Parkinson's Disease and the COVID-19 Pandemic: A Review Article on the Association between SARS-CoV-2 and α-Synucleinopathy

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ABSTRACT
There is an extensive debate on the neurological consequences of 2019 novel coronavirus disease (COVID-19) and its impact on Parkinson’s disease (PD) patients, which seems to puzzle neurologists. Links between viral infections and PD have long been suspected and studied, but the exact relationship remains elusive. Since severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters the brain through multiple routes and has a direct impact on the brain, cumulative damage occurs due to the activation of proinflammatory cytokines and chemokines. SARS-CoV-2 seems to aggravate PD due to its effects on α-synuclein, mitochondrial dysfunction, and dopamine depletion. A few studies have even highlighted the higher vulnerability of PD patients to COVID-19. The sudden dramatic change in lifestyle caused by the pandemic and the widespread lockdowns that were implemented have added to the hidden sorrows of PD patients, as they already have a compromised mechanism for coping with stress. This review summarizes insights from basic science and the clinical effect of SARS-CoV-2 infection on the human brain, with a specific focus on PD.

Keywords Angiotensin converting enzyme 2; COVID-19; Parkinson's disease; Substantia nigra pars compacta.

INTRODUCTION
The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak known as the 2019 novel coronavirus disease (COVID-19) pandemic has led to an unprecedented disruption of every aspect of life, and a return to normalcy appears to be a distant dream.1 There is an extensive debate on the neurological consequences of COVID-19 and the impact these consequences might have for patients with neurodegenerative disorders including Parkinson’s disease (PD). PD is the second most common neurodegenerative disease, which is chronic and progressive in nature and manifests as tremors, bradykinesia, rigidity, and nonmotor symptoms, including dementia, psychosis, and autonomic dysfunction.2 The global outbreak of COVID-19 cases and the heterogeneous neurological manifestations of the disease led us to review the link between PD and COVID-19 to delineate what is currently known and stimulate future research.

VIRAL INFECTIONS AND PARKINSONISM
Previous studies have supported a link between viral infections and parkinsonism, although a single pathogen seems unlikely to be responsible for the entire pathogenesis of parkinsonism.3,4 Experimental studies in rodents have revealed persistent microglial activation in the central nervous system (CNS), abnormal synu-
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clein phosphorylation and transient loss of dopamine in the substantia nigra pars compacta (SNpc) and basal ganglia after intranasal inoculation with H5N1 virus, paving the way for research on viral infections that trigger α-synucleopathies in the CNS. The earliest groundbreaking observation was made by Constantin von Economo and Rene Cruchet in 1917 on postencephalitic parkinsonism observed during the encephalitic lethargica outbreak, which overlapped with the Spanish Flu (Influenza A H1N1) pandemic in 1918. Influenza antigen was found in the brains of Spanish flu patients by Gamboa et al. However, even after 100 years, the cause of encephalitic lethargica remains unclear, although a causal relationship with influenza A H1N1 has been reported but not confirmed. Other viruses, such as Epstein-Barr virus, Japanese encephalitis virus, coxsackie virus, West Nile virus, western equine encephalomyelitis virus, avian flu virus and human immunodeficiency virus (HIV), have long been associated with parkinsonism. The presence of antibodies against coronaviruses OC-43 and 229E was reported in the cerebrospinal fluid (CSF) of PD patients two decades prior to the current pandemic, supporting the role of SARS-CoV-2 in the development of PD. More recently, the development of acute parkinsonism following COVID-19 was described in three case reports, and one of these cases involved a 45-year-old Israeli patient who developed PD soon after hospitalization with SARS-CoV-2 infection.

NEUROTROPISM OF SARS-COV-2

The first reported neurological manifestation of COVID-19 was in a PD patient. Animal studies have also indicated the particularly high vulnerability of glial and oligodendroglial cells to coronaviruses. Moriguchi et al. even detected SARS-CoV-2 RNA in CSF, suggesting its neurotropism. More than 1/3 of hospitalized COVID-19 patients exhibited neuronal involvement. Brief explanations of how the SARS-CoV-2 likely gains access to the brain and the pathogenesis of the virus are provided below.

Receptors

SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE-2) receptors, which are widely expressed in various human organs, including the CNS and striatum, and on dopaminergic neurons, preferably on their cell bodies, with lower expression on axons and dendrites. Although the Human Protein Atlas indicates minimal expression of ACE-2 RNA in the CNS, the levels of enzymatic activity of ACE-2 in the brain and CSF indicates a significant level of ACE-2 protein expression. However, ACE-2 alone may not be sufficient for SARS-CoV-2 CNS infection, as other receptors and coreceptors, such as CD147, which are expressed at higher levels in most brain cells than ACE-2, may play roles. Additionally, in silico studies have proposed that the S-protein of SARS-CoV-2 displays high binding affinity for sialic acid residues expressed on plasma membrane proteins present on neural and respiratory epithelial cells, thus providing evidence for the ability of DAS181, a sialidase fusion protein, to block viral access.

Routes of entry

While there is little evidence that SARS-CoV-2 enters the brain parenchyma, there are multiple means by which the virus might be able to do so. SARS-CoV-2-mediated direct neuroinvasion is achieved by transsynaptic transfer across infected neurons, including via the olfactory nerve, via the ocular epithelium, and via the neurovascular endothelium, or by the migration of infected leukocytes across the blood-brain barrier (BBB) along with blood-borne transport to highly vascularized brain tissues (Figure 1).

Figure 1. Different mechanisms of SARS-CoV-2 infection in the brain. BBB: blood-brain barrier, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.
Transcribal route
SARS-CoV-2 first infects the olfactory bulb, which is the only area of the CNS not protected by dura, through the olfactory epithelium and olfactory nerve. Furthermore, it is most abundant in and around the region with primary or secondary connections with the olfactory bulb, including the cortex, basal ganglia, and midbrain. This pattern explains the fact that anosmia and ageusia are prodromal symptoms of COVID-19 in approximately 50% of patients. Since axons projecting from the olfactory system to the brain are not protected by the BBB, the virus is able to spread in a rather short span of three days. However, a recent study revealed that ACE-2 and transmembrane serine protease 2, another SARS-CoV-2 receptor, are not expressed in olfactory sensory or bulb neurons but rather in olfactory epithelial cells, suggesting the involvement of other dissemination mechanisms.

Hematogenous route
Following intranasal inoculation, SARS-CoV-2 may be transported through the bloodstream across the BBB into the brain by either a transendothelial mechanism of endothelial cell infection or via destabilization of tight junctions by inflammatory processes. After crossing the BBB, SARS-CoV-2-infected cells can also invade the brain through Virchow-Robin spaces. However, the observed discrepancy between the significant incidence of neurological manifestations and the low percentage of positive blood PCR results, i.e., less than 1%, suggests that viraemia is unlikely to be a major contributor.

Serotonergic transport
SNpc infection cannot be completely explained by olfactory or oral spread. This infection type can only be established by spread along the serotonergic dorsal raphe neurotransmitter pathway, which innervates large portions of the brain, including the cerebral cortex, neostriatum, amygdala, SNpc, pons, hippocampus, entorhinal cortex, and locus coeruleus, but this hypothesis is speculative and requires in vivo testing.

Transneuronal retrograde transport
The virus first infects peripheral nerve terminals and then synapses to gain access to and invade the CNS via the axonal retrograde transynaptic route of vesicular transport and passive diffusion, syncytial induction and cell-to-cell spread via the lingual, vagus and glossopharyngeal nerves.

Other routes
Rarely, SARS-CoV-2 can also enter the CNS through lymphatics or infected leucocytes, which serve as vectors.

Impact of COVID-19 on the CNS
Even after the presence of a high viral load and severe inflammation, SARS-CoV-2 appears unlikely to exhibit direct neurotropism, and the clinical changes appear to be caused by an inflammatory-mediated brain response rather than viral invasion. Widespread neuronal infection, which causes the production of high levels of proinflammatory cytokines and chemokines, including interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF)-α, upregulates ACE-2 expression and further activates a cytokine storm in the brain. TNF-α and IL-1β concurrently mediate the breakdown of the BBB, further permitting infiltration of immune cells and viral particles into the CNS. In addition to inducing direct neuroinflammation, SARS-CoV-2 has an indirect impact related hypoxia, as acute respiratory disease predisposes the brain to edema, disturbed metabolism and subsequent structural and functional damage within the basal ganglia. Autopsy reports for 18 consecutive patients that died of SARS-CoV-2 infection showed hypoxic changes but did not reveal any signs of encephalitis. Additionally, ACE-2 present in the vasculature of the brain harbors five hypoxia-responsive elements, the expression of which is upregulated via hypoxia inducible factor-1A independent mechanisms (Figure 2).

Does PD Make Patients Prone to COVID-19 and Vice Versa?
PD patients were found to be at an augmented risk of COVID-19 due to age and multiple comorbidities. They even presented more comorbidities than their age-matched controls, and a
systemic inflammatory response along with a cytokine storm seems to be easily triggered in patients with conditions associated with chronic inflammation such as diabetes, obesity, and cardiac diseases. COVID-19 may also worsen PD through interacting with the dopaminergic system in the brain, and it is also worth noting that PD is worsened when patients acquire other infections, suggesting a vicious cycle between PD and COVID-19. PD is common in elderly patients and causes respiratory and cardiac symptoms, which places these patients at a higher risk for SARS-CoV-2 infection. Table 1 shows the results of various studies on the effect of COVID-19 on patients with PD.

However, other studies have revealed that PD patients are not at a higher risk of COVID-19. Moreover, being older (mean 78.3 years) and having a longer disease duration (mean 12.7 years) puts these patients in a higher risk category with a substantially high mortality rate of 40%, while those receiving deep brain stimulation and levodopa infusion are especially vulnerable, with a mortality rate of 50%.

**PATHOPHYSIOLOGY OF PD AND HOW SARS-COV-2 AGGRAVATES PD**

Neuroinflammation is ubiquitous in regions of neurodegeneration and seems to be the phenomenon that links infectious diseases to neurodegeneration, but whether inflammation results in neurodegeneration or the underlying disease drive inflammation remains unknown.

**α-Synuclein and SARS-CoV-2**

Braak’s dual hit hypothesis (Figure 3) proposes that α-synuclein associated pathology, a hallmark of PD, originates in the nasal and intestinal mucosa. As the digestive and respiratory systems are exposed to the external environment (e.g., SARS-CoV-2), the olfactory bulb and enteric cell plexus are specifically involved in the response to inflammation. Following pathogen infection, the first hit of PD, i.e., increased α-synuclein expression in peripheral neurons, occurs, leading to the accumulation of misfolded proteins that form high-molecular-weight aggregates. Under normal conditions, these proteins do not propagate and are cleared by normal cellular homeostatic mechanisms. However, in the context of genetic predisposition, metabolic perturbation, cellular aging and chronic inflammation, which act as a second hit, the cellular milieu facilitates the accumulation of α-synuclein. The infectious agent is escorted by α-synuclein along the vagus or olfactory nerve to either the olfactory bulb or dorsal motor nucleus of the vagus and then spreads retrogradely to neighboring neurons through the brain connectome, finally reaching the SNpc; this process represents the geographical evolution of disease.

**Table 1.** Various studies conducted on the impact of COVID-19 for patients suffering from PD and their outcomes from across the globe

| Sl. | Name of the study | Outcome |
|-----|-------------------|---------|
| 1.  | Shalash et al.36   | PD patients reported worsened stress, depression, anxiety and quality of life compared to matched controls during episodes of social lockdown. |
| 2.  | Spear et al.37     | Out of 781 PD patients, 69% complained of a lack of hands-on care, 43% reported a lack of intimacy and 37% complained of technical hassles such as poor internet and video quality during self-medication while in lockdown. |
| 3.  | Brown EG et al.38  | PD patients with COVID-19 infection had either new or worsening motor (63%) and nonmotor symptoms (75%). Among PD patients non infected with the virus, 2/3 reported adverse effects from the pandemic due to cancelled health care appointments, a reduction in home care or difficulty obtaining medications. |
| 4.  | Cilia et al.39     | COVID-19 infected PD patients experienced significant deterioration of motor symptoms compared to noninfected PD controls requiring therapy adjustment in 1/3 of cases. Among nonmotor symptoms, infected patients reported increased urinary urge and fatigue along with more daily off episodes. |
| 5.  | Schirinzi et al.39 | A total of 52% of PD patients required therapeutic changes during COVID-19 emergency. |
| 6.  | Fasano et al.40    | There was no difference in the risk of COVID-19 infection in community-dwelling PD patients; however, the risk profile of severe patients in nursing homes remained unclear. The mortality rate due to COVID-19 was higher in PD patients than in the general population. |
| 7.  | Tipton and Wszolek | Elderly PD patients with comorbidities were vulnerable to progression to severe COVID-19 infection. |
| 8.  | Antonio et al.41   | In a case report of 8 PD patients, all showed worsened motor functions and orthostatic hypotension, cognitive impairment, fatigue and psychosis, leading to increased levodopa dosage. |
| 9.  | Kumar et al.42     | A total of 42.3% PD patients reported difficulty in seeking neurology consultants and PD medications, and 31% reported a lack of transport. A total of 54.2% reported dissatisfaction with quality of life due to worsening of PD and the fear of contracting COVID-19. |
| 10. | Prasad et al.43    | Patients experienced a significant inability to access healthcare and difficulty in procuring medication along with worsening of motor symptoms. |

PD: Parkinson’s disease, COVID-19: 2019 novel coronavirus disease, SI: serial number.
This neuroinflammation triggers central PD pathology, which manifests as microglial activation and increased cytokine levels in the SNpc following viral infection.

α-Synuclein, in addition to being responsible for the pathological hallmark of PD, also functions as a native antiviral factor within neurons, as indicated by its increased neuronal expression following acute West Nile virus infection. The literature suggests that West Nile and SARS are similar; therefore, analogous α-synuclein expression upregulation might occur during SARS-CoV-2 infection, leading to widespread neurodegeneration.\(^{18,47}\) It is postulated that antiviral α-synuclein accumulation following SARS-CoV-2 infection might also compound preexisting cell-autonomous vulnerability.\(^{18}\) Studies have reported that H1N1 influenza infection obstructs protein clearance to maintain optimal viral protein load, rendering infected host cells unable to counterbalance its accumulation.\(^{48}\) SARS-CoV-2 infection might also interfere with α-synuclein clearance by binding the human protein trafficking molecule open reading frame, which is involved in endoplasmic regulation, leading to the uncontrollably aggregation of α-synuclein (Figure 4).\(^{49}\) The loss of normal α-synuclein function alters endolysosomal autophagy, leading to the accumulation of dysmorphic organelles identified as a major component of Lewy bodies.\(^{46}\) As SARS-CoV-2 proteins interact with host proteins involved in pathways that are altered during aging, inducing changes such as mitochondrial dysfunction, autophagy deficiency, endoplasmic reticulum stress, loss of proteostasis and inflammation, it is likely that SARS-CoV-2 infection may exacerbate protein misfolding and aggregation.\(^{11}\) α-Synuclein also activates Toll-like receptor-4, which binds to SARS-CoV-2, on microglia and astroglia, leading to proinflammatory activation and chronic neuroinflammation, contributing to further degen-
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Mitochondria and SARS-CoV-2

The first direct link observed between mitochondrial dysfunction and PD was a defect in mitochondrial complex I, a vital component of the electron transport chain, leading to dopaminergic cell death due to energy depletion. It is suspected that neuronal populations are not equally susceptible to neuronal insult and that dopaminergic neurons are selectively vulnerable to α-synuclein accumulation because of their intrinsic properties. This vulnerability is magnified by the high bioenergetic demand of elevated basal oxidative phosphorylation in mitochondria as a result of high axon terminal density, extensive axonal arborization, and impaired proteostasis due to large axonal size. Mitochondria are crucial in the immune response, as many viruses, including SARS-CoV-2, modulate mitochondrial function. Gardinassi et al. suspected a pivotal role of mitochondria in COVID-19 patients. Wu et al. suggested that SARS-CoV-2 RNA preferentially localizes to mitochondria, thus impairing mitochondrial function, resulting in reduced energy and increased reactive oxygen species generation. Considering the large amount of energy used by dopaminergic neurons, if additional energy reserves are unavailable in the face of cellular and bioenergetic stress of COVID-19 infection, these susceptible neurons reach the threshold for neurodegeneration.

Dopamine and SARS-CoV-2

Rodent experiments have demonstrated that dopamine may play a role in shaping lung immunity via dopamine receptors expressed by alveolar epithelial cells, lung macrophages and pulmonary terminal nerves, but the potential protective role of dopamine in the context of viral infections has been poorly investigated. The changes that occur in the dopaminergic system following viral infections were summarized by Oliver et al. ACE-2 receptors are highly expressed in dopaminergic neurons, which are already compromised in PD due to degeneration; therefore, SARS-related brain penetration may cause additional harm and worsen symptoms. ACE-2 and aromatic amino acid decarboxylase (AADC) are coregulated and are coexpressed in nonneuronal cell types; thus, a SARS-CoV-2-induced downregulation of ACE-2 expression might be paralleled by an alteration of the dopamine synthetic pathway. Since ACE-2 and AADC are both highly expressed in intestinal epithelial cells and are important sources of circulating dopamine in the blood, ACE-2 expression downregulation leads to a further reduction in blood dopamine levels in COVID-19-infected PD patients and increases the need for dopamine replacement therapy. Neuramelin in the SNpc is an immune stimulator, and the number of pigmented neuramelin-expressing neurons is significantly decreased in the HIV-1-infected brain, leading to dopaminergic pathology.

CONNECTION BETWEEN PD AND COVID-19

Hainque and Grabl documented the difficulty of detecting COVID-19 in patients suffering from PD, as some symptoms, such as fatigue, anosmia, hot flashes, and painful limbs, can also be nonmotor symptoms of PD. Anosmia, which is a prodromal symptom, is present in 90% of PD patients and approximately 50% of COVID-19 patients. COVID-19 patients who exhibit anosmia also appear to have a significantly increased risk of disease progression, and a few patients with mild cases had anosmia as the sole neurological symptom. Fever, which is a concomitant symptom of COVID-19 in 87.9% of patients, is associated with motor deterioration in PD patients and can even predispose them to Parkinsonism-hyperpyrexia syndrome, a movement disorder emergency. The increased incidence of diarrhea among those diagnosed with COVID-19 also negatively affects pharmacokinetics due to the rapid flushing of metabolites through the system during bouts of diarrhea. Aggravation of urinary symptoms, which may be ascribed to the combination of fluctuating motor symptoms due to COVID-19 and increased fatigue due to the systemic inflammatory response, has been reported.

Older patients with advanced PD suffer from respiratory muscle rigidity and impairment of the cough reflex along with pre-existing dyspnea, which increases the risk of pulmonary decompensation and pneumonia if infected by SARS-CoV-2, further making them inappropriate candidates for ventilation and intubation. The higher risk of aspiration and pneumonia also complicates COVID-19 management.

HIDDEN SORROWS OF THE PANDEMIC

The COVID-19 pandemic and the associated lockdown suddenly and profoundly changed our everyday routines. Such radical changes require the ability to adapt to new circumstances, a cognitive skill is heavily dependent upon ample functioning of dopaminergic neurons. The literature indicates that the risk of chronic stress is increased in PD patients, and approximately 30%–40% of patients experience cognitive and motor inflexibility in the form of anxiety and depression as a result of nigrostriatal dopamine depletion, even in times without crisis. Additionally, stress coping mechanisms are impaired in PD patients. This increase in stress and impairment of coping mechanisms leads to the following:

- Temporary worsening of various motor symptoms accompanied by a reduction in the efficacy of dopaminergic medication.
• Unmasking of a latent hypokinetic-rigid syndrome, possibly due to depletion of compensatory mechanisms, leading to a new PD diagnosis during the pandemic.
• An enhanced rate of dopaminergic cell loss in response to a toxin in animals have been studied (comparable studies are lacking in humans).35
Recent evidence has revealed that moderate physical activity can attenuate the clinical progression of PD.63 The negative sequelae of heightened stress, reduced physical activity and prolonged home confinement due to the fear of pandemic and lockdown has resulted in worsening of both motor and nonmotor symptoms of PD patients globally and is referred to as the “hidden sorrows of the pandemic.”11,63 Additionally, staying in confined spaces might have worsened gait and increased freezing along with a significant increase in screen time may have resulted in worsened sleep in PD patients.43 Moreover, the incidence of PD is increasing over time, particularly in males, and is projected to triple by 2030. Additionally, COVID-19 has been reported to be more prevalent and severe in males.64 Along with the factors enlisted, a shortage of neurologists, aversion to surgical procedures and delayed elective surgical procedures, such as deep brain stimulation and apomorphine pumping, especially during lockdown, have further exacerbated the symptoms of patients with PD.65

**DRUG INTERACTIONS**

Patients with mild COVID-19 have been advised to manage their symptoms at home. This is difficult for PD patients, as self-medication with over-the-counter (OTC) drugs can interfere with PD symptoms and treatments.66 The anticholinergic properties of OTC medications that include antihistamines can worsen constipation, confusion, and urinary symptoms in PD patients. If a patient is on anticholinergics for Parkinson’s symptoms and OTC antihistamines or anticholinergics are taken, the side effects can be enhanced, and close monitoring is required. For PD patients taking monoamine oxidase inhibitors (MAOIs), serious drug interactions can occur if they take cough suppressants such as dextromethorphan, as MAOIs can enhance the serotonergic effect of dextromethorphan, leading to serotonin syndrome. If MAOIs and nasal decongestants are taken together, the alpha agonist effect of the decongestant can be enhanced, leading to a long-lasting effect on patients with PD; however, longitudinal studies would be beneficial to establish this link.

**SUMMARY**

The COVID-19 pandemic has led to an unprecedented crisis for elderly people worldwide. A remarkable number of patients with COVID-19 have presented a broad spectrum of neurologi-
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