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Depression and Parkinson disease: prevalence, temporal relationship, and determinants

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Background/aim: Comorbidity of depression in Parkinson disease (PD) is a major factor that changes patients' quality of life. However, the neurobiological and sociodemographic risk factors for this comorbidity are not well studied. In this study, we aimed to define the prevalence, temporal relationship, and psychosocial and clinical determinants of depression comorbid with PD.

Materials and methods: Fifty-five PD patients were evaluated with SCID, a data form that assessed sociodemographic and PD-related variables, UPDRS III, HAM-D, HAM-A, MMSE, and the Apathy Evaluation Scale.

Results: Depression (lifetime: 45.5%, last month: 25.5%, before PD: 20%) was the most frequent psychiatric diagnosis. The major determinants of depression in the last month and depression before PD were early onset of PD and young age. Patients on pramipexole treatment were less likely to be diagnosed with depression in the last month. Other sociodemographic and PD-related variables were not significantly different for lifetime, last month, and pre-PD depression diagnosis compared to their counterparts.

Conclusion: Depression is prevalent both before and after patient gets a PD diagnosis. Depression is not only the result of PD-related life changes but it is also a preceding factor that may decrease the age of PD onset.

Key words: Parkinson disease, depression, pramipexole, age of onset

1. Introduction

Parkinson disease (PD), which was primarily defined and diagnosed according to the existence of motor symptoms (1), is receiving much more attention by having a prevalence of 1.8% among people aged over 60 (2). As new treatments for the disease have emerged, the expected time to live after diagnosis has reached up to more than 12 years (3) and nonmotor symptoms have been much more prominent and important to recognize. Nonmotor symptoms like pain, anxiety, and depression are also major factors that affect quality of life (4,5) and perceived stress (6), and they are crucial measures in the follow-up of PD.

Among the psychiatric disorders comorbid with PD, depression has the highest prevalence, followed by anxiety disorders, sleep disorders, and others (7). Patients with a PD diagnosis have a 1.89–4.26 times increased risk of depression (8,9). Despite this high risk and prevalence, studies conducted so far were not able to conclude the effect of depression on PD prognosis, the temporal relationship of the two disorders, and the determinants of depression in PD patients. Low socioeconomic status, cognitive deficits, laterality of PD motor symptoms, and anxiety disorder comorbidity were shown to increase depression vulnerability in PD patients (10–12). First-degree relatives of PD patients also have a higher risk of depressive and anxiety disorders (13), which indicates a neurobiological susceptibility. On the other hand, PD patients face many psychosocial stressors in having a chronic and progressive illness or disability (14,15), which creates an environmental risk.

In order to reach a clear conclusion about the PD/depression connection, knowing the temporal relationship and determinants of depression could help resolve the question of whether depression is the cause, prodrome, or result of PD. In this study, we aimed to determine the temporal relationship of depression and PD; to find the prevalence and determinants of lifetime depression (LD), depression in the last month (DLM), and depression before PD (DBPD) diagnosis; and to define the determinants for each type of depression diagnosis.

2. Materials and methods

2.1. Participant selection and evaluation

Patients who agreed to take part in the study and met the United Kingdom Parkinson's Disease Society Brain

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Bank Clinical Diagnostic Criteria were recruited from the Movement Disorders Clinic of Gazi University. For the 55 eligible patients, a sociodemographic data form was administered regarding PD age of onset and duration, side of onset, presenting symptom, symptom lateralization, personal and family history of psychiatric diagnosis, treatments for PD, and other medical diagnoses as well as variables like age, marital status, and monthly income. In addition, the SCID-Clinical Version, Mini Mental State Exam Test (MMSE), Hamilton Depression (HAM-D) and Hamilton Anxiety Scales (HAM-A), clinician version of the Apathy Evaluation Scale (AES), and Unified Parkinson's Disease Rating Scale part III (UPDRS III) were used to detect the psychiatric diagnosis, severity of motor symptoms, and other psychosocial predictors. Depression diagnosis before PD, lifetime depression diagnosis, and depression diagnosis in the last month were evaluated by the SCID interview. Hospital reports and information from the caregiver were also taken when needed. The Gazi University Faculty of Medicine Ethics Committee approved the study. All participants provided written informed consent. Data regarding the participant characteristics can be found in Table 1.

2.2. Statistical methods

Clinical data were analyzed with the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables. In order to assess the determinants of depression, patients that had a depression diagnosis before PD (DBPD, n = 11) were compared to the patients that did not have a DBPD diagnosis (non-DBPD, n = 44), patients that had a lifetime depression diagnosis (LD, n = 25) were compared to the patients that did not have a LD diagnosis (non-LD, n = 30), and patients that had a depression diagnosis in the last month (DLM, n = 14) were compared to the patients that did not have a DLM diagnosis (non-DLM, n = 41). $P < 0.05$ was considered significant.

3. Results

Of the 55 patients, 15 patients (27.2%) were currently using antidepressants, 11 patients (20%) had DBPD, 25 patients (45.5%) had LD, and 14 patients (25.5%) had DLM. Of the 25 patients that had a lifetime depression diagnosis, 6 patients were diagnosed with depression after PD diagnosis and they were currently in remission, 5 patients had a depression diagnosis only before PD and were currently in remission, 8 patients only had a depression diagnosis in the last month, and 6 patients had a depression diagnosis both before PD and in the last month. Generalized anxiety disorder (40%) was the second most common psychiatric diagnosis. A list of psychiatric diagnoses can be found in Table 2. None of the patients had an apathy score higher than 42.

None of the sociodemographic variables like sex, marital status, working status, and monthly income were significantly different between DBPD and non-DBPD groups, LD and non-LD groups, and DLM and non-DLM groups ($P > 0.05$). Variables regarding clinical features of PD such as side of onset, presenting symptoms, PD symptom lateralization, duration of PD diagnosis, and other clinical evaluation scales were not significantly different among the groups. However, DBPD patients were significantly younger than non-DBPD patients (56.5 ± 12 vs. 66.7 ± 9 years, $P = 0.01$) and they also had younger age of PD onset (51.9 ± 13 vs. 60.47 ± 9 years, $P = 0.04$).

DLM patients were also significantly younger (60 ± 8 vs. 66 ± 11 years, $P = 0.03$) and had significantly lower age of PD onset (53 ± 7 vs. 60.7 ± 10.7 years, $P = 0.01$) than non-DLM patients. In addition to this, depressed PD patients had higher HAM-A (9.5 ± 6 vs. 5.6 ± 7, $P = 0.03$) and AES (39.9 ± 11 vs. 32.8 ± 12, $P = 0.05$) scores, but none of the depressed patients' scores were high enough to be diagnosed with an anxiety disorder or apathy (Supplementary Table 1).

Even though levodopa equivalent doses of PD treatments were not different among the groups (517 ± 290 mg for non-DLM and 617 ± 201 mg for DLM, $P = 0.38$), based on the depression diagnosis in the last month, patients that were on ropinirole hydrochloride treatment were more likely to be diagnosed with depression (50% and 21%, respectively; $P = 0.046$) and patients that were on pramipexole treatment were less likely to be diagnosed with depression (7% and 36%, respectively; $P = 0.036$). There was not a significant difference among the patients diagnosed with DLM and non-DLM for antidepressant use ($P > 0.05$).

4. Discussion

According to the results of this study, depression is highly comorbid with PD both before and after PD diagnosis and it is more common than other psychiatric disorders. These results are in accordance with previous studies that reported a higher number of depression diagnoses in PD patients (3,7,8,16), and this comorbidity is 4–5 times higher than expected for the general population or elderly population (17) with even higher prevalence of depression in inpatient samples in Turkey (18).

By investigating lifetime, last month, and before PD diagnoses of depression, we could show that depression is not only a phenomenon that follows the PD diagnosis but it may also be a prodromal feature. Of the 45.5% of the PD patients with a lifetime depression diagnosis, 44% had depression before PD, which supports the hypothesis that depression is not just a result of the physical disturbances and psychosocial stressors associated with the disease. The fact that depression in PD is also higher than in

Table 1. Sociodemographic and clinical variables of participants.

Sex (female/male)	21/34
Marital status (married/divorced/widowed)	49/1/5
Educational status (secondary school and lower/high school and higher)	24/31
Dominant hand (right/left)	54/1
Number of comorbid diseases (0/1/2/>3)	22/24/6/3
Side of onset (right/left/bilateral)	27/25/3
Presenting symptom (tremor/rigidity/unknown)	32/22/1
Major depression before PD diagnosis (yes/no)	11/44
Age (years)	64.7 ± 10
Age at PD onset (years)	58.7 ± 10
Duration of PD symptoms (months)	71.2 ± 49.7
MMSE	27.8 ± 3
HAM-D	8.5 ± 8
HAM-A	6.6 ± 7
Apathy Evaluation Scale	34.6 ± 12
UPDRS III	13.4 ± 8

Table 2. Lifetime and last month psychiatric diagnosis of the participants.

Lifetime psychiatric diagnosis (n = 35)	Number	%
Major depression	25	71.4
Generalized anxiety disorder	11	31.4
Dysthymia	3	8.6
Panic disorder	2	5.7
Obsessive compulsive disorder	2	5.7
Posttraumatic stress disorder	2	5.7
Agoraphobia	1	2.9
Adjustment disorder	1	2.9
Psychiatric diagnosis in the last month (n = 25)	Number	%
Major depression	14	56
Generalized anxiety disorder	10	40
Dysthymia	3	12
Posttraumatic stress disorder	1	4
Agoraphobia	1	4
Adjustment disorder	1	4

other diseases with a chronic course, e.g., osteoarthritis or diabetes mellitus, that result in physical disabilities (19) also supports these results.

We found that duration of PD symptoms was not related to depression, which supports the idea that depression might be a neuropathological process occurring concomitantly or before the degeneration of motor systems. Presenting symptoms of PD were also not different among the groups, even though some studies reported higher depression prevalence among patients with tremor as the presenting symptom (2,20). One study (12) also found a negative association with tremor onset and depression. However, we have observed a significant medication effect: patients on pramipexole treatment were

less likely to be diagnosed with depression. It is suggested that by its agonist activity on D3 receptors, pramipexole might have a positive effect on the treatment of depressive symptoms (21–24). On the other hand, ropinirole, which is a monoamine oxidase inhibitor, was not protective against depression; this finding is contrary to animal and human studies that supported an antidepressant effect for ropinirole (25,26). The other PD agents that the patients were using may have led to this finding.

Among the investigated psychosocial determinants of depression before PD diagnosis and depression in the last month, young age of onset and mean age were significantly different between the groups. Early-onset PD patients have longer disease durations, experience nonmotor symptoms more often, retire earlier, and have to deal more often with marital and occupational problems (27), and that may explain higher rates of depression diagnosis in the last month. However, it is also known that chronic stress and mood disorders may lead to neurodegenerative changes in the brain as defined in Alzheimer disease (28). Glucocorticoids that are released in response to stress may increase the loss of dopaminergic neurons in PD (29). Thus, depression might also be a factor that accelerates the onset of PD in vulnerable patients. A recently published cohort study also showed that having prior depression increases the risk of having a PD diagnosis in the following year by 3.2 times (30). In animal models where depression is modeled by chronic stress paradigms, increased HPA axis and oxidative stress, increased dendritic atrophy, decreased neurogenesis, and increased inflammation are shown (31,32). Each of these neuropathological mechanisms of depression may trigger or effect the onset of PD and should be investigated further in future studies.

On the other hand, this study has limitations in addition to its strengths. The patients that took part in this study were patients in the middle phase of the disease (mean duration of illness for the sample was 71.2 months), were nondemented, and had lower levels of disability, and the research sample was relatively small, which may prevent generalization of the results for the whole PD disease duration. However, a trained physician evaluated all patients with a structured face-to-face interview and hospital records were taken into account if needed, instead of using self-evaluation scales. We think that the only way to get more reliable information about the depression/PD temporal relationship is by including nondemented PD patients. Depression was studied for diagnoses before PD, lifetime depression, and diagnoses in the last month and confounding factors like apathy and anxiety were assessed carefully, which is a major strength. Since our patient group had low anxiety and apathy scores, we could present a more clear view for the presentation of depression.

In conclusion, depression is prevalent both before and after PD diagnosis and it may be a preceding factor that decreases the age of onset of vulnerable PD patients. Further studies with larger sample sizes and examination of the effect of depression on PD progression in animal models are needed to replicate the results of this study.

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Supplementary Table 1. Sociodemographic variables and clinical scale scores of research groups.

	Mean	**Std. dev.**	**Mean**	**Std. dev.**	
Depression diagnosis before Parkinson disease (DBPD)	**DBPD- (n = 44)**		**DBPD+ (n = 11)**		**P**
Age (years)	66.75	9.34	56.55	12.35	0.01
Education level (years)	9.30	4.75	9.73	4.76	0.81
Age of PD onset (years)	60.47	9.07	51.91	13.03	0.04
Months since PD onset	75.14	52.04	55.64	37.38	0.33
MMSE score	27.64	3.07	28.55	2.34	0.23
HAM-D score	7.25	6.94	13.55	9.94	0.07
HAM-A psychological subscale score	3.05	3.17	3.45	3.05	0.52
HAM-A somatic subscale score	3.23	4.23	4.73	3.88	0.14
HAM-A total score	6.27	7.11	8.18	6.29	0.25
Apathy Evaluation Scale score	34.93	11.93	33.64	13.03	0.70
UPDRS III score	13.98	7.92	11.20	7.15	0.43
Lifetime depression diagnosis (LD)	**LD- (n = 30)**		**LD+ (n = 25)**		**P**
Age (years)	65.67	8.70	63.56	12.81	0.55
Education level (years)	9.73	4.35	8.96	5.17	0.46
Age of PD onset (years)	60.48	8.69	56.68	12.06	0.20
Months since PD onset	61.80	47.22	82.56	51.33	0.09
MMSE score	27.87	2.53	27.76	3.43	0.66
HAM-D score	4.73	3.77	13.04	9.25	0.00
HAM-A psychological subscale score	3.33	3.43	2.88	2.76	0.78
HAM-A somatic subscale score	3.20	4.18	3.92	4.20	0.44
HAM-A total score	6.53	7.38	6.80	6.54	0.72
Apathy Evaluation Scale score	32.70	11.73	37.04	12.22	0.17
UPDRS III score	13.48	8.10	13.39	7.56	0.83
Depression diagnosis in the last month (DLM)	**DLM- (n = 41)**		**DLM+ (n = 14)**		**P**
Age (years)	66.32	11.03	60.00	8.37	0.03
Education level (years)	9.22	4.75	9.86	4.74	0.83
Age of PD onset (years)	60.71	10.77	53.04	6.96	0.01
Months since PD onset	67.02	49.40	83.57	50.61	0.22
MMSE score	27.59	3.15	28.50	2.18	0.32
HAM-D score	4.54	3.94	20.14	4.33	0.00
HAM-A psychological subscale score	2.76	3.24	4.21	2.55	0.07
HAM-A somatic subscale score	2.88	4.06	5.36	4.22	0.02
HAM-A total score	5.66	6.97	9.57	6.21	0.03
Apathy Evaluation Scale score	32.88	11.82	39.93	11.51	0.05
UPDRS III score	13.13	8.37	14.50	5.66	0.22