ORIGINAL COMMUNICATION

Prevalence and impact of COVID-19 in Parkinson's disease: evidence from a multi-center survey in Tuscany region

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Abstract

Background If Parkinson's Disease (PD) may represent a risk factor for Coronavirus disease 2019 (COVID-19) is debated and there are few data on the direct and indirect effects of this pandemic in PD patients.

Objective In the current study we evaluated the prevalence, mortality and case-fatality of COVID-19 in a PD cohort, also exploring possible risk factors. We also aimed to investigate the effect of lockdown on motor/non-motor symptoms in PD patients as well as their acceptability/accessibility to telemedicine.

Method A case-controlled survey about COVID-19 and other clinical features in PD patients living in Tuscany was conducted. In non-COVID-19 PD patients motor/non-motor symptoms subjective worsening during the lockdown as well as feasibility of telemedicine were explored.

Results Out of 740 PD patients interviewed, 7 (0.9%) were affected by COVID-19, with 0.13% mortality and 14% case-fatality. COVID-19 PD patients presented a higher presence of hypertension ($p < 0.001$) and diabetes ($p = 0.049$) compared to non-COVID-19. In non-COVID-19 PD population ($n = 733$) about 70% did not experience a subjective worsening of motor symptoms or mood, anxiety or insomnia. In our population 75.2% of patients was favorable to use technology to perform scheduled visits, however facilities for telemedicine were available only for 51.2% of cases.

Conclusion A higher prevalence of COVID-19 respect to prevalence in Tuscany and Italy was found in the PD population. Hypertension and diabetes, as for general population, were identified as risk factors for COVID-19 in PD. PD patients did not experience a subjective worsening of symptoms during lockdown period and they were also favorable to telemedicine, albeit we reported a reduced availability to perform it.

Keywords COVID-19 · Parkinson's disease · Motor symptoms · Non-motor symptoms · Telemedicine

Introduction

In December 2019, a pneumonia-like illness caused by a novel Coronavirus, that has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in Wuhan-China. SARS-CoV-2 posed immediately new public health challenges to the world because Coronavirus Disease (COVID-19) rapidly spread to most countries, with more than 5,000,000 cases and more than 340.000 deaths at current time (25 May 2020) [1]

On the basis of "alarming levels of spread and severity", the World Health Organization (WHO) first declared COVID-19 as a global emergency and then characterized the COVID-19 situation as pandemic. Such pandemic is currently in its full swing in many countries, and Italy is experiencing one of the largest and most serious clusters of COVID-19 in the world, which emerged in the Lombardy region. As of early May, Italy accounts for more than 210,000 confirmed cases and more than 30,000 attributed

deaths [2]. In the same period, 10,000 cases and 880 death have been confirmed in Tuscany region [3].

Although most patients are thought to have a favorable prognosis, early identification of risk factors for severe infection is urgently needed. Indeed approximately 20% of patients develop severe COVID-19 requiring hospitalization, with some patients rapidly developing acute respiratory distress syndrome (ARDS) and other serious complications [4]. Current data suggest an increased chance of in-hospital death associated with older age (i.e., above 60), male sex, and contemporary comorbidities [5]. Comorbidities were present in nearly half of patients, with hypertension being the most common, followed by diabetes and coronary heart disease [5]. In Italy, the median age of cases was 62 years, whereas the median age of patients who died from COVID-19 was 81 years, most of which had underlying diseases, such as cardiovascular disease, diabetes, hypertension and chronic obstructive pulmonary disease [2, 6]. Interestingly, men with an age between 60 and 80 showed a higher risk of infection compared to women, but prevalence resulted to be higher for women than men in people under 60 and above 90 years [7].

Increasing age is also considered an unequivocal risk factor for Parkinson's Disease (PD) [8]. It is however still unclear whether neurodegenerative diseases, including PD, represent risk factors for COVID-19. In this framework, elderly people with advanced PD may represent a particularly vulnerable population, taking into account that the restricted pulmonary capacity due to axial akinesia can either represent a predisposing factor and lead to a major severity of pneumonia. Moreover, the emotional impact of the emergency, the social isolation and the prolonged immobility imposed by lockdown, are all factors that may indirectly exacerbate both motor and psychic symptoms of PD [9, 10].

There is currently insufficient evidence showing that PD by itself increases the risk of COVID-19, and contradictory results have been reported on small samples of PD COVID-19 patients: a first study on 10 PD patients with COVID-19 suggested that those of older age with longer disease duration were particularly susceptible to COVID-19 with a substantially high mortality rate [11]. Conversely, a recently published community-based case–control study found that mild-to-moderate COVID-19 was contracted independently of age and disease duration in PD patients [12]. They also found in mid-stage PD a similar outcome than non PD population [12]. In addition, in a study conducted in a larger sample of PD patients, younger age, obesity and chronic obstructive pulmonary disease were found to be associated to COVID-19 [13].

There is also an increasing interest about the effect of COVID-19 on motor and non-motor symptoms of PD, with a reported worsening of both these aspects in PD patients affected by COVID-19 compared to matched control subjects over the study period [12].

COVID-19 pandemic in PD patients could also have had an indirect impact on their life considering that lockdown cancelled/postponed outpatient visits and modified their access to rehabilitation programs. However, telemedicine has assumed a role of considerable importance in this period allowing a remote management of treatment-related or device-related problems [9].

The aim of our study was to evaluate the prevalence, mortality and case-fatality of COVID-19 in a large PD cohort in Tuscany and to explore the presence of risk factors for COVID-19 in PD patients. We also investigated the effects of lockdown on motor and non motor symptoms and patients acceptability/accessibility to telemedicine in a non COVID-19 PD population.

Methods

In the current study patients living in Tuscany, with PD diagnosis according to Movement Disorder Society Clinical Diagnostic Criteria for PD [14], non demented (MMSE > 23/30 at the last visit), who had performed at least one outpatient visit from January 1th to December 31th 2019 were enrolled. Consecutive patients were telephonically interviewed from the April 10th to May 4th of 2020 by a neurologist experienced in movement disorders. Investigational questions, answered by the patient or a family member when the patient was unable to answer (e.g. hospitalization) and centered on the period during the lockdown, concerned: their COVID-19 positivity, comorbidities, anti-parkinsonian therapy, the presence of flu symptoms, investigations done for flu symptoms problems, new appearance of hyposmia or ageusia and the presence of family members with COVID. In the studied population, the prevalence of COVID, mortality and case-fatality was estimated. COVID-19 and non COVID-19 PD patients matched for age and disease duration were compared regards clinical features mentioned above.

In non COVID-19 patients (patient with negative laboratory findings for COVID-19 or patients who did not perform laboratory testing according to World Health Organization criteria on March 20th indication [15]), possible worsening of motor symptoms, mood, anxiety and insomnia considering the period after the start of the lockdown were investigated. Depression Anxiety Stress Scale-21 item (DASS-21) [16], when possible, was performed, and z-score mean values were calculated according to means and standard deviation reported in literature [16]. In this non COVID-19 population, patients' acceptability to perform consultations by telemedicine was also explored. In particular we investigated the availability of devices as personal computer, mobile, with or without video connection and internet

access. Moreover patients' accessibility to the doctors and their wish to engage their General Practitioner(GP). All the questions have been formulated to obtain a yes/no answer.

Signed informed consent was obtained prior to remote assessment and collection of clinical data.

Statistical analysis

Categorical data were described by frequency, continuous data by mean and standard deviation.

COVID-19 variable was obtained stratifying COVID negative patients for age, disease duration and sex. Matched non COVID-19 patients were randomly selected. COVID-19 and non COVID-19 patients were compared using a 1:2 ratio.

To analyze quantitative and qualitative variables, t-test for independent samples (two tailed) and chi square test were performed, respectively. Significance was fixed at 0.05. All analyzes were carried out with SPSS v.26 technology.

Results

Out of a total of 740 PD patients who accepted to be interviewed, 7 (0.9%, 4 males; 3 females) were affected by COVID-19. About COVID-19 patients: three were not hospitalized, 4 were hospitalized in non intensive care unit and among them 1 patient died. According to available data provided by interviewed caregivers mortality was 0.13% and case-fatality was 14%. COVID-19 patients had a mean age of 75.71 ± 8.90 years, and a disease duration of 9.29 ± 3.59 years. Considering that all COVID-19 were older than 60 years, stratifying non COVID-19 patients for age ($n = 649$) the prevalence of COVID-19 was 1.1% and mortality of 0.15%. Demographical and clinical features of COVID-19 and non COVID-19 matched for age and disease duration were detailed in Table 1.

When comparing COVID-19 and non COVID-19 patients, COVID-19 patients presented a significantly higher presence of some comorbidities as hypertension ($p < 0.001$) and diabetes ($p = 0.049$), while no significant differences were found for the other comorbidities (see Table 2 for details). No differences were found for the use of anti-parkinsonian drugs or appearance of hyposmia or ageusia (see Table 1). We found a higher prevalence in COVID-19 group of flu symptoms ($p = 0.002$), investigations done for flu symptoms ($p = 0.001$) and the presence of a family member with COVID-19 ($p = 0.008$) (see Table 1 for details).

In non-COVID-19, DASS-21 was performed in 120 patients. We found a mean DASS-21score of 17.0 ± 11.03, considering normative value a z-score was calculated ($z = 0.57$).

Percentage of positive or negative answers about motor and non motor symptoms and the availability to perform telemedicine are shown in Table 2.

Discussion

In the current study we reported the prevalence of COVID-19, mortality and case-fatality in a large cohort of PD patients living in Tuscany. The sample of 740 patients corresponds approximately to the 7% of the entire PD population in Tuscany region, and to 10.6% of those aged 65–85, according to the last available estimate of PD prevalence based on administrative data (see Table 2 in Baldacci et al. 2015, [17]). The prevalence of COVID-19 in our PD population was 0.9%, that is higher than the national and regional prevalence. Epidemiological data indicate that the prevalence of COVID-19 in the Italy's general population between April 10th and May 4th is increased from 0.24 to 0.35%, and in Tuscany from 0.18 to 0.25% [2, 3]. Moreover, the prevalence of COVID-19 in Italy at the end of April in subjects older than 60 years was about 0.61% [2], then the prevalence of COVID-19 in our population is higher (1.1%), also taking into account age stratification. In our cohort we found only one death, with a mortality of 0.13% that is again higher than mortality in Italy and in Tuscany at the early May (0.05% and 0.02%, respectively) [2, 3], but in line with national data if considering age stratification (0.13% mortality in patients older than 60 years). Case fatality of our samples was 14%, higher than regional data in early May (9.2%), but in line with national data (14%) [2, 3].

Whether PD represents per se a risk factor for COVID-19 is unclear. The main entry pathway of the SARS-CoV-2 into human host seems to be mediated by a cellular receptor angiotensin-converting enzyme 2 (ACE2), which is highly expressed in human airway epithelia, but also in dopaminergic neurons [18]. Moreover there is increasing attention about the role of the brain angiotensin system in neurodegeneration in PD due to a pro-inflammatory pro-oxidative effects [19]. It is also interesting that the gene exhibiting the most statistically significant co-expression with ACE2 is Dopa Decarboxylase(DDC), and that ACE2 and DDC co-regulate in non-neuronal cell types [20]. In addition, a possible role of viral infection in neurodegeneration has been hypothesized years ago when antibodies against different forms of coronaviruses were detected in the cerebrospinal fluid of patients with PD compared to other neurological diseases [21].

However, considering that PD patients are usually older than 60 years, and that increased age is associated with death in patients with COVID-19 [5], age and age-related comorbidity must be considered as confounding risk factors in the PD population [22]. Our COVID-19 PD cohort has a

Table 1 Demographical and clinical features of COVID-19 and non COVID-19 patients matched for age and disease duration, expressed in means and standard deviation

	Non-Covid-19 ($n=14$)	COVID-19 ($n=7$)	p value
Sex	6F/8 M	3F/4 M	
Age (y)	75.05 ± 8.18	75.71 ± 8.90	0.871
Disease duration (y)	8.93 ± 3.05	9.29 ± 3.59	0.814
Treatment			
L-Dopa			0.469
No	1	0	
Yes	13	7	
Dopamine agonist			0.061
No	4	5	
Yes	10	2	
MAO-B inhibitors			0.999
No	8	4	
Yes	6	3	
Amantadine			0.116
No	10	7	
Yes	4	0	
Anticholinergics			0.147
No	14	6	
Yes	0	1	
Duodopa infusion/DBS			–
No	14	7	
Yes	–	–	
Comorbidities			
Hypertension			**< 0.001**
No	14	2	
Yes	0	5	
Diabetes			**0.049**
No	13	4	
Yes	1	3	
Cardiopathy			0.432
No	12	5	
Yes	2	2	
Malignancies			0.599
No	13	6	
Yes	1	1	
Renal or hepatic dysfunction			0.293
No	12	7	
Yes	2	0	
Previous chronic lung disease			–
No	14	7	
Yes	–	–	
Presence of Flu symptoms during pandemic period			**0.002**
No	13	2	
Yes	1	5	
Investigations done for flu symptoms			**0.001**
No	12	1	
Yes	2	6	
New hyposmia/ageusia			–
No	14	7	
Yes	–	–	
Presence of family members COVID-19			**0.008**

Table 1 (continued)	Non-Covid-19 ($n=14$)	COVID-19 ($n=7$)	p value
No	14	4	
Yes	0	3	

median age of 75 years, but we found a higher prevalence of COVID-19 compared to Italian population also when patients were stratified for age. Although conflicting data were initially available about the age as a risk factor for COVID-19 in PD [11, 12], younger age was found to be associated to COVID-19 in PD patients in study considering a larger sample of PD patients [13].

In our population, comparing COVID-19 and non-COVID-19 PD patients matched for age and disease duration, we found that hypertension and diabetes may be risk factors for COVID-19. Hypertension is the most common comorbidity in COVID-19 patients followed by diabetes and coronary heart disease [5]. The role of hypertension as risk factor in PD for COVID-19 is debated. Comparing COVID-19 affected with non-affected PD patients no role of hypertension was found in a single-centre case-controlled study, while the same authors reported a different result in a multicenter study [13]. In a population study considering subjects older than 55 years, PD patients have more physical and non physical comorbidities than non PD, however hypertension was significantly less prevalent than control group [22]. Then, the higher prevalence of COVID-19 in our PD population do not seems to be associated with one of the main risk factor for COVID-19. Considering the relation between diabetes and PD, conflicting data are available, indeed several studies suggest that diabetes increases the risk of developing PD, but other supported an inverse association or the lack of association [23]. So it is not clear if there is a possible relation between prevalence of COVID-19 in PD and diabetes.

None of COVID-19 PD patients were treated with Amantadine (see Table 1), an antiviral drug with anti-dyskinetic potential, however the limited sample size does not allows any suggestion on potential protective effect on viral infection.

In our non-COVID-19 cohort we also explored the effects of lockdown on motor and non motor symptoms and we found that the majority (70.0%) of patients did not experience a subjective worsening in parkinsonian symptoms, neither of mood (74.9%), anxiety (74.6%) or insomnia (77.4%). This result is in line with a published paper in which 100 PD patients were telephonically contacted for routine visit and 89 of them did not notice a worsening of motor symptoms following the onset of COVID-19 pandemic [24]. The risk of motor and non-motor symptoms worsening in PD patients during the lockdown has been hypotesized [10]. Different reasons of the negative effect of lockdown on PD have been suggested as increasing levels of stress could worsen motor symptoms, induce insomnia and mood changes, discontinuation of physiotherapy and/or reduction in physical activity and reduction of family and social contacts. However, a worsening of motor symptoms during adverse period is not obvious. An improvement of motor condition related to paradoxical kinesia that lasted up to months after the earthquake of L'Aquila in Italy in PD patients has been reported [25]. Intriguingly, in PD patients the disappearance/reduction of freezing was one of the major effects of paradoxical kinesia. Principal mechanisms proposed for paradoxical kinesia are: noradrenergic augmentation, compensatory activation of cerebellar circuitry, and activation of basal ganglia reserves [26]. In addition, the detrimental effect of stress could be contrasted by "resilience", i.e. the ability to maintain or quickly recover mental health during and after times of adversity [10]. Among the general population, older adults present a high resilience despite socioeconomic backgrounds, personal experiences, and declining health and resilience is known to correlate with outcomes, even in lesional networks brain models [27], including successful aging and lower depression [28]. In PD, resilience has been related to less disability and better scores in scales measuring disability, mental and physical health-related [29].

We cannot exclude that the stability of motor and non motor symptoms could be related to the availability of an adequate medical care using telemedicine even during the lockdown. Since their diagnosis, PD patients periodically undergo a physical evaluation and treatment adjustments to improve their motor and non motor condition. During the lockdown period many visits have been cancelled or postponed without an alternative certain date. Telemedicine is actually feasible for PD considering that most of the physical examination, except rigidity and postural instability, can be visualized [30]. In addition telemedicine could reduce travel time, distance and waiting time in patients with PD living in unserved areas [30]. Remote physical assessment of PD patients who undergo rehabilitation could be performed as evaluation and treatment of speech disorders [30].

The Telemedicine Study Group of the International Parkinson and Movement Disorders Society has recently updated a guide for how to implement telemedicine for a movement disorders. In the current study the term telemedicine was used to indicate the possibility to perform a remote evaluation of the patients using technologies as personal computer/mobile with or without video, however this term includes a wide range of clinical and diagnostic

Table 2 Data resulting from telephonically interview patients, expressed in yes/no frequencies and percentage

	Number of patients (n = 733)	Percentage
Have you noticed any worsening of motor symptoms following the onset of the COVID-19 pandemic?		
No	513	70%
Yes	217	29.6%
Missing data	3	0.4%
Have you noticed any worsening of mood following the onset of the COVID-19 pandemic?		
No	549	74.9%
Yes	181	24.7%
Missing data	3	0.4%
Have you noticed any worsening of anxiety following the onset of the COVID-19 pandemic?		
No	547	74.6%
Yes	183	25.0%
Missing data	3	0.4%
Have you noticed any new/worsening of insomnia following the onset of the COVID-19 pandemic?		
No	567	77.4%
Yes	163	22.2%
Missing data	3	0.4%
Is the patient the interlocutor during telephone conversations or mail correspondence with the doctor?		
No	332	45.3%
Yes	388	52.9%
Missing data	13	1.8
Is a family member the interlocutor during telephone conversations or mail correspondence with the doctor?		
No	405	55.3%
Yes	315	43.0%
Missing data	13	13
Does the patient have at home devices (personal computer, webcam, smart-phone) to achieve Telemedicine?		
No	343	46.8%
Yes	375	51.2%
Missing data	15	2%
Is the patient interested in realizing routine visits through Telemedicine?		
No	181	24.7%
Yes	551	75.2%
Missing data	1	0.1%
Does patient have contacts of his/her doctor?		
No	30	4.1%
Yes	650	88.7%
Missing data	53	7.2%
Does patient prefer telephone, mail or both, to contact patient's doctor?		
Telephone	510	69.6%
Mail	100	13.6%
Both	69	9.4%
NA	54	7.4%
Does patient consider more useful to engage General Practitioner trough the Telemedicine in patient management?		
No	384	52.4%
Yes	294	40.2%
Missing data	54	7.4%

possibility. Indeed telemedicine encompasses also the sharing of resources and skills of high specialty, remote interpretation of imaging or pathological data, transmission of information using wearable sensors and remotely access to therapeutic devices [30]. In our population only the 51.2% of PD patients have at home devices to perform telemedicine, and in the 75.2% they are prone to do it. In our PD population only in the 52.9% of cases the interlocutor with the specialist is the patient himself, because often the doctor is contacted by a member of the family. Considering the age of PD patients the availability of a personal computer, a webcam and the ability to use them are not given for granted. In addition, during the lockdown period in many cases sons and grandsons who do not live with patients could not help them to perform telemedicine. Nevertheless, when devices are present and operating, telemedicine in older patients presents some limitations as cognitive and visual impairment, communication barriers and hearing problems [31]. In this scenario the Neurologist could rely on the support of the GP to better manage the patients at home. Surprisingly only 40% of our PD patients thought it would be useful to involve their GP. This result is probably related to a recent modification of the perception of the role of the GP in patients medical care and to the importance of its relationship with the specialist.

Our study presents some limitations as the small number of COVID-19 patients, although significant results were found in statistical analysis. Moreover, about the effects of the lockdown on motor and non motor symptoms of PD, longer follow up periods are probably needed to confirm our data.

Conclusion

A higher prevalence of COVID-19 in the PD population respect to prevalence of COVID-19 in Italy, also when stratified for age, was found. Prevalence of COVID-19 in our PD population was also higher than prevalence of COVID-19 in Tuscany. It is not clear if PD itself could represent a risk factor for COVID-19. Our COVID-19 PD patients presented the same risk factors for COVID-19 that are found in general population, as hypertension and diabetes. We also explored the effect of lockdown on motor and non motor symptoms in PD and we did not find a subjective worsening of symptoms in this period. We also show that PD patients in Tuscany are strongly interested in Telemedicine, although it seems appropriate to widen the availability of technical facilities.

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Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics approval This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent to participate A written informed consent was obtained from all subjects before the inclusion in the study.

Consent for publication All authors have approved the version to be published.

Availability of data and material The corresponding author has full access to all data and material and can provide availability if needed.

Code availability SPSS 26.0.

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