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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

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has quickly spread globally. This crisis has received significant attention in the medical literature with approximately 30,000 related publications on PubMed (and many more in online archives of preprints) in the first 6 months of 2020. Recently, the specific neurological manifestations of COVID-19, as well as the impact of the pandemic on patients with neurological disease, has garnered interest [1, 2].

Many of these studies have focused on the relationship between SARS-CoV-2, COVID-19, and Parkinson's disease (PD). Intuitively, older people with advanced PD are particularly vulnerable to an acute respiratory pandemic. The effects of stress, anxiety and social isolation are also likely to have a negative impact on parkinsonian symptoms, leading to secondary deterioration. Nevertheless, data on outcome

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in PD patients with COVID-19 is inconclusive. It has been suggested that dopamine may be involved in pathophysiology of COVID-19 [3], that amantadine and α-synuclein may 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
FDA-approved drugs for the treatment of Parkinson's disease and their reported potential impact on SARS-CoV-2 infection

Drug/Class	Potential effect	Comment
Levodopa	Alteration in dopamine synthetic pathways may be involved in the pathophysiology of SARS-CoV-2 [3].	
DDC inhibitors	Co-expression of *DDC* and *ACE2*, the gene encoding the main receptor to SARS-CoV2 [3].	
Dopamine Agonists	Association with worse outcome reported in two studies [8, 10].	Confounded by tendency to not using them in patients with higher baseline frailty
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	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 in 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, COV ID-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 dropped 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 influence 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

Table 2
Current studies reporting mortality figures relating to COVID-19 in PD

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
Kobylecki 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
Hainque & Grabli, 2020 [34]	Case series	2 (2 COVID+)	100%	NA	STN DBS?

*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 opsoclonus, 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 'akinetic 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 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-rel ated 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]
Akinetic Mutism/ Catatonia	In setting of encephalitis, some cases unclear if true akinetic-mutism	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 Episodic opsoclonus Ocular flutter Slow Saccades Vertical supranuclear gaze palsy (“round the houses”)	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	
Atazanavir	None	Can potentiate some antipsychotics
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	
Lopinavir/ritonavir	Serotonin syndrome, parkinsonism with concomitant buspirone	Can potentiate some antidepressants, antipsychotics, BDZ, donepezil, galantamine, TBZ. Can inhibit some AEDs
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; BDS, 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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REFERENCES

[1] Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, Kneen R, Defres S, Sejvar J, Solomon T (2020) Neurological associations of COVID-19. *Lancet Neurol* **19**, 767-783.

[2] Wood H (2020) New insights into the neurological effects of COVID-19. *Nat Rev Neurol* **16**, 403.

[3] Nataf S (2020) An alteration of the dopamine synthetic pathway is possibly involved in the pathophysiology of COVID-19. *J Med Virol* **92**, 1743-1744.

[4] Araújo R, Aranda-Martínez JD, Aranda-Abreu GE (2020) Amantadine treatment for people with COVID-19. *Arch Med Res* **51**, 739-740.

[5] Ait Wahmane S, Achbani A, Ouhaz Z, Elatiqi M, Belmouden A, Nejmeddine M (2020) The possible protective role of α-synuclein against severe acute respiratory syndrome coronavirus 2 infections in patients with Parkinson's disease. *Mov Disord* **35**, 1293-1294.

[6] Lippi A, Domingues R, Setz C, Outeiro TF, Krisko A (2020) SARS-CoV-2: At the crossroad between aging and neurodegeneration. *Mov Disord* **35**, 716-720.

[7] Filatov A, Sharma P, Hindi F, Espinosa PS (2020) Neurological complications of coronavirus disease (COVID-19): Encephalopathy. *Cureus* **12**, e7352.

[8] Fasano A, Cereda E, Barichella M, Cassani E, Ferri V, Zecchinelli AL, Pezzoli G (2020) COVID-19 in Parkinson's disease patients living in Lombardy, Italy. *Mov Disord* **35**, 1089-1093.

[9] Zipprich HM, Teschner U, Witte OW, Schönenberg A, Prell T (2020) Knowledge, attitudes, practices, and burden during the COVID-19 pandemic in people with Parkinson's disease in Germany. *J Clin Med* **9**, 1643.

[10] Sainz-Amo R, Baena-Álvarez B, Pareés I, Sánchez-Díez G, Pérez-Torre P, López-Sendón JL, Fanjul-Arbos S, Monreal E, Corral-Corral I, García-Barragán N, Martínez-Castrillo JC, Fasano A, Alonso-Cánovas A (2020) COVID-19 in Parkinson's disease: What holds the key? *J Neurol*, doi: 10.1007/s00415-020-10272-0

[11] Cilia R, Bonvegna S, Straccia G, Andreasi NG, Elia AE, Romito LM, Devigili G, Cereda E, Eleopra R (2020) Effects of COVID-19 on Parkinson's disease clinical features: A community-based case-control study. *Mov Disord* **35**, 1287-1292.

[12] Aranda Abreu GE, Hernández Aguilar ME, Herrera Covarrubias D, Rojas Durán F (2020) Amantadine as a drug to mitigate the effects of COVID-19. *Med Hypotheses* **140**, 109755.

[13] Smieszek SP, Przychodzen BP, Polymeropoulos MH (2020) Amantadine disrupts lysosomal gene expression: A hypothesis for COVID19 treatment. *Int J Antimicrob Agents* **55**, 106004.

[14] Rejdak K, Grieb P (2020) Adamantanes might be protective from COVID-19 in patients with neurological diseases: Multiple sclerosis, parkinsonism and cognitive impairment. *Mult Scler Relat Disord* **42**, 102163.

[15] Cortés Borra A (2020) Does amantadine have a protective effect against COVID-19? *Neurol Neurochir Pol* **54**, 284-285.

[16] Aranda-Abreu GE, Aranda-Martínez JD, Araújo R (2020) Use of amantadine in a patient with SARS-CoV-2. *J Med Virol*, doi: 10.1002/jmv.26179

[17] Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, White KM, O'Meara MJ, Rezelj VV, Guo JZ, Swaney DL, Tummino TA, Hüttenhain R, Kaake RM, Richards AL, Tutuncuoglu B, Foussard H, Batra J, Haas K, Modak M, Kim M, Haas P, Polacco BJ, Braberg H, Fabius JM, Eckhardt M, Soucheray M, Bennett MJ, Cakir M, McGregor MJ, Li Q, Meyer B, Roesch F, Vallet T, Mac Kain A, Miorin L, Moreno E, Naing ZZC, Zhou Y, Peng S, Shi Y, Zhang Z, Shen W, Kirby IT, Melnyk JE, Chorba JS, Lou K, Dai SA, Barrio-Hernandez I, Memon D, Hernandez-Armenta C, Lyu J, Mathy CJP, Perica T, Pilla KB, Ganesan SJ, Saltzberg DJ, Rakesh R, Liu X, Rosenthal SB, Calviello L, Venkataramanan S, Liboy-Lugo J, Lin Y, Huang XP, Liu Y, Wankowicz SA, Bohn M, Safari M, Ugur FS, Koh C, Savar NS, Tran QD, Shengjuler D, Fletcher SJ, O'Neal MC, Cai Y, Chang JCJ, Broadhurst DJ, Klippsten S, Sharp PP, Wenzell NA, Kuzuoglu-Ozturk D, Wang HY, Trenker R, Young JM, Cavero DA, Hiatt J, Roth TL, Rathore U, Subramanian A, Noack J, Hubert M, Stroud RM, Frankel AD, Rosenberg OS, Verba KA, Agard DA, Ott M, Emerman M, Jura N, von Zastrow M, Verdin E, Ashworth A, Schwartz O, d'Enfert C, Mukherjee S, Jacobson M, Malik HS, Fujimori DG, Ideker T, Craik CS, Floor SN, Fraser JS, Gross JD, Sali A, Roth BL, Ruggero D, Taunton J, Kortemme T, Beltrao P, Vignuzzi M, García-Sastre A, Shokat KM, Shoichet BK, Krogan NJ (2020) A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* **583**, 459-468.

[18] Bone NB, Liu Z, Pittet J-F, Zmijewski JW (2017) Frontline Science: D1 dopaminergic receptor signaling activates the AMPK-bioenergetic pathway in macrophages and

alveolar epithelial cells and reduces endotoxin-induced ALI. *J Leukoc Biol* **101**, 357-365.

[19] Riva L, Yuan S, Yin X, Martin-Sancho L, Matsunaga N, Pache L, Burgstaller-Muehlbacher S, De Jesus PD, Teriete P, Hull MV, Chang MW, Chan JF-W, Cao J, Poon VK-M, Herbert KM, Cheng K, Nguyen T-TH, Rubanov A, Pu Y, Nguyen C, Choi A, Rathnasinghe R, Schotsaert M, Miorin L, Dejosez M, Zwaka TP, Sit K-Y, Martinez-Sobrido L, Liu W-C, White KM, Chapman ME, Lendy EK, Glynne RJ, Albrecht R, Ruppin E, Mesecar AD, Johnson JR, Benner C, Sun R, Schultz PG, Su AI, García-Sastre A, Chatterjee AK, Yuen K-Y, Chanda SK (2020) Discovery of SARS-CoV-2 antiviral drugs through large-scale compound repurposing. *Nature* **586**, 113-119.

[20] de Siqueira JVV, Almeida LG, Zica BO, Brum IB, Barceló A, de Siqueira Galil AG (2020) Impact of obesity on hospitalizations and mortality, due to COVID-19: A systematic review. *Obes Res Clin Pract* **14**, 398-403.

[21] Alqahtani JS, Oyelade T, Aldhahir AM, Alghamdi SM, Almehmadi M, Alqahtani AS, Quaderi S, Mandal S, Hurst JR (2020) Prevalence, severity and mortality associated with COPD and smoking in patients with COVID-19: A rapid systematic review and meta-analysis. *PloS One* **15**, e0233147.

[22] Mitchell F (2020) Vitamin-D and COVID-19: Do deficient risk a poorer outcome? *Lancet Diabetes Endocrinol* **8**, 570.

[23] Ilie PC, Stefanescu S, Smith L (2020) The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging Clin Exp Res* **32**, 1195-1198.

[24] Ding H, Dhima K, Lockhart KC, Locascio JJ, Hoesing AN, Duong K, Trisini-Lipsanopoulos A, Hayes MT, Sohur US, Wills A-M, Mollenhauer B, Flaherty AW, Hung AY, Mejia N, Khurana V, Gomperts SN, Selkoe DJ, Schwarzschild MA, Schlossmacher MG, Hyman BT, Sudarsky LR, Growdon JH, Scherzer CR (2013) Unrecognized vitamin D3 deficiency is common in Parkinson disease: Harvard Biomarker Study. *Neurology* **81**, 1531-1537.

[25] Hribar CA, Cobbold PH, Church FC (2020) Potential role of vitamin D in the elderly to resist COVID-19 and to slow progression of Parkinson's disease. *Brain Sci* **10**, 284.

[26] Massey AR, Beckham JD (2016) Alpha-synuclein, a novel viral restriction factor hiding in plain sight. *DNA Cell Biol* **35**, 643-645.

[27] Labrie V, Brundin P (2017) Alpha-synuclein to the rescue: Immune cell recruitment by alpha-synuclein during gastrointestinal infection. *J Innate Immun* **9**, 437-440.

[28] Xiao W, Shameli A, Harding CV, Meyerson HJ, Maitta RW (2014) Late stages of hematopoiesis and B cell lymphopoiesis are regulated by α-synuclein, a key player in Parkinson's disease. *Immunobiology* **219**, 836-844.

[29] Zheng KS, Dorfman BJ, Christos PJ, Khadem NR, Hencheliffe C, Piboolnurak P, Nirenberg MJ (2012) Clinical characteristics of exacerbations in Parkinson disease. *Neurologist* **18**, 120-124.

[30] Brugger F, Erro R, Balint B, Kägi G, Barone P, Bhatia KP (2015) Why is there motor deterioration in Parkinson's disease during systemic infections - a hypothetical view. *NPJ Parkinsons Dis* **1**, 15014.

[31] Umemura A, Oeda T, Tomita S, Hayashi R, Kohsaka M, Park K, Sugiyama H, Sawada H (2014) Delirium and high fever are associated with subacute motor deterioration in Parkinson disease: A nested case-control study. *PLoS One* **9**, e94944.

[32] Artusi CA, Romagnolo A, Imbalzano G, Marchet A, Zibetti M, Rizzone MG, Lopiano L (2020) COVID-19 in Parkinson's disease: Report on prevalence and outcome. *Parkinsonism Relat Disord* **80**, 7-9.

[33] Helmich RC, Bloem BR (2020) The impact of the COVID-19 pandemic on Parkinson's disease: Hidden sorrows and emerging opportunities. *J Parkinson Dis* **10**, 351-354.

[34] Hainque E, Grabli D (2020) Rapid worsening in Parkinson's disease may hide COVID-19 infection. *Parkinsonism Relat Disord* **75**, 126-127.

[35] Schirinzi T, Cerroni R, Di Lazzaro G, Liguori C, Scalise S, Bovenzi R, Conti M, Garasto E, Mercuri NB, Pierantozzi M, Pisani A, Stefani A (2020) Self-reported needs of patients with Parkinson's disease during COVID-19 emergency in Italy. *Neurol Sci* **41**, 1373-1375.

[36] International Parkinson and Movement Disorder Society (2020) Repository of COVID-19 and movement disorder observations.

[37] Santos García D, Oreiro M, Pérez P, Fanjul G, Paz González JM, Feal Painceiras M, Cores Bartolomé C, Valdés Aymerich L, García Sancho C, Castellanos Rodrigo M (2020) Impact of COVID-19 pandemic on Parkinson's disease: A cross-sectional survey of 568 Spanish patients. *Mov Disord* 35(10):1712-1716.

[38] Del Prete E, Francesconi A, Palermo G, Mazzucchi S, Frosini D, Morganti R, Coleschi P, Raglione LM, Vanni P, Ramat S, Novelli A, Napolitano A, Battisti C, Giuntini M, Rossi C, Menichetti C, Ulivelli M, De Franco V, Rossi S, Bonuccelli U, Ceravolo R, Tuscany Parkinson COVID-19 Participants (2020) Prevalence and impact of COVID-19 in Parkinson's disease: Evidence from a multi-center survey in Tuscany region. *J Neurol*, doi: 10.1007/s00415-020-10002-6

[39] Salari M, Zali A, Ashrafi F, Etemadifar M, Sharma S, Hajizadeh N, Ashourizadeh H (2020) Incidence of anxiety in Parkinson's disease during the coronavirus disease (COVID-19) pandemic. *Mov Disord* **5**, 1095-1096.

[40] Prasad S, Holla VV, Neeraja K, Surisetti BK, Kamble N, Yadav R, Pal PK (2020) Parkinson's disease and COVID-19: Perceptions and implications in patients and caregivers. *Mov Disord* **35**, 912-914.

[41] WHO Coronavirus Disease (COVID-19) Dashboard.

[42] Shalash A, Roushdy T, Essam M, Fathy M, Dawood NL, Abushady EM, Elrassas H, Helmi A, Hamid E (2020) Mental health, physical activity, and quality of life in Parkinson's disease during COVID-19 pandemic. *Mov Disord* **35**, 1097-1099.

[43] Brown EG, Chahine LM, Goldman SM, Korell M, Mann E, Kinel DR, Arnedo V, Marek KL, Tanner CM (2020) The effect of the COVID-19 pandemic on people with Parkinson's disease. *J Parkinsons Dis* **10**, 1365-1377.

[44] van der Kolk NM, de Vries NM, Kessels RPC, Joosten H, Zwinderman AH, Post B, Bloem BR (2019) Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson's disease: A double-blind, randomised controlled trial. *Lancet Neurol* **18**, 998-1008.

[45] Kintz N, Petzinger GM, Jakowec MW (2017) Treadmill exercise modifies dopamine receptor expression in the prefrontal cortex of the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse model of Parkinson's disease. *Neuroreport* **28**, 987-995.

[46] Petzinger GM, Fisher BE, McEwen S, Beeler JA, Walsh JP, Jakowec MW (2013) Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. *Lancet Neurol* **12**, 716-726.

[47] Palermo G, Tommasini L, Baldacci F, Del Prete E, Siciliano G, Ceravolo R (2020) Impact of COVID-19 pandemic

on cognition in Parkinson's disease. *Mov Disord* **35**, 1717-1718.

[48] Snyder AM, Stricker EM, Zigmond MJ (1985) Stress-induced neurological impairments in an animal model of parkinsonism. *Ann Neurol* **18**, 544-551.

[49] Goetz CG, Stebbins GT (1991) Effects of head trauma from motor vehicle accidents on Parkinson's disease. *Ann Neurol* **29**, 191-193.

[50] Tarakad A, Jankovic J (2017) Anosmia and ageusia in Parkinson's disease. *Int Rev Neurobiol* **133**, 541-556.

[51] Jo T, Yasunaga H, Michihata N, Sasabuchi Y, Hasegawa W, Takeshima H, Sakamoto Y, Matsui H, Fushimi K, Nagase T, Yamauchi Y (2018) Influence of parkinsonism on outcomes of elderly pneumonia patients. *Parkinsonism Relat Disord* **54**, 25-29.

[52] Antonini A, Leta V, Teo J, Chaudhuri KR (2020) Outcome of Parkinson's disease patients affected by COVID-19. *Mov Disord* **35**, 905-908.

[53] Kobylecki C, Jones T, Lim CK, Miller C, Thomson AM (2020) Phenomenology and outcomes of in-patients with Parkinson's disease during the coronavirus disease 2019 pandemic. *Mov Disord* **35**(8), 1295-1296.

[54] Fasano A, Elia AE, Dallocchio C, Canesi M, Alimonti D, Sorbera C, Alonso-Canovas A, Pezzoli G (2020) Predictors of COVID-19 outcome in Parkinson's disease. *Parkinsonism Relat Disord* **78**, 134-137.

[55] Sainz-Amo R, Baena-Álvarez B, Pareés I, Sánchez-Díez G, Pérez-Torre P, López-Sendón JL, Fanjul-Arbos S, Monreal E, Corral-Corral I, García-Barragán N, Martínez-Castrillo JC, Fasano A, Alonso-Cánovas A (2020) COVID-19 in Parkinson's disease: What holds the key? *J Neurol*, doi: 10.1007/s00415-020-10272-0

[56] García-Azorín D, Martínez-Pías E, Trigo J, Hernández-Pérez I, Valle-Peñacoba G, Talavera B, Simón-Campo P, de Lera M, Chavarría-Miranda A, López-Sanz C, Gutiérrez-Sánchez M, Martínez-Velasco E, Pedraza M, Sierra Á, Gómez-Vicente B, Guerrero Á, Ezpeleta D, Peñarrubia MJ, Gómez-Herreras JI, Bustamante-Munguira E, Abad-Molina C, Orduña-Domingo A, Ruiz-Martin G, Jiménez-Cuenca MI, Juarros S, Del Pozo-Vegas C, Dueñas-Gutierrez C, de Paula JMP, Cantón-Álvarez B, Vicente JM, Arenillas JF (2020) Neurological comorbidity is a predictor of death in Covid-19 disease: A cohort study on 576 patients. *Front Neurol* **11**, 781.

[57] Pilotto A, Benussi A, Libri I, Masciocchi S, Poli L, Premi E, Alberici A, Baldelli E, Bonacina S, Brambilla L, Benini M, Caratozzolo S, Cortinovis M, Costa A, Cotti Piccinelli S, Cottini E, Cristillo V, Delrio I, Filosto M, Gamba M, Gazzina S, Gilberti N, Gipponi S, Giunta M, Imarisio A, Liberini P, Locatelli M, Schiano F, Rao R, Risi B, Rozzini L, Scalvini A, Vergani V, Volonghi I, Zoppi N, Borroni B, Magoni M, Leonardi M, Zanusso G, Ferrari S, Mariotto S, Pezzini A, Gasparotti R, Paolillo C, Padovani A (2020) COVID-19 impact on consecutive neurological patients admitted to the emergency department. *J Neurol Neurosurg Psychiatry*, doi: 10.1136/jnnp-2020-323929

[58] Frontera JA, Sabadia S, Lalchan R, Fang T, Flusty B, Millar-Vernetti P, Snyder T, Berger S, Yang D, Granger A, Morgan N, Patel P, Gutman J, Melmed K, Agarwal S, Bokhari M, Andino A, Valdes E, Omari M, Kvernland A, Lillemoe K, Chou SH-Y, McNett M, Helbok R, Mainali S, Fink EL, Robertson C, Schober M, Suarez JI, Ziai W, Menon D, Friedman D, Friedman D, Holmes M, Huang J, Thawani S, Howard J, Abou-Fayssal N, Krieger P, Lewis A, Lord AS, Zhou T, Kahn DE, Czeisler BM, Torres J, Yaghi S, Ishida K, Scher E, de Havenon A, Placantonakis D, Liu M, Wisniewski T, Troxel AB, Balcer L, Galetta S (2020) A prospective study of neurologic disorders in hospitalized COVID-19 patients in New York City. *Neurology*, doi: 10.1212/WNL.0000000000010979

[59] Fasano A, Antonini A, Katzenschlager R, Krack P, Odin P, Evans AH, Foltynie T, Volkmann J, Merello M (2020) Management of advanced therapies in Parkinson's disease patients in times of humanitarian crisis: The COVID-19 experience. *Mov Disord Clin Pract* **7**, 361-372.

[60] Papa SM, Brundin P, Fung VSC, Kang UJ, Burn DJ, Colosimo C, Chiang H-L, Alcalay RN, Trenkwalder C, MDS-Scientific Issues Committee (2020) Impact of the COVID-19 pandemic on Parkinson's disease and movement disorders. *Mov Disord* **35**, 711-715.

[61] Schneider RB, Biglan KM (2017) The promise of telemedicine for chronic neurological disorders: The example of Parkinson's disease. *Lancet Neurol* **16**, 541-551.

[62] Goetz CG, Stebbins GT, Luo S (2020) Movement Disorder Society–Unified Parkinson's Disease Rating Scale Use in the Covid-19 Era. *Mov Disord* **35**, 911-911.

[63] Abdolahi A, Bull MT, Darwin KC, Venkataraman V, Grana MJ, Dorsey ER, Biglan KM (2016) A feasibility study of conducting the Montreal Cognitive Assessment remotely in individuals with movement disorders. *Health Informatics J* **22**, 304-311.

[64] Espay AJ, Hausdorff JM, Sánchez-Ferro Á, Klucken J, Merola A, Bonato P, Paul SS, Horak FB, Vizcarra JA, Mestre TA, Reilmann R, Nieuwboer A, Dorsey ER, Rochester L, Bloem BR, Maetzler W, Movement Disorder Society Task Force on Technology (2019) A roadmap for implementation of patient-centered digital outcome measures in Parkinson's disease obtained using mobile health technologies. *Mov Disord* **34**, 657-663.

[65] Motolese F, Magliozzi A, Puttini F, Rossi M, Capone F, Karlinski K, Stark-Inbar A, Yekutieli Z, Di Lazzaro V, Marano M (2020) Parkinson's disease remote patient monitoring during the COVID-19 lockdown. *Front Neurol* **11**, 567413.

[66] Mulroy E, Menozzi E, Lees AJ, Lynch T, Lang AE, Bhatia KP (2020) Telemedicine in movement disorders: Leçons du coronavirus disease 2019. *Mov Disord* **35**, 1893-1896.

[67] Kumar A (2020) Experience of video consultation during the COVID-19 pandemic in elderly population for Parkinson's disease and movement disorders. *Postgrad Med J*, doi: 10.1136/postgradmedj-2020-138846

[68] Xu J, Wang J, Keith S, Zhang M, Yang C, Yuan Q, Qiu Y, Hu X, Wu X (2020) Management of Parkinson's disease patients after DBS by remote programming: Preliminary application of single center during quarantine of 2019-nCoV. *J Neurol*, doi: 10.1007/s00415-020-10273-z

[69] Kostick K, Storch EA, Zuk P, Blumenthal-Barby JS, Torgerson L, Yoshor D, Sheth S, Viswanathan A, Tarakad A, Jimenez-Shahed J, Goodman W, Lázaro-Muñoz G (2020) Strategies to mitigate impacts of the COVID-19 pandemic on patients treated with deep brain stimulation. *Brain Stimulat* **13**, 1642-1643.

[70] Fazzini E, Fleming J, Fahn S (1992) Cerebrospinal fluid antibodies to coronavirus in patients with Parkinson's disease. *Mov Disord* **7**, 153-158.

[71] Boika AV (2020) A post-COVID-19 parkinsonism in the future? *Mov Disord* **35**, 1094.

[72] Singal CMS, Jaiswal P, Seth P (2020) SARS-CoV-2, more than a respiratory virus: Its potential role in neuropathogenesis. *ACS Chem Neurosci* **11**, 1887-1899.

[73] Hoffman LA, Vilensky JA (2017) Encephalitis lethargica: 100 years after the epidemic. *Brain* **140**, 2246-2251.

[74] Chiesa-Estomba CM, Lechien JR, Radulesco T, Michel J, Sowerby LJ, Hopkins C, Saussez S (2020) Patterns of smell recovery in 751 patients affected by the COVID-19 outbreak. *Eur J Neurol* **27**, 2318-2321.

[75] Li Y, Bai W, Hashikawa T (2020) The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol* **92**, 552-555.

[76] Kantonen J, Mahzabin S, Mäyränpää MI, Tynninen O, Paetau A, Andersson N, Sajantila A, Vapalahti O, Carpén O, Kekäläinen E, Kantele A, Myllykangas L (2020) Neuropathologic features of four autopsied COVID-19 patients. *Brain Pathol* **30**, 1012-1016.

[77] Matschke J, Lütgehetmann M, Hagel C, Sperhake JP, Schröder AS, Edler C, Mushumba H, Fitzek A, Allweiss L, Dandri M, Dottermusch M, Heinemann A, Pfefferle S, Schwabenland M, Sumner Magruder D, Bonn S, Prinz M, Gerloff C, Püschel K, Krasemann S, Aepfelbacher M, Glatzel M (2020) Neuropathology of patients with COVID-19 in Germany: A post-mortem case series. *Lancet Neurol* **19**, 919-929.

[78] Brundin P, Nath A, Beckham JD (2020) Is COVID-19 a perfect storm for Parkinson's disease? *Trends Neurosci* **43**, 931-933.

[79] da S G Pedrosa C, Goto-Silva L, Temerozo JR, Gomes IC, Souza LRQ, Vitória G, Ornelas IM, Karmirian K, Mendes MA, Sacramento CQ, Fintelman-Rodrigues N, Soares VC, da Silva Gomes Dias S, Salerno JA, Puig-Pijuan T, Veríssimo C, Furtado DR, Borges HL, Bozza PT, Rehen S, Souza TML, Guimarães MZP (2020) Non-permissive SARS-CoV-2 infection of neural cells in the developing human brain and neurospheres. *bioRxiv*, doi: 10.1101/2020.09.11.293951. Preprint

[80] Sulzer D, Antonini A, Leta V, Nordvig A, Smeyne RJ, Goldman JE, Al-Dalahmah O, Zecca L, Sette A, Bubacco L, Meucci O, Moro E, Harms AS, Xu Y, Fahn S, Ray Chaudhuri K (2020) COVID-19 and possible links with Parkinson's disease and parkinsonism: From bench to bedside. *NPJ Parkinsons Dis* **6**, 18.

[81] Chaudhry ZL, Klenja D, Janjua N, Cami-Kobeci G, Ahmed BY (2020) COVID-19 and Parkinson's disease: Shared inflammatory pathways under oxidative stress. *Brain Sci* **10**, 807.

[82] Rodriguez-Perez AI, Garrido-Gil P, Pedrosa MA, Garcia-Garrote M, Valenzuela R, Navarro G, Franco R, Labandeira-Garcia JL (2020) Angiotensin type 2 receptors: Role in aging and neuroinflammation in the substantia nigra. *Brain Behav Immun* **87**, 256-271.

[83] Joglar B, Rodriguez-Pallares J, Rodriguez-Perez AI, Rey P, Guerra MJ, Labandeira-Garcia JL (2009) The inflammatory response in the MPTP model of Parkinson's disease is mediated by brain angiotensin: Relevance to progression of the disease. *J Neurochem* **109**, 656-669.

[84] Gagne JJ, Power MC (2010) Anti-inflammatory drugs and risk of Parkinson disease. *Neurology* **74**, 995-1002.

[85] Cohen ME, Eichel R, Steiner-Birmanns B, Janah A, Ioshpa M, Bar-Shalom R, Paul JJ, Gaber H, Skrahina V, Bornstein NM, Yahalom G (2020) A case of probable Parkinson's disease after SARS-CoV-2 infection. *Lancet Neurol* **19**, 804-805.

[86] Faber I, Brandão PRP, Menegatti F, de Carvalho Bispo DD, Maluf FB, Cardoso F (2020) Coronavirus disease 2019 and parkinsonism: A non-post-encephalitic case. *Mov Disord* **35**, 1721-1722.

[87] Méndez-Guerrero A, Laespada-García MI, Gómez-Grande A, Ruiz-Ortiz M, Blanco-Palmero VA, Azcarate-Diaz FJ, Rábano-Suárez P, Álvarez-Torres E, de Fuenmayor-Fernández de la Hoz CP, Pérez DV, Rodríguez-Montalbán R, Pérez-Rivilla A, Catalán JS, González AR-, González de la Aleja J (2020) Acute hypokinetic-rigid syndrome following SARS-CoV-2 infection. *Neurology* **95**, e2109-e2118.

[88] Beach SR, Praschan NC, Hogan C, Dotson S, Merideth F, Kontos N, Fricchione GL, Smith FA (2020) Delirium in COVID-19: A case series and exploration of potential mechanisms for central nervous system involvement. *Gen Hosp Psychiatry* **65**, 47-53.

[89] Pilotto A, Odolini S, Masciocchi S, Comelli A, Volonghi I, Gazzina S, Nocivelli S, Pezzini A, Focá E, Caruso A, Leonardi M, Pasolini MP, Gasparotti R, Castelli F, Ashton NJ, Blennow K, Zetterberg H, Padovani A (2020) Steroid-responsive encephalitis in coronavirus disease 2019. *Ann Neurol* **88**, 423-427.

[90] Hirsch L, Jette N, Frolkis A, Steeves T, Pringsheim T (2016) The incidence of Parkinson's disease: A systematic review and meta-analysis. *Neuroepidemiology* **46**, 292-300.

[91] Yang L, Han Y, Nilsson-Payant BE, Gupta V, Wang P, Duan X, Tang X, Zhu J, Zhao Z, Jaffré F, Zhang T, Kim TW, Harschnitz O, Redmond D, Houghton S, Liu C, Naji A, Ciceri G, Guttikonda S, Bram Y, Nguyen D-HT, Cioffi M, Chandar V, Hoagland DA, Huang Y, Xiang J, Wang H, Lyden D, Borczuk A, Chen HJ, Studer L, Pan FC, Ho DD, tenOever BR, Evans T, Schwartz RE, Chen S (2020) A human pluripotent stem cell-based platform to study SARS-CoV-2 tropism and model virus infection in human cells and organoids. *Cell Stem Cell* **27**, 125-136.e7.

[92] Beatman EL, Massey A, Shives KD, Burrack KS, Chamanian M, Morrison TE, Beckham JD (2015) Alpha-synuclein expression restricts RNA viral infections in the brain. *J Virol* **90**, 2767-2782.

[93] Bantle CM, Phillips AT, Smeyne RJ, Rocha SM, Olson KE, Tjalkens RB (2019) Infection with mosquito-borne alphavirus induces selective loss of dopaminergic neurons, neuroinflammation and widespread protein aggregation. *Npj Parkinsons Dis* **5**, 1-15.

[94] Qin X-Y, Zhang S-P, Cao C, Loh YP, Cheng Y (2016) Aberrations in peripheral inflammatory cytokine levels in Parkinson disease: A systematic review and meta-analysis. *JAMA Neurol* **73**, 1316-1324.

[95] Pilotto A, Masciocchi S, Volonghi I, Crabbio M, Magni E, De Giuli V, Caprioli F, Rifino N, Sessa M, Gennuso M, Cotelli MS, Turla M, Balducci U, Mariotto S, Ferrari S, Ciccone A, Fiacco F, Imarisio A, Risi B, Benussi A, Premi E, Focá E, Caccuri F, Leonardi M, Gasparotti R, Castelli F, Zanusso G, Pezzini A, Padovani A, ENCOVID Study Group (2020) Clinical presentation and outcomes of SARS-CoV-2 related encephalitis: The ENCOVID multicentre study. *J Infect Dis*, doi: 10.1093/infdis/jiaa609

[96] Paterson RW, Brown RL, Benjamin L, Nortley R, Wiethoff S, Bharucha T, Jayaseelan DL, Kumar G, Raftopoulos RE, Zambreanu L, Vivekanandam V, Khoo A, Geraldes R, Chinthapalli K, Boyd E, Tuzlali H, Price G, Christofi G, Morrow J, McNamara P, McLoughlin B, Lim ST, Mehta PR, Levee V, Keddie S, Yong W, Trip SA, Foulkes AJM,

Hotton G, Miller TD, Everitt AD, Carswell C, Davies NWS, Yoong M, Attwell D, Sreedharan J, Silber E, Schott JM, Chandratheva A, Perry RJ, Simister R, Checkley A, Longley N, Farmer SF, Carletti F, Houlihan C, Thom M, Lunn MP, Spillane J, Howard R, Vincent A, Werring DJ, Hoskote C, Jäger HR, Manji H, Zandi MS (2020) The emerging spectrum of COVID-19 neurology: Clinical, radiological and laboratory findings. *Brain* **143**, 3104-3120.

[97] Anwar F, Naqvi S, Al-Abbasi FA, Neelofar N, Kumar V, Sahoo A, Kamal MA (2020) Targeting COVID-19 in Parkinson's patients: Drugs repurposed. *Curr Med Chem*, doi: 10.2174/0929867327666200903115138

[98] Xiong W, Mu J, Guo J, Lu L, Liu D, Luo J, Li N, Liu J, Yang D, Gao H, Zhang Y, Lin M, Shen S, Zhang H, Chen L, Wang G, Luo F, Li W, Chen S, He L, Sander JW, Zhou D (2020) New onset neurologic events in people with COVID-19 infection in three regions in China. *Neurology* **95**, e1479-e1487.

[99] Diezma-Martín AM, Morales-Casado MI, García-Alvarado N, Vadillo Bermejo A, López-Ariztegui N, Sepúlveda Berrocal MA (2020) [Tremor and ataxia in COVID-19]. *Neurologia* **35**, 409-410.

[100] Chaumont H, Etienne P, Roze E, Couratier C, Roger P-M, Lannuzel A (2020) Acute meningoencephalitis in a patient with COVID-19. *Rev Neurol (Paris)* **176**, 519-521.

[101] Fadakar N, Ghaemmaghami S, Masoompour SM, Shirazi Yeganeh B, Akbari A, Hooshmandi S, Ostovan VR (2020) A first case of acute cerebellitis associated with coronavirus disease (COVID-19): A case report and literature review. *Cerebellum* **19**, 911-914.

[102] Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B (2020) Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* **77**, 1-9.

[103] Balestrino R, Rizzone M, Zibetti M, Romagnolo A, Artusi CA, Montanaro E, Lopiano L (2020) Onset of Covid-19 with impaired consciousness and ataxia: A case report. *J Neurol* **267**, 2797-2798.

[104] Khoo A, McLoughlin B, Cheema S, Weil RS, Lambert C, Manji H, Zandi MS, Morrow JM (2020) Postinfectious brainstem encephalitis associated with SARS-CoV-2. *J Neurol Neurosurg Psychiatry* **91**, 1013-1014.

[105] Grimaldi S, Lagarde S, Harle J-R, Boucraut J, Guedj E (2020) Autoimmune encephalitis concomitant with SARS-CoV-2 infection: Insight from 18F-FDG PET imaging and neuronal autoantibodies. *J Nucl Med* **61**, 1726-1729.

[106] Rábano-Suárez P, Bermejo-Guerrero L, Méndez-Guerrero A, Parra-Serrano J, Toledo-Alfocea D, Sánchez-Tejerina D, Santos-Fernández T, Folgueira-López MD, Gutiérrez-Gutiérrez J, Ayuso-García B, González de la Aleja J, Benito-León J (2020) Generalized myoclonus in COVID-19. *Neurology* **95**, e767-e772.