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Covid-19 and Parkinson's disease: Acute clinical implications, long-COVID and post-COVID-19 parkinsonism

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Contents

Abstract

The Coronavirus Disease 2019 (Covid-19), caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has led to unprecedented challenges for the delivery of healthcare and has had a clear impact on people with chronic neurological conditions such as Parkinson's disease (PD). Acute worsening of motor and non-motor symptoms and long-term sequalae have been described during and after SARS-CoV-2 infections in people with Parkinson's (PwP), which are likely to be multifactorial in their origin. On the one hand, it is likely that worsening of symptoms has been related

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to the viral infection itself, whereas social restrictions imposed over the course of the Covid-19 pandemic might also have had such an effect. Twenty cases of post-Covid-19 para-infectious or post-infectious parkinsonism have been described so far where a variety of pathophysiological mechanisms seem to be involved; however, a Covid-19-induced wave of post-viral parkinsonism seems rather unlikely at the moment. Here, we describe the interaction between SARS-CoV-2 and PD in the short- and long-term and summarize the clinical features of post-Covid-19 cases of parkinsonism observed so far.

1. Introduction

The Coronavirus Disease 2019 (Covid-19), caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has led to major and unprecedented challenges for the delivery of healthcare with a clear impact on patients, both directly through symptoms and morbidity caused by an active SARS-CoV-2 infection and indirectly by effects of pandemic-related restrictions. From an initial focus on the symptomatology, morbidity, and mortality caused by a SARS-CoV-2 infection, the focus of research has moved towards the interaction of this virus with pre-existing conditions, including movement disorders. The specific impact of Covid-19 on movement disorders, also in relation to Parkinson's disease (PD), has increased steadily over the course of the pandemic (Ellul et al., 2020; Wood, 2020).

Many hypotheses have been put forward to explain the worsening of symptoms observed in people with PD (PwP) after contracting a SARS-CoV-2 infection. At first sight, at least some of the symptomatology might be explained by the effects of stress, anxiety, and isolation (van Wamelen, Wan, Chaudhuri, & Jenner, 2020), with the inevitable overlap related to restrictions imposed by the Covid-19 pandemic in combination with the often more advanced age of PwP compared to the general population. Some have suggested a role for infection-induced altered dopaminergic neurotransmission (Ait Wahmane et al., 2020; Araújo, Aranda-Martínez, & Aranda-Abreu, 2020; Nataf, 2020) and others that the infection might even lead to secondary neurodegeneration (Lippi, Domingues, Setz, Outeiro, & Krisko, 2020). Nevertheless, the relation between Covid-19 and PD is likely to be more complex than this and many uncertainties remain.

Here, we aim to review the available evidence and implications of Covid-19 in PwP in the acute phase of the infection and possible

long-term effects, as well as mechanisms that might underlie the potential worsening of symptoms in PwP. We also summarize the available evidence on post-Covid-19 cases of parkinsonism.

2. The acute effects of SARS-CoV-2 infection in people with Parkinson's disease

Several studies have reported a worsening of motor and non-motor symptoms in PwP during the acute phase of SARS-CoV-2 infection, which often required therapy adjustments. Not unimportantly, although many PwP present with typical Covid-19 symptoms, some have a more atypical presentation with isolated worsening of parkinsonian symptoms (Fearon & Fasano, 2021). However, most of these studies consisted of case series and observational studies with relatively small participant cohort numbers only, while prospectively collected data is largely lacking. In addition, it is sometimes difficult to separate the effects of the SARS-CoV-2 infection per se from the consequences of social restrictions imposed over the course of the Covid-19 pandemic (Table 1).

Worsening of PD symptomatology is often observed over the course of an acute infection and might be mediated by several putative mechanisms of action, including altered central dopamine metabolism, pharmacodynamic and pharmacokinetic changes to dopaminergic medication, as well as direct effects of pathogens endotoxins (Brugger et al., 2015) (Fig. 1). Exacerbation of PD symptomatology over the course of an acute infection is usually transient, but might persist even after resolution of the infection, including persisting motor deterioration (Umemura et al., 2014). Whether the worsening of PD symptomatology in the acute phase of a SARS-CoV-2 infection does have peculiarities compared to the commonly observed exacerbations of motor and non-motor symptoms triggered by other infections remains unclear. The proposed neurotropism of SARS-CoV-2 is currently debatable, and it is possible to argue that systemic inflammation in combination with pandemic-related stress (van Wamelen et al., 2020) might contribute to the exacerbation of the PD symptomatology. Moreover, the pandemic-induced social isolation in association with reduced access to healthcare services and rehabilitation can per se have a detrimental impact on PD symptoms, including motor disability, anxiety and depression as it has been discussed in Chapters 9 and 10.

Table 1 Overview of studies looking at the acute effect of SARS-CoV-2 infection in people with Parkinson's disease.

Study population and design	Main findings	Reference
Case series • 10 Hospitalized PwP with a SARS-CoV-2 infection	Worsening of motor and non-motor symptoms, including: • Anxiety • Fatigue • Orthostatic hypotension • Cognitive impairment • Psychosis Therapy adjustment in half of the cases.	Antonini, Leta, Teo, and Chaudhuri (2020)
Community-based, case-control study • 12 Non-hospitalized PwP with SARS-CoV-2 infection • 36 Patients PwP without SARS-CoV-2 infection	Worsening of motor symptoms: • Increased daily OFF-time Worsening of non-motor symptoms: • Urinary problems • Fatigue Therapy adjustment in 1/3 of the cases.	Cilia et al. (2020)
Telephone survey • 8 PwP with a SARS-COV-2 infection.	Worsening of motor symptoms. Therapy adjustment in 1/4 of cases.	Artusi et al. (2020)
Case report • 2 PwP (with DBS) and a SARS-CoV-2 infection	Worsening of motor symptoms. Worsening of non-motor symptoms. • Cognitive impairment	Hainque and Grabli (2020)
Telephone survey, cross-sectional study • 15 PwP with a SARS-CoV-2 infection	• Hallucinations (23% in PwP with SARS-CoV-2 vs 0% in PwP without) • Motor fluctuations (61% in PwP with SARS-CoV-2 vs 36% in PwP without)	Santos-García et al. (2020)

• 553 PwP without a SARS-CoV-19 infection	• Dementia (16% in PwP with SARS-CoV-2 vs 7% in PwP without) • Behavioral problems (34% in PwP with SARS-CoV-2 vs 15% in PwP without)	
Case-control study • 7 PwP with a SARS-CoV-2 infection • 733 PwP without a SARS-CoV-2 infection	PwP did not experience a subjective worsening of symptoms during lockdown period. No description of possible differences between PwP with and without a SARS-CoV-2 infection.	Del Prete et al. (2021)
Case-control study • 51 PwP with a SARS-CoV-2 infection • 26 Healthy participants with a SARS-CoV-2 infection • 7158 PwP without a SARS-CoV-2 infection • 9736 Healthy participants without a SARS-CoV-2 infection	PwP with a SARS-CoV-2 infection: • Worsening of motor (63%) and non-motor (75%) symptoms. PwP without SARS-CoV-2 infection: • Worsening of motor (43%) and non-motor (52%) symptoms.	Brown et al. (2020)

PwP: people with Parkinson's disease; DBS: deep brain stimulation; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; vs: versus.

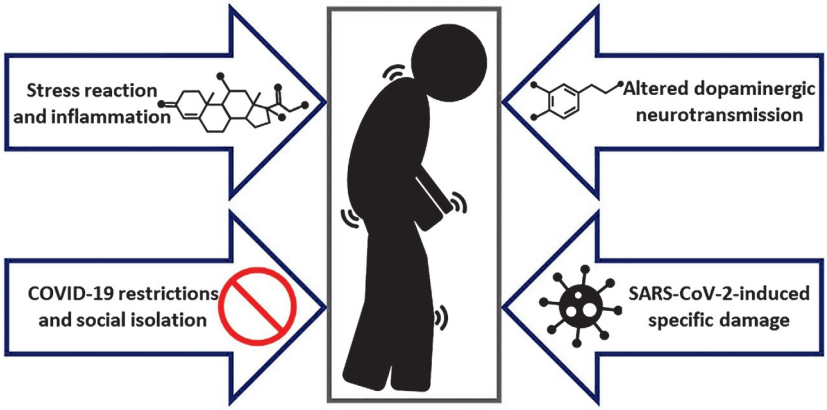

Fig. 1 Possible mechanisms for worsening of symptoms in the acute phase of COVID-19 in people with Parkinson's disease. Abbreviations: COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

2.1 Dopaminergic signaling during infections

Given the clear role of dopamine in PD, it is not surprising to see that altered dopaminergic neurotransmission has been put forward as a possible culprit for symptoms worsening during infections, and SARS-CoV-2 infection in particular. In part, this motor deterioration might be caused by dosing or administration errors of dopaminergic medication drugs (Gerlach, Broen, & Weber, 2013), as well as changes in cognition and psychosis interfering with medication intake which could be particularly bothersome in unsupervised situations at home (Daley, Deane, Gray, Hill, & Myint, 2015). Nonetheless, it seems likely that other factors play a role in symptoms worsening during active SARS-CoV-2 infection, including disturbances in dopamine metabolism and dopaminergic signaling. For example, a retrospective analysis of 675 PwP showed that in 17 out of the 26 PwP who developed acute akinesia, infection was identified as the precipitating factor. With levodopa serum levels detected within normal range, it seems unlikely that malabsorption of the medication could explain this observation (Onofrj et al., 2009). More likely causes include alterations in dopaminergic drug transportation across the blood–brain barrier (BBB) where levodopa enters the brain through selective transporters (Okura, Ito, Ishiguro, Tamai, & Deguchi, 2007). Moreover, cytokines, which are released during infection, reduce the expression of type 2 vesicular monoamine transporters (VMAT2), involved in transferring cytosolic dopamine into vesicles (Kazumori et al., 2004). Also dopamine transporters, which are responsible

for the reuptake of released dopamine, seem to be regulated by cytokines (Felger et al., 2013; Felger & Miller, 2012). Finally, at least in non-human primates, chronic exposure to interferon-α decreases presynaptic dopamine 2 receptor expression in the striatum (Felger et al., 2013; Felger & Miller, 2012). It could be reasoned that, similar to infections in general, the same mechanisms apply for SARS-CoV-2 infections.

2.2 The role of stress

The notion of stress, related changes in cortisol levels, and worsening of symptoms in PwP is not new. In fact, even Gowers in the late 19th century wrote 'Prolonged anxiety and severe emotional shock often precede the onset of PD' (Gowers, 1888). While motor performance often seems to improve under conditions of acute stress, chronic anxiety and stress on the other hand tend to characteristically aggravate motor symptoms in PwP, particularly resting tremor (Moore, Rose, & Grace, 2001). It is, therefore, of interest that a SARS-CoV-2 infection, in particular more severe infections, have consistently increased serum cortisol levels, as demonstrated in a recent meta-analysis and systematic review by Amiri-Dashatan and colleagues (Amiri-Dashatan, Koushki, Parsamanesh, & Chiti, 2022). Although the effects of increased cortisol levels on motor symptoms in PwP remain elusive (van Wamelen et al., 2020), higher serum cortisol levels appear to be more consistently associated with anxiety levels, risk-taking, sleep problems, and depressive symptoms in PwP (Breen et al., 2014; Djamshidian et al., 2011; Muller & Muhlack, 2007; Ruzicka et al., 2015). In the case of psychological stress, mainly induced by restrictions imposed during the Covid-19 pandemic, the overlap with the concept of exhaustion (a state of excessive fatigue and irritability often attributed to stress) is interesting (Clark, Ritz, Prescott, & Rod, 2013). Fatigue has been a commonly reported symptom in PwP during the pandemic, and the related vital exhaustion (a psychological response reflecting a breakdown of the adaption to stress) has been associated with a higher risk of hospitalization in PwP in an exposure-dependent manner (Clark et al., 2013), suggesting that at least some of the symptoms observed in PwP as related to Covid-19 might be stress-mediated. As the response to stress and the related regulation of cortisol levels are altered in PwP (van Wamelen et al., 2020), the pandemic and SARS-CoV-2 infection, as well as infections in general, might make them particularly prone to worsening of their symptoms in such situations.

3. Parkinson's disease and Long-COVID

While acute implications of Covid-19 in PwP have been widely reported (Fearon & Fasano, 2021), possible long-term sequelae of the viral infection in the general population, and specifically in patients with chronic neurogenerative diseases, such as PD, remain to be further elucidated. Given the potentially relevant implications in terms of clinical management and societal burden, on the 18th of December 2020, the National Institute for Health and Care Excellence (NICE) in conjunction with the Scottish Intercollegiate Guidelines Network (SIGN) and the Royal College of General Practitioners (RCGP) published the "Covid-19 rapid guideline" to identify, assess and manage possible long-term effects of Covid-19, often referred to as "Long-COVID" (NICE, 2020). The guidelines have been recently updated and provide recommendations to a variety of healthcare professionals about care for adults and children who have new or ongoing symptoms 4 weeks or more after the start of acute Covid-19 (NICE, 2020). Common long-COVID clinical manifestations are respiratory symptoms of breathlessness and cough, but also generalized, cardiovascular, psychological/psychiatric, neurological, gastrointestinal, dermatological, musculoskeletal, ear, nose and throat symptoms (Table 2) (NICE, 2020).

According to a recent metanalysis of 37 published articles, fatigue (16–64%), dyspnea (15–61%), cough (2–59%), arthralgia (8–55%), and thoracic pain (5–62%) have been reported as the most prevalent and persistent symptoms 4 weeks after a severe form of SARS-CoV-2 infection (i.e., requiring hospitalization), while for patients with milder forms (i.e. not requiring hospitalization) the persistence of the above mentioned symptoms was lower and 3% to 74% of the latter group of patients had prolonged smell and taste disorders (Nguyen et al., 2022). Risk factors for long-COVID symptoms were female sex, older age, presence of comorbidities and severity at the acute phase of the infection (Nguyen et al., 2022).

As far as long-COVID symptoms in PwP are concerned, only a few reports are available to the best of our knowledge. In addition to the case report of a 73-year-old male patient with a diagnosis of PD who developed severe and persistent oropharyngeal dysphagia after a severe form of Covid-19 (no dysphagia reported before Covid-19) (Boika, Sialitski, Chyzhyk, Ponomarev, & Fomina, 2021), a multicentre, international case series described the prevalence of persistent post-Covid-19 symptoms in 27 PwP (Leta et al., 2021). According to this series, 23 PwP (85%) developed

Table 2 Most common clinical manifestations of long-COVID (NICE, 2020).

Respiratory symptoms	**Breathlessness**
	Cough
Cardiovascular symptoms	Chest tightness
	Chest pain
	Palpitations
Generalized symptoms	Fatigue
	Fever
	Pain
Neurological symptoms	Cognitive impairment ('brain fog', loss of concentration or memory issues)
	Headache
	Sleep disturbance
	Peripheral neuropathy symptoms (pins and needles and numbness)
	Dizziness
	Delirium (in older populations)
	Mobility impairment
	Visual disturbance
Gastrointestinal symptoms	Abdominal pain
	Nausea and vomiting
	Diarrhea
	Weight loss and reduced appetite
Musculoskeletal symptoms	Joint pain
	Muscle pain
Ear, nose and throat symptoms	Tinnitus
	Earache
	Sore throat
	Dizziness
	Loss of taste and/or smell
	Nasal congestion

Continued

Table 2 Most common clinical manifestations of long-COVID (NICE, 2020).—cont'd

	Breathlessness
Respiratory symptoms	**Cough**
Dermatological symptoms	Skin rashes
	Hair loss
Psychological/psychiatric symptoms	Symptoms of depression
	Symptoms of anxiety
	Symptoms of post-traumatic stress disorder

prolonged post–Covid-19 symptoms and the most common long-term effects of Covid-19 were worsening of motor symptoms (52%), increased levodopa daily dose requirements (48%), fatigue (41%), cognitive disturbances (such as "brain fog", loss of concentration and memory deficits, 22%), and sleep disturbances (22%). Interestingly, a severe acute infection (as indicated by a history of hospitalization), was not a prerequisite for the development of persistent post–Covid-19 symptoms in PwP (Boika et al., 2021; Leta et al., 2021). Although recent evidence seems to suggest that chronic immunological changes might be involved in the long-COVID syndrome in PwP (Boika et al., 2021), whether viral illness-related worsening of pre-existing PD features, as well as lockdown-related stress combined with reduced access to health care services also contribute, needs to be further explored.

4. Post-covid-19 cases of Parkinsonism

The excessive dimensions of the Covid-19 pandemic have recently triggered discussions as to whether it could serve as a "perfect storm" for a post-Covid-19 emergence of new-onset parkinsonism in susceptible individuals (Beauchamp, Finkelstein, Bush, Evans, & Barnham, 2020; Brundin, Nath, & Beckham, 2020). Infectious agents, including viruses, have long been presumed to play a role in the pathogenesis of PD (Hawkes, Del Tredici, & Braak, 2007; Sulzer, 2007), while the association of numerous viruses with the development of transient or persistent parkinsonism has been well-documented in the literature (Jang, Boltz, Webster, & Smeyne, 2009; Xing, Marsili, & Truong, 2022). The idea of Covid-19 unmasking parkinsonism constitutes a source of concern to many and has been fuelled by historically documented parkinsonism cases appearing

during the acute or chronic phase of encephalitis lethargica (EL), an entity which affected more than one million people in Europe, India and America from 1916 to 1930 (Hoffman & Vilensky, 2017). The causative substrate of EL constitutes one of the greatest medical mysteries with many researchers acknowledging an epidemiological link to the Spanish influenza, a pandemic with a death toll exceeding 40 million people globally in 1918–1919 (Hoffman & Vilensky, 2017). The Spanish influenza strains disappeared in 1933, coinciding with the end of the EL period, while people born between 1888 and 1924 were found to have an increased risk of developing PD compared to those born before or after this time period (Henry, Smeyne, Jang, Miller, & Okun, 2010).

Up to now, 20 cases have been reported in the literature with new-onset symptoms of parkinsonism (bradykinesia and/or rigidity), manifesting during or shortly after a diagnosis of Covid-19 (Table 3) (Akilli & Yosunkaya, 2021; Ayele et al., 2021; Cavallieri et al., 2021; Cohen et al., 2020; Faber et al., 2020; Fearon et al., 2021; Ghosh et al., 2021; Makhoul & Jankovic, 2021; Méndez-Guerrero et al., 2020; Morassi et al., 2021; Ong et al., 2022; Pilotto et al., 2021; Rao et al., 2022; Rass et al., 2021; Roy et al., 2021; Tiraboschi et al., 2021). Only one of these patients (patient 6) had mentioned prior symptoms of prodromal PD (constipation), while none of the above cases had a family history of PD. Hyposmia or anosmia in the context of Covid-19 was identified in nine patients, although the significance of this feature remains unclear given its high prevalence in SARS-CoV-2 infection. Genetic testing was performed on three occasions, with patients 9 and 10 testing positive for a heterozygous mutation in the genes of glucocerebrosidase (GBA) and leucine-rich repeat kinase 2 (LRRK2), respectively. A genetic substrate was not confirmed for patient 3.

In 11 of these cases, parkinsonism appeared in the context of encephalopathy (patients 2, 4, 5, 7–9, 11–14, 17), while four patients developed post-infectious parkinsonism without encephalopathy (patients 1, 18, 19, 20). The remaining four patients presented with parkinsonism and were clinically diagnosed with probable PD (patients 3, 6, 15, 16), as they bore significant similarities to typical PD. The severity of Covid-19 was mild in four cases, moderate in four cases and severe in 11 cases. Eight of these patients had to be admitted in the Intensive Care Unit (ICU) and, with one exception, parkinsonism was detected after their level of consciousness was improved and they were discharged from the ICU. Eleven patients underwent a lumbar puncture, which revealed signs of subjacent inflammation (increased protein, oligoclonal bands) in two cases (patients 14 and 17).

Table 3 Published papers of new-onset post-Covid-19 parkinsonism and patients' characteristics.

First author, date	Country	Patient's ID	Age, Gender	Past medical history	Covid severity	Onset	Encephalopathy
Faber et al. (2020)	Brazil	#1	35F	–	Mild	10 d	–
Méndez-Guerrero et al. (2020)	Spain	#2	58 M	Hypertension, hypercholesterolemia	Severe/ ICU	38 d	+
Cohen et al. (2020)	Jerusalem	#3	45 M	Hypertension, asthma	Moderate	14–21 d	–
Pilotto et al. (2021)	Italy	#4	73 M			0	+
Akilli and Yosunkaya (2021)	Turkey	#5	72 M	Hypertension, DM, peripheral artery disease	Severe/ ICU	2 d	+
Makhoul & Jankovic, 2021	USA	#6	64F		Mild	5 d	–
Roy, Song, Awad, and Zamudio (2021)	USA	#7	60 M	Hypertension, DM, hypercholesterolemia	Severe/ ICU	8 d	+
Fearon, Mikulis, and Lang (2021)	Canada	#8	46 M		Severe/ ICU	38 d	+
Tiraboschi et al. (2021)	Italy	#9	40F	Overweight	Severe/ ICU	22 d	+
Rass et al. (2021)	Austria	#10			Severe/ ICU	3 mo	
Ghosh et al. (2021)	India	#11	65F	Diabetes mellitus	Moderate	6 d	+
Ayele et al. (2021)	Ethiopia	#12	35F	–	Severe/ ICU	7–14 d	+

Morassi et al. (2021)	Italy	#13	70F	Hypertension, anxiety-depressive disorder	Severe	31 d	+
		#14	73F	Hypertension, DM, anxiety-depressive disorder	Mild	0	+
Cavallieri et al. (2021)	Italy	#15	67 M		Moderate	4 mo	–
		#16	45 M	–	Mild	3 mo	–
Ong, Nor, Yusoff, and Sapuan (2022)	Malaysia	#17	31 M	–	Severe	6 d	+
Rao, Hidayathullah, Hegde, and Adhikari (2022)	India	#18	72 M	–	Severe	14 d	–
		#19	66 M	Hypertension, DM, seizures	Severe/ ICU	14 d	–
		#20	74 M		Moderate	21 d	–

Covid-19: Coronavirus Disease 2019; d: days; DM: diabetes mellitus; F: female; ICU: Intensive Care Unit; ID: identification number; M: male; mo: months; USA: United States of America.

Polymerase chain reaction (PCR) tests and cultures for various pathogens in the cerebrospinal fluid (CSF) were negative on all occasions. Interestingly, an acute SARS-CoV-2 infection of the central nervous system (CNS), which would be achieved by detecting the virus via PCR, was not confirmed on any occasion. Such findings in the CSF are consistent with the majority of Covid-19 patients, who have been investigated for various types of neurological manifestations (Neumann et al., 2020). Seven patients (patients 2, 3, 9, 11, 13, 14, 17) were screened for a range of serum and/or CSF antibodies related to autoimmune encephalitis with negative results on all occasions. Seven patients (patients 1, 2, 3, 6, 14, 15, 16) underwent dopaminergic uptake imaging (either 6-[18F]-L-fluoro-L-3,4-dihydroxyphenylalanine (F-FDOPA)-based positron emission tomography (PET) or dopamine transporter single-photon emission computerized tomography (SPECT) imaging with ioflupane I-123 injection (DaTscan)), with all of them having a decreased dopamine uptake either in one or both putamina, similarly to typical PD. Four patients (patients 1, 9, 13, 14) underwent a brain FDG (2-deoxy-2-[18F]fluoro-D-glucose)-based PET scan with only one of them exhibiting normal findings. A brain magnetic resonance imaging (MRI) was performed on all but three cases (patients 6, 10, 18), and was found abnormal on six occasions (Table 4).

Although duration of follow-up varied greatly, ranging from 1 month to 1 year and missing in almost half of the cases, most patients in this case series exhibited a favorable outcome (Table 5). Like already mentioned, 11 of them presented with encephalopathy, with the majority of them well-fitting the concept of general viral post-encephalitic parkinsonism, as has been already described in the past (Jang et al., 2009).

The frequency of encephalopathy in the context of Covid-19 seems to vary widely (7–69%) (Ellul et al., 2020), while in a large group of 129,008 SARS-CoV-2 positive patients of all ages, 138 cases of encephalitis have been confirmed, generating an incidence of 0.215% (Siow, Lee, Zhang, Saffari, & Ng, 2021). However, the definition of encephalitis might vary in different publications. Under these circumstances, corticosteroids, intravenous immune globulin (IVIG), convalescent plasma therapy, monoclonal antibodies administration or plasmapheresis have been included in the treating protocols across different clinical settings (usually with supportive imaging indications), recently including Covid-19-related encephalitis with concurrent neurological manifestations (Huo, Xu, & Wang, 2021; Sonneville, Klein, de Broucker, & Wolff, 2009). Five of the above cases were treated with immunomodulatory/ immunosuppressive therapy

Table 4 Imaging diagnostic means (if applicable) used in patients with new-onset post-Covid-19 parkinsonism.

Patient's ID	MRI	Dopaminergic uptake imaging	FDG PET scan
#1 (Faber et al., 2020)	Unremarkable findings.	DaTscan: ↓DA uptake of the L putamen*	Unremarkable findings.
#2 (Méndez-Guerrero et al., 2020)	Unremarkable findings.	DaTscan: ↓DA uptake of both putamina asymmetrically*	
#3 (Cohen et al., 2020)	Unremarkable findings.	F-FDOPA PET: ↓DA uptake of both putamina (L > R) & L caudate	
#4 (Pilotto et al., 2021)	↑T2 signal of the frontal lobes.		
#5 (Akilli & Yosunkaya, 2021)	Unremarkable findings.		
#6 (Makhoul & Jankovic, 2021)		DaTscan: ↓DA uptake of the R putamen*	
#7 (Roy et al., 2021)	Ischemic stroke in the basal ganglia and corona radiata.		
#8 (Fearon et al., 2021)	Oedema of the globus pallidus and microbleeds in cerebellar nuclei attributed to hypoxia. Atrophy of the above regions in subsequent imaging.		
#9 (Tiraboschi et al., 2021)	Unremarkable findings.		↑glu metabolism in the mesial temporal lobes & subthalamic nuclei (normalization of signal after IVIg).
#10 (Rass et al., 2021)			

Continued

Table 4 Imaging diagnostic means (if applicable) used in patients with new-onset post-Covid-19 parkinsonism.—cont'd

Patient's ID	MRI	Dopaminergic uptake imaging	FDG PET scan
#11 (Ghosh et al., 2021)	Symmetrical lesions of the caudate and putamen, sparing the globus pallidus, with ↑T2 signal and diffusion restriction, attributed to extra-pontine osmotic demyelination.		
#12 (Ayele et al., 2021)	Symmetrical, non-enhancing lesions with ↑T2 signal in the pallidum, possibly attributed to silent hypoxia.		
#13 (Morassi et al., 2021)	Unremarkable findings.	DaTscan: ↓DA uptake of both putamina asymmetrically*	Diffuse cortical hypo-metabolism, ↑glu metabolism in the mesial temporal lobes, basal ganglia, brainstem (indicative of encephalitis)
#14 (Morassi et al., 2021)	Unremarkable findings.		
#15 (Cavallieri et al., 2021)	Unremarkable findings.	DaTscan: ↓DA uptake of both putamina	
#16 (Cavallieri et al., 2021)	Unremarkable findings.	DaTscan: ↓DA uptake of both putamina	
#17 (Ong et al., 2022)	↑T2 signal of both thalami with hemosiderin deposition and patchy enhancement and ↑T2 signal of the pons attributed to ANEC.		
#18 (Rao et al., 2022)			
#19 (Rao et al., 2022)	Unremarkable findings.		
#20 (Rao et al., 2022)	Unremarkable findings.		

ANEC: Acute Necrotizing Encephalitis; Covid-19: Coronavirus Disease 2019; DA: dopamine; DaTscan: dopamine transporter single-photon emission computerized tomography (SPECT) imaging with ioflupane I-123 injection; FDG: 2-deoxy-2-[18F]fluoro-D-glucose; F-FDOPA: 6-[18F]-L-fluoro-L-3,4-dihydroxyphenylalanine; glu: glucose; ID: identification; IVIg: intravenous immunoglobulin therapy; L: left; MRI: magnetic resonance imaging; PET: positron emission tomography; R: right.

Table 5 Treatment, possible diagnosis and clinical course with follow-up assessment (if applicable) in patients with new-onset post-Covid-19 parkinsonism.

Patient's ID	Response to immunomodulatory/ immunosuppressive treatment	Response to anti-parkinsonian therapy	Possible diagnosis/ Clinical course—Follow-up
#1 (Faber et al., 2020)	–	200/50 mg of levodopa/ benserazide TD.	A probable diagnosis of Covid-related post-infectious parkinsonism without encephalopathy. Significant improvement after few days of therapy. No follow-up.
#2 (Méndez-Guerrero et al., 2020)	–	Adverse events & no clinical response to Apo test (3 mg initially, 2 mg after 5 day).	A probable diagnosis of Covid-related post-encephalitic parkinsonism. Significant, spontaneous improvement, although symptoms persisted (follow-up at 53 day).
#3 (Cohen et al., 2020)	High-dose of methylprednisolone without any consistent effect.	0.375 mg ER pramipexole OD, 2 mg biperiden resulted in parkinsonism improvement.	Authors suggested a diagnosis of probable PD. Improvement with dopaminergic therapy. No follow-up is specified.
#4 (Pilotto et al., 2021)	–	–	–
#5 (Akilli & Yosunkaya, 2021)	Convalescent plasma therapy (twice), patient improvement. Plasmapheresis due to ARDS.	–	A probable diagnosis of Covid-related post-encephalitic parkinsonism. No symptoms found at 2 month follow-up.
#6 (Makhoul & Jankovic, 2021)	–	–	Authors suggested that the patient's prodromal PD became symptomatic due to Covid-19 stress. No follow-up.
#7 (Roy et al., 2021)	–	Levodopa/ carbidopa & modafinil for 1mo with symptoms improvement.	Authors suggested a 'locked in'/parkinsonian state due to Covid-related encephalopathy and an acute ischemic stroke in the basal ganglia. Full recovery at 1mo follow-up.

Continued

Table 5 Treatment, possible diagnosis and clinical course with follow-up assessment (if applicable) in patients with new-onset post-Covid-19 parkinsonism.—cont'd

Patient's ID	Response to immunomodulatory/ immunosuppressive treatment	Response to anti-parkinsonian therapy	Possible diagnosis/ Clinical course—Follow-up
#8 (Fearon et al., 2021)	–	No response to 450 mg levodopa.	Probable diagnosis of hypoxic-ischemic injury. Parkinsonism persisted at 1y follow-up.
#9 (Tiraboschi et al., 2021)	2 IVIg cycles, significant improvement.	–	Authors suggested a diagnosis of immune-mediated Covid-related encephalopathy. Full resolution of clinical and imaging findings at 4mo follow-up.
#10 (Rass et al., 2021)	–	–	–
#11 (Ghosh et al., 2021)	Low doses of dexamethasone as per Covid-19 treatment protocol before parkinsonism manifestation.	Levodopa/carbidopa 100/25 mg BD, pramipexole 1.5 mg OD with parkinsonism improvement.	Probable diagnosis of osmotic demyelination due to hyperglycemic state, triggered by dexamethasone. Significant improvement at 4mo follow-up assessment, while on dopaminergic therapy.
#12 (Ayele et al., 2021)	–	Levodopa/ carbidopa 200/50 mg TD with parkinsonism improvement.	Probable diagnosis of silent hypoxia. Significant improvement on follow-up (not specified when) while on dopaminergic therapy.
#13 (Morassi et al., 2021)	1 IVIg cycle & corticosteroids followed by improvement.	Levodopa/ carbidopa 100/25 mg BD with moderate response of parkinsonism.	Possible immune-mediated substrate of encephalopathy. At 9mo follow-up, parkinsonism persisted, cognitive & ADL worsening.
#14 (Morassi et al., 2021)	2 cycles of corticosteroids and 1 cycle of IVIg.	Amantadine 100 mg BD, levodopa/ carbidopa 100/25 mg QD.	Probable post-encephalitic parkinsonism. No improvement with therapy, death 30d after discharge (aspiration pneumonia, bedsores).

#15 (Cavallieri et al., 2021)	–	–	Diagnosis of probable PD. No information on treatment or follow-up.
#16 (Cavallieri et al., 2021)	–	–	
#17 (Ong et al., 2022)	High doses of methylprednisolone.	Trihexyphenidyl 2 mg TD.	Diagnosis of Covid-induced ANEC. Full resolution of parkinsonism and cognitive impairment.
#18 (Rao et al., 2022)	–	Levodopa 50 mg TD, improvement.	Significant improvement at 4mo (pt 18), 1mo (pt 19), 6mo (pt 20) on dopaminergic therapy. Probable diagnosis of post-infectious parkinsonism (patients' characteristics did not account for PD).
#19 (Rao et al., 2022)	–	Levodopa/ carbidopa titration, improvement.	
#20 (Rao et al., 2022)	–	Levodopa/ carbidopa, improvement.	

ADL: activities of daily living; ANEC: acute necrotizing encephalopathy; Apo: apomorphine; ARDS: acute respiratory distress syndrome; BD: twice per day; Covid: Coronavirus disease 2019; d: day; ER: extended release; ID: identification; mg: milligrams; IVIg: intravenous immunoglobulin therapy; mo: month; OD: once daily; PD: Parkinson's disease; pt.: patient; QD: four times per day; TD: three times per day; y: year.

(Table 5) with three of them demonstrating full resolution of their symptoms (patients 5, 9, 17) and one of them (patient 13) exhibiting a good response to therapy, although parkinsonism and cognitive decline persisted in the follow-up assessment after 9 months. Interestingly, patient 17 was diagnosed with COVID-19-precipitated acute necrotizing encephalopathy (ANEC), a rare, but distinctive kind of typically virus-related acute encephalopathy, which has been classically managed with immunomodulatory/ immunosuppressive therapy, especially corticosteroids (Wu et al., 2015).

An immune-mediated substrate has been suggested in the above cases. SARS-CoV-2 has the potential of causing a cytokine release and triggering an excessive immune response in the periphery (Wan et al., 2021). Such processes might affect the BBB permeability, thus, allowing infected immune cells or the virus per se to invade the CNS and induce a secondary cytokine storm (Williams et al., 2021). Interestingly, increased proinflammatory cytokines and a high titre of anti-SARS-CoV-2 IgG antibodies were detected in the CSF of patient 9, which is a previously described, although rare phenomenon (Lewis et al., 2021). Whether these antibodies were locally produced or crossed the BBB due to the systemic inflammation remains unclear. Neuroinflammation has been suspected to promote neurodegeneration and significantly contribute to PD pathogenesis with midbrain dopamine neurons being particularly vulnerable to systemic inflammation due to high energy requirements (Pissadaki & Bolam, 2013; Tufekci, Meuwissen, Genc, & Genc, 2012).

Trials of dopaminergic therapy have also been classically attempted in cases of post-virus parkinsonism, whether encephalopathy was present or not (Bopeththa & Ralapanawa, 2017; Guan, Lu, & Zhou, 2012). Eleven patients in this case series were treated with dopaminergic therapy due to assumed post-Covid-19 parkinsonism, with (patients 2, 7, 8, 11–14) or without encephalopathy (patients 1, 18–20). One patient manifested full recovery, six of them exhibited a significant and one of them a moderate response of their parkinsonian features (Table 5), suggesting an underlying, occasionally reversible, impairment of the dopaminergic pathway. Secondary causes of parkinsonism should be investigated, although the underlying cause might not, ultimately, differentiate the therapeutic strategy followed. In two of the above cases (patients 8, 12) silent hypoxia was identified as the potential subjacent cause of parkinsonism due to the imaging findings; dopaminergic therapy led to significant improvement of one patient's symptoms, but had no clinical effect for the other. Parkinsonism

in patient 11, who had a history of diabetes mellitus, was attributed to extra-pontine osmotic demyelination, triggered by uncontrolled hyperglycemia after dexamethasone administration in the context of Covid-19 treatment. Authors suggested that Covid-19-precipitated inflammation could have also contributed to the BBB disruption, although osmotic demyelination per se has been associated with de novo movement disorders due to impairment of the striato-thalamo-cortical network (de Souza, 2013). Symptoms in this occasion have also improved with dopaminergic therapy. Imaging studies in patient 7 revealed an ischemic stroke in the basal ganglia, which could also have accounted for the patient's acute hemiparkinsonism and hemiparesis. Finally, four patients had a history of neuroleptic drugs use prior to the emergence of parkinsonism (patients 9, 13, 14, 17), thus, the possibility of drug-induced parkinsonism cannot be overlooked.

The temporal proximity of new-onset parkinsonism with a Covid-19 diagnosis, along with the co-existent encephalopathy in some cases, led the authors to assume an etiological connection between them. In summary, different mechanisms underlying these cases of supposedly para- or post-infectious parkinsonism, including structural or functional impairment of the nigrostriatal pathway, inflammatory or vascular damage and unmasking of already active, though asymptomatic, prodromal PD, have been described in the literature (Merello, Bhatia, & Obeso, 2021). However, with more than 5300 confirmed cases of Covid-19 per 100,000 globally (as of February 2022) (Worldmeter.info, 2021) and an annual incidence of about 15 PD cases per 100,000 (Tysnes & Storstein, 2017), anticipating a parkinsonism wave based solely on the current 20 published cases may be premature, as the possibility of chance or exterior factors cannot be overlooked. Moreover, the popularity of the topic might have led to publication bias, favoring the publication of post-Covid parkinsonism cases, while others might argue that parkinsonism might be underdiagnosed, as full neurologic examination might not take place in the Covid-19 wards or Covid-19 patients are usually managed by non-neurological specialties. Finally, it is conceivable that the combination of inflammation, fever and respiratory symptoms may amplify clinical manifestations particularly in the premotor and prodromal phase of PD. Greater vigilance is recommended in order to timely recognize and address potential neurological manifestations of SARS-CoV-2, including parkinsonism, especially in the long-term.

5. Conclusions

SARS-CoV-2 and the restrictions imposed during the Covid-19 pandemic have had a clear impact on PwP. As expected, many have seen their symptoms worsen and it is likely that multiple factors have contributed to this. On the one hand, some of the symptomatology might be explained by the effects of reduced mobility, stress, anxiety, and isolation during the pandemic which may have negative consequences on PD symptoms, including gait dysfunction and risk of falls (Luis-Martínez et al., 2021); on the other hand, SARS-CoV-2 infection may also impact dopaminergic neurotransmission or could even be associated to secondary neurodegeneration.

The relation between Covid-19 and PD is likely to be more complex and many uncertainties remain, although some might argue that it provides an unprecedented opportunity to study the effects of viral infections on PwP and the short- and long-term impact of infection and social restrictions on symptoms of PD and quality of life.

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