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Anxiety, depression and worries in advanced Parkinson Disease during COVID-19 pandemic

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ABSTRACT

Background: The psychological impact of the COVID-19 outbreak and lockdown on frail populations with advanced Parkinson disease (APD) and their caregivers may have peculiar features and require particular attention.

Methods: We enrolled here 100 APD patients and 60 caregivers. Seventy-four patients were treated with device-aided therapies (DAT) and 26 with standard medical treatment (SMT). Through a telephonic interview, subjects underwent the Hospital Anxiety and Depression Scale (HADS-A and HADS-D) to quantify depression and anxiety, and an ad-hoc questionnaire to explore thoughts and emotions related to the pandemic.

Results: Depression was observed in 35% of APD patients and anxiety in 39%, with a significant reduction of the latter after the lockdown ($p= 0.023$). We found a significant correlation between the type of therapy and the HADS-A score ($p= 0.004$). Patients' main worries were: a possible higher risk of COVID-19 infection (25%), interruption of non-pharmacological interventions (35%), interruption of outpatient clinics (38%), PD complications related to COVID-19 (47%). Patients treated with DAT showed specific worries related to device issues and risk for caregivers' infection. The 40% of caregivers showed anxiety while the 21.7% of them showed depression.

Limitations: The lack of an assessment of anxiety and depression before the pandemic represents the main limitation of the study.

Conclusion: Our study reveals a higher prevalence of anxiety and the presence of peculiar worries and needs in APD patients during the pandemic alongside behavioural abnormalities of their caregivers. These findings are important for neurologists and healthcare services to foster strategies for the management of psychological distress in both patients and caregivers.

KEYWORDS

Parkinson disease; COVID-19; Anxiety; Worries; Depression

1. INTRODUCTION

On 11th March 2020, the World Health Organization declared COVID-19 a global pandemic (World Health Organization, 2020). To prevent contagion, many countries adopted extraordinary measures such as a lockdown of social and working activities, with significant psychological effects on the population (Brooks et al., 2020). Particular attention should be paid to the impact of COVID-19 pandemic on more vulnerable individuals who suffer from chronic diseases, such as people with Parkinson's disease (PD). Due to their pathological condition, PD patients are indeed at higher risk for developing neuropsychiatric symptoms (Weintraub et al., 2019).

During pandemic, an increase of psychological distress, depression, and anxiety have been observed in PD patients (Oppo et al., 2020; Salari et al., 2020; Shalash et al., 2020), which are at least partially related to individual perception of higher risk for a worse infection outcome (Artusi et al., 2020) and reduced access to healthcare services (Schirinzi et al., 2020). Importantly, higher distress was observed also in caregivers of patients with PD (Oppo et al., 2020). In such a complex picture, a more specific characterization of the psychological impact of COVID-19 on patients with PD and their family members is needed, with a special focus on the interaction with the heterogeneous motor and nonmotor symptoms that occur in PD at different clinical stages. Advanced PD (APD) is characterized by an increased frailty related to symptoms' severity and motor complications that require frequent therapeutic adjustments (Antonini et al., 2018). Moreover, APD patients may be treated by device-aided therapies (DAT), which require regular follow-up visits in highly specialized clinical settings.

Here, we investigated the psychological impact of the COVID-19 outbreak on APD patients and their caregivers by assessing distress, worries, depressive, and anxious symptoms; in addition, we evaluated potential differences between patients treated with DAT compared to those on standard medical treatment (SMT). We hypothesized an increasing impact of COVID-19 outbreak on PD patients and their caregivers according to disease severity and complexity of treatment.

2. METHODS

2.1 Study population

Using the electronic database of the Movement Disorder Center of the University Hospital of Turin (Italy) we randomly-selected a group of non-demented PD patients treated with DAT over the previous 5 years, a group of non-demented APD patients treated with SMT, and a group of caregivers who were balanced for the level of patients' disease severity. APD was defined as persistence of motor fluctuations and/or troublesome dyskinesia limiting the activities of daily living in spite of repeated adjustments of medication (Antonini et al., 2018).

Patients and caregivers enrolled in the current study were evaluated by phone interview from April 2020 to May 2020 (T0), which was the lockdown interval decided by the Italian Government.

Patients were re-evaluated after lockdown conclusion from June 2020 to August 2020 (T1). The Local Ethical Committee approved the study protocol, and each participant gave verbal informed consent before entering the study.

2.2 Data collection

We administered all participants with the Hospital Anxiety and Depression Scale (HADS) at T0 and T1 to obtain a validated and formal quantification of their depressive and anxious symptoms (Zigmond and Snaith, 1983) considering values ≥ 8 as pathological cut-off. We also administered a questionnaire specifically developed to investigate thoughts, fears, and emotional states related to COVID19 outbreak and lockdown (Supplementary Material 1). The patients' cognitive status was assessed at T0 using the Mini Mental State Examination (MMSE) (Folstein et al., 1975).

2.3 Statistical analysis

Descriptive statistics was used for continuous variables and frequency distribution for categorical data. Spearman Correlation Tests were performed to analyze correlations between HADS scores with age, disease duration, MMSE score, presence of caregivers, type of therapy, and QUEST-1-PD

mean score, calculated by answers related to agreement or disagreement (10 questions; range score 1-5). Comparisons between patients and caregivers for sex, age, education, and HADS scores were analyzed by Mann-Whitney U Test and Chi Square Test. Differences in the HADS scores and QUEST-1-PD at T0 between the three groups of patients were analyzed by the non-parametric Kruskal-Wallis Test and the post hoc analysis for multiple comparisons. Wilcoxon test was used to compare patients' HADS scores between T0 and T1. All p-values reported are two-tailed and a $p < 0.05$ was considered statistically significant. Data were analyzed using SPSS 26 (Chicago, IL).

3. RESULTS

We enrolled 100 APD patients and 60 caregivers; 54% of patients were treated with DBS, while 20% of them were on LCIG and 26% were on SMT; patients were from 14 Italian regions (Supplementary Material 2). The 11% of patients spent the lockdown period in isolation, while the 89% of them were overseen by at least one caregiver. Demographic and clinical characteristics of patients and caregivers are summarized in Table 1 and 2.

3.1 Anxiety and depression assessment

At T0, HADS scores revealed that 39% of patients showed anxiety and 35% depression. At T1, the percentage was reduced for the anxiety (30.6%; $p = 0.023$) but not for depression (34.1%; $p = 0.807$). The QUEST-1-PD mean score showed a significant correlation with anxiety ($p = 0.001$) and a trend toward significance with depression ($p = 0.077$) at T0. The type of treatment was significantly correlated to the HADS-A score ($p = 0.004$), with LCIG and SMT patients showing the highest prevalence of anxiety.

At T0, we found no correlation between both, anxiety and depression, and age (HADS-A score: $p = 0.158$; HADS-D score: $p = 0.193$), PD duration (HADS-A score: $p = 0.987$; HADS-D score: $p = 0.559$), number of caregivers (HADS-A score: $p = 0.256$; HADS-D score: $p = 0.493$), and MMSE score (HADS-A score: $p = 0.821$; HADS-D score: $p = 0.057$).

The 40% of caregivers showed anxiety and the 21.7% depression (T0). A significant difference between patients and caregivers was found for HADS-D score ($p= 0.001$).

3.2 Specific worries and distress related to COVID-19 and lockdown

The 25% of patients were feared for a possible higher risk of infection, the 47% expressed worries about a possible PD symptom worsening related to the COVID-19 disease, the 20% about drug supplies, the 38% about the limitation of hospital access, and the 24% about the difficulty to consult with physicians or carers (Supplementary Material 3). Moreover, the 35% of patients were worried about the interruption of non-pharmacological treatments, such as physiotherapy, psychological support or cognitive stimulation, and the 48% about the possible worsening of symptoms consequent to the limitation of the outdoor physical activity. The 39% of patients expressed a positive opinion about telemedicine, as well as webinars and toll-free numbers (Supplementary Material 3).

3.3 Impact of different therapies

Patients treated with SMT, LCIG and DBS showed slight, albeit significant, differences for demographic and clinical features (Table 1).

At T0, the anxiety score was significantly higher in SMT and LCIG patients (HADS-A score: DBS vs LCIG $p= 0.028$; DBS vs SMT: $p= 0.050$). At T1, the anxiety score was significantly higher in LCIG patients ($p= 0.002$) and maintained a trend toward the significance in SMT patients ($p= 0.065$). The three groups of patients did not differ for the presence of a caregiver during the COVID-19 outbreak and for the mean QUEST-1-PD score.

DBS patients referred specific worries about possible device-related issues: a percentage of 20.4% ($n= 11$) of patients were worried about the difficulty to consult the neurologist for a modification of the stimulation parameters, a percentage of 24.1% ($n= 13$) about the stimulator charge and the

possible difficulty for a replacement, a percentage of 40.7% (n= 22) about the interruption of regular follow-up visits. In addition, a group of 35.2% (n= 19) of patients were worried for a COVID-19 disease of the caregiver.

LCIG patients reported worries about the infection of the stoma (35%, n= 7) or a probe block or dislocation (30%, n= 6), while a percentage of 40% (n= 8) about the possible block of the intestinal infusion of levodopa or the COVID-19 disease of the caregiver (30%, n=6).

4. DISCUSSION

We evaluated the psychological impact of the COVID-19 pandemic on APD patients and their caregivers, analyzing specific worries in the whole sample and referring to different treatments. Anxiety and depression occurred in more than 30% of patients during the lockdown, with a reduction of the anxiety in the following months, confirming previous data on the negative effect of COVID-19 outbreak in PD patients (Oppo et al., 2020; Salari et al., 2020; Shalash et al., 2020), even in advanced stages.

Our study highlighted a differential psychological impact in relation to the treatment of APD patients. Anxiety correlated with specific distress/worries, investigated by an ad-hoc questionnaire, in particular: a possible higher risk to develop COVID-19 with a worse outcome, a difficulty to have hospital access, and the interruption of non-pharmacological treatments. Patients treated with DAT showed also specific worries related to the device and the possible COVID-19 disease of the caregiver. In addition, we reported significant anxiety and depression in a relevant group of caregivers (40% and 21.7%, respectively).

Probably the absence of definitive data about PD and risk of COVID-19 disease (Artusi et al., 2020) and the poor information increased feelings of doubts and uncertainty, rising the levels of anxiety; indeed, the need of a correct information during the outbreak has been claimed by a recent study (Schirinzi et al., 2020). Worries and distress about PD symptoms could also arise from the restrictions of the lockdown. Physical activity and non-pharmacological treatments are relevant

tools for managing PD symptoms and the interruption or limitation of these activities contributed to the increase of negative feelings in our patients. Moreover, APD patients need frequent outpatient visits; in fact, one of the major concerns reported in our interview was related to the limitation of outpatient clinics and the possible difficulties to consult physicians. The limitation of the access to healthcare services can be replaced by the telemedicine (Schirinzi et al., 2020; Miele et al., 2020), and this was appreciated or advocated by almost half of the patients, underlying the relevance of this different modality of assistance.

Interestingly, our data showed a correlation between the type of treatment and anxiety, while no correlation was observed for depression; probably anxiety was related to the strain for PD symptoms management during the outbreak. Indeed, patients treated with DAT expressed fears about the possibility to obtain adequate and rapid healthcare assistance in case of device issues. Another frequent concern was the possibility of the COVID-19 disease of the caregiver, considered as an essential resource both for the symptoms management and for the psychological support. Noteworthy, anxiety levels were lower in DBS-treated patients than in LCIG and SMT-treated patients, probably for the relative independent management of the DBS device.

Our data confirm the findings of other studies that investigated the psychological impact of COVID-19 on PD patients, highlighting significant emotional sequelae of the pandemic. In particular, depression was reported in a percentage of 21% of patients (Xia et al., 2020), anxiety in a percentage from 21% to 81.7% (Xia et al., 2020) of patients and 57.9% of caregivers (Salari et al., 2020). In addition, an increased distress was reported in a percentage of 43.8% of patients and 53.1% of caregivers (Oppo et al., 2020).

Our data assessed the psychological consequences of COVID-19 pandemic in a specific group of PD patients, such as APD patients, highlighting different emotional and behavioural responses in relation to the type of treatment. Then, specific needs should be taken into account for APD patients.

The main limitation of our study is the lack of a baseline evaluation of anxiety and depression before the COVID-19. However, the comparison between two assessment (T0 and T1) probably revealed the effects of the pandemic.

In conclusion, we found multiple reactions and emotional states in the different groups of APD patients, underlying the necessity to strictly monitor the psychological impact of the pandemic in a such frail population. Finally, specific strategies of information and education seem to be necessary to reduce distress and anxiety for both patients and caregivers.

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Table 1: Patients demographic and clinical features.

	All patients (n= 100)	DBS group (n= 54)	LCIG group (n= 20)	SMT group (n= 26)	p-value
Age	62.4 ± 9.0 (38-78)	60.6 ± 9.0 (38-74)	69.6 ± 8* (47-78)	60.7 ± 7.1# (43-72)	0.000 <i>DBS vs LCIG:</i> <i>p= 0.000</i> <i>DBS vs SMT:</i> <i>p= 1.000</i> <i>LCIG vs SMT:</i> <i>p= 0.000</i>
Sex (male/female)	60/40	31/23	13/7	16/10	n.a.
Education (years)	11.3 ± 4.2 (5-27)	12.1 ± 3.8 (5-27)	8.2 ± 4.7* (5-24)	12.2 ± 3.9# (8-18)	0.000 <i>DBS vs LCIG:</i> <i>p= 0.000</i> <i>DBS vs SMT:</i> <i>p= 1.000</i> <i>LCIG vs SMT:</i> <i>p= 0.001</i>
Employment	Employed n= 21	Employed n=12	Employed n= 2	Employed n= 7	n.a.

	Not employed n= 14 Retired n= 65	Not employed n= 10 Retired n= 32	Not employed n= 0 Retired n= 18	Not employed n= 4 Retired n= 15	
Disease duration (years)	13.4 ± 4.6 (6-31)	13.9 ± 4.9° (7-31)	14.7 ± 4.1 (8-23)	11.2 ± 3.7# (6-20)	0.007 <i>DBS vs LCIG:</i> <i>p= 1.000</i> <i>DBS vs SMT:</i> <i>p= 0.028</i> <i>LCIG vs SMT:</i> <i>p= 0.010</i>
CT duration (months)	n.a.	32.4 ± 21.1 (2-72)	35.7 ± 20.8 (4-74)	n.a.	n.a.
MMSE	28.5 ± 1.6 (22-30)	29.2 ± 1.1° (26-30)	27.4 ± 2.4* (22-30)	28.0 ± 1.3 (26-30)	0.000 <i>DBS vs LCIG:</i> <i>p= 0.001</i> <i>DBS vs SMT:</i> <i>p= 0.001</i> <i>LCIG vs SMT:</i> <i>p= 1.000</i>
Symptoms observed from February 2020 to T0 <i>Flu symptoms</i>	n= 6	n= 4	n= 1	n= 1	n.a.

<i>Fever</i>	n= 7	n= 4	n= 1	n= 2	
<i>Cough</i>	n= 8	n= 7	n= 0	n=1	
<i>Cold</i>	n=11	n=8	n=0	n=3	
<i>Respiratory difficulties</i>	n=5	n=3	n=1	n=1	
<i>Diarrhea</i>	n=7	n=5	n=0	n=2	
<i>Urinary burning</i>	n=2	n=1	n=0	n=1	
<i>Pneumonia</i>	n=0	n=0	n=0	n=0	
<i>(Further) smell reduction</i>	n=0	n=0	n=0	n=0	
<i>Taste reduction</i>	n=0	n=0	n=0	n=0	
Execution of nasopharyngeal swab (from February 2020 to T0)	n=0	n=0	n=0	n=0	n.a.
Diagnosis of Covid-19 (from February 2020 to T0)	n=0	n=0	n=0	n=0	n.a.
HADS (T0)					
HADS-A	6.7 ± 3.9 (0-16)	5.8 ± 3.7° (0-15)	8.1 ± 3.2* (3-15)	8.2 ± 4.4 (1-16)	0.008 <i>DBS vs LCIG:</i> <i>p= 0.028</i>
<i>Normal (0-7)</i>	n= 61	n= 39	n= 9	n= 13	

<i>Mild (8-10)</i>	n= 19	n= 7	n= 7	n= 5	<i>DBS vs SMT:</i> <i>p= 0.049</i>
<i>Moderate (11-15)</i>	n= 19	n= 8	n= 4	n= 7	
<i>Severe (≥16)</i>	n= 1	n= 0	n= 0	n= 1	
					<i>LCIG vs SMT:</i> <i>p= 1.000</i>
HADS-D	6.5 ± 3.3 (0-17)	6.3 ± 3.6 (0-14)	7.3 ± 3.4 (1-17)	6.3 ± 2.5 (1-13)	0.494 <i>No significant differences across samples</i>
<i>Normal (0-7)</i>	n= 65	n= 33	n= 12	n= 20	
<i>Mild (8-10)</i>	n= 25	n= 13	n= 7	n= 5	
<i>Moderate (11-15)</i>	n= 9	n= 8	n= 0	n= 1	
<i>Severe (≥16)</i>	n= 1	n= 0	n= 1	n= 0	
HADS (T1)					
	n=85	n= 47	n= 18	n= 20	
HADS-A	5.9 ± 3.7 (0-17)	4.9 ± 3.6 (0-17)	7.7 ± 2.8* (3-13)	6.6 ± 3.8 (1-17)	0.005 <i>DBS vs LCIG:</i> <i>p= 0.002</i>
<i>Normal (0-7)</i>	n= 59	n= 38	n= 9	n= 12	<i>DBS vs SMT:</i> <i>p= 0.065</i>
<i>Mild (8-10)</i>	n= 18	n= 6	n= 6	n= 6	<i>LCIG vs SMT:</i> <i>p= 0.251</i>
<i>Moderate (11-15)</i>	n= 6	n= 2	n= 3	n= 1	
<i>Severe (≥16)</i>	n= 2	n= 1	n= 0	n= 1	
HADS-D	6.6 ± 3.1 (1-14)	6.4 ± 2.8 (1-13)	7.9 ± 3.6 (3-14)	5.8 ± 2.9 (2-12)	0.159 <i>No significant differences across samples</i>
<i>Normal (0-7)</i>	n= 56	n= 30	n= 11	n= 15	
<i>Mild (8-10)</i>	n= 20	n= 15	n= 2	n= 3	

<i>Moderate (11-15)</i>	n= 9	n= 2	n= 5	n= 2	
<i>Severe (≥ 16)</i>	n= 0	n= 0	n= 0	n= 0	

Table 1: All data are reported as mean \pm standard deviation (range), with the exception of sex, employment, HADS anxiety and depression severity levels, symptoms observed from February 2020 to T0, execution of nasopharyngeal swab, and diagnosis of Covid-19. n.a., not applicable; MMSE, Mini Mental State Examination; T0, data collected from April 2020 to May 2020, during the lockdown; T1, data collected after the end of the lockdown in Italy from June 2020 to August 2020; HADS, Hospital Anxiety and Depression Scale; HADS-A, HADS Anxiety subscale; HADS-D, HADS Depression subscale. Bold values mean statistically significant difference. Significant values adjusted by the Bonferroni correction for multiple tests are reported in Italics.

* Significant difference between DBS and LCIG

Significant difference between LCIG and SMT

° Significant difference between DBS and SMT

Table 2: Caregivers demographic and clinical features.

Age	62.1 ± 9.2 (43-83)
Sex (male/female)	21/39
Education (years)	11 ± 3.9 (4-23)
Employement	Employed n= 20 Not employed n= 6 Retired n= 34
Symptoms observed from February 2020 to T0	
<i>Flu symptoms</i>	n=4
<i>Fever</i>	n=6
<i>Cough</i>	n=4
<i>Cold</i>	n=3
<i>Respiratory difficulties</i>	n=3

<i>Diarrhea</i>	n=7
<i>Urinary burning</i>	n=2
<i>Pneumonia</i>	n=1
<i>Smell reduction</i>	n=2
<i>Taste reduction</i>	n=1
Execution of nasopharyngeal swab (from February 2020 to T0)	n=1
Diagnosis of Covid-19 (from February 2020 to T0)	n=1
HADS	
HADS-A	6.6 ± 4.6 (0-17)
<i>Normal (0-7)</i>	n= 36
<i>Mild (8-10)</i>	n= 12
<i>Moderate (11-15)</i>	n= 11
<i>Severe (≥16)</i>	n= 1
HADS-D	5 ± 3.7 (1-17)
<i>Normal (0-7)</i>	n= 47
<i>Mild (8-10)</i>	n= 8
<i>Moderate (11-15)</i>	n= 3
<i>Severe (≥16)</i>	n= 2

Table 2: All data are reported as mean \pm standard deviation (range), with the exception of sex, employment, HADS anxiety and depression severity levels, symptoms observed from February 2020 to T0, execution of nasopharyngeal swab, and diagnosis of Covid-19. HADS, Hospital Anxiety and Depression Scale; HADS-A, HADS Anxiety subscale; HADS-D, HADS Depression subscale; T0, data collected from April 2020 to May 2020, during the lockdown.