Review

Parkinson’s Disease and the COVID-19 Pandemic

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Abstract. Studies focusing on the relationship between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), coronavirus disease 2019 (COVID-19), and Parkinson’s disease (PD) have provided conflicting results. We review the literature to investigate: 1) Are PD patients at higher risk for contracting COVID-19 and are there specific contributing factors to that risk? 2) How does COVID-19 affect PD symptoms? 3) How does COVID-19 present in PD patients? 4) What are the outcomes in PD patients who contract COVID-19? 5) What is the impact of COVID-19 on PD care? 6) Does COVID-19 increase the risk of developing PD? A literature search was performed from 1979 to 2020 using the terms: ‘Parkinson’s disease’ and ‘parkinsonism’ combined with: ‘COVID-19’, ‘SARS-CoV-2’ and ‘coronavirus’. It does not appear that PD is a specific risk factor for COVID-19. There is evidence for direct/indirect effects of SARS-CoV-2 on motor/non-motor symptoms of PD. Although many PD patients present with typical COVID-19 symptoms, some present atypically with isolated worsening of parkinsonian symptoms, requiring increased anti-PD therapy and having worse outcomes. Mortality data on PD patients with COVID-19 is inconclusive (ranging from 5.2% to 100%). Patients with advanced PD appear to be particularly vulnerable. Single cases of acute hypokinetic-rigid syndrome have been described but no other convincing data has been reported. The rapidity with which COVID-19 has swept across the globe has favored the proliferation of studies which lack scientific rigor and the PD literature has not been immune. A coordinated effort is required to assimilate data and answer these questions in larger PD cohorts.

Keywords: Parkinson’s disease, COVID-19, review
in PD patients with COVID-19 is inconclusive. It has been suggested that dopamine may be involved in the pathophysiology of COVID-19 [3], that amantadine and α-synuclein may be protective against COVID-19 [4, 5], whereas some authors have suggested that SARS-CoV-2 infection may potentially lead to secondary neurodegeneration [6]. The global explosion of COVID-19 has necessitated rapid dissemination of information regarding SARS-CoV-2 in order to provide adaptive care. Unfortunately, study design and recruitment have at times occurred in a rapid and ad hoc fashion, leading to conflicting results scattered across a number of small studies.

Therefore, we sought to review the current literature on the complex relationship between PD and COVID-19 in order to clarify what we know so far and where future studies should be heading.

A literature search was performed using Medline from January 1979 to October 2020 using the terms: ‘Parkinson’s disease’ and ‘parkinsonism’ combined with terms: ‘COVID-19’; ‘SARS-CoV-2’ and ‘coronavirus’. Only English-language publications were considered. Systematic checking of references from review articles and other reports was also performed. Publications were grouped to answer six specific questions: 1) Are PD patients at higher or lower risk for contracting COVID-19 and are there specific contributing factors which may put them at higher or lower risk? 2) How does COVID-19 affect PD symptoms? 3) How does COVID-19 present in PD patients? 4) What are the outcomes in PD patients who contract COVID-19? 5) What is the impact of COVID-19 on the care of PD patients? and 6) Does COVID-19 increase the risk of developing PD?

ARE PD PATIENTS AT HIGHER OR LOWER RISK FOR CONTRACTING COVID-19 AND ARE THERE SPECIFIC CONTRIBUTING FACTORS WHICH MAY PUT THEM AT HIGHER OR LOWER RISK?

The first reported neurological presentation of COVID-19 was in a PD patient [7]. The authors noted that COVID-19 affects elderly patients with chronic conditions to a greater extent, but it was unknown whether PD itself was a risk factor. The most complete data on COVID-19 risk in PD comes from Lombardy in Italy where one-third of Italian cases of SARS-CoV-2 occurred. A case-control study of 1,486 PD patients and 1,207 family members demonstrated no difference in COVID-19 rates (7.1% vs 7.6%) [8]. The PD cohort were older than controls but less likely to be hospitalized. The only potential contributing factor was that PD patients had fewer weekly outings. This may have been the result of cocooning an at-risk population and could have masked an increased risk of COVID-19 infection in PD. Accordingly, another study conducted in Germany, reported up to 73% of PD patients were compliant with social distancing, and that the proportion was higher in older patients, probably in light of perceived higher risk [9].

Another retrospective case-control study from Spain compared demographics of 39 COVID-19-positive PD patients with 172 COVID-19-negative PD controls [10]. There was no significant difference in vitamin D levels, but COVID-19 cases were more likely to be institutionalized, have co-existent dementia (36% vs. 14%, \(p=0.0013\)) and less likely to be on a dopamine agonist, although only institutionalization survived the multivariate analysis. Other studies, however, found no significant differences in disease severity or duration or concomitant medication use [8, 11]. Importantly, a number of PD medications have a proposed benefit against SARS-CoV-2. Amantadine is FDA approved for influenza A and its antiviral properties have led its consideration as a treatment for COVID-19 [4]. A number of mechanisms of action of amantadine targeting SARS-CoV-2 have been proposed [12, 13]. A small number of COVID-19-positive PD patients taking amantadine did not manifest symptoms of the disease [14] and other case reports have reported similar [15, 16]. However, it is clear that larger series are required to draw conclusions. An interactome analysis of drug targets and potential drug repurposing for SARS-CoV-2 identified entacapone among 69 existing drugs with potential effect against the virus [17]; however, no clinical data is available to support this hypothesis. An alteration in dopamine synthetic pathways may be involved in the pathophysiology of SARS-CoV-2 which raises the question of whether levodopa may modulate COVID-19 risk. A co-expression link has been demonstrated between *DDC* (encoding for dopa decarboxylase), which encodes a major enzyme in dopamine synthetic pathways, and *ACE2*, the gene encoding the main receptor to SARS-CoV-2 [3]. Furthermore, fenoldopam, a D1-receptor agonist, dampens inflammation following endotoxin-induced acute lung injury in mouse models [18]. The D2/D3-receptor antagonist elopiprazole also reduces SARS-CoV-2 infectivity in vitro (but combination with a competitive D2/D3 agonist did...
Table 1

| Drug/Class       | Potential effect                                                                 | Comment                                                                 |
|------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Levodopa         | Alteration in dopamine synthetic pathways may be involved in the pathophysiology of SARS-CoV-2 [3]. | Confounded by tendency to not using them in patients with higher baseline frailty |
| DDC inhibitors   | Co-expression of DDC and ACE2, the gene encoding the main receptor to SARS-CoV2 [3]. |-confirmed by studies [8, 10].                                      |
| Dopamine Agonists| Association with worse outcome reported in two studies [8, 10].                  |                                                                       |
| COMT inhibitors  | Interactome analysis of potential drug repurposing for SARS-CoV-2 identified entacapone as drug potential effect against the virus [17] |                                                                       |
| MAO-B inhibitors | Antimuscarnics None                                                              |                                                                       |
| Amantadine       | Small number of COVID-19-positive PD patients taking amantadine did not manifest symptoms of the disease [14–16] | Antiviral properties by downregulation of cathepsin L, lysosomal pathway disturbance and change in pH necessary to uncoat the viral proteins [97]. |
| Antimuscarinics  | None                                                                             |                                                                       |

DDC, Dopa-decarboxylase; COMT, catechol-O-methyl transferase; MAO-B, monoamine oxidase B.

not significantly reverse this reduction) [19]. As those with more severe disease tend to take higher levodopa doses and also have worse outcomes, controlling for such confounders in small datasets is difficult. In addition, levodopa is always prescribed with a dopa decarboxylase inhibitor, which can theoretically have a negative impact. Interestingly, two studies have found that patients with a worse outcome are less likely to be on dopamine agonists, but—again—this most likely mirrors the attitude of not using them in patients with higher baseline frailty [8, 10]. A summary of FDA-approved drugs for PD and proposed effects on SARS-CoV-2 is shown in Table 1.

PD patients who contract COVID-19 are more likely to be obese, have underlying COPD, and less likely to be taking vitamin D supplementation than those who do not contract COVID-19 [8]. Obesity and chronic lung disease are well described risk factors in other populations [20, 21] and the negative association with vitamin D supports the suspicion that hypovitaminosis D may contribute to COVID-19 susceptibility [22, 23]. Vitamin D deficiency is common in PD [24] and some authors have proposed vitamin D therapy as protective against both COVID-19 and PD [25], although the jump from correlation to causation requires scrutiny in the absence of convincing data.

It has been postulated that α-synuclein itself may be protective against SARS-CoV-2 [5]. Neuronal expression of α-synuclein in the peripheral nervous system inhibits viral CNS invasion and restricts replication of RNA viruses in the brain [26]. Physiological α-synuclein also plays a role in immune cell recruitment and protection against pro-inflammatory responses to other infections [27]. Finally, α-synuclein knockout mice demonstrate B-cell and T-cell deficiencies [28]. Given this, it was proposed that overexpression of α-synuclein in PD may prevent neuroinvasion of SARS-CoV-2 [5]. However, assuming the roles of physiological α-synuclein (a protein with myriad synaptic functions) will be augmented in PD patients who have an excess of aggregated α-synuclein may be speculative.

Overall, the data collected so far do not indicate that PD is a risk factor for developing COVID-19.

HOW DOES COVID-19 AFFECT PD SYMPTOMS?

Infections are a common cause of exacerbations of parkinsonian symptoms [29]. The mechanism for this remains unclear although altered cerebral dopamine metabolism, pharmacodynamic changes and direct effects of endotoxins have been implicated [30]. Although usually reversible, motor deterioration may persist following this period of systemic inflammation [31]. A severe infection such as COVID-19 will have a direct detrimental effect on PD motor symptoms. One study demonstrated that PD symptoms worsened in all eight patients with COVID-19 infection, either early before or early after infection [32]. In addition, indirect effects such as social isolation, pharmacodynamic effects, dramatic changes in routine, the impact of stress and anxiety as well as
prolonged immobility are all likely to have negative effects on motor and non-motor symptoms and quality of life in PD [33].

A community-based case-control study compared twelve PD patients with COVID-19 with 36 age-, sex-, and disease-matched COVID-negative controls and found worsening of levodopa-responsive motor symptoms and increased daily OFF-time in the COVID-19 group [11]. Half of the COVID-positive cases experienced diarrhea and—when regression models were adjusted, authors found that motor worsening and daily OFF-time (but not worsening of motor disability and activities of daily living) were predominantly explained by diarrhea. Thus, altered pharmacodynamics of dopaminergic medications may explain the increase in motor fluctuations. This symptomatic worsening required medication adjustment in one-third of cases. Needs for medications adjustments in one-third to one-half of cases have been reported in other series and also online among the cases reported in the web-based repository promoted by the International Parkinson and Movement Disorders Society [11,34–36].

A telephone-based survey of 568 Spanish patients found 65.7% of patients reported worsening of their symptoms during the pandemic [37]. However, COVID-19 status was only confirmed by patient report and only 15 patients reported COVID-19 positivity. The COVID-19-negative group were more likely to experience motor fluctuations (61% vs. 35.7%, \(p = 0.052\)) and hallucinations (23.4% vs. 0%, \(p = 0.025\)), and a trend towards more prevalent dementia and behavioral disorders was seen but this should be interpreted with great caution given the size of the COVID-19-positive cohort. Another study examined queries and correspondence from PD patients in Rome during the pandemic [35]. Most queries (46%) were regarding scheduled activities (clinic visits, prescriptions, etc.). They also found 28% of patients reported acute clinical worsening. Although none of these was affected by COVID-19, 50% of these reported worsening of motor symptoms (requiring augmentation of dopaminergic therapy in one-third) but 25% reported augmented anxiety. In a case-controlled survey in Tuscany, 29.6% of non-COVID PD cohort (\(N = 733\)) experienced worsening of motor symptoms during the COVID-19 pandemic with similar worsening of mood (24.7%), anxiety (25%), and poor sleep (22.2%) [38].

Anxiety is the most common neuropsychiatric comorbidity in PD. Quantification of anxiety levels during the pandemic in PD patients and the age-matched general population in Iran showed that severe anxiety was recorded in 25.5% of the cases and 4.8% of controls [39]. There was a strong correlation between severity of anxiety in PD patients and fear of COVID-19 infection, and this was significantly higher than in controls. In contrast, during a similar period in India, a telephone questionnaire reported that patients and caregivers were “well informed and coping well” [40]. Only 11% of patients reported worsening of motor and non-motor symptoms. The discrepancy between these two studies may be explained by the fact in the month prior to the submission dates of both articles, 3088 people had died from COVID-19 in Iran, whereas only 156 people had died in India [41]. An Egyptian telephone study showed that anxiety, depression, physical inactivity and reduced quality of life were all more prevalent in PD compared with controls [42].

More recently, large online studies such as Fox Insight have been utilized to assess the effect of the pandemic on patients with COVID-19. Data collated from 5429 PD patients (51 SARS-CoV-2-positive) found that, among those infected, 18% reported new motor symptoms and 55% reported worsening of at least one existing motor symptom [43]. New or worsening non-motor symptoms were also noted, including mood (71%), cognition (49%), sleep (62%) and dysautonomia (38%). Among those who were not infected, 6.2% reported new motor symptoms and 41% reported worsening of existing motor symptoms in addition to changes in mood (36.5%), cognition (18.5%), sleep (36.5%) and dysautonomia (20.6%).

This co-existence of anxiety, stress, isolation and physical inactivity is a particularly detrimental combination for PD patients [33]. Chronic stress accelerates dopaminergic cell loss in experimental models of PD which could exacerbate the neuropathological changes which give rise to PD. Whether chronic stress can truly permanently worsen PD, however, remains unknown. On the other hand, aerobic exercise protects against progression of parkinsonian symptoms [44] and may even enhance neuroplasticity and dopamine receptor expression in PD [45, 46]. Subjective worsening of anxiety and cognitive symptoms was demonstrated among 28 PD patients along with a mean mini-mental state examination score drop of 0.5 points before vs. during lockdown [47].

The precise mechanism by which worsening of parkinsonism occurs is not yet clear and proposed mechanisms of SARS-CoV-2-related neurodegeneration remain hypothetical. These are outlined in a
subsequent section and may have some relevance for explaining worsening of existing PD symptoms. Although cytokine storm in the setting of severe infection may worsen symptoms, the mechanism by which COVID-19 influences parkinsonian symptoms in PD may be much more straightforward. Rodents with greater than 90% nigrostriatal dopamine deficiency clinically recover completely from the 6-hydroxydopamine treatment only to become grossly symptomatic when they are exposed to a stressful environment [48]. The neurological impairments were related both to the extent of dopamine depletion and to the intensity of the stress. Similar studies in motor vehicle accidents have shown acute worsening of symptoms which recover over weeks to baseline [49]. For this reason, the combination of infection alone in the setting of stress may be sufficient to explain the observed worsening without inciting more complex mechanisms.

There is thus good evidence for direct and indirect effects of SARS-CoV-2 on motor and non-motor symptoms of PD. These indirect effects of COVID-19 may thus prove to be more detrimental to PD patients than the virus itself.

HOW DOES COVID-19 PRESENT IN PD PATIENTS?

Worsening of motor symptoms in PD may be the only presenting symptom and hence, mask the symptoms of COVID-19 infection. A study of two PD patients treated with subthalamic nucleus deep brain stimulation (STN-DBS) whose COVID-19 infections presented atypically and had poor outcomes [34]. Both patients died within days of ARDS. Hence, early and accurate diagnosis of COVID-19 in PD may be challenging. In addition, COVID-19 symptoms such as fatigue, anosmia, hot flushes or painful limbs also belong to the spectrum of non-motor PD signs. Anosmia is present in over 96% of PD patients and taste loss occurs in up to 40% [50]. Any worsening in these senses in the setting of COVID-19 is therefore subjective and may be unreliable.

Worsening of motor and non-motor symptoms in PD and a predominance of typical COVID-19 symptoms (fever 83%, cough 75%, dyspnea 33%, anosmia 33%) has been demonstrated [11]. High rates of typical symptoms among PD patients (fever 70%, cough 59%, diarrhea 27%, olfactory dysfunction 16%) which were not significantly different to those in controls with COVID-19 have been confirmed in other studies [8]. Interestingly, the rates of reported dyspnea were lower in the PD group (16.2% vs. 28.3%, \( p = 0.004 \)). This might represent a lack of awareness of the symptom as many PD patients experience breathlessness as a wearing off phenomenon and, thus, may underreport it. On the other hand, it might truly mirror lower rates of breathlessness during COVID-19. One study found similar symptoms among those with and without PD except more frequent chills \( (p = 0.048) \), cough \( (p = 0.02) \) and lower pulmonary symptoms \( (p = 0.004) \) among those without PD [43]. Atypical presentations including subacute dystonia in a 58-year-old woman with PD for 8 years and worsening of gait and balance in a 65-year-old man with PD for 4 years have been reported in absence of any respiratory symptoms [36].

In summary, although many PD patients present with typical symptoms of COVID-19, a proportion of patients present atypically with isolated worsening of parkinsonian symptoms. These patients may be diagnosed late, require increased anti-PD therapy and have worse outcomes.

WHAT IS THE OUTCOME OF PD PATIENTS WHO CONTRACT COVID-19?

Older patients with advanced PD, impaired cough reflex and respiratory muscle involvement may be particularly vulnerable to a severe acute respiratory syndrome. A Japanese study from the pre-COVID-19 era of elderly patients with pneumonia, however, showed that patients with parkinsonism had significantly lower in-hospital mortality than those without [51], suggesting PD patients may not be as vulnerable as one intuitively expects them to be. Only 8 studies have examined mortality in PD in the setting of COVID-19. Five of these studies are case series with numbers of COVID-19 cases ranging from two to 117 cases.

A series of 10 COVID-19-positive PD patients from the UK and Italy showed four of these died but all had advanced disease and were of older age (mean 78.3 years) [52]. Two of these four had been treated with intrajejunal levodopa. However, two of the six patients who recovered also had advanced therapies, suggesting other factors may predict mortality.

Comparing hospital admissions in PD patients during the pandemic with a three-year period of control data revealed 13 deaths (22.4% of hospitalizations) during the pandemic compared with 6.5% of hospitalizations prior [53]. Only three deaths related to
COVID-19 (in-hospital mortality 5.2%). This highlights the crucial secondary effect of possible delay in seeking medical attention for other illnesses (e.g., cardiac issues).

The true burden of the COVID-19 crisis for PD will therefore be represented not merely by COVID-19-related mortality but by total excess of morbidity and mortality associated during this period. A multi-center study of 117 community-dwelling PD patients with COVID-19 in Italy, Iran, Spain and the UK examined predictors of outcomes [54]. Overall mortality was 19.7% and predictors of poor outcome included coexistent dementia (26.1% vs. 8.5%, \( p = 0.049 \)) and duration of PD (11.7 ± 8.8 vs. 6.6 ± 5.4 years, \( p = 0.029 \)). There was a trend towards increased mortality with hypertension (63.6% vs. 37.6%, \( p = 0.054 \)). Thus again, patients with advanced PD are most at risk, although the overall mortality was lower than in previous studies. In their previous study, no significant difference in death rates from COVID-19 was observed between PD patients and familial controls (5.7% vs. 7.6%, \( p = 0.20 \)) [8]. Two further Italian studies with reported mortality rates of 14% (1 of 7 COVID-19-positive PD patients) and 75% (6 of 8 COVID-19-positive PD patients) respectively [32, 38]. The small numbers of infected patients included in these studies clearly highlights the difficulties in calculating meaningful estimates for outcomes.

A comparison of outcomes in 29 PD patients with severe COVID-19 (hospitalized or death) with 182 mild COVID-19/COVID-19-negative patients and found a positive association between poor outcome and institutionalization (28% vs. 5%, \( p < 0.0001 \)), dementia (38% vs. 15%, \( p = 0.0026 \)), co-existent neoplasm (10% vs. 2%, \( p = 0.0353 \)) and a negative association with use of dopamine agonists (17% vs. 74%, \( p = 0.0155 \)), although the association with dementia and dopamine agonists use did not survive the multivariate analysis [55]. The overall mortality in this study was 21%.

The data on mortality in PD patients with COVID-19 is inconclusive with figures ranging from 5.2% to 100% (Table 2). Patients with chronic neurological diseases admitted to hospital have been demonstrated to have higher COVID-19-related mortality compared to non-neurological patients, with figures ranging from 29.7% to 44.8% [56–58]. These studies were also confounded by age, baseline disability, comorbidities and one study showed that rate of intubation and multiple organ failure was higher among patients with neurological disorders [58] but others showed no difference [56, 57]. Questionnaire and telephone-based surveys are at risk of bias as more severely affected patients with longer disease duration may be missed [8]. Similarly, small case series of hospitalized patients may overestimate overall mortality in such a selected cohort.

**WHAT IS THE IMPACT FOR PATIENT CARE IN PD?**

The pandemic has required drastic adaptive changes to PD care. The majority of multidisciplinary care is currently performed remotely. Care of patients with advanced therapies has been interrupted or delayed in many centers during the pandemic [59]. Concerns over medication supply and surgical interventions for patients who require them have been raised [43, 60]. Hence, adaptive strategies and reallocation of resources have had to take place in an ad hoc fashion in many centers. The breadth of disruption to PD care, irrespective of COVID-19 status has been clearly shown [43]. In particular, those with

| Reference | Study Design | Total PD sample | PD | Controls | Risk factors |
|-----------|--------------|-----------------|----|----------|--------------|
| Fasano et al., 2020 [8] | Phone survey | 1486 (105 COVID+) | 5.7% | 7.6% | NA |
| Artusi et al., 2020 [32] | Phone survey | 1407 (8 COVID+) | 75% | NA | NA |
| Del Prete et al., 2020 [38] | Phone survey | 740 (7 COVID+) | 14% | NA | NA |
| Sainz Amo et al., 2020 [55] | Single-center case series | 211 (33 COVID+) | 21% | NA | Cancer, hospital admission (no DA use, dementia)* |
| Fasano et al., 2020 [54] | Multi-center case series | 117 (117 COVID+) | 19.7% | NA | Dementia, hypertension, disease duration |
| Kobyakci et al., 2020 [53] | Inpatients | 58 (3 COVID+) | 5.2% | NA | NA |
| Antonini et al., 2020 [52] | Case series | 10 (10 COVID+) | 40% | NA | Age, disease duration, use of advanced therapies |

*lack of DA use and dementia did not survive the multivariate analysis, DA, dopamine agonist; STN DBS, subthalamic nucleus deep brain stimulation.
longer disease duration and those who lived alone had increased risk of disruption to medical care and other essential activities. Interruptions were seen in exercise (28.9%), seeing family (46%) and friends (54%), support group attendance (21.5%) and community activities (57%), while 41% and 38% of patients found alternate means to exercise and see family, respectively.

Telemedicine is validated as a feasible way to assess PD [61]. However, it has its limitations. The assessment of rigidity, postural reflexes, cognition, mood and anxiety, are difficult, if not impossible [62, 63]. Hence, monitoring symptoms at home using wearable devices and smartphone applications may replace more traditional methods of physical examination in PD, allowing more continuous data-driven management of PD [64, 65]. Home-based exercise and psychological programs represent further adaptive opportunities for management [44]. Significant concerns have been raised regarding the use of telemedicine to properly assess patients with movement disorders [66]. In particular, the sustainability of the doctor-patient relationship, effectiveness of treatment plans instituted remotely, and diagnostic ability of the virtual environment have all been questioned. Although it has been assumed that the elderly population may not be able to adapt to video consultations, early studies have received generally positive feedback [67]. However, lower income was associated with ability to find alternative means of exercise and use of telemedicine [43].

Other adaptive strategies such as remote DBS programming based on the online evaluation of patient’s symptoms have been shown to help improve motor symptoms of postsurgical DBS patients with PD during quarantine [68]. Other decision algorithms for patients with advanced therapies have been published in order to help with rapid dissemination of management strategies during the peak of the pandemic crisis [59, 69]. These strategies entail a greater level of involvement and participation from patients in managing their own care. Thus, the challenges created by the current crisis may present new opportunities for PD care.

DOES COVID-19 INCREASE THE RISK OF DEVELOPING PD?

The finding of elevated coronavirus antibody levels in the cerebrospinal fluid of PD patients compared has suggested a possible role for viral infections in neurodegeneration [70]. However, this study is problematic for a number of reasons. Only murine coronavirus antibodies were significantly elevated. Thus, the findings may merely represent an epiphenomenon. Furthermore, no matched serum samples were taken raising the possibility that these antibodies were filtered from blood rather than synthesized intrathecally. Given that most people are seropositive for coronaviruses (many of which cause common colds) by adulthood, one expects all participants were seropositive.

Nevertheless, this concept has experienced a resurgence in the current pandemic and raised concern that incidence of post-infectious parkinsonism may rise (similar to encephalitis lethargica in the wake of the Spanish flu) [6, 71, 72]. However, drawing parallels with encephalitis lethargica should be undertaken with caution, since, notwithstanding the coincidence in time, these are different viruses and the causal role of influenza H1N1 virus on the development of post-encephalitic parkinsonism is debated [73]. The fact that anosmia, a common prodromal feature of PD, is one of the most common presenting symptoms of COVID-19 has fueled concerns regarding neuroinvasion via the olfactory bulb and potential triggering of neurodegeneration [71]. Given that olfactory dysfunction recovers in the majority of COVID-19 patients, however, this suggests neuronal loss is unlikely to be the cause of anosmia [74]. Additionally, although translational models and studies in other coronaviruses have suggested SARS-CoV-2 may be neuroinvasive [75], a recent postmortem series of four patients (one of whom had PD) showed only hypoxia-associated neuropathological features and no olfactory bulb involvement or evidence of neurotropism [76]. A larger neuropathological study of 43 patients with COVID-19 found that any changes appear to be mild [77]. Although varying degrees of astrogliosis and microglial activation was seen, which raises the possibility of future neurodegeneration, there was no evidence for CNS damage directly caused by SARS-CoV-2.

Multiple potential mechanisms have been proposed for how COVID-19 infection may affect or even cause PD. These have been elegantly summarized recently [78]. Firstly, vascular damage to the nigrostriatal system in the setting of severe SARS-CoV-2 infection could theoretically cause parkinsonism. Secondly, considering the association between inflammation and PD risk, it is possible that severe neuroinflammation could lead to loss of nigral dopaminergic neurons which may be particularly...
susceptible to systemic inflammation. Finally, the presence of viral RNA in postmortem brains of some patients with COVID-19 supports the potential that SARS-CoV-2 may be neurotropic [77, 79].

The inflammatory hypothesis has garnered significant support due to overlap between inflammatory cascades associated with COVID-19 and those reported to be potentially implicated in the pathogenesis of PD [78, 80, 81]. Aside from the “viral hypothesis” of PD, the renin-angiotensin system, which is implicated in the pathophysiology of COVID-19, may play a role in neuroinflammatory mediated-neurodegeneration in PD [82, 83]. Pro-inflammatory cytokines (TNF and IL-1β) have been associated with increased PD risk, while use anti-TNF biologics may reduce the risk [84]. Finally, oxidative stress and NF-κB have also been suspected to play a role in the development of both COVID-19 and PD [81].

Whether coronavirus can truly precipitate nigrostriatal degeneration remains unknown. To date, three cases of parkinsonism in the setting of SARS-CoV-2 infection have been reported [85–87]. All patients were young (between 35 and 58 years old), had not reported symptoms of parkinsonism prior to infection and all had nigrostriatal dopamine transporter imaging abnormalities. Two of these patients presented with symptoms typical of idiopathic PD and both patients responded to dopaminergic therapy [85, 86]. On the other hand, the third case of a 58-year-old man who developed asymmetric tremor, rigidity and bradykinesia with spontaneous improvement after 14 days is a little more suggestive of a virally-mediated presentation [87]. Dopamine transporter (DAT) SPECT imaging confirmed bilateral asymmetric decrease in presynaptic dopamine uptake involving both putamina and the authors hypothesized direct invasion by SARS-CoV-2 and selective involvement of dopaminergic midbrain neurons. The patient’s brain MRI and metaiodobenzylguanidine (MIBG) cardiac SPECT were normal, ruling out structural damage and peripheral dysautonomia as seen in PD. In addition, his clinical picture was enriched by atypical features not seen in PD, such as fluctuating encephalopathy, distal myoclonus not elicitable with common stimuli, episodic opsomolus, limited vertical gaze (with ‘round the houses’ phenomenon). To date the patient still presents with a milder asymmetric parkinsonism and a repeated DAT SPECT is planned (personal communication with authors). No other similar cases have been described to date although ‘akinet mutism’ of unclear nature has been reported in a number of studies in the setting of encephalitis [88, 89]. It is important to consider that, based on recent estimates of the incidence of PD and documented global burden of SARS-CoV-2 infection, one would expect approximately 10,000 newly-diagnosed cases of PD among those infected over the age of 40 [41, 90].

Midbrain dopamine neurons express high levels of ACE2 receptor, which could facilitate SARS-CoV-2 entry [91] and many viruses have been associated with transient parkinsonism including Epstein Barr virus, West Nile Virus, Western Equine virus, Japanese Encephalitis, Coxsackie virus and HIV. Although not yet demonstrated with SARS-CoV-2, other neurotropic viruses such as West Nile virus and Western Equine virus can upregulate alpha-synuclein [92, 93]. Since sustained elevated alpha-synuclein levels can promote aggregation of the protein, for example in patients with SNCA gene multiplications, it has been hypothesized that, if SARS-CoV-2 similarly upregulated alpha-synuclein in a similar manner, this could predispose an infected patient to PD down the line, although this remains speculative [78]. Furthermore, the presence of SARS-CoV-2 RNA is not associated with the severity of neuropathological changes and other post-mortem case series have not found viral RNA [76].

Experimental models also suggest that SARS-CoV-2 interacts with a number of proteins in age-related pathways (mitochondrial function, proteostasis, lipid metabolism and stress responses) [17]. Dysfunction of these pathways could lead to selective neurodegeneration and alpha-synuclein aggregation, as has been demonstrated with the H1N1 virus [6]. The causative role of viral infections in the genesis of PD has gained attention in recent years. There has also been recent interest in the role of cytokines (the primary mediators of inflammation in SARS-CoV-2) in accelerating neurodegeneration in PD [94].

The list of movement disorders caused by COVID-19 is growing (Table 3). However, it should be noted that multicenter studies and large case series of SARS-CoV-2-related encephalopathies indicated that movement disorders are still an uncommon manifestation of the disease [1, 95, 96]. Many confounders need to be taken into account, such as ICU-related complications and use of anti-viral medications. In addition, a number of medications used in treatment of SARS-CoV-2 can cause movement disorders as side effects (Table 4). The long-term consequences of the SARS-CoV-2 infection and the impact, if any, that the current pandemic will have on burden of PD remains unknown.
### Table 3
Movement disorders reported in association with COVID-19 infection

| Movement Disorder | Comment | No. of reported cases | Reference |
|-------------------|---------|------------------------|-----------|
| Action tremor     | Progressive upper and lower limb tremor | 2 | Xiong et al., 2020 [98] Diezma-Martin et al., 2020 [99] |
| Akinesia/ Catatonia | In setting of encephalitis, some cases unclear if true akinesia-catatonia | 6 | Mendez-Guerrero et al., 2020 [87] Beach et al., 2020 [88] Pilotto et al., 2020 [89] |
| Ataxia            | Gait disturbance and falls, acute cerebellitis | 8 | Chaumont et al., 2020 [100] Fadaker et al., 2020 [101] Mao et al., 2020 [102] Diezma-Martin et al., 2020 [99] Balestrino et al., 2020 [103] |
| Myoclonus         | Generalized (limbs, face, tongue), exaggerated startle (possible brainstem/reticular origin). | 7 | Khoo et al., 2020 [104] Mendez-Guerrero et al., 2020 [87] Grimaldi et al., 2020 [105] Rabano-Suarez et al., 2020 [106] Beach et al., 2020 [88] |
| Oculomotor disorders | Convergent spasm | 2 | Khoo et al., 2020 [104] Mendez-Guerrero et al., 2020 [87] |
| Parkinsonism      | Rest tremor, bradykinesia, rigidity | 3 | Mendez-Guerrero et al., 2020 [87] Cohen et al., 2020 [85] Faber et al., 2020 [86] |
| Tics              |          | 1 | Xiong et al., 2020 [98] |

### Table 4
Drugs used in the treatment of SARS-CoV-2 which have been reported to have movement disorders side effects or relevant drug interactions

| Drug                     | Side effects | Drug interactions |
|--------------------------|--------------|-------------------|
| Anakinra                 | None         | Can potentiate some antipsychotics |
| Atazanavir               | None         |                   |
| Azithromycin             | Akathisia, choreoathetosis |                   |
| Dipyridamole             | Tremor and ataxia (likely vestibular), potentiates parkinsonism in MPTP mice |                   |
| Famotidine               | Trialled as anti-PD medication without effect. Induces parkinsonism in ET? |                   |
| Favapiravir              | None         |                   |
| Hydroxychloroquine/ chloroquine | Cinchonism (ataxia, tremor, dystonia), parkinsonism in a 5-year-old child, myoclonus? theoretical anti-PD effects via inhibiting autophagy | Can potentiate donepezil, some antidepressants, antipsychotics? |
| Interferon beta          | None         | Can potentiate some antidepressants, antipsychotics, BDZ, donepezil, galantamine, TBZ. Can inhibit some AEDs |
| Lopinavir/ritonavir      | Serotonin syndrome, parkinsonism with concomitant buspirone |                   |
| Nitazoxanide             | May mitigate experimental parkinsonism in mice |                   |
| Remdesivir               | None         |                   |
| Ribavirin                | Parkinsonism with interferon alpha and ribavirin in chronic HVC |                   |
| Sarilumab                | None         |                   |
| Tocilizumab              | Myoclonus (toxic levels) | Can increase levodopa levels |

AEDs, antiepileptic drugs; BDZ, benzodiazepines; ET, essential tremor; HCV, Hepatitis C virus; MPTP, 1-methyl-4-phenyl-1,2,3,6–tetrahydropyridine; TBZ, tetrabenazine.
CONCLUSIONS

The uncertainty created by the COVID-19 pandemic has affected every area of medical care. PD patients represent a particularly vulnerable group both to the direct and indirect effects of SARS-CoV-2. The rapidity with which COVID-19 has swept across the globe has made constructing large well-designed studies to examine these questions in a rigorous fashion problematic. As a result, the evidence is scattered diffusely among a relatively small number of studies and the many questions remain unanswered. A coordinated effort is required to assimilate data to answer the questions contained here in larger PD cohorts. Dedicated databases of PD cohorts with and without COVID-19 may aid in answering many of the above questions.

CONFLICT OF INTEREST

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