COVID-19 in Parkinson's Disease Patients Living in Lombardy, Italy

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ABSTRACT: Background: It is unknown whether patients with PD are at greater risk of COVID-19, what their risk factors are, and whether their clinical manifestations differ from the general population.
Objectives: The study aimed to address all these issues.
Methods: In a case-controlled survey, we interviewed 1,486 PD patients attending a single tertiary center in Lombardy, Italy and 1,207 family members (controls).
Results: One hundred five (7.1%) and 92 controls (7.6%) were identified as COVID-19 cases. COVID-19 patients were younger, more likely to suffer from chronic obstructive pulmonary disease, to be obese, and vitamin D nonsupplemented than unaffected patients. Six patients (5.7%) and 7 family members (7.6%) died from COVID-19. Patients were less likely to report shortness of breath and require hospitalization.
Conclusions: In an unselected large cohort of non-advanced PD patients, COVID-19 risk and mortality did not differ from the general population, but symptoms appeared to be milder. The possible protective role of vitamin D supplementation warrants future studies. © 2020 International Parkinson and Movement Disorder Society

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Severe acute respiratory syndrome coronavirus 2 (SARS Co-V2) emerged in the region of Wuhan in China around December last year and spread so rapidly that the World Health Organization declared coronavirus disease 2019 (COVID-19) a pandemic on 11 March 2020.[1] Specific pre-existing medical conditions and advanced age appear to be linked to more severe manifestations of the infection,[1,2] thus raising the question of whether Parkinson's disease (PD) poses an increased risk of morbidity and mortality in COVID-19 patients.[3]

The first reported case of COVID-19 in a 74-year-old PD patient complicated by encephalopathy has recently been described.[4] A series of 10 PD patients collected in Padua, Italy and London, United Kingdom reported a high mortality rate (40%), and worsening of anxiety and other nonmotor features,[5] in keeping with a recent survey among patients and caregivers.[6] We recently gathered clinical information on 117 community-dwelling PD patients with COVID-19 followed in 21 tertiary centres in Italy, Iran, Spain, and the United Kingdom.[7] We found an overall mortality of 19.7%, with a significant effect of concomitant dementia, hypertension, and PD duration.[7]

Many questions remain unanswered: (1) Are PD patients more at risk of being infected by SARS Co-V2 and developing COVID-19? (2) What are the risk factors for COVID-19 infection in PD patients? (3) How is the clinical expression of COVID-19 in PD patients? (4) What is the COVID-19 outcome in an unselected cohort of PD patients?

In order to answer these questions, we conducted a phone survey of all PD patients and family members included in the database of one of the largest tertiary centers for PD in Italy, located in Milan–Lombardy, the region with the highest incidence of COVID-19 in the country.[8,9]

Patients and Methods

We contacted (using all available phone numbers, up to three attempts on 3 different days) a total of 1,926 patients fulfilling the following inclusion criteria: (1) clinical diagnosis of PD[10]; (2) at least one evaluation at the Parkinson Institute (Pini-CTO, Milan, Italy) in 2019; and (3) living in Lombardy. Patients were asked about COVID-19-related symptoms during the previous 3 months, the execution of nasopharyngeal swabs, chest radiograph, or computed tomography, and hospitalization. Interviews were standardized using an electronic case report form and conducted in the presence of 1 family member for support and in the event of patient hospitalization or death at the moment

of the survey. In order to gather data from a control population with a similar environmental exposure, the survey also involved 1,207 family members willing to participate.

A positive nasopharyngeal swab was needed for a "confirmed" diagnosis of COVID-19, whereas a "probable" diagnosis was formulated using the following criteria: presence of persistent COVID-19-related symptoms (≥3 including fever or ≥5 without fever) or ≥1 symptom in the presence of suggestive chest radiological signs and/or living with a family member with a confirmed diagnosis of COVID-19. If needed, the regional register of health care data was also accessed to obtain laboratory and radiological findings as well as hospitalization data and confirm the date and cause of death.

Finally, relevant demographic and clinical data were extracted from the institutional electronic chart of the patient and confirmed during the interview.

Between-group comparisons (COVID-19 PD cases vs. unaffected PD patients and PD with COVID-19 vs. controls with COVID-19) were initially performed using Fisher's exact test for categorical variables and Student's *t* test or the Mann-Whitney U test (depending on data distribution) for continuous variables. Then, given the significant difference in age among these groups, dichotomous variables and outcomes were compared using age-adjusted logistic regression analysis (an independent model for each variable/outcome) to calculate odds ratio (OR) with 95% confidence interval (95% CI). All analyses were conducted using STATA statistical software (version 15.1; StataCorp LP, College Station, TX).

Results

Data on 1,486 patients were collected (response rate: 77.2%). Reasons of exclusion from the analysis were: patient unreachable (N = 302), refusal (N = 98), and patient died before the pandemic or during it for causes other than COVID-19 (N = 40). Among unreachable patients, 139, 129, and 54 had one, two, and three available phone numbers, respectively; in 15%, the number appeared to be wrong. No differences were detected when comparing responders versus nonresponders except for longer disease duration in the latter group (Supporting Information Table S1).

We identified 32 confirmed and 73 probable cases of COVID-19 among the PD patients (total, 105; 7.1%).

TABLE 1. Features of PD patients by COVID-19 status

		Confirmed/Probable COVID-19 Cases (N = 105)	Unaffected PD Patients (N = 1,381)	*P* Value*	Age-Adjusted OR [95% CI]**	*P* Value**
Feature	Male sex	55 (52.4%)	790 (57.2%)	0.36	—	—
	Age (years)	**70.5 ± 10.1**	**73.0 ± 9.5**	**0.017**	—	—
	Disease duration (years)	9.9 ± 6.4	9.5 ± 6.8	0.51	—	—
	H & Y stage	2.2 ± 0.8	2.2 ± 0.9	0.94	—	—
	Body mass index (kg/m^2)	25.6 ± 4.9	25.0 ± 4.1	0.24	—	—
	Current smoking	6 (5.7%)	64 (4.6%)	0.63	—	—
	Outings (n/week)	0.8 ± 1.9	0.8 ± 1.9	0.88	—	—
Comorbidities	**Obesity**	**19 (18.1%)**	**151 (10.9%)**	**0.037**	**1.72 [1.00–2.94]**	**0.048**
	Hypertension	44 (41.9%)	535 (38.7%)	0.53	1.29 [0.86–1.95]	0.22
	COPD	**6 (5.7%)**	**24 (1.7%)**	**0.016**	**3.82 [1.51–9.65]**	**0.005**
	Diabetes	8 (7.6%)	111 (8.0%)	1.00	1.03 [0.48–2.17]	0.95
	Cancer	1 (0.9%)	45 (3.3%)	0.25	0.31 [0.04–2.25]	0.24
Drugs/ supplements	L-dopa	100 (95.2%)	1,324 (95.9%)	0.80	1.19 [0.45–3.13]	0.72
	Dopamine agonists	50 (47.6%)	649 (47.0%)	0.92	1.05 [0.69–1.61]	0.82
	MAO-B inhibitors	23 (21.9%)	271 (19.6%)	0.61	1.09 [0.67–1.77]	0.72
	COMT inhibitors	6 (5.7%)	66 (4.8%)	0.64	1.19 [0.67–2.11]	0.56
	Amantadine	1 (1.0%)	28 (2.0%)	0.72	0.41 [0.05–3.08]	0.39
	ACE inhibitors	15 (14.3%)	173 (12.5%)	0.65	0.79 [0.42–1.48]	0.46
	ARBs	13 (12.4%)	125 (9.0%)	0.29	1.02 [0.53–1.97]	0.95
	Immunosuppressive agents	5 (4.8%)	42 (3.0%)	0.38	1.41 [0.49–4.03]	0.52
	NSAIDs	6 (5.7%)	70 (5.1%)	0.82	1.11 [0.47–2.63]	0.82
	Vitamin D	**13 (12.4%)**	**316 (22.9%)**	**0.010**	**0.56 [0.32–0.99]**	**0.048**

Values are mean ± SD or n (%), significant data are bold-typed. Between-group comparisons of continuous variables were initially performed using the unpaired Student's *t* test (normal distribution) or the Mann-Whitney U test (non-normal distribution), whereas categorical variables were analyzed by Fisher's exact test.
*Then, given the significant between-group age difference, age-adjusted ORs were calculated.
**to fully investigate differences in comorbidities and drugs/supplements (an independent model for each variable).
ACE, angiotensin-converting enzyme; ARBs, angiotensin-receptor blockers; COMT, catechol-O-methyltransferase; COPD, cchronic obstructive pulmonary disease; COVID-19, coronavirus disease 19; MAO-B, monoamine oxidase B; NSAIDs, nonsteroidal anti-inflammatory drugs.

TABLE 2. Clinical features of COVID-19 among affected PD and non-PD controls (family members)

		PD With COVID-19 (N = 105)	Controls With COVID-19 (N = 92)	P Value*	Age-Adjusted OR [95% CI]**	*P* Value**
Clinical features	Total reported symptoms	3.4 ± 1.8	3.5 ± 1.8	0.70	—	—
	Fever	74 (70.5%)	67 (72.8%)	0.75	0.85 [0.45–1.61]	0.61
	Cough	62 (59.0%)	55 (59.8%)	1.00	0.91 [0.50–1.63]	0.74
	Shortness of breath	17 (16.2%)	26 (28.3%)	0.06	**0.33 [0.15–0.70]**	**0.004**
	Nasal congestion	44 (41.9%)	35 (38.0%)	0.66	1.39 [0.76–2.52]	0.29
	Olfactory dysfunction	17 (16.2%)	17 (18.5%)	0.71	0.78 [0.36–1.67]	0.52
	Gustatory dysfunction	19 (18.1%)	16 (17.4%)	1.00	1.08 [0.51–2.30]	0.84
	Nausea or vomiting	15 (14.3%)	15 (16.3%)	0.70	1.05 [0.47–2.35]	0.91
	Diarrhea	28 (26.7%)	20 (21.7%)	0.74	1.58 [0.80–3.14]	0.19
	Myalgia or arthralgia	35 (33.3%)	30 (32.6%)	1.00	1.14 [0.62–2.11]	0.67
	Fatigue	40 (38.1%)	31 (33.7%)	0.55	1.31 [0.71–2.38]	0.39
	Conjunctivitis	10 (9.5%)	7 (7.6%)	0.80	1.18 [0.42–3.32]	0.75
Pattern of symptoms	Respiratory	50 (47.6%)	52 (56.5%)	0.25	0.64 [0.36–1.14]	0.13
	Gastrointestinal	13 (12.4%)	10 (10.9%)	0.83	1.42 [0.57–3.56]	0.45
	Systemic	22 (21.0%)	11 (12.0%)	0.12	2.05 [0.91–4.59]	0.08
	Unspecific/mild	18 (17.1%)	14 (15.2%)	0.85	1.18 [0.54–2.57]	0.68
	Asymptomatic	2 (1.9%)	5 (5.4%)	0.25	0.27 [0.05–1.50]	0.14
Outcome	Death	6 (5.7%)	7 (7.6%)	0.77	0.45 [0.13–1.53]	0.20
	Hospitalization	18 (17.1%)	25 (27.2%)	0.12	**0.41 [0.20–0.86]**	**0.018**

Values are mean ± SD or n (%), significant data are bold-typed. Between-group comparisons of clinical features, pattern of symptoms, and outcomes were performed using the unpaired Student's *t* test whereas categorical variables were analyzed by the Fisher's exact test.
*Given the significant between-group age difference (Supporting Information Table S2), age-adjusted ORs.
**were used to further explore these comparisons (an independent model for each variable/outcome).

Compared to unaffected PD patients, COVID-19 PD cases were younger, more likely to suffer from chronic obstructive pulmonary disease, to be obese, and vitamin D non-supplemented (Table 1). Fever, cough, and nasal congestion were the most frequent symptoms (Table 2). Eighteen patients (17.1%) were hospitalized and 6 died (5.7%).

Ninety-two family members were diagnosed with COVID-19 (7.6%; $P = 0.60$ vs. PD patients). Their demographic and clinical characteristics were similar to PD patients, with the exception of younger age and higher number of weekly outings (Table 2 and Supporting Information Table S2). When analyzing COVID-19 cases among PD patients and family members, the former were less likely to report shortness of breath (SOB) and require hospitalization after adjusting for age.

Discussion

This single-center case-controlled survey described the clinical features and predictors of COVID-19 infection and outcome in a relatively unselected and homogeneous large cohort of PD patients and controls (their family members). Our study sought to answer important questions.

Are PD Patients More at Risk of Being Infected by SARS Co-V2 and Developing COVID-19?

All interviewees live in Lombardy, the region where the first Italian patient was diagnosed with COVID-19 on 20 February 2020. Since then, the increasing number of cases recorded in Lombardy, and subsequently throughout the country, led Italy to be the third-most affected country worldwide.[9] More than 36% of Italian COVID cases are to this date (3 May) in Lombardy, where roughly 0.8% of the population has been diagnosed with COVID-19.[9] However, the accuracy of prevalence data is hampered by the existence of asymptomatic cases and the lack of population screening campaigns. In this survey, COVID-19 prevalence was similar in PD patients and study controls (7.1% vs. 7.6%).

What Are the Risk Factors of COVID-19 Infection in PD Patients?

Older age, longer disease duration, and use of advanced therapies in one study[5] and dementia, hypertension, and—again—disease duration in another study[7] have been found to predict poor COVID-19 outcome in PD patients. Our study expands these notions, focusing on the risk of getting infected. The most interesting result is the seemingly protective effect of vitamin D intake, as hypothesized by several researchers during the past weeks.[11-17] Vitamin D can reduce the risk of infections through several mechanisms, for example, by reducing concentrations of proinflammatory cytokines. Evidence supporting this role of vitamin D has been confirmed by two recent studies. One study found significant negative correlations ($r = -0.44$) between the average vitamin D levels of different European countries and the national prevalence of COVID-19 cases and associated mortality.[18] Another

age-stratified study in Swiss patients has found significantly lower vitamin D levels in SARS-CoV-2 PCR-positive versus -negative cases (median of 11.1 vs. 24.6 ng/mL, respectively; $P = 0.004$).[19]

When comparing COVID-19 affected with non-affected PD patients, the former were younger, more frequently obese, and suffering from chronic obstructive pulmonary disease. Whereas obesity and comorbid respiratory disorders are well-known COVID-19 risk factors,[20] the younger age of affected patients might rely on the more aggressive preventive measures adopted for older patients. No role for hypertension was detected, in contrast with reports in non-PD[20] and other PD cohorts.[7] Hypertension in PD is rare and related to the occurrence of dysautonomia. Likewise, smoking is not common in PD, thus explaining why it did not increase COVID-19 risks in spite of what has been observed in the general population.[20]

In keeping with another PD series,[7] we did not find any significant effect of anti-PD drugs in spite of the hypothesized protective role of levodopa,[21] entacapone,[22] and amantadine.[23,24] The same was true for angiotensin-receptor blockers and angiotensin-converting-enzyme inhibitors.[25] Finally, although the role of nonsteroidal anti-inflammatory drugs is still unclear,[26] we did not find any significant effect.

How Is the Clinical Expression of COVID-19 in PD Patients?

No study has, so far, evaluated the clinical manifestation of COVID-19 in PD patients. Worsening of PD-related symptoms has been hypothesized,[27,28] as later confirmed by a small series.[5] In our study, we found that the clinical expression of COVID-19 largely overlaps with that of non-PD patients with few exceptions. The reason for the reduced occurrence of SOB is only speculative at the moment and probably related to the poorly understood pathophysiology of respiratory function in PD.[29] Uncontrolled studies have focused on the occurrence of dyspnea, reaching the overall conclusion that it is a common PD symptom, although patient self-reporting seems reduced.[30,31] Alternatively, given that SOB has been associated with anxiety or complications of L-dopa therapy,[32] it is conceivable that surveyed PD patients found it difficult to attribute their respiratory symptoms to COVID-19 alone. In this survey, we also found that hospitalization was required in PD patients less often, possibly because of the aforementioned reduced occurrence of SOB and the tendency for frail patients to be treated at home.[33]

What Is the COVID-19 Outcome in an Unselected Cohort of PD Patients?

COVID-19 mortality in PD patients is still far from being elucidated. So far, two studies have reported figures of 19.7%[7] and 40%.[5] Although PD patients might be at risk in light of their frailty and advanced age, we believe that the available data are misled by the ascertainment methods. Our survey found a much lower figure (5.7%) that did not differ importantly from the rate in the non-PD control population. Italian data suggest an overall mortality of 9.5% for all patients >50 and of 12.8% for all patients aged ≥70 years.[2] Our mortality rate is probably underrepresented for the reasons detailed below.

Study Limitations and Conclusions

Besides the well-known limitation of a telephone survey, our study has two other major limitations: (1) We directed our attention toward community-dwelling PD patients because we could not reach patients living in nursing homes or other long-term care facilities, where outbreaks with high mortality rates have been reported.[34] (2) Some patients could not be reached for unknown reasons, thus raising the possibility of patient death attributed to COVID-19. Furthermore, COVID-19 diagnosis could not be confirmed in many cases, which is in line with the challenge of population screening during this unprecedented crisis. Other limitations include the younger age of non-PD COVID-19 cases, which we mitigated statistically and the small size for some comparisons.

In conclusion, this is the first case-controlled study on a relatively unselected and homogeneous large cohort of PD patients. Overall, we confirmed that COVID-19 risk, morbidity, and mortality in patients with mild-to-moderate PD do not differ from the general population. Interestingly, we found a possible protective role of vitamin D intake, which should be confirmed by appropriate randomized controlled trials.[35]

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.