effects of COVID-19 on neurodegeneration that have been reported in the literature.

2. SARS-CoV-2 invasion routes in CNS
Accumulating investigations have found SARS-CoV-2 infection in CNS of COVID-19 patients' postmortem brain, experimental animals, and cell cultures [3, 4]. It has been reported that SARS-CoV-2 potentially penetrates in CNS via direct neural pathway or indirect hematogenous route. In first 2 to 3 days after onset of symptoms, viral RNA was obtained from blood samples of patients with COVID-19. Existence of SARS-CoV-2 in blood permits it to enter neuronal circulation, at which sluggish blood flow could help SARS-CoV-2 S protein to interact with ACE2 localized on vascular endothelium. Following viral particle emerging from vascular endothelium, endothelial lining damage occurs, perhaps facilitating viral entry to brain [5, 6]. An efficient 3D microfluidic model of human blood-brain barrier has confirmed this hypothesis [7]. In this model, SARS-CoV-2 proteins induce a pro-inflammatory activity in cerebral endothelial cells and increases barrier disruption, which promotes SARS-CoV-2 entry in brain. According to in-vitro studies, SARS-CoV-2 interfaces with ACE2 and disrupt neurons [8, 4]. Viral infection of neurons was greatly reduced when treated with ACE2 antibodies or cerebrospinal of COVID-19 patient. Notably, endothelial fractures in cerebral capillaries and hemorrhage inside cerebral tissue may cause fatalities in SARS-CoV-2 infected patient prior to emergence of postulated neuronal damage [6, 4].

(a) Hematogenous route
This approach can describe cerebrovascular symptoms, but it does not describe well about neurological symptoms including olfactory or gustatory
dysfunctions, which can appear before respiratory symptoms in some COVID-19 individuals [9].

(b) Olfactory route

In previous research, SARS-CoV-2 has been shown to infect brain of a genetic mouse express human ACE2 via nose, near to olfactory system. Intranasal administration of SARS-CoV-2 was reported to invade brains of mutant mice with human ACE2 expression, validating olfactory pathway for SARS-CoV-2 entry into brain. Research suggests that TMPRSS2 and ACE2 are produced in olfactory sensory neurons, stem cells olfactory epithelium supporting, and CNS cells adds to evidence that SARS CoV-2 potentially penetrate brain via nose [10, 11, 12].

(c) Enteric and vagal nerves route

SARS-CoV-2 showed that it was possible to enter in CNS through enteric and vagus nerves, as ACE2 and TMPRSS2 expression in enteric neurons and glia has been demonstrated. SARS-CoV-2 potentially enters and multiplies in intestinal absorptive cells of human. As a result, another invasion route appears to be dissemination of SARS-CoV-2 in brain via vagus nerve, which connects gastrointestinal neurons. To summarize, SARS-CoV-2 has potential to penetrate CNS via olfactory and enteric vagal pathway [13, 14].

3. Impact of COVID-19 on Patients with Alzheimer’s disease

Alzheimer’s disease is a neurological illness that primarily affects the older population. Severe cognitive function and memory deterioration are the most common clinical manifestations [15]. Neurofibrillary tangles and amyloid deposition in brain are the primary pathological causes. In affected brain regions, inflammatory response and neuron loss also detected. Approximately 50% Alzheimer’s patients require long-term care at home or from an expert. Alzheimer’s patients are found to be adversely affected during the COVID-19 pandemic. According to the New York Times report, up to 80% COVID-19 people died in long-term treatment centers, implying that every fourth of people who died had Alzheimer’s disease [16]. Certain characteristics of Alzheimer’s patients have been found to enhance likelihood of SARS-CoV-2 illness, according to some research data. Alzheimer’s patients are often unable to pursue public health strategies for reducing SARS-CoV-2 transmission such as hand hygiene, coughing while covering mouth and nose, reporting and monitoring symptoms of COVID-19, self-isolation at home by itself and maintaining physical distance from others [17].

In addition, COVID-19 disease has great impact on emotional and psychological health of Alzheimer’s patients, which cannot be neglected. During COVID-19, Boutoleau’s research team reported for the first time that home isolation had considerable influence on mental and physical condition of Alzheimer’s patients. Researchers discovered that increasing emotional stress speeds up degradation of cognitive ability. The more time individuals are isolated, worse form of the illness is usually the outcome. During home confinement, this behavior may be linked to a decrease in social contact and an increase
in physical activity. Apolipoprotein E4 (APOE4) is a most prominent vulnerable gene for Alzheimer's disease genetically linked to prevalent late-onset familial and sporadic forms of the disease. This behavior has been connected to a loss of social contact and an increase in physical activity when people are confined to their homes [18, 19].

Further, APOE4 homozygous genome is found to be linked to a higher incidence of Alzheimer's disease among European ancestral populations. According to a recent study, persons who are homozygous for APOE4 have a 2.2-fold greater COVID-19 risk of reoccurrence and a 4.3-fold greater mortality compared to people who are homozygous for ApoE3, with a considerable occurrence of APOE4 in individuals with symptomatic COVID-19 illness [20]. Approximately 2.36 percent of those with European descent were APOE4 homozygous, whereas 5.13 percent of those with SARS-CoV-2 positive were APOE4 homozygous, indicating that risk of SARS-CoV-2 infection was 2 fold in APOE4 homozygous persons. However, researchers concluded that APOE4 variations were not really a standalone potential risk in chronic COVID-19 disease. Vulnerability of AD patients to SARS-CoV-2 virus makes them more prone to develop a severe condition [21].

Additionally, whereas respiratory complications are typical mostly in elderly AD patients and SARS-CoV-2 virus affects mainly respiratory tract; indications in AD patients having SARS-CoV-2 infection become much more serious. It is worth noting that affected individual's likelihood contracting with SARS-CoV-2 exposure, AD is not primary source of COVID-19 vulnerability. Mutations in HLA and ACE2 gene on cells and hosts have also been linked to COVID-19 severity or vulnerability, according to preliminary research [16].

COVID-19 has been linked to virus invasion of brain tissue in numerous investigations. Binding with ACE2, cellular receptors mostly found in small intestine, kidney, brain, vascular and respiratory epithelium, allows SARS-CoV-2 to enter cells. SARS-CoV-2 can initially infect peripheral nerve terminals subsequently penetrate to brain through synapses associated routes, according to growing evidence. Gustatory (88.0%) and olfactory (85.6%) dysfunctions abnormalities were found in mild and intermediate COVID-19 individuals. Anosmia developed in about 11% of those patients before other indication [9]. ACE2 has also been shown to have significant expression in ciliated cells and nasal goblet, suggesting that SARS-CoV-2 virus could penetrate CNS by olfactory neurons [22]. SARS-CoV-2 could also infiltrate CNS and cerebrospinal fluid through ventricular choroid plexus. Increased level of ACE2 in posterior ventricle choroid plexus raises risk of SARS-CoV-2 virus penetration into brain. SARS-CoV-2 was recently discovered in a CSF sample of 24 year patient of COVID-19 from Japan by genomic sequencing. SARS-CoV-2 infection and invitation in CNS may have unforeseen effects on neurodegenerative disorders. SARS-CoV-2 infection has recently been proposed as a possible cause of neurodegeneration. Cells that express ACE2 like glial and neurons cells could be exploited as SARS-CoV-2 infecting targets.
SARS-CoV-2 activates glial cells which release inflammatory mediators and potentially cause a strong innate immune response and long-term inflammatory elevation. Furthermore, long-term SARS-CoV-2 exposure can trigger innate and adaptive immune reactions [23, 24]. Corticosteroids were more often used for treatment of hospitalized patients of COVID-19, according to retrospective studies, but it's important to note that inadequate corticosteroid medication caused symptoms of mental illness in around 35% of COVID-19 individual, including psychosis, depression and delirium. Because Alzheimer's disease has a long-term clinical history, influence of COVID-19 on disease development, whether caused by direct virus infection or incorrect therapy, warrants long-term monitoring [25].

Figure 1: Impact of COVID-19 pandemic on patients with neurodegenerative diseases.

4. Impact of COVID-19 on patients with Parkinson’s disease

Parkinson’s disease (PD) is another most common neurological disorder which
corresponds to the degradation of dopamine neurons in intense portion of substantia nigra and presence of inclusion bodies in remaining neurons as key pathogenic hallmarks [26]. The most common clinical symptoms are tremor, myotonia, tardiness and irregular gait. In addition, it has been found that several non-motor symptoms such as sleep difficulties, depression, anxiety, hypoxia and memory impairment can have serious influence on PD patients’ clinical condition. During COVID-19 pandemic, mitigation measures or social containment had a substantial impact on life expectancy [27, 28].

Dopaminergic neurons also have a high level of angiotensin-converting enzyme 2. Despite the fact that ACE2 expression in brains of patients with PD has diminished due to neurodegeneration and loss of dopamine neurons, there is an evidence that indicates SARS-CoV-2 could potentially infiltrate brain of PD patients that could exacerbate brain trauma and clinical conditions. A 74-year-old patient with COVID-19 and PD was recently described as first example of encephalopathic sequelae. COVID-19 was found to be particularly dangerous to Parkinson's disease patients with a higher age and prolonged duration of disease, with high death rate of up to 40%. Unfortunately, study’s representative samples are somewhat limited and more findings are required to be clarified using a larger sample size. It's also unclear whether rate of SARS-CoV-2 incidence in Parkinson's patients is rising or falling. COVID-19 risk, mortality and morbidity in mild to moderate PD patients are not different from overall population, according to a new large prospective cohort study of generally randomly selected individuals with homogenous PD [29, 30]. Because frequent clinical symptoms of COVID-19 such as tiredness, flushing and anosmia were all non-motor PD symptoms, Hainque et al. concluded that early assessment of COVID-19 in PD patients was difficult. Furthermore, exact seriousness of SARS-CoV-2 illness in Parkinson's disease person needs to be determined. Although SARS-CoV-2 is rare to induce PD, it is found that it can exacerbate several non-motor and motor abnormalities [31].

5. Impact of COVID-19 on patients with amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal neurological illness that deteriorates motor neurons in spinal cord and brain. Spasms, muscle weakness, ineffective communication and respiratory distress are all symptoms of ALS. ALS has a prevalence of 9.62 instances per 100,000 individuals worldwide, with an incidence rate of 2.76 per 100,000 patients [32]. ALS can affect by a variety of genetic, environmental variable and aging-related malfunctioning, similar to certain other neurological disorders. Patient records, physical assessment, neuroimaging and electro-diagnostic screening are used to diagnose ALS. Clinical management for ALS patients has been complicated by COVID-19. COVID-19 had an effect on diagnosis and findings of ALS, including numerous clinical studies, because diagnostic process, monitoring of efficacy and safety that results in clinical studies totally depend on face-to-face meetings. COVID-19 has heightened demand for telemedicine and technical gadgets, making it more complicated to give best possible care to person [33, 34, 35].
COVID-19 crisis and its management have implications for health condition of ALS, especially those within early phases and much more harsh progression of disorder, according to outcomes of information survey that included self-perceived depression, anxiety, motor aggravate and modification in patients care. 3 patients with no history of autoimmune or neurologic illnesses have been identified with muscular dystrophy after contracting COVID-19, implying that COVID-19 disease can disrupt autoimmune consciousness [36, 37].

There is currently no reliable information on patients with SARS-CoV-2 and ALS. COVID-19 appears to have a large indirect influence on ALS patients, based on its effect on diagnosis, clinical care and associated experimental research.

6. Impact of COVID-19 on patients with Prion disease

Prion disorder is a type of unusual neurodegenerative illnesses with a prolonged incubation time and a brief clinical manifestation. It produces neuronal death in infected brain regions, generation of vasicles like tumors and recruitment of microglia and astrocytes on a pathological level. Nearly 85 percent of people had Creutzfeldt-Jakob disease (CJD) that was unpredictable. SARS-CoV-2 infection was recently reported in a patient with a possible CJD diagnosis. The patient was a 60-year-old male who became infected while at a family event. Psychomotor retardation, right hemiplegia, sudden multifocal myoclonic seizures, drowsiness, and restlessness were among the neurological symptoms he encountered soon after. He died within two months following commencement of his illness. Tau protein, MRI and EEG tests all strongly suggested the identification of spontaneous CJD. In comparison to the most of sCJD cases, he progressed quickly and had a short duration [38]. COVID-19 has been found to cause non-specific inflammatory responses in brain. Activated astrocytes and microglia with expression of inflammatory mediators like interleukine-6, interleukine-1, TNF-α and interleukine-12are commonly observed in CNS of sCJD victims and several prion contaminated animal models at preliminary and lateral stages. More research is needed to see if COVID-19 infection can exacerbate neuroinflammation and, as a result, accelerate human prion illnesses [39].

7. Impact of COVID-19 on progression/severity of stroke

Both COVID-19 and stroke may interact in a substantial way. COVID-19 patients may have a number of vascular complications like thromogenesis and other diseases, which might results in prolonged hospital stays leading to ICU hospitalizations. Strokes have been documented in COVID-19 individuals in several investigations. Mild neurological disorders were observed in 2.8 percent of 214 COVID-19 individual in a Wuhan investigation. One intracerebral haemorrhage and four ischemic stroke patients and victim with serious COVID-19 were included in study, compare with one ischemic individual suffering with non-severe COVID-19. Cerebrovascular disorders were found in 5.1 percent of 138 COVID-19 individuals in another Wuhan investigation [40]. In a study of 219 COVID-19 people in Wuhan, Li et al. (2020)
discovered that 10 (4.6%) encounter with acute ischemic stroke and 1 (0.5%) developed ICH. In another Chinese investigation, cerebrovascular disorder was found in 1.4% of COVID-19 patients within 552 hospitals of 30 regions [41]. Carfi et al. (2020) found that 2 (1.4 percent) out of 143 COVID-19 patients in Italy had a stroke. However, in Spain, 14 (1.7%) of the 841 SARS-CoV-2 infected patients had cerebrovascular illness, including 11 with ischemic stroke and three persons with ICH. COVID-19–linked coagulopathy, which can be caused by inflammation, including proinflammatory cascade, may develop in these patients [42]. Moreover, SARS-CoV-2 causes ACE2 downregulation, which leads traditional RAS axis in brain while underactivating the alternative RAS signalling. The oxidative stress, vasodilation, neuroinflammation, and thrombogenesis imbalances that result may lead to COVID-19 stroke pathogenesis [43, 44].

8. Conclusion
Several mechanisms have been proposed so far for COVID-19’s impact on the central nervous system, including direct SARS-CoV-2 infection of neurons, pro-inflammatory response stimulated by chronic inflammation inundation into CNS, thrombosis, respiratory failure-related brain hypoxia, stroke and so on. Patients of COVID-19, general public and medical professionals frequently experience psychological stress [45]. Worldwide magnitude of COVID-19 is unexpected, potentially putting entire population at risk until COVID-19 vaccinations are reached to a substantial population and also readily accessible [46]. As a distinct population, patients having neurodegenerative disorders require extra care. Several potential effects of COVID-19 on neurodegenerative illnesses have already been hypothesized, despite the fact that the scale and data of existing studies on this topic are still insufficient (Figure 1). Patients with various neurological disorders, such as Alzheimer’s disease, have previously shown a considerably higher mortality rate and are more vulnerable to SARS-CoV-2 than the aged population with underlying conditions. Secondly, COVID-19 already has strong impacts on normal processes of assessment, management, and regular care of patients with neurodegenerative disorders like amyotrophic lateral sclerosis, and it is expected to have even greater consequences in future. Furthermore, inflammatory response and immune storm triggered by SARS-CoV-2 illness appears to enhance the probability of more chronic COVID-19 instances in individuals with neurological illnesses like prion disease. Moreover, COVID-19 can hasten advancement of neurodegenerative disorders, while the processes are unknown and may differ amongst neurodegenerative disorders like Parkinson’s disease and Alzheimer’s disease. Despite the fact that several types of COVID-19 vaccines are being used over the world, it is still unclear when the pandemic will decelerate, if not comes to a halt. As a result, in order to offer relevant treatments, more long-term monitoring and analysis of COVID-19’s consequences on neurodegenerative disorders are required.

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