New-onset non-motor symptoms in patients with Parkinson's disease and post-COVID-19 syndrome: A prospective cross-sectional study

ANASTASIA BOUGEA[1], VASILIKI EPAMEINONDAS GEORGAKOPOULOU[2], MYRTO PALKOPOULOU[3], EFTHYMIA EFTHYMIOPOULOU[1], EFTHALIA ANGELOPOULOU[1], DEMETRIOS A. SPANDIDOS[4] and PANAGIOTIS ZIKOS[5]

[1]1st Department of Neurology, Eginition Hospital, Medical School, National and Kapodistrian University of Athens, 11528 Athens; [2]Department of Infectious Diseases-COVID-19 Unit, Laiko General Hospital, 11527 Athens; [3]Department of Neurology, Rhodes General Hospital, 85133 Rhodes; [4]Laboratory of Clinical Virology, School of Medicine, University of Crete, 71003 Heraklion; [5]Department of Neurology, 251 Air Force General Hospital, 11525 Athens, Greece

Received March 3, 2023; Accepted April 10, 2023

DOI: 10.3892/mi.2023.83

Abstract. The clinical range of post-coronavirus disease 2019 (COVID-19) symptoms in patients with Parkinson's disease (PD) has not yet been thoroughly characterized, with the exception of a few small case studies. The aim of the present study was to investigate the motor and non-motor progression of patients with PD (PWP) and post-COVID-19 syndrome (PCS) at baseline and at 6 months after infection with COVID-19. A cross-sectional prospective study of 38 PWP+/PCS+ and 20 PWP+/PCS- matched for age, sex and disease duration was conducted. All patients were assessed at baseline and at 6 months using a structured clinicodemographic questionnaire, the Unified Parkinson's Disease Rating Scale Part III (the UPDRS III), the Montreal Cognitive Assessment, the Hoehn and Yahr scale, the Geriatric Depression Scale and the levodopa equivalent daily dose (LEDD). There was a statistically significant difference in the LEDD (P=0.039) and UPDRS III (P=0.001) at baseline and at 6 months after infection with COVID-19 between the PWP with PCS groups. The most common non-motor PCS symptoms were anosmia/hyposmia, sore throat, dysgeusia and skin rashes. There was no statistically significant difference in demographics or specific scores between the two groups, indicating that no prognostic factor for PCS in PWP could be identified. The novelty of the present study is that it suggests the new onset of non-motor PCS symptoms of PWP with a mild to moderate stage.

Correspondence to: Dr Anastasia Bougea, 1st Department of Neurology, Eginition Hospital, Medical School, National and Kapodistrian University of Athens, 72-74 Vassilisis Sophias Avenue, 11528 Athens, Greece
E-mail: annita139@yahoo.gr

Key words: post-coronavirus disease 2019 syndrome, Parkinson's disease, motor symptoms, non-motor symptoms

Introduction

Chronic or post-coronavirus disease 2019 (COVID-19) syndrome (PCS) refers to symptoms and abnormalities that persist or are present >12 weeks following the onset of acute COVID-19 infection and are not attributable to other diagnoses (1,2). However, the clinical spectrum of post-COVID-19 symptoms in Parkinson's disease (PD) has yet not been fully described, apart from a limited number of small case series (3,4). Previous studies have focused on the chronic worsening of the motor and non-motor symptoms (NMS) in PD following infection with COVID-19 (5-8). These findings need to be carefully interpreted in light of the limitations of the studies, as regards both the methodology and design (small sample, lack of a control group and follow-up).

The main aim of the present study was to compare the long-term incidence of clinical outcomes between patients with PD (PWP) and PCS, and those without PCS at a 6-month follow-up.

Patients and methods

A total of 38 PWP exhibiting PCS symptoms were compared with 20 consecutive patients with PD with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, but no ongoing symptoms, between May 1, 2020 (the lockdown period) and December 31, 2021 (the post-lockdown period), from the 251 Air Force General Hospital (Athens, Greece) and the Rhodes General Hospital (Rhodes, Greece). The inclusion criteria were as follows: Clinical manifestations of PCS were considered as new-onset following initial recovery from an acute COVID-19 episode by a Delphi consensus. The exclusion criteria were the following: Severe comorbidities. A 6-month period was selected to minimize the effects of PD progression on the changes in clinical features and the recall bias. The following data were collected: Demographics, disease duration, motor and non-motor clinical measures, vaccination status at the baseline timepoints of 0 and 6 months, and the

Table I. Demographics and clinical characteristics of the study population.

Parameter	Patients with PCS	Patients without PCS	P-value
Sex, n (%)			0.999[a]
Male	18 (47.3)	9 (45)	
Female, n (%)	20 (52.6)	11 (55)	
Vaccinated			0.916[b]
No	10 (26.3)	5 (25)	
Partially	13 (34.2)	6 (30)	
Fully	15 (39.5)	9 (45)	
Hospitalization due to COVID-19, n (%)			0.777[a]
Yes	24 (63.1)	14 (70)	
No	14 (36.9)	6 (30)	
Age (years), mean (SD)	61.08 (8.70)	60.90 (10.53)	0.945[c]
LEDD before COVID-19, mean (SD)	716.76 (321.24)	702.40 (353.64)	0.876[c]
LEDD after COVID-19, mean (SD)	891.55 (399.05)	759.90 (365.92)	0.225[c]
PD duration at time of COVID-19 diagnosis (years), median (range)	4 (1-12)	4 (1-13)	0.637[d]
HY before COVID-19, median (range)	2 (1-3)	2 (1-3)	0.278[d]
HY after COVID-19, median (range)	2 (1-3)	2 (1-3)	0.838[d]
UPDRS III (off) before COVID-19, median (range)	21.50 (10-49)	24 (16-49)	0.321[d]
UPDRS III after COVID-19, median (range)	31.50 (15-92)	27.5 (19-63)	0.359[d]
MoCA before COVID-19, median (range)	27 (18-30)	26 (20-30)	0.980[d]
MoCA after COVID-19, median (range)	24.50 (11-40)	24.5 (19.3)	0.605[d]

P-values for the differences between groups were obtained using [a]the Chi-squared test; [b]Fisher's exact test; [c]the t-test and [d]the Mann-Whitney U test. PD, Parkinson's disease; COVID-19, coronavirus disease 2019; SD, standard deviation; HY, Hoehn and Yahr Scale; LEDD, levodopa equivalent daily dose; MoCA, Montreal Cognitive Assessment; PCS, post-COVID syndrome; UPDRSIII, Unified Parkinson's Disease Rating Scale Part III.

levodopa equivalent daily dose (LEDD). Motor impairment was evaluated with the Unified Parkinson's Disease Rating Scale part III (UPDRS III) (off phase; i.e., flares of symptoms between regularly scheduled doses of levodopa). NMS were assessed using the Montreal Cognitive Assessment (MoCA) and the Geriatric Depression Scale (GDS). The severity of PD was assessed using the Hoehn and Yahr (HY) scale. The study protocol was approved by health authorities and local independent ethics committees at each participating center (Rhodes General Hospital, no. 199/2020; 251 Air Force General Hospital, no. 251AFH/19-2020), in accordance with the Declaration of Helsinki and the current European Data Protection Regulation. Written informed consent was obtained from all participants.

Statistical analysis. The assessment of the normal distribution of continuous variables was performed with the use of the Shapiro-Wilk test. Continuous variables with normal distribution are presented as the mean (standard deviation), and continuous variables with non-normal distribution are presented as the median (range). The comparison of normally distributed continuous variables was performed using the unpaired t-test and the comparison of not normally distributed continuous variables was performed using an unpaired non-parametric two-tailed Mann-Whitney U test. Categorical variables were examined using Fisher's exact or Chi-squared tests, and are presented as absolute numbers (frequency and percentage). P-values <0.05 were considered to indicate statistically significant differences. Statistical analysis was conducted using IBM SPSS-Statistics version 26.0 (IBM Corp.).

Results

The demographic and clinical characteristics of the patients at baseline were similar between the PD cases and matched controls (Table I). The most common symptoms reported by the patients with PCS were anosmia/hyposmia and a sore throat (73.7%), followed by dysgeusia and skin rashes (65.8%) (Table II).

No significant associations of age, PD duration, vaccination against COVID-19 and hospitalization due to COVID-19 with PCS symptoms were observed (Tables III-V). However, there was a statistically significant association between the male sex, and pain, headaches and sleep disturbances (P=0.020, P=0.047 and P=0.008, respectively) in patients with PCS (Table VI).

Of note, there was a statistically significant difference in the mean value of LEDD (P=0.039) and in the median UPDRS III score at baseline and 6 months later (P=0.001) in the patients with PD with PCS symptoms (Table VII).

There was no statistically significant difference in demographics or specific scores between the two groups, indicating

Table II. New-onset symptoms related to post-COVID-19 syndrome.

Breathlessness	Frequency	Percentage
No	14	36.8
Yes	24	63.2
Cough		
No	20	52.6
Yes	18	47.4
Chest pain		
No	16	42.1
Yes	22	57.9
Palpitations		
No	14	36.8
Yes	24	63.2
Fatigue		
No	19	50
Yes	19	50
Pain		
No	14	36.8
Yes	24	63.2
Fever		
No	15	39.5
Yes	23	60.5
Headache		
No	22	57.9
Yes	16	42.1
Sleep disturbances		
No	20	52.6
Yes	18	47.4
Peripheral neuropathy symptoms		
No	16	42.1
Yes	22	57.9
Dizziness		
No	18	47.4
Yes	20	52.6
Abdominal pain		
No	18	47.4
Yes	20	52.6
Nausea		
No	16	42.1
Yes	22	57.9
Diarrhea		
No	16	42.1
Yes	22	57.9
Myalgia		
No	18	47.4
Yes	20	52.6
Anosmia/hyposmia		
No	10	26.3
Yes	28	73.7
Dysgeusia		
No	13	34.2
Yes	25	65.8
Sore throat		
No	10	26.3
Yes	28	73.7
Skin rashes		
No	13	34.2
Yes	25	65.8

COVID-19, coronavirus disease 2019.

that no prognostic factor for PCS in PWP could be identified (Table I).

Discussion

To the best of our knowledge, the present study is the first prospective cross-sectional study describing the effects of PCS on PD motor symptoms and NMS. First, patients with PD with PCS were not older or had a longer disease duration than those without PCS, although males more frequently reported pain, headaches, and sleep disturbances than females. As regards the primary objective of the present study, an aggravation of motor and the new onset of non-motor PD symptoms were observed in the PCS group over the study period.

To date, at least to the best of our knowledge, only two studies have described PCS symptoms in PWP. The most common long-term effects of COVID-19 reported are the deterioration of motor symptoms (52%), increased LEDD (48%), fatigue (41%), cognitive disturbances (22%), and sleep disturbances (22%) (3,4). A severe acute infection (as indicated by a history of hospitalization) is not a prerequisite for the development of persistent post-COVID-19 symptoms in PWP (4). Of note, in the present study, the most frequently reported new symptoms were anosmia/hyposmia and a sore throat (73.7%), followed by dysgeusia and skin rashes, in accordance with previous PCS non-PD cases (9). The present study demonstrated that the LEDD and UPDRS III scores exhibited significant difference at baseline and at 6 months following infection with COVID-19 in PWP with PCS symptoms. The deterioration of motor symptoms may be explained by stress, physical inactivity, pharmacodynamic effects, marked changes in routine and social isolation with a subsequent increase in LEDD. All previous studies (3,4,7-9) were small, lacked a control group, included exacerbated pre-existing symptoms that were previously stable, and recruited only participants infected during the first wave of the pandemic. Although chronic immunological changes may have caused the clinical worsening of PWP after the COVID-19 lockdown, these studies did not adjust for confounders that influence PD motor and non-motor symptoms, such as physical immobility, stress, anxiety, and sleep disturbances during COVID-19 lockdown.

Table III. Associations of Parkinson's disease duration and age of the patients with post-COVID-19 symptoms.

	PD duration (years)			Age (years)		
Symptom	Median	Range	P-value[a]	Mean	Standard deviation	P-value[b]
Breathlessness				0.622		0.125
No	4	1-12		63.93	9.49	
Yes	3	1-10		59.42	7.94	
Cough			0.126			0.246
No	4	1-12		62.65	8.63	
Yes	3	1-10		59.33	8.69	
Chest pain			0.271			0.861
No	3	1-10		61.38	6.96	
Yes	4	1-12		60.86	9.93	
Palpitations			0.709			0.765
No	3.5	1-10		61.64	8.55	
Yes	4	1-12		60.75	8.96	
Fatigue			0.686			0.475
No	3	1-10		62.11	7.29	
Yes	4	1-12		60.05	10.01	
Pain			0.893			0.702
No	3	2-12		60.36	10.40	
Yes	4	1-10		61.50	7.76	
Fever			0.300			0.799
No	4	2-12		61.53	8.38	
Yes	3	1-10		60.78	9.08	
Headache			0.445			0.272
No	4	1-12		62.41	9.30	
Yes	3	1-10		59.25	7.72	
Sleep disturbances			0.654			0.726
No	4	1-10		60.60	8.76	
Yes	3.5	1-12		61.61	8.86	
Peripheral neuropathy symptoms			0.849			0.719
No	4	1-10		61.69	9.00	
Yes	4	1-10		60.64	8.66	
Dizziness			0.828			0.231
No	4	1-10		59.28	8.12	
Yes	3.5	1-12		62.70	9.09	
Abdominal pain			0.573			0.153
No	4	1-10		63.22	8.70	
Yes	3	1-12		59.15	8.46	
Nausea			0.942			0.597
No	4	1-10		60.19	8.34	
Yes	3	1-12		61.73	9.09	
Diarrhea			0.298			0.157
No	4	1-12		63.44	8.34	
Yes	3	1-7		59.36	8.74	
Myalgia			0.740			0.419
No	4	1-10		62.28	6.89	
Yes	3.5	1-12		60.00	10.12	
Anosmia/hyposmia			0.526			0.255
No	3	1-7		63.80	7.71	
Yes	4	1-12		60.11	8.96	

Table III. Continued.

	PD duration (years)			Age (years)		
Symptom	Median	Range	P-value[a]	Mean	Standard deviation	P-value[b]
Dysgeusia			0.272			0.538
No	4	1-8		62.31	9.34	
Yes	3	1-12		60.44	8.48	
Sore throat			0.584			0.434
No	4	1-12		59.20	8.33	
Yes	3.5	1-10		61.75	8.88	
Skin rashes			0.097			0.969
No	5	1-10		61.00	10.00	
Yes	3	1-12		61.12	8.17	

P-values for the difference between groups were obtained using [a]the Mann-Whitney U test and [b]the t-test. PD, Parkinson's disease; COVID-19, coronavirus disease 2019.

Table IV. Association of vaccination against COVID-19 with post-COVID-19 symptoms.

	Vaccination against COVID-19			
Parameter	No	Partially	Fully	P-value
Breathlessness				0.490
No	5	5	4	
Yes	5	8	11	
Cough				0.318
No	4	9	7	
Yes	6	4	8	
Chest pain				0.542
No	4	7	5	
Yes	6	6	10	
Palpitations				0.393
No	5	3	6	
Yes	5	10	9	
Fatigue				0.931
No	5	7	7	
Yes	5	6	8	
Pain				0.217
No	5	6	3	
Yes	5	7	12	
Fever				0.703
No	5	5	5	
Yes	5	8	10	
Headache				0.363
No	4	9	9	
Yes	6	4	6	
Sleep disturbances				0.143
No	6	4	10	
Yes	4	9	5	
Peripheral neuropathy symptoms				0.838
No	5	5	6	
Yes	5	8	9	

Table IV. Continued.

Parameter	Vaccination against COVID-19			P-value
	No	Partially	Fully	
Dizziness				0.803
No	4	7	7	
Yes	6	6	8	
Abdominal pain				0.440
No	3	7	8	
Yes	7	6	7	
Nausea				0.227
No	5	3	8	
Yes	5	10	7	
Diarrhea				0.542
No	4	7	5	
Yes	6	6	10	
Myalgia				0.590
No	6	5	7	
Yes	4	8	8	
Anosmia/hyposmia				0.307
No	3	5	2	
Yes	7	8	13	
Dysgeusia				0.199
No	4	2	7	
Yes	6	11	8	
Sore throat				0.932
No	3	3	4	
Yes	7	10	11	
Skin rashes				0.173
No	2	7	4	
Yes	8	6	11	

P-values for the differences between groups were obtained using the Fisher's exact test. COVID-19, coronavirus disease 2019.

The differentiation between PCS in PD and the general worsening of PD symptoms due to COVID-19 remains challenging. There are several potential mechanisms underlying the aggravation of PD-related neurodegeneration due to SARS-CoV-2 as follows: i) The poor absorption of anti-parkinsonian medications due to drug interaction with cough suppressants for SARS-CoV-2 (10); ii) SARS-CoV-2 neurotropism of particularly vulnerable substantia nigra involved in the onset and progression of PD *in vitro* and human post-mortem studies (11,12); iii) enhanced neurodegeneration due to the persisting neuroinflammation process; SARS-CoV-2-related exosomes, in particular, have the potential to transmit SARS-CoV-2 fragments, transcriptional factors, and inflammatory mediators to brain cells, resulting in prolonged neuroinflammation and α-synuclein aggregation, which may lead to the worsening of PD symptoms. α-synuclein can enhance the SARS-CoV-2-mediated activation of microglia and the NLR family pyrin domain containing 3 inflammasome via the angiotensin converting enzyme 2/NF-κB pathway (13,14). Dopamine or inflammatory marker levels were not assessed in the present study; however, the authors aim to examine these in future studies.

The main limitation of the present study was the small cohort of patients with COVID-19. However, the present study has several strengths: First, the potentially harmful effects of lockdown restrictions on PD motor and non-motor symptoms were excluded. Second, the selection bias was minimized by excluding patients with advanced PD and comorbidities, who are more likely to develop neurological complications.

In conclusion, these novel findings raise critical questions for future analyses. Anosmia in COVID-19 may represent a true viral invasion of the olfactory bulbs (15). This new-onset post-COVID-19 symptom, which often predicts PD-associated clinical and pathological changes (16), may shed light on the possibility of SARS-CoV-2 infection triggering long-term neurodegeneration. Other NMS, such as pain, headaches and sleep disturbances, have been found to be more common in males than in females with PD and PCS, as evidenced in males

Table V. Associations of hospitalization due to COVID-19 with post-COVID-19 symptoms.

	Hospitalization for COVID-19		
Parameter	No	Yes	P-value
Breathlessness			0.298[a]
No	7	7	
Yes	7	17	
Cough			0.999[a]
No	7	13	
Yes	7	11	
Chest pain			0.510[a]
No	7	9	
Yes	7	15	
Palpitations			0.729[a]
No	6	8	
Yes	8	16	
Fatigue			0.737[a]
No	8	11	
Yes	6	13	
Pain			0.298[a]
No	7	7	
Yes	7	17	
Fever			0.999[b]
No	5	10	
Yes	9	14	
Headache			0.510[a]
No	7	15	
Yes	7	9	
Sleep disturbances			0.745[b]
No	8	12	
Yes	6	12	
Peripheral neuropathy symptoms			0.999[b]
No	6	10	
Yes	8	14	
Dizziness			0.999[a]
No	7	11	
Yes	7	13	
Abdominal pain			0.745[a]
No	6	12	
Yes	8	12	
Nausea			0.187[a]
No	8	8	
Yes	6	16	
Diarrhea			0.187[a]
No	8	8	
Yes	6	16	
Myalgia			0.179[a]
No	9	9	
Yes	5	15	
Anosmia/hyposmia			0.315[b]
No	5	5	
Yes	9	19	

Table V. Continued.

Parameter	Hospitalization for COVID-19		P-value
	No	Yes	
Dysgeusia			0.881[b]
No	5	8	
Yes	9	16	
Sore throat			0.315[b]
No	5	5	
Yes	9	19	
Skin rashes			0.448[b]
No	2	11	
Yes	12	13	

P-values for the differences between groups were obtained using athe Chi-squared test and bFisher's exact test. COVID-19, coronavirus disease 2019.

Table VI. Associations of sex with post-COVID-19 symptoms.

Parameter	Gender		P-value
	Female	Male	
Breathlessness			0.745[a]
No	8	6	
Yes	12	12	
Cough			0.516[a]
No	12	8	
Yes	8	10	
Chest pain			0.512[a]
No	7	9	
Yes	13	9	
Palpitations			0.179[b]
No	5	9	
Yes	15	9	
Fatigue			0.999[a]
No	10	9	
Yes	10	9	
Pain			**0.020[b]**
No	11	3	
Yes	9	15	
Fever			0.999[a]
No	8	7	
Yes	12	11	
Headache			**0.047[b]**
No	15	7	
Yes	5	11	
Sleep disturbances			**0.008[b]**
No	15	5	
Yes	5	13	
Peripheral neuropathy symptoms			0.112[b]
No	11	5	
Yes	9	13	

Table VI. Continued.

Parameter	Gender		P-value
	Female	Male	
Dizziness			0.757[a]
No	10	8	
Yes	10	10	
Abdominal pain			0.999[a]
No	9	9	
Yes	11	9	
Nausea			0.752[a]
No	9	7	
Yes	11	11	
Diarrhea			0.752[a]
No	9	7	
Yes	11	9	
Myalgia			0.999[a]
No	9	9	
Yes	11	9	
Anosmia/hyposmia			0.095[b]
No	3	7	
Yes	17	11	
Dysgeusia			0.506[b]
No	8	5	
Yes	12	13	
Sore throat			0.200[b]
No	7	3	
Yes	13	15	
Skin rashes			0.999[a]
No	7	6	
Yes	13	12	

P-values for the differences between groups were obtained using [a]the Chi-squared test and [b]Fisher's exact test. Values in bold font indicate significant differences (P<0.05). COVID-19, coronavirus disease 2019.

Table VII. Comparison of LEDD, HY, UPDRS III and MoCA before and 6 months after COVID-19 in patients with PD reporting post-COVID-19 syndrome.

Parameter measured	Before COVID-19	After COVID-19	P-value
LEDD, mean (SD)	716.76 (321.24)	891.55 (399.05)	0.039[a]
HY, median (range)	2 (1-3)	2 (1-3)	0.251[b]
UPDRS III, median (range)	21.50 (10-49)	31.50 (15-92)	0.001[b]
MoCA, median (range)	27 (18-30)	24.50 (11-40)	0.612[b]

P-values for the difference between groups were obtained using [a]the t-test and [b]the Mann-Whitney U test. PD, Parkinson's disease; COVID-19, coronavirus disease 2019; SD, standard deviation; H&Y, Hoehn and Yahr Scale; LEDD, levodopa equivalent daily dose; MoCA, Montreal Cognitive Assessment; UPDRSIII, Unified Parkinson's Disease Rating Scale Part III.

with PD without PCS (17,18). However, the reason that males are more vulnerable than females to PD and PCS remains to be elucidated.

Moreover, the fact that these new-onset NMS were not associated with the vaccination status in the cohort of wild-type, alpha, and delta variant patients with

SARS-CoV-2 suggests a more complex interplay between the immunological response and neurodegeneration. It also remains to be determined whether the current available vaccines against SARS-CoV-2 prevent PWP from PCS.

There is a clear need to distinguish the PCS in PWP from the chronic worsening of PD symptoms due to COVID-19. The diagnostic and treatment tools of PCS are currently insufficient, and numerous clinical trials are warranted to address the hypothesized underlying biological mechanisms, including viral persistence, neuroinflammation and autoimmunity.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AB and PZ conceptualized the study. AB, VEG, MP, EE, EA, DAS and PZ made a substantial contribution to the analysis and interpretation of the data, and wrote and prepared the draft of the manuscript. VEG and AB analyzed the data, and provided critical revisions. AB and PZ confirm the authenticity of all the raw data. All authors contributed to manuscript revision, and have read and approved the final version of the manuscript.

Ethics approval and consent to participates

The present study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the ethics committees of each participating center (Rhodes General Hospital, no. 199/2020; 251 Air Force General Hospital, no. 251AFH/19-2020). Written informed was obtained from the patients for publication of their data.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. National Institute for Health and Care Excellence (NICE). COVID-19 rapid guideline: Managing the long-term effects ofCOVID-19. https://www.nice.org.uk/guidance/NG188. Accessed February 1, 2023.
2. Soriano JB, Murthy S, Marshall JC, Relan P and Diaz JV; WHO Clinical Case Definition Working Group On Post-COVID-19 Condition: A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect Dis 22: e102-e107, 2022.
3. Leta V, Rodríguez-Violante M, Abundes A, Rukavina K, Teo JT, Falup-Pecurariu C, Irincu L, Rota S, Bhidayasiri R, Storch A, *et al*: Parkinson's disease and post-COVID-19 syndrome: The Parkinson's Long-COVID spectrum. Mov Disord 36: 1287-1289, 2021.
4. Boika AV, Sialitski MM, Chyzhyk VA, Ponomarev VV and Fomina EG: Post-COVID worsening of a Parkinson's disease patient. Clin Case Rep 9: e04409, 2021.
5. D'Iorio A, Baiano C, Maraucci G, Vitale C, Amboni M and Santangelo G: A longitudinal study on the effects of COVID-19 pandemic on non-motor symptoms in Parkinson's disease. Neurol Sci 43: 4605-4609, 2022.
6. Khoshnood RJ, Zali A, Tafreshinejad A, Ghajarzadeh M, Ebrahimi N, Safari S and Mirmosayyeb O: Parkinson's disease and COVID-19: A systematic review and meta-analysis. Neurol Sci 43: 775-783, 2022.
7. Antonini A, Leta V, Teo J and Chaudhuri KR: Outcome of Parkinson's disease patients affected by COVID-19. Mov Disord 35: 905-908, 2020.
8. Montanaro E, Artusi CA, Rosano C, Boschetto C, Imbalzano G, Romagnolo A, Bozzali M, Rizzone MG, Zibetti M and Lopiano L: Anxiety, depression, and worries in advanced Parkinson disease during COVID-19 pandemic. Neurol Sci 43: 341-348, 2022.
9. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, Cook JR, Nordvig AS, Shalev D, Sehrawat TS, *et al*: Post-acute COVID-19 syndrome. Nat Med 27: 601-615, 2021.
10. Goerttler T, Kwon EH, Fleischer M, Stettner M, Tönges L and Klebe S: SARS-CoV-2, COVID-19 and Parkinson's disease-many issues need to be clarified-a critical review. Brain Sci 12: 456, 2022.
11. Yang L, Han Y, Nilsson-Payant BE, Gupta V, Wang P, Duan X, Tang X, Zhu J, Zhao Z, Jaffré F, *et al*: 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, 2020.
12. Emmi A, Rizzo S, Barzon L, Sandre M, Carturan E, Sinigaglia A, Riccetti S, Barbera MD, Boscolo-Berto R, Cocco P, *et al*: Detection of SARS-CoV-2 viral proteins and genomic sequences in human brainstem nuclei. NPJ Parkinsons Dis 9: 25, 2023.
13. Mysiris DS, Vavougios GD, Karamichali E, Papoutsopoulou S, Stavrou VT, Papayianni E, Boutlas S, Mavridis T, Foka P, Zarogiannis SG, *et al*: Post-COVID-19 parkinsonism and parkinson's disease pathogenesis: The exosomal cargo hypothesis. Int J Mol Sci 23: 9739, 2022.
14. Angelopoulou E, Karlafti E, Georgakopoulou VE, Papalexis P, Papageorgiou SG, Tegos T and Savopoulos C: Exploring the role of ACE2 as a connecting link between COVID-19 and Parkinson's disease. Life (Basel) 13: 536, 2023.
15. Braak H, Rüb U, Gai WP and Tredici KD: Idiopathic Parkinson's disease: Possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. J Neural Transm (Vienna) 110: 517-536, 2003.
16. Pfeiffer RF: Non-motor symptoms in Parkinson's disease. Parkinsonism Relat Disord 22 (Suppl 1): S119-S122, 2016.
17. Miller IN and Cronin-Golomb A: Gender differences in Parkinson's disease: Clinical characteristics and cognition. Mov Disord 25: 2695-2703, 2010.
18. Angelopoulou E, Papadopoulos AN, Spantideas N and Bougea A: Migraine, tension-type headache and Parkinson's disease: A systematic review and meta-analysis. Medicina (Kaunas) 58: 1684, 2022.