

Effects of COVID-19 on Parkinson's Disease Clinical Features: A Community-Based Case-Control Study

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ABSTRACT: The impact of coronavirus disease 2019 (COVID-19) on clinical features of Parkinson's disease (PD) has been poorly characterized so far. Of 141 PD patients resident in Lombardy, we found 12 COVID-19 cases (8.5%), whose mean age and disease duration (65.5 and 6.3 years, respectively) were similar to controls. Changes in clinical features in the period January 2020 to April 2020 were compared with those of 36 PD controls matched for sex, age, and disease duration using the clinical impression of severity index for PD, the Movement Disorders Society Unified PD Rating Scale Parts II and IV, and the nonmotor symptoms scale. Motor and nonmotor symptoms significantly worsened in the COVID-19 group, requiring therapy adjustment in one third of cases. Clinical deterioration was explained by both infection-related mechanisms and impaired pharmacokinetics of dopaminergic therapy. Urinary issues and fatigue were the most prominent nonmotor issues. Cognitive functions were marginally involved, whereas none experienced autonomic failure. © 2020 International Parkinson and Movement Disorder Society

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Since the first patient was diagnosed with coronavirus disease 2019 (COVID-19) in Lombardy, on February 20, 2020, Italy has become the third most affected country (>215,000 cases and 30,000 deaths) in the world.¹ COVID-19 neurotropic properties may underlie a worsening of chronic neurological diseases, such as Parkinson's disease (PD). COVID-19 may worsen PD by a number of mechanisms,²⁻⁴ including pharmacodynamics changes (eg, reciprocal interactions between the dopaminergic and renin-angiotensin systems in the substantia nigra and striatum⁵) as well as systemic inflammatory responses.⁶⁻⁹ Patients with PD are frailer than the general population because of disease-related factors and age-related comorbidities.^{2-4,10,11} A higher COVID-19 mortality rate has been described in advanced PD patients in association with older age and longer disease duration.¹²

Our primary objective was to investigate the effects of COVID-19 on motor and nonmotor symptoms in a community-based PD cohort. In addition, we explored whether older age and longer disease duration represented risk factors for developing symptomatic COVID-19.

Materials and Methods

In the present observational, community-based, case-control study, we investigated the demographic and clinical features in a cohort of patients with idiopathic PD¹³ and COVID-19 when compared with controls with PD between the preoutbreak period in Italy (January 1, 2020) and the end of lockdown restrictions (May 4, 2020). A 3-month period was chosen to minimize the effect of PD progression on the change in clinical features and the recall bias. The diagnosis of COVID-19 was performed according to the clinical and laboratory criteria for probable and confirmed cases released by the World Health Organization criteria on March 20, 2020.¹⁴ In symptomatic cases fulfilling criteria for "probable case,"^{14,15} we included only patients with close and protracted contacts (ie, caregivers) with laboratory-confirmed cases.

Out of the 1092 records obtained by searching the Besta Institute clinical software for patients fulfilling the following criteria: (1) International Classification of Diseases, Ninth Revision, clinical modification code for parkinsonism 332.0; (2) resident in the Lombardy region, northern Italy (which is by far the most affected area [>80,000 cases] with the highest case fatality [>15,000 deaths] in Italy as of May 11, 2020)¹⁶; and (3) visited at least once by a neurologist from January 1, 2019 to December

31, 2019, we performed a random selection of 150 PD for subsequent remote interview by a neurologist experienced in movement disorders (by video consultation or telephone),^{2,17,18} which was performed between April 15 and May 4, 2020. Signed informed consent was obtained prior

to the remote assessment and collection of clinical data, as approved by the local ethics committee.

Of a total of 141 patients who agreed to be interviewed, 12 (8.5%) were affected by COVID-19.¹⁴ Compared with the overall cohort of 129 control

TABLE 1. Characteristics of the study population

Variable	Cases, N = 12	Controls, N = 36	P Value*
General features			
Male sex, N (%)	5 (41.7)	15 (41.7)	1.00
Age, y, mean (SD)	65.5 (8.9)	66.3 (8.1)	0.78
Current smoking, N (%)	0 (0.0)	3 (8.3)	0.56
Past smoking, N (%)	5 (41.7)	10 (27.8)	0.48
Frequency of smoking, cigarettes/day, N (%)	10.0 (8.7)	9.1 (7.3)	0.82
Body mass index, kg/m ² , mean (SD)	25.1 (3.8)	25.5 (3.8)	0.77
Body weight, kg, mean (SD)	67.0 (11.5)	71.3 (14.5)	0.36
Seasonal vaccinations in 2019, total N (%)	3 (25.0)	9 (25.0)	1.00
Anti-H1N1, N (%)	3 (25.0)	9 (25.0)	1.00
Antipneumococcus, N (%)	1 (8.3)	2 (5.5)	1.00
PD-related features^a			
Age at PD onset, y, mean (SD)	59.0 (8.1)	60.4 (7.8)	0.58
Tremor-dominant phenotype, N (%)	6 (50)	18 (50)	1.00
Disease duration, y, mean (SD)	6.3 (3.6)	6.1 (2.9)	0.79
Hoehn and Yahr stage, mean (SD)	1.8 (0.7)	1.8 (0.6)	0.95
Dementia, N (%)	0 (0.0)	3 (8.3)	0.56
Therapy			
Levodopa, N (%)	10 (83.3)	28 (77.8)	1.00
Levodopa dose, mg/day, mean (SD)	400.0 (119.3)	433.6 (227.1)	0.09
DA, N (%)	9 (75.0)	23 (63.9)	0.73
iMAO-B, N (%)	6 (50.0)	16 (44.4)	0.75
iCOMT, N (%)	0 (0.0)	4 (11.1)	0.56
Amantadine, N (%)	0 (0.0)	0 (0.0)	1.00
Advanced-stage invasive therapies, N (%) ^b	1 (8.3)	1 (2.8)	0.44
Total LEDD, mg/day, mean (SD)	571 (517)	487 (327)	0.52
Therapy adjustment during the study period, N (%)	4 (33.3)	2 (5.5)	0.028
Risk factors for COVID-19			
Contact with confirmed or suspect COVID-19, total N (%) ^c	8 (66.7)	4 (11.1)	<0.001
Confirmed COVID-19, N (%)	6 (50.0)	0 (0.0)	<0.001
Suspect COVID-19, N (%)	2 (16.7)	4 (11.1)	0.63
Comorbidities			
Any	9 (75)	24 (66.7)	0.73
COPD	1 (8.3)	4 (11.1)	1.00
Hypertension, N (%)	4 (33.3)	16 (44.4)	0.74
Obesity, N (%)	1 (8.3)	2 (5.5)	1.00
Diabetes mellitus, N (%)	0 (0.0)	2 (5.5)	1.00
Cardiopathy, N (%)	1 (8.3)	5 (13.9)	1.00
Malignancies, N (%)	2 (16.7)	3 (8.3)	0.59
Immune system diseases, N (%)	1 (8.3)	1 (2.8)	1.00
Immune-modulating therapies, N (%) ^d	2 (16.7)	2 (5.5)	0.26
Renal or hepatic dysfunction, N (%)	1 (8.3)	5 (13.9)	1.00
Other neurological diseases, N (%) ^e	1 (8.3)	4 (11.1)	1.00
COVID-19 symptoms			
Fever, N (%)	10 (83.3)	2 (5.5)	<0.001
Cough, N (%)	9 (75%)	3 (8.3)	<0.001
Dyspnea, N (%)	4 (33.3)	0 (0.0)	0.003
Dizziness, N (%)	2 (16.6)	1 (2.8)	0.15
Headache, N (%)	4 (33.3)	3 (8.3)	0.055
Anorexia, N (%)	5 (41.6)	1 (2.8)	0.002
Diarrhea, N (%)	6 (50)	2 (5.5)	0.002
Fatigue, N (%)	7 (58.4)	3 (8.3)	<0.001

(Continues)

TABLE 1. Continued

Variable	Cases, N = 12	Controls, N = 36	P Value*
Skeletal muscle pain, N (%)	7 (58.4)	2 (5.5)	<0.001
Nausea/vomiting, N (%)	2 (16.6)	1 (2.8)	0.15
Smell loss, N (%)	4 (33.3)	1 (2.8)	0.011
Taste loss, N (%)	2 (16.6)	1 (2.8)	0.15
Hypotension, N (%)	2 (16.6)	1 (2.8)	0.15

*These data refer to the baseline state (January 2020) before the COVID-19 outbreak in Italy.

^bOne case was on levodopa/carbidopa gel infusion; 1 control was on subthalamic nucleus stimulation.

^cDefined according to the World Health Organization criteria.¹⁴

^dIncluding daily intake of drugs targeting rheumatic diseases or malignancies (eg, steroids, hydroxychloroquine, methotrexate, azathioprine, etc.) prior to the baseline assessment.

^eOne patient with meningioma among cases, 4 patients with chronic cerebrovascular disease among controls.

*Between-group comparisons of continuous variables were performed using the unpaired Student's *t* test, whereas categorical variables were analyzed by Fisher's exact test. Significant values ($P < 0.05$) are in bold.

H1N1, haemagglutinin type 1 and neuraminidase type 1; PD, Parkinson's disease; DA, dopamine agonists; iMAO-B, monoamine oxidase type B inhibitors; iCOMT, catechol-O-methyltransferase inhibitors; LEDD, levodopa equivalent daily dose; COVID-19, coronavirus disease 2019; COPD, chronic obstructive pulmonary disease, including asthma.

patients with PD (men, 56.6%; age, 69.1 ± 10.1 years; PD duration, 8.2 ± 5.0 years; any comorbidity, 62.8%), the cases has similar sex distribution ($P = 0.37$), age ($P = 0.24$), PD duration ($P = 0.20$), and comorbidities ($P = 0.54$). Among the 129 patients screening negative for COVID-19, a group of 36 control patients with PD matched for sex, age, and disease duration (± 1 year) was used for subsequent statistical analysis. A 1:3 ratio was chosen to minimize the effects related to biological variability and the potential presence of asymptomatic COVID-19 among controls.¹⁹ Cases and matched controls underwent in-depth assessment using internationally validated scales. Motor aspects of experiences of daily living and the severity of treatment-related motor complications were assessed using the Movement Disorders Society Unified PD Rating Scale (MDS-UPDRS) Parts II and IV, respectively²⁰; nonmotor symptoms were assessed using of the Italian version of the Non-Motor Symptoms Scale (NMSS)²¹; and overall changes of motor and nonmotor features were additionally rated using the Clinical Impression of Severity Index for Parkinson's Disease (CISI-PD).²²

Descriptive statistics were provided for continuous (mean and standard deviation) and categorical (count and percentage) variables, which were compared between groups using Student's *t* test and Fisher's exact test. Between-visit changes in study parameters (January to April 2020) were compared between COVID-19 cases and controls using repeated-measure linear regression models. The role of potential confounders was addressed by Multivariate Analysis of Variance (MANOVA). All statistical analyses were performed using STATA statistical software release 15.1 (Stata Corporation, College Station, TX) setting the level of significance at a 2-tailed $P < 0.05$.

Results

Demographic and clinical features at baseline were similar between PD cases and matched controls except

for the greater need to increase dopaminergic therapy dosing and higher rate of contacts with confirmed COVID-19 among cases (Table 1). COVID-19 symptoms were mild, managed at home without symptomatic therapy in 3 cases (25%); 8 cases (66.7%) had moderate illness, pharmacologically managed at home by the general practitioner; only 1 patient was hospitalized (8.3%) as a result of pneumonia. COVID symptoms remitted in 10 of 12 (83.3%) cases and were still ongoing in 2 patients (16.7%; both remitted at subsequent follow-up on May 15); nobody died.

In the within-group comparisons, cases evidenced a significant worsening of the CISI-PD total and motor-signs scores, MDS-UPDRS Part II score, the NMSS total score, and the urinary domain subscore (Table 2, footnote c). Between-group case-control analysis additionally revealed greater motor disability (at CISI-PD), motor fluctuations (at MDS-UPDRS Part IV), and nonmotor complaints. The involvement of cognitive functions was marginal (no change at CISI-PD), and autonomic cardiovascular and sexual functions remained unaffected (Table 2).

Finally, considering the greater rate of diarrhea among COVID-19 cases (Table 1) and its detrimental effect on the pharmacokinetics of dopaminergic medications (particularly levodopa), we adjusted a selected subset of models for this symptom and found that worsening of the CISI-PD total and motor signs scores was partially mediated by diarrhea ($P = 0.002$ for both), although COVID-19 status was still a significant contributor ($P = 0.025$ and 0.026 , respectively). Worsening of MDS-UPDRS Part II and the Part IV total scores and the NMSS total score were explained by COVID-19 alone ($P = 0.008$, $P = 0.034$, $P = 0.008$, respectively); interestingly, an increase in daily *off* time was fully explained by diarrhea ($P = 0.019$). We additionally explored whether urinary dysfunction and fatigue were attributed to COVID-19 or to diminished dopaminergic drive (Table 2) and found that urinary problems worsening was the result of both motor fluctuations ($P < 0.001$)

TABLE 2. Analysis of study end points (CISI-PD, MDS-UPDRS, NMSS)

Variable	Cases, N = 12			Controls, N = 36			Statistics	
	Baseline*	End of Study*	Change**	Baseline*	End of Study*	Change**	Between-Group Difference in Change***	P Value***
CISI-PD								
Total score	6.2 (4.1)	7.4 (4.1)	1.3 (0.3–2.2) ^d	7.5 (4.7)	7.6 (4.8)	0.1 (0.0–0.2)	1.2 (0.6–1.7)	<0.001
Motor signs	2.3 (1.4)	3.0 (1.3)	0.7 (0.2–1.2) ^d	2.7 (1.4)	2.7 (1.4)	0.0 (–0.0 to 0.1)	0.6 (0.3–0.9)	<0.001
Disability	2.1 (1.1)	2.4 (1.4)	0.3 (–0.1 to 0.7)	2.4 (1.4)	2.4 (1.4)	0.0 (0.0–0.0)	0.3 (0.1–0.5)	0.003
Motor complications	0.6 (1.2)	0.7 (1.4)	0.1 (–0.1 to 0.3)	1.0 (1.4)	1.0 (1.4)	0.0 (–0.1 to 0.1)	0.1 (–0.1 to 0.2)	0.42
Cognitive status	1.2 (1.2)	1.3 (1.2)	0.1 (–0.1 to 0.4)	1.5 (1.5)	1.5 (1.5)	0.0 (–0.1 to 0.1)	0.1 (–0.0 to 0.3)	0.089
MDS-UPDRS								
UPDRS Part II	11.9 (7.6)	13.7 (9.4)	1.8 (0.4–3.1) ^c	12.0 (8.3)	12.2 (8.3)	0.2 (0.0–0.4) ^c	1.6 (0.8–2.3)	<0.001
UPDRS Part IV	3.0 (6.2)	4.2 (8.1)	1.2 (–0.2 to 2.5)	4.8 (6.6)	4.8 (6.6)	0.0 (0.0–0.0)	1.2 (0.5–2.9)	0.002
UPDRS Part IV, off ^f	1.1 (2.0)	1.5 (2.8)	0.4 (–0.2 to 1.0)	1.7 (2.5)	1.7 (2.5)	0.0 (0.0–0.0)	0.4 (0.1–0.7)	0.014
UPDRS Part IV–DYSK ^a	0.3 (1.2)	0.5 (1.7)	0.2 (–0.2 to 0.5)	0.6 (1.2)	0.6 (1.2)	0.0 (0.0–0.0)	0.2 (–0.0 to 0.4)	0.083
NMSS								
Total score	39.3 (28.1)	49.7 (43.1)	10.4 (0.2–20.6) ^c	41.9 (40.8)	41.8 (41.1)	–0.1 (–0.7 to 0.5)	10.5 (5.2–15.9)	<0.001
Cardiovascular	1.5 (1.3)	1.8 (3.3)	0.3 (–1.1 to 1.6)	1.3 (2.3)	0.9 (1.9)	–0.4 (–0.6 to –0.2) ^c	0.6 (–0.2 to 1.4)	0.13
Sleep/fatigue	8.3 (6.4)	10.5 (7.1)	2.2 (–0.2 to 4.6)	10.0 (9.7)	9.8 (9.7)	–0.1 (–0.4 to 0.1)	2.3 (1.0–3.6)	0.001
Mood/apathy	8.6 (14.3)	11.8 (17.9)	3.2 (–1.2 to 7.5)	7.6 (11.0)	7.6 (11.3)	0.0 (–0.4 to 0.4)	3.1 (0.8–5.5)	0.010
Perceptual problems	0.9 (1.6)	0.9 (1.6)	0.0 (0.0–0.0)	0.7 (1.6)	0.7 (1.6)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	1.00
Attention/memory	3.2 (4.1)	4.7 (7.8)	1.5 (–1.1 to 4.1)	4.9 (7.1)	4.9 (7.1)	0.0 (–0.1 to 0.2)	1.4 (0.1–2.8)	0.038
Gastrointestinal ^b	3.3 (5.1)	3.2 (5.2)	–0.1 (–0.8 to 0.5)	3.0 (3.8)	3.2 (3.9)	0.2 (–0.0 to 0.4)	–0.4 (–0.9 to 0.2)	0.17
Urinary	8.6 (7.5)	10.8 (9.3)	2.2 (0.1–4.4) ^c	8.3 (9.0)	8.3 (9.0)	0.0 (0.0–0.0)	2.3 (1.1–3.4)	<0.001
Sexual function	1.3 (2.0)	1.3 (2.0)	0.0 (0.0–0.0)	2.1 (4.5)	2.1 (4.5)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	1.00
Miscellaneous	3.5 (3.3)	4.8 (3.7)	1.3 (–0.5 to 3.0)	4.2 (5.9)	4.3 (5.9)	0.1 (–0.0 to 0.2)	1.2 (0.2–2.1)	0.014

*Data are provided as mean (standard deviation).

**Data are provided as mean (95% confidence interval).

***According to repeated-measures linear regression model.

^aOff-related subscore was calculated as the sum of items 4.3, 4.4, and 4.5. Dyskinesia subscore was calculated as the sum of items 4.1 and 4.2.

^bNote that the gastrointestinal domain of the NMSS does not include an assessment of diarrhea.

^cSignificantly different compared with baseline (test for within-group comparison).

CISI-PD, Clinical Impression of Severity Index for Parkinson’s Disease; MDS-UPDRS, Movement Disorders Society Unified PD Rating Scale; NMSS, Non-Motor Symptoms Scale; UPDRS, Unified Parkinson’s Disease Rating Scale; DYSK, dyskinesia.

and COVID-19 ($P = 0.005$), whereas fatigue was attributed to COVID-19 alone ($P < 0.001$).

Discussion

To our knowledge, this is the first community-based case-control study describing the effects of symptomatic COVID-19 on PD motor and nonmotor symptoms. First, patients with PD who developed symptomatic COVID-19 were neither older age nor had longer disease duration than those who screened negative, but had nonsignificant 3.5-year younger age and 2.0-year shorter disease durations. The lack of case fatalities is consistent with the Italian case fatality rate of 3.5% at 60 to 69 years of age.¹⁵ Similarly, only 1 patient (8.3%) needed to be admitted to the hospital for severe COVID-19 illness, which is consistent with the frequency of hospitalization previously reported in the general population of the Lombardy region.²³ We expand previous report in advanced PD¹² and show

that mild to moderate COVID-19 may be contracted independently of age and PD duration and that patients with PD with mid-stage PD do not seem to have an overall worse outcome than the non-PD population.¹⁵ Concerning the primary objective of the study, we found a worsening of motor and nonmotor symptoms of PD during the study period in the COVID-19 group when compared with the matched controls.

Motor Symptoms

COVID-19 induced a significant worsening of motor performance, motor-related disability, and experiences of daily living. Worsening of levodopa-responsive motor symptoms and increased daily off time, caused either by the effects of acute systemic inflammatory response⁶⁻⁹ or by changes in pharmacokinetics, was so pronounced in one third of cases to prompt neurologists to increase dopaminergic therapy. We explored the relative contribution of suboptimal absorption of oral therapy by adjusting motor end points for diarrhea, which was

present in 50% of cases. According to multivariate analysis, concomitant diarrhea explained the increase in motor fluctuations, but could not entirely explain the worsening of motor disability and motor aspects of experiences of daily living.

Nonmotor Symptoms

COVID-19 significantly aggravated a number of nonmotor symptoms. Increased fatigue in our cohort was fully explained by COVID-19, confirming that it is a common COVID-19 symptom,²⁴ as described in PD following systemic inflammation.²⁵ Urinary urge/incontinence and nicturia were explained by the infection as well as increased motor fluctuations, which were partly a result of pharmacokinetic issues. COVID-19 was neither a major cause of cognitive dysfunction nor autonomic failure in our cohort of mid-stage PD. Although there was an effect of COVID-19 on attention, it was not severe enough to be detected by CISI-PD. We did not find changes in cardiovascular, gastrointestinal, or sexual function domains in the NMSS or differences in hypotension between the groups.

Strengths and Limitations

The main limitation of this study is the small cohort of COVID-19 patients, albeit statistical analysis could detect several significant changes. There are a number of strengths worth mentioning. First, our case-control study protocol excluded the detrimental effects that quarantine and lockdown restrictions might have played on a number of confounders that influence PD motor and nonmotor symptoms, such as reduced physical activity, enhanced stress, confusion, anxiety, and sleep disturbances.²⁶ Second, a community-based survey minimized selection bias related to the inclusion of hospitalized patients with severe illness or institutionalized patients with advanced PD and comorbidities who are more susceptible to a worst outcomes of neurological manifestations.^{27,28} Our cohort with mild to moderate illness is likely representative of the majority of patients with PD affected by COVID-19, considering that only a minority of cases required hospitalization.²⁹⁻³¹ Third, we excluded secondary and atypical parkinsonisms (including dementia with Lewy bodies), minimizing the risk of overestimating either fluctuating or drug-induced worsening of cognitive dysfunction, visual hallucinations, and autonomic failure. Finally, our comprehensive assessment performed by experienced neurologists in a single tertiary referral clinic ensured a homogeneous and standardized approach. Larger multicenter studies would have requested longer time for data collection, increasing patient/caregiver recall bias.

Conclusions

Patients with PD may experience substantial worsening of motor and nonmotor symptoms during mild to moderate COVID-19 illness, independent of age and disease duration. Clinicians should take pharmacokinetic changes into consideration before adjusting therapy regimens (eg, management of dehydration secondary to fever, diarrhea, anorexia with reduced water intake). Although we speculate that subacute clinical changes in PD associated with nonsevere COVID-19 illness are likely caused by systemic inflammatory response^{8,9} rather than a direct invasion of the central nervous system,^{27,28} further studies in larger PD populations are warranted to clarify the cause-effect relationship among clinical changes and the severity of COVID-19 illness, cytokine levels, and virus detection in the cerebrospinal fluid. ■

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