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ORIGINAL ARTICLE

Parkinson disease following COVID-19: Report of six cases

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Abstract

Background and purpose: Core clinical manifestations of COVID-19 include influenza-like and respiratory symptoms. However, it is now evident that neurological involvement may occur during SARS-CoV-2 infection, covering an extensive spectrum of phenotypical manifestations. A major challenge arising from this pandemic is represented by detecting emerging neurological complications following recovery from SARS-CoV-2 infection. To date, a few post-COVID-19-infected subjects diagnosed with Parkinson disease (PD) have been described, raising the possibility of a connection between the infection and neurodegenerative processes. Here, we describe a case series of six subjects who developed PD after COVID-19.

Methods: Patients were observed at Scientific Institute for Research and Health Care Mondino Foundation Hospital, Pavia (Italy), and San Paolo University Hospital of Milan (Italy) between March 2021 and June 2022. In all subjects, SARS-CoV-2 infection was confirmed by means of reverse transcriptase polymerase chain reaction from a nasopharyngeal swab. Subjects underwent an accurate neurological evaluation, and neuroimaging studies were performed.

Results: We describe six subjects who developed PD with an average time window after SARS-CoV-2 infection of 4–7 weeks. Apparently, no relationship with COVID-19 severity emerged, and no overt structural brain abnormalities were found. All subjects experienced unilateral resting tremor at onset and showed a satisfactory response to dopaminergic treatment.

Conclusions: Immune responses to SARS-CoV-2 infection have been shown to shape the individual susceptibility to develop long-term consequences. We hypothesize that, in these subjects, COVID-19 has unmasked a latent neurodegenerative process. Characterization of the neuroinflammatory signatures in larger cohorts is warranted, which might provide novel insights into the pathogenesis of PD.

KEYWORDS
COVID-19, neurodegeneration, Parkinson disease, parkinsonism, SARS-CoV-2

INTRODUCTION

Human coronaviruses, including SARS-CoV-2, are primarily respiratory pathogens. However, compelling evidence has demonstrated a neurological involvement during the course of the COVID-19 outbreak. The variety of neurological presentation has been extensively described, ranging from smell and taste disorders, which often represent the first symptom of the infection, to multiple central and peripheral manifestations [1–3]. Both viral invasion of the central nervous system (CNS) and cytokine response generated by an abnormal immune response have been considered key factors for the development of neurological symptoms. Combined clinical, neuropathological, and neurophysiological findings in severe COVID-19 patients also supported the notion of a direct viral involvement of both brainstem and midbrain nuclei, as well as astrocytes, possibly triggering the respiratory distress [4–6]. However, to date, the role of each of these distinct components remains to be established [7, 8]. This is of relevance, as it places SARS-CoV-2 infection in a unique position as compared to other viral infections. Consistently, infected patients exhibit a significantly heterogeneous phenotype, from being asymptomatic to displaying a lethal disease, suggesting genetically or otherwise predisposing elements involved in the individual clinical manifestation. In addition, the specificity of T cell responses, and their relations to humoral immunity and cytokine profile, highlight the importance of host immune response in disease outcome [9]. Independently from the ability to develop an enduring immunity, a large number of patients recovering from COVID-19 experience the persistence of specific symptoms, termed postacute sequelae of COVID-19 (PASC; or long COVID [10]). Current understanding points again to the specific CD4+ and CD8+ T cell responses to SARS-CoV-2 infection, depending on initial risk factors, but ultimately indicating an individual susceptibility to develop long-term consequences [9]. If the time proximity between hyposmia, hypogeusia, "brain fog," and SARS-CoV-2 infection enables establishment of a potential link between these neurological symptoms and the individual response to the infection, it is more complex to understand whether SARS-CoV-2 has a causative/triggering role for neurological diseases diagnosed in the months following COVID-19 recovery.

To date, 11 post-COVID-19-infected subjects diagnosed with Parkinson disease (PD) have been described, raising the possibility of a connection between the infection and neurodegenerative process [11]. Neuroinflammation has been reported in infected COVID-19 patients as well as in postmortem samples, and represents a key element in PD pathophysiology [12, 13]. Moreover, SARS-CoV-2 has been shown to exhibit a peculiar tropism for the olfactory mucosa, which is also one of the first sites affected by alpha-synuclein (α-syn) accumulation in PD.

Here, we describe a cases series of six subjects who developed PD after COVID-19 infection. A striking common feature shared by our patients is the narrow time window between infection and symptom onset (4–7 weeks). No apparent relationship with COVID-19 severity emerges, and no overt structural brain abnormalities were found. In addition, they all exhibited subtle unilateral tremor as a symptom at onset and showed a satisfactory response to dopaminergic treatment.

In conclusion, further effort is required to better understand the host-mediated immune regulatory mechanisms and their relationship to neurodegenerative processes.

MATERIALS AND METHODS

Six patients with onset of PD following COVID-19 were independently observed at the Scientific Institute for Research and Health Care Mondino Foundation Hospital, Pavia (Italy) and San Paolo University Hospital of Milan (Italy) between March 2021 and June 2022. In all subjects, SARS-CoV-2 infection was confirmed by means of reverse transcriptase polymerase chain reaction (RT-PCR) from a nasopharyngeal swab (NPS). All patients underwent a complete cycle of anti-SARS-CoV-2 vaccination (three doses). At onset of neurological manifestation, in four cases, they had not started the vaccination cycle (Cases 1, 4, 5, and 6) yet; in two cases they had already completed it (Cases 2 and 3). The severity of COVID-19 was classified as follows: severe, for patients in an intensive care unit requiring ventilatory assistance; moderate, for patients hospitalized in inpatient wards (with no ventilatory assistance) or treated at home with low-molecular-weight (LMW) heparin and corticosteroids; mild, for patients requiring minimal or no medication.

No patient had a previous history of neurological or neurodegenerative disease, cranial or spinal injury, or exposure to neuroleptic medication, or family history of PD.

All neurological assessments were conducted using the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS)-III scale. PD was diagnosed for all patients through MDS diagnostic criteria [14]. All patients underwent brain magnetic resonance imaging (MRI); four patients were subjected to dopamine transporter single-photon emission computerized tomography imaging with ioflupanel-123 injection (DaTscan). Genetic testing was performed in two subjects, with Patient 1 testing negative for a glucocerebrosidase (*GBA*) mutation, and Patient 3 testing negative for a panel including parkin (*PARK2*) and leucine-rich repeat kinase 2 (*LRRK2*) genes.

Details of demographics, clinical and medical history, and instrumental findings of the subjects enrolled in this case series are reported in Table 1. Neurological evaluation, parkinsonian features, and treatment are shown in Table 2.

RESULTS

Case 1

A 66-year-old man, in October 2020, presented SARS-CoV-2 infection with acute onset of severe asthenia, hyposmia, and dyspnea with recurrent episodes of desaturation that required hospitalization in an intensive care unit. He was treated with continuous positive

TABLE 1 Demographic characteristics, clinical and medical history, and instrumental findings of the subjects enrolled.

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age, years/gender	66/M	64/F	35/M	62/M	55/M	73/F
Previous medical history	Type II diabetes mellitus, essential hypertension	None	None	None	None	Essential hypertension, hypothyroidism
Home therapy	Insulin therapy, losartan 50 mg/daily	None	None	None	None	Ramipril 5 mg/daily, Levothyroxine 75 μg/daily
COVID-19 presentation treatment	Asthenia, hyposmia, and dyspnea with recurrent episode of desaturation; oxygen therapy (cPAP), corticosteroids, antibiotics, LMW heparin, and hyperimmune plasma	Fever, hyposmia, and dysgeusia; antibiotics, LMW heparin, and oral corticosteroids	Fever, cough, and profound myalgia; antibiotics	Severe myalgias, anosmia, ageusia and high fever, interstitial pneumonia; Prednisone 50 mg, ciprofloxacin 500 mg, amoxicillin/clavulanic acid 2 g, LMW heparin 4000 IU	Asymptomatic, none	Hyposmia, none
COVID-19 severity	Severe/ICU	Moderate	Mild	Moderate	Mild	Mild
Neurological Symptoms during SARS-CoV-2 Infection	Hyposmia	Hyposmia and dysgeusia	None	Anosmia, ageusia, mental slowing, distractibility, memory impairment	Frequent nocturnal awakenings and worsening of preexisting RBD	Hyposmia and worsening of preexisting RBD
Prodromal Symptoms of PD (preexisting COVID)	RBD	None	None	None	RBD	RBD, constipation
Onset of PD symptoms (weeks after COVID recovery)	3–5	3	7	6–8	7	6
Clinical presentation of PD	Right hand rest tremor	Right hand rest tremor	Left foot and hand rest tremor	Lower lip tremor	Mild rest tremor of the left hand	Right hand rest tremor
Brain MRI	Unremarkable findings	Unremarkable findings	Unremarkable findings	Unremarkable findings	Unremarkable findings	Chronic diffuse microangiopathy

Abbreviations: cPAP, continuous positive airway pressure; F, female; ICU, intensive care unit; IU, international units; LMW, low-molecular-weight; M, male; MRI, magnetic resonance imaging; RBD, rapid eye movement sleep behavior disorder.

TABLE 2 Neurological evaluation, parkinsonian features, and treatment of the subjects enrolled.

Case	DaTscan	Levodopa challenge test	Cognitive evaluation [MMSE]	Neurological examination and MDS-UPDRS-III at onset [off-state]	Antiparkinsonian therapy	MDS-UPDRS-III at follow-up [on-state]
1	N/A	100 mg of oral LD (MDS-UPDRS-III pretest: 35; MDS-UPDRS-III posttest: 18)	MMSE 28/30	Upper and lower limbs mild rigidity (predominantly on the right side), bradykinesia in both hands, inconstant rest tremor in the right hand (MDS-UPDRS-III: 35)	Levodopa/benserazide (200 mg/day) and rasagiline 1 mg/day	14
2	Reduced uptake in the striatum bilaterally	N/A	N/A	Hypomimia, mild bradykinesia, upper and lower limbs rigidity and right-sided inconstant rest tremor (MDS-UPDRS-III: 21)	Levodopa/benserazide (150 mg/day) and rasagiline 1 mg/day	9
3	Reduced uptake in the right striatum	N/A	MMSE 30/30	Left foot inconstant tremor, mild-to-moderate rest tremor at the hand, marked hypomimia, global bradykinesia, and upper and lower limbs rigidity (MDS-UPDRS-III: 25)	Levodopa/benserazide (300 mg/d) and pramipexole RP 0.52 mg/day	7
4	N/A	N/A	N/A	Lip and chin tremor, mild hypomimia, mild hypophonia, bradykinesia, and mild resting tremor and rigidity in the right harm (MDS-UPDRS-III: 34)	Levodopa 100 mg/benserazide 25 mg t.i.d., pramipexole RP 1.05 mg	20
5	Reduced uptake in the right striatum	MDS-UPDRS-III pretest: 17; MDS-UPDRS-III posttest: 5	MMSE 30/30	Mild hypomimia, hypophonia upper and lower limbs rigidity, tremor in both hands, predominantly on the left side (MDS-UPDRS-III: 17)	Ropinirole 8 mg/day	5
6	Reduced uptake in caudate nucleus bilaterally	100 mg of oral LD (MDS-UPDRS-III pretest: 22; MDS-UPDRS-III posttest: 9)	MMSE 29/30	Hypomimia, bradylalia, right limbs rigidity, mild rest and postural tremor at upper limbs on the right side (MDS-UPDRS-III: 22)	Levodopa/benserazide 200/50 mg (50 mg q.i.d.)	7

Abbreviations: DaTscan, dopamine transporter single-photon emission computerized tomography imaging with ioflupanel-123 injection; MDS-UPDRS, Movement Disorder Society–Unified Parkinson's Disease Rating Scale; N/A, not applicable; q.i.d., four times per day; t.i.d., three times per day. LD, levodopa. RP, releasing prolonged.

airway pressure and corticosteroids, antibiotics, LMW heparin, and hyperimmune plasma with a positive outcome.

Four to five weeks after the resolution of the pulmonary symptoms, the patient noticed the appearance of occasional tremor in his right hand that worsened in intensity over time. He came to our observation nearly 5 months after SARS-CoV-2 infection. Neurological examination revealed mild rigidity of the upper and lower limbs bilaterally (predominantly on the right side), mild bradykinesia in the right hand, slight bradykinesia in the left hand, and an inconstant rest tremor in the right hand. Gait was characterized by short steps and reduced arm swing on the right side. A 10-year history of rapid eye movement sleep behavior disorder (RBD) emerged from a clinical interview. The patient underwent levodopa challenge test, which provided significant improvement (48%). Cognitive performance was normal. Brain MRI was unremarkable, showing just mild enlargement of the sulci. Medication with levodopa/benserazide (200 mg/day) and rasagiline (1 mg/day) was started, with a significant improvement of clinical symptoms. At 2-month follow-up, good motor control persisted under the antiparkinsonian treatment.

Case 2

A 64-year-old female subject with no past comorbidities displayed COVID-19 infection in March 2021 with fever, hyposmia, and dysgeusia. She was treated at home (details in Table 1) with stable oxygen saturation during the entire disease course. She presented an episode of ventricular tachycardia treated with sotalol 40 mg twice daily.

Approximately 4 weeks after symptom resolution, she reported onset of a resting tremor in her right arm and mild impaired movement of both hands. Neurological examination revealed slight hypomimia, mild bradykinesia, upper and lower limbs rigidity, and right-sided inconstant rest tremor. DaTscan showed reduced uptake in the striatum bilaterally (Figure 1), whereas brain MRI was normal. Treatment with levodopa/benserazide (150 mg/day) and rasagiline 1 mg/day was introduced with a rapid and substantial clinical improvement that was still present after 6 months of treatment at follow-up visit.

Case 3

A 35-year-old male without any comorbidity displayed fever, cough, and profound myalgia. The RT-PCR NPS was positive for SARS-CoV-2 in January 2022, and he was treated at home with antibiotics for 1 week. He did not report hyposmia or hypogeusia at onset or during disease progression; the fever lasted for 3 days and NPS tested negative 2 weeks after symptom onset.

Six to seven weeks after the diagnosis of COVID-19, he developed a rest tremor on the left side, together with global motor bradykinesia. He was referred to neurological consultation 2 months after the development of resting tremor. Neurological examination revealed an abduction–adduction tremor in the left foot, a mild-to-moderate rest tremor in the hand, marked hypomimia, global bradykinesia, and upper and lower limbs rigidity. He denied falls or dysphagia/dysarthria. The cognitive status was normal, and no behavioral features were described by parents. During the interview, no premotor symptoms were reported, including RBD, constipation, or smell disturbances, and his family history was negative for PD or other suspected neurodegenerative disorders. DaTscan showed a reduced uptake in the right striatum, whereas brain MRI was normal. A genetic screening was negative for mutations in *PARK2*, *LRRK2*, and *GBA* genes.

Treatment with levodopa/benserazide (300 mg/day) and pramipexole (prolonged release tablets) 0.52 mg/day was introduced, with clinical improvement at a 4-month follow-up visit. Rasagiline has been recently added (1 mg/day).

Case 4

A 62-year-old man with a previously negative medical history was diagnosed with COVID-19 in December 2021 with severe myalgias, anosmia, ageusia, and high fever; lung computed tomography was positive for interstitial pneumonia. The patient was treated at home with prednisone, antibiotics, and LMW heparin. After 1 week, dyspnea improved, fever disappeared, and fatigue and myalgia decreased. Since the beginning of the COVID-19 symptomatology, the patient reported cognitive symptoms, with mental slowing, distractibility, loss of concentration, and reduced speed of memory recall.

After 6–7 weeks, he reported a subjective slowing in daily activities and noticed the appearance of a mild lower lip tremor. A change in writing and a slight motor impairment in the right upper limb were observed. Neurological examination confirmed the presence of a lip and chin tremor, mild hypomimia, a reduced blinking rate, mild hypophonia, bradykinesia, and mild resting tremor and rigidity in the right harm. Brain MRI was unremarkable.

Levodopa/benserazide (300 mg/day) and pramipexole prolonged release (1.05 mg) were started with a substantial improvement of motor symptoms. Two months after the beginning of the treatment, a follow-up evaluation showed a stable beneficial effect of pharmacological treatment, except for the persistence of a mildly reduced blinking rate and occasional lip tremor.

Case 5

A 55-year-old man tested positive for SARS-CoV-2 infection in March 2021, although asymptomatic. Immediately after recovery, he reported frequent nocturnal awakenings, along with a concomitant worsening of a preexisting RBD (previous diagnosis confirmed by polysomnography).

Moreover, 6–7 weeks after the SARS-CoV-2 infection, he reported the development of mild rest tremor in both hands, predominantly on the left side, hypophonia, and bradykinesia. Neurological examination

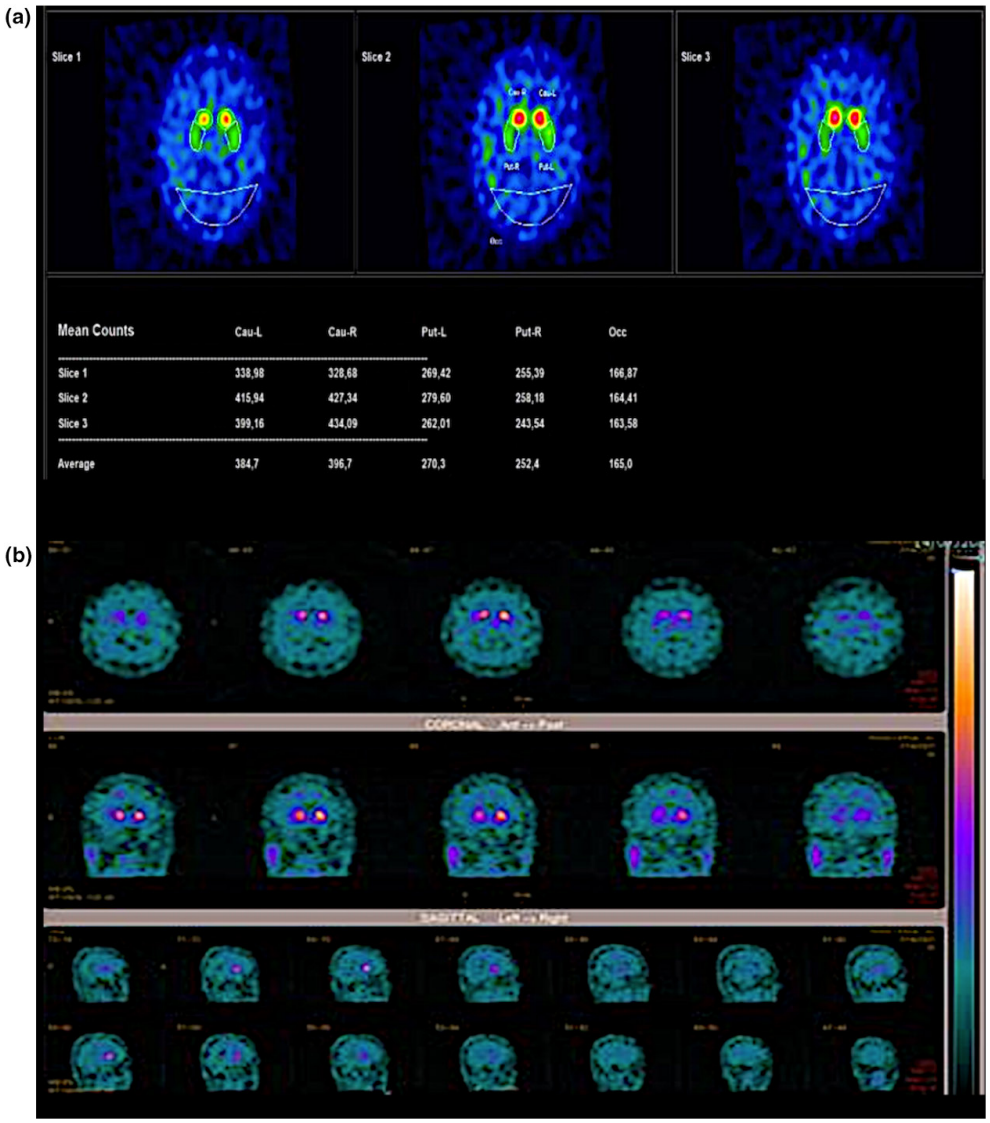

FIGURE 1 (a) DaTscan images related to Case 2. (b) DaTscan images related to Case 5. DaTscan documented severe reduced radiopharmaceutical uptake within the caudate and putamen bilaterally, more pronounced on the right side (caudate: left = 2.18, right = 1.86, normal value > 4.23; putamen: left = 1.09, right = 0.87, normal value > 3.64). DaTscan, dopamine transporter single-photon emission computerized tomography imaging with ioflupanel-123 injection.

confirmed these findings and revealed mild hypomimia and upper and lower limbs rigidity. Brain MRI was negative, whereas DaTscan demonstrated a reduced uptake in the right striatum (Figure 1).

The cognitive evaluation was normal, and no behavioral features were reported. Levodopa challenge test determined a significant improvement of MDS-UPDRS-III (70%).

Case 6

A 73-year-old woman with a mild COVID-19 infection in September 2020 (hyposmia without experiencing respiratory phenomena) reported a worsening of RBD during the disease course and developed rest tremor in her right hand, micrography, and global bradykinesia 6 weeks after recovery. Her neurological examination showed hypomimia, bradylalia, right limbs rigidity, and mild rest and postural tremor in the upper limbs predominantly on her right site. DaTscan showed a reduced uptake in caudate nucleus bilaterally. Brain MRI showed chronic diffuse microangiopathy. Cognitive performance was normal.

She was treated with levodopa/benserazide (200 mg/day) with a substantial clinical improvement. A follow-up visit at 6 months confirmed the beneficial effect of levodopa treatment.

DISCUSSION

Since the beginning of the COVID-19 pandemic in 2020, many cases of postinfectious neurological conditions (i.e., cognitive impairment,

persistent muscle weakness, hyposmia, and headache, referred to as PASC or long COVID) have emerged [10, 15]. Of interest, a number of new onset movement disorders such as myoclonus, chorea, and ticlike disorders have also been reported [16]. Exploiting the biological cause–effect correlation between the SARS-CoV-2 infection and these manifestations is challenging, but the abnormal immune-mediated response to the viral infection seems to have a prominent role in the pathophysiology of PASC. A growing literature has emerged, depicting this postinfectious neuroinflammatory state as a potential condition able to trigger or accelerate latent neurodegenerative diseases [11, 17].

To date, 11 COVID-19-related cases of parkinsonism have been reported [18–24]. Here, we describe a case series of six patients who developed parkinsonian symptoms between 4 and 7 weeks after SARS-CoV-2 infection. A number of peculiar features in their clinical presentations are worth mentioning. (1) Our cases apparently differ from those described in the early phase of the pandemic [17], in which an acute symptom onset occurred, and consistently, a lack of both history of RBD and hyposmia prior to the infection was reported. In our cases, the temporal relationship between infection and symptom onset differs, with a rather homogeneous time window of 4–7 weeks after infection. (2) In all our cases, resting tremor was the predominant clinical manifestation at onset. To our knowledge, 6 of the 11 described cases presented resting tremor at onset. (3) In line with previous evidence [11], no clear relationship emerges between severity of COVID-19 and development of parkinsonian symptoms.

MRI scans (with standard morphological acquisition sequences) were unremarkable in all our patients, an interesting finding when compared to some of the previously reported cases, in which hypoxic–ischemic lesions were observed [11]. Nonetheless, none of the patients described was referred to a neurological consultation previously. Conversely, DaTscan showed unilateral reduced uptake in the striatum in Cases 3 and 5, and bilateral reduction in the striatum and bilateral reduction in the caudate in Cases 2 and 6, respectively. As suggested by Makhoul and Jankovic [20], these data must be carefully interpreted, because a decreased uptake would be unlikely to occur within such a short period of time (days or weeks). However, in our cases, the onset of motor symptoms occurred later (weeks to months) than in previously described acute/postacute cases. Moreover, three of them had a history of RBD, thus suggesting that the infection uncovered a latent neurodegenerative substrate in vulnerable subjects and made it clinically manifest.

The available evidence does not allow us to draw a well-defined hypothesis on the dominance of tremor as an early symptom in these cases. In principle, there is no need to suspect pathophysiological mechanisms other than those already well described, which include both imbalance in basal ganglia neurochemistry and a synchronous oscillatory activity in cerebellothalamocortical and basal ganglia–cortical loops [25]. One of the possible interpretations lies in the role of stress in patients who have experienced COVID-19. An increase in serum cortisol levels has been consistently shown in SARS-CoV-2 infection, an observation that matches with the evidence for an altered stress response and related modulation of cortisol levels in PD patients [26]. Expectedly, stress tends to aggravate motor symptoms in PD, particularly resting tremor [27]. An alternative explanation is related to the potential, direct viral invasion of brainstem nuclei. Recently, aberrant cholinergic/noradrenergic transmission between the hypothalamic paraventricular nucleus and different brainstem nuclei (including reticular formation, locus coeruleus, dorsal raphe nucleus, and motor nucleus of the vagus) has been postulated, and indicated as a possible source of tremor, in early, prodromal PD [28]. Finally, the contribution of the isolation resulting from lockdown during the pandemic, and the ensuing neurochemical changes caused by a depressive state remain to be determined [29].

Because our cases were heterogenous for COVID-19 infection manifestations, including both completely asymptomatic patients and those that required hospitalization and assisted ventilation, a correlation between COVID-19 severity and the development of PD appears unlikely. The role of neuroinflammation in the PD pathogenesis is now well established. Inflammation is a key factor in the initiation and propagation of α-syn aggregates, and the contribution of microglial activation to α-syn pathology has been put forward [30]. Moreover, elevated α-syn-specific T cell response may be present years before the diagnosis of motor PD [31]. In addition, cytokines, which are released during infection, reduce the expression of monoamino-2 vesicular carriers [32], suggesting that SARS-CoV-2 infection, per se, may play a role in dopaminergic dysregulation. Moreover, recent studies show that the olfactory system exhibits inflammatory signatures, which might spread to the CNS and trigger degenerative processes [33].

To establish a possible etiological connection between viral infections and PD, both a careful medical history in de novo PD and a larger surveillance of post-COVID-19 patients, including a detailed neurological examination, are warranted. This would highlight possible previous infections and their temporal relationship with the movement disorder onset, and would represent useful and powerful tools to clarify the link between SARS-CoV-2 infection, neuroinflammation, and PD. In this respect, neuroimaging and positron emission tomography studies will certainly contribute to a better understanding of PASC and their possible long-term consequences [34, 35].

We are aware that our study has some limitations that require several notes of cautions. Above all, the limited number of cases does not allow us to establish a clear causal link between COVID-19 and PD. Similarly, the lack of genetic testing (except in Cases 1 and 3) prevents drawing conclusions on a potential genetic predisposition that, to some extent, could have justified the precipitating effect of inflammation. However, the growing number of cases and a better understanding of the immune signature that characterizes individual patients provide further hints in interpreting with greater clarity these phenomena, representing a unique opportunity to better understand PD pathogenesis.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. Informed consent was verbally obtained from each patient. The authors confirm that the approval of an institutional review board was not required for this work.

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