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BRIEF REPORT

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The potential association between COVID-19 and Parkinson's disease-like symptoms

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Abstract: Although the initial triggers of Parkinson's disease (PD) remain largely unknown, viral infections have been implicated in some cases. In this study, we investigated the neurological sequelae and explored the potential association between post COVID-19 conditions and the development of Parkinson's disease-like symptoms by conducting a questionnaire survey on patients with COVID-19. We surveyed patients who had recovered from COVID-19 and visited the outpatient service of the institution from February 2020 to November 2021. Demographic and clinical data and data regarding the presence and duration of post COVID-19 conditions were obtained. The most common symptom was insomnia, experienced by 141 participants (27.9%). Bradykinesia was the next most common symptom, experienced by 66 participants (13.1%). Moreover, 18 (3.6%) participants reported persistence for > 180 days. Notably, the median duration of bradykinesia was 90 days. The proportions of patients with dysbasia, resting tremor, not previously noted constipation, and somniloquy were 9.1%, 5.0%, 4.8%, and 2.8%, respectively. Few participants had any of these symptoms lasting for more than 180 days. None of the participants was first diagnosed with PD, other neurological diseases, or dementia after COVID-19. Longitudinal follow-up surveys are needed to better understand the relationship between COVID-19 and PD.

***Keywords*:** Parkinson's disease (PD), neurological Sequelae, post COVID-19 Conditions

Introduction

The Coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread worldwide since early 2020 (*1*). Approximately 10–20% of people experience various mid- and long-term effects after recovering from COVID-19 (*2*). Notably, the sequelae of COVID-19 are known as post COVID-19 conditions. Frequent symptoms of post COVID-19 conditions include fatigue, cough, and dysosmia; however, multiple symptoms often overlap and persist (*3-6*). Furthermore, post COVID-19 is known to affect neurological and motor functions, and myalgic encephalomyelitis/chronic fatigue syndrome occurs in the nervous system after recovery from COVID-19 (*7*). A recent study demonstrated that SARS-CoV-2 infection may lead to cognitive decline and brain atrophy including olfactory pathways (*8*), further highlighting the association between COVID-19 and neurodegenerative disorders.

Parkinson's disease (PD), a progressive neurodegenerative disorder, is characterized by a range of motor and non-motor symptoms. Importantly, years or even decades before the onset of the typical motor symptoms, the PD process is associated with a characteristic prodrome (*9*). Although the initial triggers of PD are largely unknown, viral infections have been implicated in some cases (*10*). Notably, patients developed clinical parkinsonism a few weeks after contracting COVID-19 (*11-13*).

One of the well-known sequelae of COVID-19 is dysosmia, which is an early symptom in the onset of PD (*14*). We hypothesized that COVID-19 might trigger the onset of PD. In this study, we investigated the neurological sequelae and the potential association between post COVID-19 conditions and development of Parkinson's disease-like symptoms by conducting a questionnaire survey on patients with COVID-19.

Patients and Methods

This study was designed as a single-center, cross-sectional survey in which a self-reported, online, or paper-based questionnaire was sent to eligible patients in February 2022 without reminders (*4*). Participation in this survey was voluntary, but not anonymous. Participants who recovered from COVID-19 were requested to complete and return the questionnaire. Informed consent was obtained through a consent checkbox,

either online or *via* a paper-based questionnaire. The study was reviewed and approved by the institutional ethics committee, specifically the Ethics Committee of National Center for Global Health and Medicine (NCGM) (NCGM-S-004406-00). Furthermore, the study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients who recovered from COVID-19 and visited the outpatient service of the institution between February 2020 and November 2021 to undergo a pre-donation screening test for COVID-19 convalescent plasmapheresis were recruited (*15*). Most participants had received acute-phase treatment for COVID-19 in other hospitals. Furthermore, all participants in this study were Japanese, as the screening test was specifically designed for Japanese patients.

We developed a questionnaire based on findings from our previous study on prolonged- and late-onset symptoms of COVID-19 and comprehensive discussions among the authors. Moreover, we attempted to minimize the number of questions required to maximize the response rate. Five nonmedical employees of NCGM were included in the pilot study and provided feedback on the items' content, clarity, and format and whether the survey questions were self-explanatory. Minor revisions were made in response to the feedback.

Patient characteristics were investigated, including information regarding the acute phase of COVID-19 and the presence and duration of symptoms related to COVID-19. Disease severity was categorized as follows: mild, requiring no oxygen therapy; moderate, necessitating oxygen therapy but not mechanical ventilation; and severe, involving mechanical ventilation with or without extracorporeal membrane oxygenation. Post-acute phase symptoms related to PD included insomnia, somniloquy (Rapid eye movement sleep behavior disorder [RBD] like symptoms), resting tremors, bradykinesia, dysbasia, and not previously noted constipation. This information was obtained using an online/paper-based questionnaire, as it was difficult to obtain this information from medical records, given that many participants in this study were treated for the acute phase of COVID-19 at other hospitals.

Patient characteristics, the presence of pneumonia, disease severity, and treatments administered during the acute phase of COVID-19 were described using the median and interquartile range for continuous variables and as absolute values (*n*) accompanied by percentages (%) for categorical variables.

The proportions of patients with prolonged symptoms, those with symptoms lasting for at least 30 days within 180 days of symptom onset, and those with symptoms lasting beyond 180 days were described.

Results and Discussion

A total of 505 responses were obtained. All patients were diagnosed with COVID-19 between February 2020 and December 2021. The median number of days (interquartile range) from COVID-19 diagnosis to completion of the questionnaire survey was 392 (243–473 days). Moreover, the median age of the participants was 48 years, and 59.6% were women. Notably, all participants were Japanese. In terms of disease severity, 393 (77.8%), 58 (11.5%), and 5 (1.0%) participants had mild, moderate, and severe disease, respectively. Furthermore, 59 (11.7%) patients received corticosteroids, and 57 (11.3%) received antivirals. A total of 237 (46.9%) participants had no underlying medical conditions. Only one participant reported an underlying neurological disease (Table 1).

The most common symptom was insomnia, experienced by 141 participants (27.9%). However, none of the participants reported that it persisted for more than 180 days, with a median duration of insomnia of 45 days. Bradykinesia was the next most common symptom, experienced by 66 participants (13.1%). Additionally, 18 (3.6%) patients reported persistence for > 180 days; the median duration of bradykinesia was 90 days. The proportions of patients

Table 1. Demographic and clinical characteristics of the participants (*n* = 505)

Characteristics	Value
Age, median (IQR), years	48.0 (42.0, 55.0)
Female sex, *n* (%)	301 (59.6)
Ethnicity, *n* (%)	
Japanese	505 (100)
Timing of the interview	
Days since symptom diagnosis of COVID-19, median (IQR)	392 (243, 473)
Individual comorbidity, *n* (%)	
No underlying medical conditions	237 (46.9)
Hypertension	70 (14.9)
Bronchial asthma	69 (14.7)
Dyslipidemia	59 (12.6)
Diabetes	19 (4.1)
Malignancy	13 (2.6)
Connective tissue disease	4 (0.8)
Chronic kidney disease	3 (0.6)
Immunodeficiency	2 (0.4)
Neurological disease	1 (0.2)
Highest severity during clinical course of COVID-19	
Mild	393 (77.8)
Moderate	58 (11.5)
Severe	5 (1.0)
Unknown	49 (9.7)
Pharmacological treatments	
Antiviral	57 (11.3)
Corticosteroids	59 (11.7)
Casirivimab/ imdevimab	4 (0.8)
Sotrovimab	4 (0.8)

with dysbasia, resting tremor, not previously noted constipation, and somniloquy were 9.1%, 5.0%, 4.8%, and 2.8%, respectively. Notably, few participants had any of these symptoms lasting for more than 180 days. Finally, none of the participants was first diagnosed with PD, other neurological diseases, or dementia after COVID-19 (Table 2).

Direct tissue damage by SARS-CoV-2 infection, constitutive inflammatory responses including autoimmunity, and psychiatric impairment have been suggested as underlying etiologies of long COVID-19 (*16*). Furthermore, it has already been reported that COVID-19 exacerbates motor function and neurological deficits in existing patients with PD and causes new symptoms (*17*). Specifically, it is thought that the insufficient response to dopaminergic drugs after infection altered transport of dopaminergic drugs through the blood-brain barrier (BBB) after systemic infection, and altered dopamine metabolism and receptor signaling are due to the response to proinflammatory cytokines (*18*). Another possibility is that extracerebral inflammatory processes can exacerbate pre-existing neuroinflammatory processes (*19*). Moreover, COVID-19 may indirectly influence symptoms in PD through factors such as substantial changes in routine life, social isolation, stress, anxiety, and prolonged immobility (*20*). However, the causal relationship between COVID-19 and the onset of PD and the mechanism by which COVID-19 triggers neurodegeneration remain determined (*18*). Importantly, studies on the risk of developing PD have shown that patients with viral or bacterial infections have a 20% higher risk of developing PD than controls do (*21*), and COVID-19 may be involved in developing PD.

SARS-CoV-2 enters the brain through the olfactory bulb, axonal transport from peripheral nerves, and hematogenous pathways through the BBB (*22*). Post-infection, immune-mediated processes play an important role in the development of PD (*23*). Interestingly, 13.1% of the participants in this study reported bradykinesia, and 3.6% reported that their symptoms persisted for more than 180 days. Bradykinesia emerged as a distinct long-term sequela, in contrast to other items in the study, which few participants reported as persisting beyond 180 days. While the direct relationship between bradykinesia and early symptoms of PD remains unclear, such manifestation may be a transient symptom of disuse and muscle weakness linked to COVID-19. Notably, all participants who reported dysbasia improved within the 180-day timeframe. Therefore, bradykinesia is considered a significant symptom of post-COVID-19, and continued follow-up is recommended.

Olfactory dysfunction is an early and sensitive marker of the preclinical phase of PD (*14*). α-synuclein pathology in PD is thought to originate from enteric or peripheral autonomic nervous system, or brain regions such as olfactory bulb and amygdala (*24*). In a prior study, 57.8% of COVID-19 patients reported olfactory disturbances; notably, 20.1% of these persisted for several months, and 10.3% continued for more than a year. Although olfactory disturbances are a frequent sequela of COVID-19, none of the patients in this study developed PD after contracting COVID-19. One reason is that this study's median period from onset to investigation was as short as 392 days, which was not long enough to lead to PD onset. Notably, previous studies examining the association between viral infections and the development of PD have reported that a period of 5–10 years after infection is associated with the development of PD (*25*).

This study had some limitations. First, there may be recall bias because the questionnaire survey was conducted on subjects who had been infected with COVID-19 for some time. Second, the participants may have reported resting tremors that they confused with COVID-19 chills. Third, difficulties in walking and movement may be caused by disuse after contracting COVID-19. Fourth, the period from the onset of COVID-19 to the investigation was short, and the time to the onset of PD may have been too short. COVID-19 is a disease with rising prevalence globally. It should also be noted that the questionnaire survey used in this study, which asked about subjective symptoms, is not a diagnostic criterion for PD on its own. The Japanese Ministry of Health, Labour and Welfare defines

Table 2. Number of participants with post-acute COVID-19 symptoms and the persistence of symptoms

Number of patients with the symptom (%)	Number of patients with the symptom (%)	Lasting less than 30 days (%)	Lasting at least 30 days within 180 days since the onset (%)	Lasting more than 180 days (%)	Duration of symptoms in days (median, IQR)
Insomnia	141 (27.9)	115 (22.8)	10 (2.0)	0 (0)	45 (10,255)
Bradykinesia	66 (13.1)	22 (4.4)	21 (4.2)	18 (3.6)	90 (30,255)
Dysbasia	46 (9.1)	40 (7.9)	4 (0.8)	0 (0)	90 (14,240)
Rest tremor	25 (5.0)	22 (4.4)	2 (0.4)	0 (0)	30 (9, 90)
Not previously noted constipation	24 (4.8)	17 (3.4)	4 (0.8)	1 (0.2)	30 (14,270)
Somniloquy	14 (2.8)	10 (2.0)	1 (0.2)	0 (0)	7 (7, 180)
First diagnosed with Parkinson's disease or other neurological disease or dementia	0 (0.0)	-	-	-	-

diagnostic criteria include the presence of parkinsonism, absence of specific abnormalities on the head computed tomography or magnetic resonance imaging, absence of exposure to drugs or toxic substances that cause parkinsonism, and improvement of parkinsonism with antiparkinsonian drugs (*26*). Dopamine transporter positron emission tomography (PET) data or dopamine receptor PET data, and a more commonly used tool such as the unified parkinson's disease rating scale is also useful for diagnosis. Therefore, it is necessary to conduct a follow-up survey to determine whether the number of patients with PD will increase.

Conclusion

In this study, none of the patients developed PD after COVID-19 infection. Long-term follow-up with more patients may clarify the relationship between COVID-19 and PD. Therefore, longitudinal follow-up surveys are warranted to better understand the relationship between COVID-19 and PD.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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