PD Symptoms Have A Distinct Impact on Caregivers' and Patients' Stress: A Study Assessing the Consequences of COVID-19 Lockdown

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The high morbidity and mortality rates of COVID-19 have led many countries to impose a lockdown as an extreme measure to prevent contagion. Accordingly, concerns were raised about worsening of Parkinson's disease (PD) patients' symptoms[1-3], as well as for their caregivers' mental health. We hypothesized that different PD features may impact on patients' and caregivers' stress under lockdown. To this aim, we prospectively carried out a series of structured telephone interviews to each pair (PD/caregivers), conducted by the treating neurologist during the last 10 days of lockdown in Italy. The study was approved by the ethical committee of Brotzu General Hospital (PG/2020/11022). Patient and caregivers provided written consent by email.

Inclusion criteria were diagnosis of PD according to MDS clinical criteria[4] and having a family member as caregiver. Change of stress level of PD and caregivers was compared to the time prior to home confinement and assessed with a self-reported judgement (verbal rating scale, VRS). Answers were transposed on a scale from 0 (severely worsened) to 6 (much improved), where 3 stood for unchanged. VRS for each item were categorized in worsened (score 0-2) and unchanged/improved (score 3-6). The following clinical variables were assessed in PD: Unified Parkinson's Disease Rating Scale part II (UPDRS-II), Non-Motor Symptoms Scale (NMSS), Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale, Parkinson's disease questionnaire-8. Hospital Anxiety and Depression Scale (HADS) were retrieved in PD and caregivers, who also underwent Zarit burden interview (ZBI). PD patients were also categorized in two groups based on whether or not they continued to practice at least 45' per day of physical activity during the home confinement. Full methods, including statistical analysis, are in supplementary material.

We enrolled 32 PD and 32 caregivers (supplementary table 1). Level of stress during home confinement was rated as worsened in 43.8% of PD and 53.1% of caregivers. PD experiencing increased stress level had worse HADS-anxiety (p=0.006) and NMSS (p=0.012). In PD the increase in stress due to NMSS was driven by mood/cognition score.

Patients' features associated to higher level of stress in caregivers were worse NMSS (p=0.018). Specifically, cardiovascular, mood/cognition, urinary and miscellaneous domain of NMSS scored higher in PD patients whose caregivers had worsened stress (Figure 1). On multivariate binary logistic regression, worsening stress were associated to patients' HADS-anxiety (p=0.032) in PD and NMSS (p=0.018) in caregivers. Similarly, on multivariate linear regression analysis a higher ZBI was associated with a higher NMSS (p=0.029) (supplementary table 2). PD practicing daily physical activity had lower anxiety compared with those who were inactive (6.0 ±3. vs 8-7 ±3, *p*=0.044). The two groups were similar for other clinical and demographic features. Multivariate linear regression showed a significant association between HADS-anxiety in PD and lack of physical activity during home confinement, even when controlling for age, disease duration, total Levodopa equivalent daily dose, UPDRS-II, NMSS and QUIP-RS (supplementary tables 3 and 4).

The binary and multiple regression models adequately fitted the data. There was no evidence of collinearity between NMSS and UPDRS-II (supplementary material).

NMS particularly neuropsychiatric[5] and sleep disturbances[6], are known predictors of caregiver burden. COVID-19 related confinement period resulted in an additional load of pressure on the caregiver, especially caused by NMSS belonging to the neuropsychiatric and autonomic domain. Differently, only anxiety was a significant determinant of worsening stress in PD patients, as recently reported[2]. Limitations of our study are the small sample size and the use of telephone interviews.

Despite the small sample size and the use of a non-validated outcome measure such as VRS, we believe these findings should be taken into account in the post-pandemic time. The maintenance of a minimum level of physical activity should represent an essential non-pharmacological measure also for the management of PD anxiety. Moreover, our study highlights that, under strict home confinement, different PD symptoms has a distinct but significant impact not only on patients' but also on caregivers' stress. Post-pandemic health

care systems should take care of such unpaid compassionate group that bears a huge and growing burden on society.

Figure 1. Panels A-C: Parkinson's disease (PD) experiencing increased stress level during lockdown had worse NMSS (*p=0.012) and HADS-anxiety (*p=0.006). Patients' features associated to higher level of stress in caregivers (CVG) were worse NMSS (*p=0.018). UPDRS-II was not associated to higher stress level in both PD and caregivers. Panel D: Cardiovascular, mood/cognition, urinary and miscellaneous domain of NMSS scored higher in caregivers with worsened stress. Panel E: In PD, increased stress by NMSS was driven by mood/cognition score.

Supplemental Material.

This file includes additional details about the methods, analysis, and results related to this paper. Four Supplemental Tables are also provided

ETHICAL COMPLIANCE STATEMENT

Institutional ethics approval was obtained from AOU Brotzu, Cagliari Ethical committee (PG/2020/11022). The study was conducted in accordance with the Declaration of Helsinki. Each participant provided written informed consent which was scanned and sent by email.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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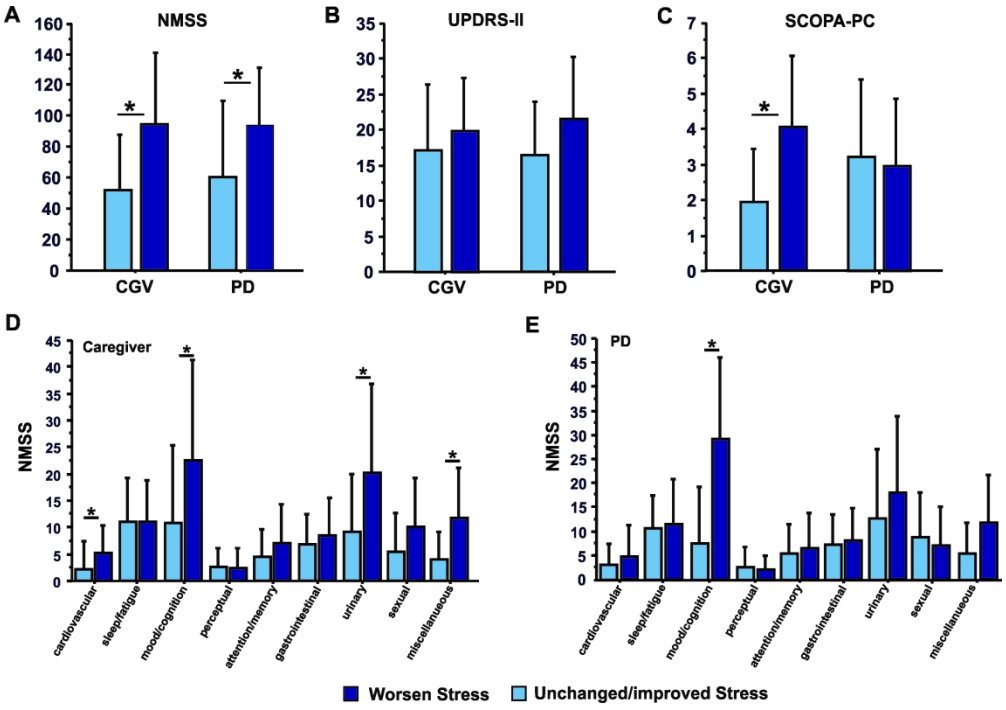

Panels A-C: Parkinson's disease (PD) experiencing increased stress level during lockdown had worse NMSS (*p=0.012) and HADS-anxiety (*p=0.006). Patients' features associated to higher level of stress in caregivers (CVG) were worse NMSS (*p=0.018). UPDRS-II was not associated to higher stress level in both PD and caregivers.

Panel D: Cardiovascular, mood/cognition, urinary and miscellaneous domain of NMSS scored higher in caregivers with worsened stress.

Panel E: In PD, increased stress by NMSS was driven by mood/cognition score.

SUPPLEMENTARY METHODS

The telephone interview included two distinct sections, designed to separately assessing PD and caregivers. For those patients having problems in completing the interview themselves, (e.g. due to dysarthria, hypophonia or cognitive impairment), this was conducted with the help of caregivers. The interview had a duration of approximately 50 minutes.

STATISTICAL ANALYSIS

Pearson Test was used to run correlation between continuous variables. Spearman test was used to evaluate correlation between non-parametric variables. Unpaired t-test for independent sample was employed to compare means of non-parametric continuous variables.

Linear Regression analysis was used to evaluate relationship between ZARIT total score (dependent variable) and motor score UPDRS II total and NMSS (independent variable). Linear regression analysis was also employed to assess the association between HAM-A (dependent variable) and the following independent variables: physical activity (Yes/No), age (years), disease duration (years), Total Levodopa Equivalent Daily Dose (LEDD) (mg), UPDRS II, NMSS, PDQ8, QUIP-RS.

Binary Logistic regression was used to evaluate the relationship between presence of a worsened VRS (dependent variable) and UPDRS II total score and NMSS (independent variable). Results were considered significant when $P \leq 0.05$.

Analyses were performed using SPSS 20.0 for Mac.

SUPPLEMENTARY RESULTS

We evaluated the fit of the model for the binary logistic regression reported in supplementary table 2 with Hosmer-Lemeshow test. This test indicates a poor fit if the significance value is I< 0.05. We found a p-value, respectively, of 0.32 (for the dependent variable worsened VRS for patient's stress) and of 0.62 (for dependent variable worsened VRS for caregiver's stress), indicating that the model adequately fits these data.

The fit of the model for the reported linear regressions was evaluated by ANOVA test. For linear regression with dependent variable ZBI, the R Square was 0.38 (p=0.001). For linear regression with dependent variable HADS, the R Square was 0.48 (p=0.03). These results support the hypothesis that the model adequately fits the data.

We also tested collinearity between UPDRS-II and NMSS. Lack of collinearity was confirmed by the correlation test between NMSS and UPDRS II, which showed statistically significant correlation values (rho = 0.72) but lower than those generally indicative of collinearity (i.e. rho= 0.8-0.9) (H. Mayers. Classical and Modern Regression with Applications. PWS10 Kent Publishing Company. 1990).

Moreover, we performed a collinearity diagnostic test regarding the linear regression reported in supplementary table 2 (dependent variable: ZBI score. Independent variable: NMSS. UPDRS II). The variance inflation factor (VIF) values (1.9) and the condition index results (1.0, 4.2 and 6.9) were not indicative of collinearity.

Finally, statistical analysis performed on supplementary table 4 variables did not support the possibility of collinearity between the variables, showing VIF value between 1.1 and 4.1.

SUPPLEMENTARY TABLE 1.

DEMOGRAPHICAL AND CLINICAL FEATURES OF PATIENTS WITH PARKINSON'S DISEASE (PD) AND THEIR CAREGIVERS

	PD (N=32)	Caregivers (N=32)	p-value
M/F (%)	24/8 (75)	6/26 (18.8)	**<0.0001***
Age, years	72.5 ± 8.7	64.63 ± 10.32	**0.024***
Education, years	11.38 ± 5.24	12.78 ± 5.31	0.236
HADS Anxiety	6.78 ± 3.34	6.78 ± 4.52	0.808
HADS Depression	7.72 ± 4.18	5.97 ± 3.93	0.126
Lockdown Stress (worsened /unchanged or improved) (%)	14/18 (43.8)	17/15 (53.1)	0.617
Age at onset, years	60.58 ± 10.53	-	
Disease duration, years	11.62 ± 4.51	-	
Total LEDD, mg	959.31 ± 344.95	-	
D-ag LEDD, mg	135.41 ± 162.69	-	
UPDRS-II	18.44 ± 8.33	-	
Schwab and England	62.19 ± 17.54	-	
NMSS	73.56 ± 47.04	-	
QUIP-RS	4.84 ± 4.62		
PDQ8	12.63 ± 6.42	-	
ZARIT BURDEN INTERVIEW	-	18.16 ± 17.07	

D-Ag= dopamine agonist; HADS = Hospital Anxiety and Depression Scale; LEDD = levodopa equivalent daily dose; NMSS = Non-Motor Symptoms Scale; PDQ-8; Parkinson's disease questionnaire-8 ; QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale; UPDRS = Unified Parkinson's Disease Rating Scale.
All continuous data given as mean ± standard deviation. * Significant values are bolded.

SUPPLEMENTARY TABLE 2.

BINARY LOGISTIC REGRESSION AND LINEAR REGRESSION ANALYSES ON FACTORS ASSOCIATED TO WORSENING OF STRESS AND CAREGIVER BURDEN DURING LOCKDOWN DUE TO COVID-19.

BINARY LOGISTIC REGRESSION ANALYSIS - Dependent variable VRS for stress worsening							
			B	**Exp(B)**	**P-value**	**95% CI - LB**	**95% CI - UB**
PD	**NMSS**		-0.011	0.989	0.380	0.964	1.014
	UPDRS II		-0.008	0.992	0.904	0.865	1.137
	HADS-A		-0.365	0.694	**0.032***	0.497	0.970
CAREGIVER	**NMSS**		-0.048	0.953	**0.018***	0.916	0.992
	UPDRS II		0.124	1.132	0.136	0.962	1.333
LINEAR REGRESSION ANALYSIS - Dependent variable ZBI							
	UC		**SC**				
	B	**SE**	**Beta**	**t**	**P-value**	**95% CI - LB**	**95% CI - UB**
UPDRS II	0.399	0.414	0.195	0.963	0.344	-0.449	1.246
NMSS	0.169	0.073	0.464	2.294	**0.029***	0.018	0.319

CI= confidence interval; HADS-A: Hospital Anxiety and Depression scale, Anxiety score; LB= lower bound; NMSS = Non-Motor Symptoms Scale; UB= upper bound; SC= Standardized Coefficients; UC = Unstandardized Coefficients; UPDRS = Unified Parkinson's Disease Rating Scale; ZBI = Zarit Burden Interview.
* Significant values are bolded.

SUPPLEMENTARY TABLE 3.

DEMOGRAPHICAL AND CLINICAL FEATURES OF PARKINSON'S DISEASE (PD) CATEGORIZED ON PRACTIZING HOME PHYSICAL ACTIVITY

	Physical Activity-YES (N=23)	Physical activity-NO (N=9)	P Value
Age, years	73.4 ± 8	70.1 ±11	0.342
Disease duration, years	11.9 ± 4	10.9 ± 6	0.572
Total LEDD, mg	905 ± 303	1096 ±424	0.163
UPDRS II	17.5 ± 8	20.9 ± 10	0.306
Schwab & England	63.0 ± 17	60.0 ± 20	0.666
NMSS	73.2 ± 50	74.6 ± 42	0.942
HADS-A	6.0 ± 3	8.7 ± 3	**0.044**
HADS-D	8.0 ± 5	7.0 ± 3	0.552
PDQ-8	12.4 ± 7	13.2 ± 6	0.748
QUIP-RS	4.7 ± 5	5.1 ± 5	0.842

HADS = Hospital Anxiety and Depression Scale; LEDD = levodopa equivalent daily dose; NMSS = Non-Motor Symptoms Scale; PDQ-8; Parkinson's disease questionnaire-8 ; QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale; UPDRS = Unified Parkinson's Disease Rating Scale.
All continuous data given as mean ± standard deviation. * Significant values are bolded.

SUPPLEMENTARY TABLE 4.

LINEAR REGRESSION ANALYSIS OF VARIABLES ASSOCIATED TO ANXIETY IN PD UNDER LOCKDOWN

LINEAR REGRESSION ANALYSIS - Dependent variable HADS-ANXIETY							
	UC		SC				
	B	SE	Beta	t	P-value	95% CI - LB	95% CI - UB
Physical activity (Yes/No)	-2.932	1.320	-0.404	-2.222	**0.037**	-5.669	-0.195
Age (years)	0.046	0.087	0.122	0.531	0.600	-0.134	0.226
Disease duration (years)	-0.094	0.174	-0.127	-0.541	0.594	-0.455	0.267
Total LEDD (mg)	-0.001	0.003	-0.079	-0.278	0.784	-0.006	0.005
UPDRS II	-0.049	0.102	-0.125	-0.484	0.633	-0.261	0.162
NMSS	0.000	0.022	0.004	0.013	0.989	-0.044	0.045
PDQ8	0.241	0.161	0.470	1.500	0.148	-0.092	0.575
QUIP-RS	0.234	0.121	0.322	1.928	0.067	-0.018	0.485

CI= confidence interval; HADS-A: Hospital Anxiety and Depression scale, Anxiety score; LB= lower bound; NMSS = Non-Motor Symptoms Scale; UB= upper bound; SC= Standardized Coefficients; UC = Unstandardized Coefficients; UPDRS = Unified Parkinson's Disease Rating Scale;
* Significant values are bolded.