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Apathy and Depression in Parkinson Disease

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Abstract

The purpose of this study was to investigate the prevalence and clinical correlates of apathy and depression in Parkinson disease (PD), and to clarify whether apathy can be dissociated from depression. One hundred fifty patients with PD completed the Beck Depression Inventory Second Edition (BDI-II), Starkstein's Apathy Scale (AS), and a quality of life (QOL) battery. Hoehn and Yahr (HY) staging, the Unified Parkinson's Disease Rating Scale (UPDRS), and the Mini-Mental State Examination (MMSE) were performed on the same day. Apathy (AS score $\geq$ 16) was diagnosed in 60% of patients and depression (BDI-II score $\geq$ 14) in 56%. Apathy coexisted with depression in 43% of patients, compared with depression without apathy in 13% and apathy without depression in 17%. Apathy scale score was significantly correlated with UPDRS scores, HY stage, and age, whereas BDI-II score was correlated only with UPDRS scores. Both AS and BDI-II scores were negatively correlated with QOL. However, multiple regression analysis revealed that depression was strongly and negatively associated with emotional well-being and communication, whereas apathy was mainly associated with cognition and stigma. These findings suggest that apathy and depression may be separable in PD, although both are common in patients with PD and are associated with QOL.

Keywords

Parkinson disease, apathy, depression, QOL, cognitive impairment

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Introduction

Although Parkinson disease (PD) is primarily a movement disorder, it is accompanied by various nonmotor symptoms including psychiatric and behavioral problems. Among such symptoms, apathy and depression are among the most frequently reported.[1,2] Because depressive patients often have symptoms of apathy, it remains unclear whether apathy is a distinct syndrome or merely a symptom of depression. Apathy may, therefore, be one of the clinical signs of depression[3]; in this case, apathy would be a symptom resulting from depression. However, in many medical situations, apathy can be totally independent of depression. For example, in Alzheimer disease (AD), apathy can occur in the absence of depression, and depression can occur in the absence of apathy.[4] Kirsch-Darrow et al[5] suggest that apathy is a core feature of PD and support the notion that apathy can be dissociated from depression as it can in AD.

The purpose of this study was to confirm the findings in patients with PD and, further, to examine cognitive function and quality of life (QOL) in these patients. Although recent studies have shown that depression is an important factor impacting QOL in patients with PD,[6-9] few studies have been conducted in regard to apathy in PD patients. Thus, we also examined the relationship between apathy or depression and QOL.

Methods

Patients

One-hundred and sixty consecutive patients with idiopathic PD who attended 4 outpatient clinics (Hyogo College of Medicine Hospital, Toda Neurology and Orthopedics Clinic, NHO South Kyoto Hospital, and Ehime Prefectural Central Hospital) between June 2007 and January 2008 were enrolled in the

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study. Parkinson disease was diagnosed according to the UK Parkinson's Disease Society Brain Bank Criteria.[10] Treatment with antiparkinsonian drugs had improved the parkinsonian symptoms and signs in all treated patients. At the time of the study, 5 patients had never received parkinsonian medication, although the efficacy of levodopa was subsequently confirmed in these patients. Patients with secondary parkinsonism or evidence of more generalized neurological disease were excluded. Participants were excluded if they declined to participate later, or could not complete the self-administered questionnaires because of dementia.

As a result, we obtained data from 150 patients with PD. Of these patients, 5 were being treated for depression with antidepressant drugs. None of the patients underwent deep brain stimulation (DBS) surgery during the course of the study. Informed consent was obtained from all study participants.

Assessment Instruments/Questionnaires

Patients were assessed clinically using assessment instruments comprising both neurologist-administered rating scales and self-administered questionnaires. The neurologist-administered assessments were the modified Hoehn and Yahr Scale (HY)[11] to stage PD severity in the patient's best "on" state, the Unified Parkinson's Disease Rating Scale (UPDRS),[12] and the Mini-Mental State Examination (MMSE).[13] These examinations were performed by a neurologist on the same day. The self-administered scales included the Beck Depression Inventory (BDI),[14] an apathy scale (AS)[15] and 2 QOL instruments: the EuroQoL (EQ-5D)[16] and the 39-item Parkinson's disease questionnaire (PDQ-39).[17]

Dementia was diagnosed on the basis of an MMSE score <21, which is recommended as a cutoff for dementia.[13] Depression was evaluated with the Japanese version of the BDI Second Edition (BDI-II),[18] which has been used widely in Japan to assess depression and is reported to have excellent reliability and validity.[18] The cutoff score for the BDI-II was set at 14, as is standard in Japan[18] and indicated in the original version.[14] To assess apathy, the Japanese version[19] of Starkstein's Apathy Scale[15] was used. This scale[15] was chosen based on a review of apathy and anhedonia rating scales in PD by Leentjens et al[20] in which they recommended only this scale be used to assess apathy in PD. The cutoff score was set at 16 rather than 14 as indicated in the original scale because the Japanese version demonstrated high reliability (sensitivity 81.3%, specificity 85.3%) with a cutoff of 16.[19] The Japanese version of the EQ-5D, a 5-item questionnaire, and the PDQ-39, a 39-item questionnaire, were used for QOL assessments. The EQ-5D is a generic health-related QOL measure developed by the European Quality of Life Group, which was translated into Japanese and validated.[21] It includes 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and psychological status, with 3 possible answers for each item (1 = *no problem*, 2 = *moderate problem*, 3 = *severe problem*). A summary index with a maximum score of 1 can be derived from these 5 dimensions by conversion with a table of scores. The maximum score of 1 indicates the best health state, in contrast with the scores of individual questions where higher scores indicate more severe or frequent problems. The PDQ-39 is a widely used disease-specific health-related QOL measure and was translated and validated in Japan by Kohmoto et al.[22] The PDQ-39 is comprised of 39 questions, each with 5 different answer options, from which 8 subscores (mobility, activity of daily living [ADL], emotional well-being, stigma, social support, cognition, communication, and bodily discomfort) and 1 summary index (SI) can be calculated. The maximum score of 100 indicates the worst quality of life.

Statistical Analysis

Group differences of clinical variables between males and females were analyzed using nonparametric tests (Mann-Whitney *U* test). Spearman's rank correlation coefficients were used to assess the degree of correlations between BDI-II or AS scores and the following variables: age, age at onset, disease duration, HY stage, UPDRS total and individual subscale score, MMSE score, Levodopa dose, PDQ-39 score, and EQ-5D score. Total levodopa dose equivalent[23] was calculated as follows: (regular levodopa dose × 1) + (pramipexole dose × 67) + (ropinirole dose × 16.67) + (pergolide dose × 100) + (bromocriptine dose × 10) + (regular levodopa dose × 0.1 if taking entacapone). To identify apathy and depression determinants, stepwise multiple regression analysis was used. In this model, AS and BDI scores were considered dependent variables, and independent (explanatory) variables were chosen on the basis of Spearman's rank correlations, where only statistically significant factors were included. Interaction and colinearity effects were taken into account when building the regression models. All data were analyzed using Dr SPSS (SPSS version 11.0). Statistical significance was set at $P < .05$.

Results

Table 1 shows the clinical characteristics of the 150 PD study patients. There were no differences in clinical variables between males and females.

Figure 1 shows the prevalence of depression, apathy, and dementia in all 150 participants. Apathy was present in 90 patients (60%) and depression was present in 84 patients (56%). Apathy in the absence of depression was evident in 25 patients (17%) and depression in the absence of apathy was evident in 19 patients (13%). Twelve patients (8%) were diagnosed as having dementia. Apathy only was present in 23 patients (15%) and depression only was present in 18 patients (12%). No patients with dementia only were noted. Apathy coexisted with depression and dementia in 9 patients (6%).

Table 2 shows the relationship between score on the AS or BDI-II and several clinical variables. A significant correlation was noted between AS and BDI-II scores (rs = .547, $P < .001$). Apathy scale score showed significant correlations with age and onset age (rs = .229, $P = .006$ and rs = .176, $P = .038$, respectively). In contrast, there was no correlation between BDI-II score and age or onset age. In regard to duration of

Table 1. Characteristics of Study Patients

	Total (n = 150)		Male (n = 70)		Female (n = 80)	
	Mean	SD	Mean (Range)	SD	Mean (Range)	SD
Age (yr)	69.7	8.6	68.3 (47-86)	9.2	70.9 (0-87)	8.0
Age at onset (yr)	63.4	9.8	61.9 (35-82)	10.2	64.7 (43-82)	9.3
Duration of disease (yr)	6.3	4.4	6.3 (1-16)	3.9	6.3 (1-17)	4.8
Hoehn-Yahr stage	2.9	0.9	2.8 (1-5)	0.8	3.0 (1-5)	1.0
UPDRS I (Mentation)	2.5	2.6	2.4 (0-13)	2.6	2.5 (0-12)	2.6
UPDRS II (ADL)	12.0	8.7	12.0 (0-41)	7.9	12.0 (0-45)	9.4
UPDRS III (motor)	29.2	16.2	28.0 (1-70)	14.0	30.0 (7-84)	18.0
UPDRS IV (complications)	3.0	3.2	2.9 (0-14)	3.1	3.1 (0-14)	3.3
UPDRS total	46.7	25.5	45.0 (3-125)	23.0	48.0 (11-138)	28.0
MMSE	26.6	3.9	26.6 (16-30)	4.0	26.6 (14-30)	3.9
Beck Depression Inventory	16.9	10.6	16.0 (0-61)	10.0	18.0 (0-49)	11.0
AS	17.0	7.5	17.0 (0-42)	8.0	16.9 (2.36)	7.1
Anti-PD medication	340.1	209.3	337.8 (0-1200)	234.9	342.3 (0-935)	185.4
PDQ-39						
Mobility	46.5	32.5	42.6 (0-100)	31.8	49.8 (0-100)	32.9
ADL	39.8	31.4	38.4 (0-100)	30.5	40.9 (0-100)	32.3
Emotional well-being	39.0	27.8	35.2 (0-100)	25.3	42.1 (0-100)	29.5
Stigma	25.1	25.2	22.6 (0-100)	21.5	27.1 (0-100)	27.8
Social support	15.6	21.4	12.6 (0-100)	19.5	18.0 (0-92)	22.6
Cognition	34.3	24.4	37.8 (0-100)	27.5	31.5 (0-100)	21.4
Communication	22.5	25.0	24.1 (0-100)	25.9	21.2 (0-100)	24.3
Bodily discomfort	32.1	24.9	32.2 (0-100)	23.7	32.0 (0-100)	26.0
Summary index	31.9	21.5	30.7 (0-100)	21.2	32.8 (2-89)	21.8
EQ-5D						
Mobility	1.7	0.5	1.7 (0-3)	0.5	1.7 (0-3)	0.5
ADL	1.6	0.6	1.6 (0-3)	0.6	1.6 (0-3)	0.6
Work	1.9	0.6	1.8 (0-3)	0.6	1.9 (0-3)	0.6
Pain	1.8	0.6	1.7 (0-3)	0.6	1.8 (0-3)	0.6
Anxiety	1.6	0.7	1.6 (0-3)	0.6	1.7 (0-3)	0.7
Summary	0.6	0.2	0.6 (−0.11-1)	0.2	0.6 (0.37-1)	0.2

NOTES: ADL = activity of daily living; EQ-5D = EuroQoL; MMSE = Mini-Mental State Examination; PDQ-39 SI = Parkinson's disease questionnaire; UPDRS = Unified Parkinson's Disease Rating Scale.

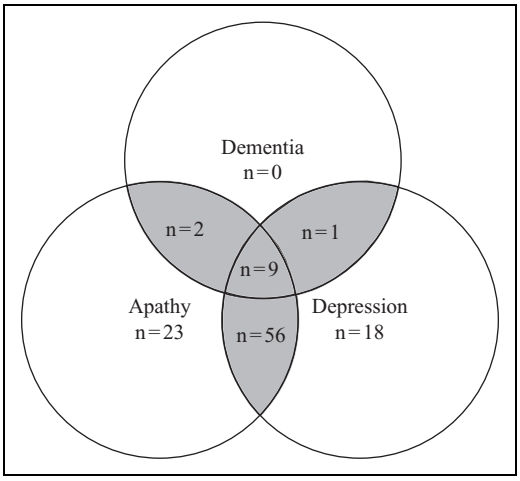

Figure 1. Prevalence of depression, apathy, and dementia in 150 patients with Parkinson disease (PD).

disease, no significant correlation was found with either apathy or depression. Apathy scale score showed significant correlation with HY stage ($rs = 0.256$, $P = .002$), while only a trend

Table 2. Relationships Between AS or BDI-II Scores and Clinical Variables

	AS		BDI-II	
	rs	*P*	*rs*	*P*
Age	.229[a]	.006	.116	.173
Age at onset	.176[a]	.038	.091	.288
Duration of disease	.063	.459	.032	.713
Hoehn-Yahr stage	.256[a]	.002	.154[a]	.070
UPDRS I (Mentation)	.485[a]	<.001	.469[a]	<.001
UPDRS II (ADL)	.239[a]	.004	.301[a]	<.001
UPDRS III (Motor)	.282[a]	.001	.242[a]	.004
UPDRS IV (complications)	.105	.215	.192[a]	.023
UPDRS total	.326[a]	<.001	.343[a]	<.001
MMSE	−.321[a]	<.001	−.140	.101
Levodopa dose equivalents	.053	.579	0.139	.140
PDQ-39	.513[a]	<.001	0.727[a]	<.001
EQ-5D summary	−.358[a]	<.001	−0.555[a]	<.001

[a]significant

NOTES: ADL = activity of daily living; AS = Apathy Scale; BDI-II = Beck Depression Inventory Second Edition; EQ-5D = EuroQoL; MMSE = Mini-Mental State Examination; PDQ-39 SI = Parkinson's disease questionnaire; UPDRS = Unified Parkinson's Disease Rating Scale. *rs* = Spearman's rho correlation coefficient.

Table 3. Results of Stepwise Multiple Regression Analysis

Predictors	*R*	R^2	Adjusted R^2	R^2 change	β-weight	τ Value	*P* value
A. Dependent variable: AS score (Independent variables: age at onset, age, Yahr stage, UPDRS parts I, II, III, total, EQ-5D, PDQ-39 SI)							
PDQ-39 SI	.532	.282	.277	.282	.532	7.263	<.001
age at onset					.159[a]	2.177	.031
age					.148[a]	2.041	.043
Yahr stage					.017	0.206	.837
UPDRS I					.318[a]	3.679	<.001
UPDRS II					–.003	–0.031	.975
UPDRS III					.077	0.947	.345
UPDRS total					.081	0.950	.344
MMSE					–2.31[a]	–3.086	.002
EQ-5D					–1.04	–0.985	.326
B. Dependent variable: BDI-II score (Independent variables: UPDRS parts I, II, III, IV, total, EQ-5D, PDQ-39 SI)							
PDQ-39 SI	.747	.558	.555	.558	.747	13.155[a]	<.001
UPDRS I					.141[a]	2.041	.043
UPDRS II					–.034	–.530	.597
UPDRS III					–.035	–.555	.580
UPDRS IV					.027	.474	.636
UPDRS total					–.020	–.297	.173
EQ-5D					–.111	–1.371	.173

NOTES: AS = Apathy Scale; BDI-II = Beck Depression Inventory Second Edition; EQ-5D = EuroQoL; MMSE = Mini-Mental State Examination; PDQ-39 SI = Parkinson's disease questionnaire; UPDRS = Unified Parkinson's Disease Rating Scale.
[a]Significant.

was noted between BDI-II score and HY stage (rs = .154, P = .07). Both AS and BDI-II scores showed significant correlations with UPDRS subscale scores and total score (AS: P < .05 for UPDRS subscales I ([rs = .485),], II ([rs = .282),], III ([rs = .326),], and total score ([rs = .326)]; BDI-II: P < .05 for each of the UPDRS subscales ([I: rs = .469, II: rs = .301, III: rs = .242, IV: rs = .192)] and total score [rs = .343]), although no significant correlation was found between the UPDRS subscale IV score and AS score. Regarding MMSE score, only AS score showed a significant correlation (rs = –.321, P < .001). Neither AS nor BDI-II score showed significant association with levodopa dose equivalent. Both AS and BDI-II scores showed significant correlations with PDQ-39 SI score (rs = .513, P < .001 and rs = .727, P < .001, respectively) and EQ-5D total score (rs = –.358, P < .001 and rs = –.555, P < .01, respectively).

To determine which factors contributed most to BDI-II or AS score, multiple stepwise regression analyses were performed, entering factors that correlated significantly with BDI-II or AS score (Table 3). A multiple regression model that included AS score as the dependent variable and age, onset age, HY stage, UPDRS I, II, and III subscale scores, MMSE score, EQ-5D score, and PDQ-39 SI score as independent variables showed PDQ-39 SI score as explaining the most variation in AS score (R^2 = .282, P < .001). The regression model that included BDI as the dependent variable, and UPDRS I, II, III, and IV subscale scores, EQ-5D score, and PDQ-39SI score as the independent variables also showed PDQ-39SI score as explaining the most variation in BDI-II score (R^2 = .558, P < .001). Because this variable was the most strongly related factor to both AS and BDI-II scores, we examined the correlation between AS or BDI-II score and PDQ-39 subdimension scores. To identify determinants of apathy and depression, a multiple regression analysis was carried out. In these models, the dependent variables were AS and BDI-II scores, and the 8 subdimension scores of the PDQ-39 were the independent variables. As shown in Table 4, AS score was mainly explained by cognition and stigma, while BDI-II score was mainly explained by emotional well-being and communication.

Discussion

In the present study, among the 60% of the 150 patients who had apathy, 17% had no concomitant depression. Among the 56% of patients who had depression, 13% had no concomitant apathy. Forty-three percent had both depression and apathy. These findings suggest that both apathy and depression are core features of PD, and that apathy can be present in the absence of depression. Apathy was correlated with higher depression scores and impaired cognitive functioning. After excluding patients with depression and dementia, 15% of the 150 patients presented with apathy as an independent behavioral disorder. These findings indicate that apathy is common and may occur as an independent behavioral disturbance in the patient with PD.

The high prevalence of apathy and depression reported in this study is consistent with the current literature[5,14-28] and underscores that apathy and depression are key neuropsychiatric features of PD. Although frequency of apathy in our series is slightly higher than reported elsewhere (Table 5), differences in the apathy rating scales[28-30] and the size and selection of the study population employed in each study could explain the discrepancies in results. In regard to the characteristics of patients in the present study, there were a slightly higher number of

Table 4. Results of Stepwise Multiple Regression Analysis

Predicators	*R*	R^2	Adjusted R^2	R^2 change	β-weight	t value	*P* value
A. Dependent variable: AS score (Independent variables: subdimensions of PDQ-39)							
Cognition	.553	.306	.301	.306	.553	7.859	<.001
Mobility					.062	.711	.478
ADL					.163	1.652	.101
Emotional well-being					.219[a]	2.533	.012
Stigma					.214[a]	2.736	.007
Social support					.090	1.053	.294
Communication					.272[a]	2.469	0.015
Bodily discomfort					−.019	−.224	.823
B. Dependent variable: BDI-II score (Independent variables: subdimensions of PDQ-39)							
Emotional well-being	.725	.526	.523	.526	.725	12.38[a]	<.001
Mobility					.091	1.199	.233
ADL					.159	1.893	.060
Stigma					.237[a]	2.999	.003
Social support					.251[a]	3.440	.001
Cognition					.236[a]	3.259	.001
Communication					.352[a]	5.233	<.001
Bodily discomfort					.157[a]	2.460	.015

NOTES: ADL = activity of daily living; AS = Apathy Scale; BDI-II = Beck Depression Inventory Second Edition; PDQ-39 = Parkinson Disease Questionnaire 39.
[a]Significant.

Table 5. Prevalence (%) of Apathy and Depression in PD

		Instruments to access							
Author	No. of cases	Apathy	Depression	Apathy	Depression	Both	Apathy only	Depression only	Neither
Starkstein et al[15]	50	Starkstein's AS	HAMD	42	56	30	12	26	32
Levy et al[4]	40	NPI	NPI	32.5	55	11	5	28	40
Aarsland et al[25]	139	NPI	NPI	16.5	38	–	–	–	–
Pluck et al[26]	45	MarinAS	BDI	38	43	–	–	–	–
Kirsh-Darrow et al[5]	80	MarinAS	BDI	51	26	22	29	4	44
Dujardin et al[28]	159	LARS	MADRS	32	25	19	13	6	62
Pederson et al[29]	232	UPDRS I	MADRS	38	30	21	17	9	52
Our study, 2009	150	Starkstein's AS	BDI-II	60	56	43	17	13	27

NOTES: AS = Apathy Scale; BDI-II = Beck Depression Inventory Second Edition; HAMD = Hamilton Rating Scale for Depression; LARS = Lille Apathy Rating Scale; MADRS = Montgomery and Asberg Depression Rating Scale; NPI = Neuropsychiatric Inventory; PD = Parkinson disease.

females than males, which is consistent with the higher prevalence of PD reported among females in the Japanese population.[31] Another point of note is that there was no difference in BDI-II score between males and females. This result is also in good agreement with previous reports[32,33] that depressive symptoms equally affected females and males, although some authors have reported that depression in PD was more common in females.[8,34] Eight percent of our patients with PD had concomitant dementia, which may have led to an overestimate of the prevalence of apathy in PD alone. In addition, a high frequency of apathy may contribute to the prevalence of depression, because a significant correlation was found between apathy and depression and the severity of depression symptoms contributes to the overall level of apathy.

We also found a significant correlation between apathy and lower cognitive function. Apathy is generally considered a sign of frontal dysfunction and can be seen with focal lesions of the frontal lobe or as part of more widespread dysfunction such as in AD.[26,35] Therefore, we used the MMSE, which is not sensitive to cognitive deficits due to subcortical or frontal lobe disturbances, in this study. Previous studies[4,29] also found significant correlations between apathy and lower MMSE scores, although others did not,[15,26] or instead used cognitive tests of executive function or attention problems.[27] Different findings could also be related to case selection, that is, whether patients with dementia were included or not, and the use of different scales to measure the level of apathy.[20,28] In contrast to AS score, BDI-II score was not significantly associated with MMSE score in the present study, although previous studies[36,37] demonstrated a significant correlation between depression and cognitive impairment. Wichowicz et al[38] reported that PD patients with depression scored lower on the

MMSE compared to those without depression, although the difference was not statistically significant, as shown in our study. Pluck et al[26] have also demonstrated that apathy is more clearly associated with cognitive dysfunction than depression in PD and have suggested that this link is related to disruption of frontosubcortical circuits. Although it remains unclear whether separate neural systems underlie depression and apathy, it may be that orbitofrontal-subcortical connections underlie depression in PD, whereas mesial frontal-anterior cingulate subcortical connections underlie apathy.[39] These possible anatomical differences may result in some differences in the relationships between apathy or depression and MMSE score.

The current study showed significant correlations between apathy and more severe motor symptoms estimated by the UPDRS scores on subscales II and III and HY stage. These results are concordant with previous studies.[1,29] Similar correlations were noted for depression in our study. Several investigators[40,41] have reported that depressed patients with PD had more severe motor symptoms, more advanced HY staging, and a more severe global clinical condition (determined by UPDRS) than nondepressed patients with PD. These findings may support the hypothesis[1] that dysfunction of the nigrostriatal pathway plays an important role in the pathophysiology of apathy and depression in PD, although later stages (in which gait and balance are disturbed) are generally associated with more global brain involvement.

A dopaminergic deficit has previously been used to explain the pathogenesis of apathy or depression because dopaminergic agonists are reported to improve apathy[1] or depression[2] in some patients as well as in groups of patients with PD treated with levodopa in the "on" state versus the "off" state. Poewe[2] describes that dopaminergic cell loss in the ventral tegumental area (VTA) with subsequent orbitofrontal dopaminergic denervation may contribute to apathy and anhedonia, which are typical of parkinsonian depression. However, not all patients with PD become apathetic or depressive, indicating that neither symptom should necessarily be considered a dopamine-dependent syndrome in PD. Dujardin et al[28] suggest that nondopaminergic circuits participate in the pathophysiology of apathy in PD because the apathy level is mainly determined by cognitive impairment and not by association with the severity of motor symptoms. PD-specific pathology with multiple transmitter deficiencies in mesocortical monoaminergic systems plays a major role, which includes those of the mesocorticolimbic dopamine projection and the mesocortical noradrenergic and serotonergic projections, in the pathogenesis of apathy and depression.

As for UPDRS subscale IV score, a correlation was shown with BDI-II score but not with AS score. These results may be the result of apathetic patients being less sensitive to dyskinesia and motor fluctuation than depressive patients.

In the current study, both BDI-II and AS scores were significantly correlated with QOL scores as determined by the EQ-5D and PDQ-39. In addition, multiple regression analysis showed that both BDI-II and AS scores were more strongly associated with the PDQ-39 (disease-specific QOL) SI score than the UPDRS or MMSE score. In accordance with these results, Lemke[42] reported that depression reduced QOL independently of motor symptoms. Many studies[6-8,43] have also found depression to be a predictor of QOL. However, few studies have investigated the relationship between apathy and QOL in patients with PD. The current study has revealed that both depression and apathy are closely associated with QOL in PD. However, multiple regression analysis using the subdimension scores of the PDQ-39 suggested some differences between apathy and depression, namely, that AS was mainly explained by cognition and stigma, whereas BDI was mainly determined by emotional well-being and communication.

In this study, AS score, but not BDI-II score, was significantly associated with patient age and age at onset. These results also suggest pathophysiological differences between apathy and depression.

In conclusion, apathy as well as depression are common behavioral disturbances in patients with PD and are associated with impaired cognitive functioning and more severe motor symptoms. However, apathy may occur independently of depression. Apathy and depression are not similar in terms of their associations with other clinical variables. Our study indicates that apathy may be a "core" feature of PD and a distinct syndrome, not merely a symptom of depression.

The recognition that apathy can be present without depression is important in avoiding inappropriate diagnosis and treatment as a depressive disorder that is not in fact present. Although patients with PD themselves generally do not complain of apathy, it needs to be systematically diagnosed and considered in their care and management because it may contribute to a reduction of QOL for both patients and caregivers.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

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References

1. Levy R, Czernecki V. Apathy and the basal ganglia. *J Neurol*. 2006;253(suppl 7):VII/54-VII/61.
2. Poewe W. Depression in Parkinson's disease. *J Neurol*. 2007; 254(suppl 5):49-55.
3. Marin RS, Firinciogullari S, Biedrzycki RC. Group differences in the relationship between apathy and depression. *J Nerv Ment Dis*. 1994;182(4):235-239.
4. Levy ML, Cummings JL, Fairbanks LA, et al. Apathy is not depression. *J Neuropsychiatry Clin Neurosci*. 1998;10(3):314-319.
5. Kirsch-Darrow L, Fernandez HF, Marsiske M, et al. Dissociating apathy and depression in Parkinson's disease. *Neurology*. 2006; 67(1):33-38.
6. Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease? *J Neurol Neurosurg Psychiatry*. 2000;69(3):308-312.
7. Slaweka J, Derejko M, Lass P. Factors affecting the quality of life of patients with idiopathic Parkinson's disease—a cross-sectional

study in outpatient clinic attendees. *Parkinsonism Relat Disord*. 2005;11(7):465-468.
8. Carod-Artal FJ, Vargous AP, Martinez-Martin P. Determinants of quality of life in Brazilian patients with Parkinson's disease. *Mov Disord*. 2007;22(10):1408-1415.
9. Rahman S, Griffin KJ, Quinn NP, Jahanshahi M. Quality of life in Parkinson's disease: the relative importance of the symptoms. *Mov Disord*. 2008;23(10):1428-1434.
10. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry*. 1992;55(3):181-184.
11. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med*. 2006;355(9):896-908.
12. Fahn S, Elton RL. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne D, et al., eds. *Recent developments in Parkinson's disease.* Florham Park, NJ: McMillan Health Care Information; 1987:153-163.
13. Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.
14. Levin BE, Lllabre MM, Weiner WJ. Parkinson's disease and depression: psychometric properties of the Beck Depression Inventory. *J Neurol Neurosurg Psychiatry*. 1988;51(11):1401-1404.
15. Starkstein SE, Mayberg HS, Preziosi T, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neurophychiatry Clin Neurosci*. 1992;4(2):134-139.
16. Schrag A, Selai C, Jahanshahi M, Quinn NP. The EQ-5D-a generic quality of life measure is a useful instrument to measure quality of life in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2000;69(1):67-73.
17. Hagell P, Nygren C. The 39-item Parkinson's disease questionnaire (PDQ-39) revisited: implications for evidence based medicine. *J Neurol Neurosurg Psychiatry*. 2007;78(11):1191-1198.
18. Beck AT, Steer RA, Brown GK. Japanese version BDI-II (Beck Depression Inventory, Second Edition), Nihon Bunka Kagakusho, Tokyo, 2003:2-11.
19. Okada K, Kobayashi S, Aoki K, et al. Assessment of motivational loss in poststroke patients using the Japanese version of Starkstein's Apathy Scale. *Jpn J Stroke*. 1998;20(3):318-323.
20. Leentjens AFG, Dujardin K, Marsh L, et al. Apathy and anhedonia rating scales in Parkinson's disease. Critique and recommendations. *Mov Disord*. 2008;23(14):2004-2014.
21. Japanese EuroQoL Translation Team. The development of the Japanese EuroQoL instrument. *Iryo to Shakai*. 1998;8(1):109-123.
22. Kohmoto J, Ohbu S, Nagaoka M, et al. Validation of the Japanese version of the Parkinson's disease questionnaire. *Clin Neurol*. 2003;43(3):71-76.
23. Hobson DE, Lange AE, Martin WR, Razmy A, Rivest J, Fleming J. Excessive daytime sleepiness and sudden-onset sleep in Parkinson's disease: a survey by the Canadian Movement Disorders Group. *JAMA*. 2002;287(4):455-463.
24. Shulman LM, Taback RL, Bean J, Weiner WJ. Comorbidity of the nonmotor symptoms of Parkinson's disease. *Mov Disord*. 2001;16(3):507-510.
25. Aarsland D, Larsen JP, Lim NG, et al. Range of neuropsychiatric disturbances in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1999;67(4):492-496.
26. Pluck GC, Brown RG. Apathy in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2002;73(6):636-649.
27. Isella V, Melzi P, Grimaldi M, et al. Clinical, neuropsychological, and morphometric correlates of apathy in Parkinson's disease. *Mov Disord*. 2002;17(2):366-371.
28. Dujardin K, Sockeel P, Deros D, et al. Characteristics of apathy in Parkinson's disease. *Mov Disord*. 2007;22(6):778-784.
29. Pederson KFm Larsen JP, Alves G, Aarsland D. Prevalence and clinical correlates of apathy in Parkinson's disease: a community-based study. *Parkinsonism Relat Disord*. 2009; 15(4):295-299.
30. Sockeel P, Dujardin K, Devos D, et al. The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2006;77(5):579-584.
31. Kusumi M, Nakashima K, Harada H, Nakayama H, Takahashi K. Epidemiology of Parkinson's disease in Yonago city, Japan -comparison with a study carried out 12 years ago. *Neuroepidemiology*. 1996;15(4):201-207.
32. Cole SA, Woodard JL, Juncos JL, Kogos JL, Youngstrom EA, Watts RL. Depression and disability in Parkinson's disease: a quantitative and qualitative analysis. *J Neuropsychiatry Clin Neurosci*. 1996;8(1):20-25.
33. Starkstein SE, Preziosi TJ, Bolduc PL, Robinson RG. Depression in Parkinson's disease. *J Nerv Ment Dis*. 1990;178(1):27-31.
34. Fleminger S. Left-sided Parkinson's disease is associated with greater anxiety and depression. *Psychol Med*. 1991;21(3): 629-638.
35. Richard IH. Apathy does not equal depression in Parkinson's disease. Why we should care. *Neurology*. 2006;67(1):10-11.
36. Mayeux R, Stern Y, Rosen J, Leventhal J. Depression, intellectual impairment, and Parkinson's disease. *Neurology*. 1981;31(6): 645-650.
37. Starkstein SE, Preziosi TJ, Nerthier ML, Bolduc PL, Mayberg HS, Robinson RG. Depression and cognitive impairment in Parkinson's disease. *Brain*. 1989;112(pt 5):1141-1153.
38. Wichowicz HM, Stawek J, Derejko M, Cubała WJ. Factors associated with depression in Parkinson's disease: a cross-sectional study in a Polish population. *Eur Psychiatry*. 2006; 21(8):516-520.
39. Stella F, Banzato CE, Barasnevicius Quagliato EM, Viana MA. Depression in patients with Parkinson's disease: impact on functioning. *J Neurol Sci*. 2008;272(1-2):158-163.
40. Ehmann TS, Beninger RJ, Gawel MJ, Riopelle RJ. Depression synptoms in Parkinson's disease: a comparison with disabled control subjects. *J Geriatr Psychiatry Neurol*. 1990;3(1):3-9.
41. Kanda F, Oishi K, Sekiguchi K, et al. Characteristics of depression in Parkinson's disease: evaluating with Zung's self-rating depression scale. *Parkinsonism Relat Disord*. 2008;14(1):19-23.
42. Lemke MR. Depressive symptoms in Parkinson's disease. *Eur J Neurol*. 2008:(suppl 1):21-25.
43. Den Oudsten B, Van Heck GL, De Vries J. Quality of life and related concepts in Parkinson's disease: a systematic review. *Mov Disord*. 2007;22(11):1528-1537.