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Clinical determinants of apathy and its impact on health-related quality of life in early Parkinson disease

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Abstract

Apathy is a common non-motor symptom of Parkinson disease (PD) that can affect the health-related quality of life (HRQoL) of patients and caregivers. This study aimed to investigate the clinical determinants of apathy and its impact on HRQoL in patients with early PD.

We enrolled 324 patients with early PD with modified Hoehn–Yahr stages 1 to 3 and a disease duration ≤5 years. Demographic information was obtained, and motor and non-motor symptoms were evaluated with relevant scales.

Apathy was present in 110 of 324 (33.9%) patients. Compared with patients with non-apathetic PD, those with apathetic PD had significantly higher modified Hoehn–Yahr stage, Unified Parkinson's Disease Rating Scale-II (UPDRS-II) score, Non-Motor Symptoms Scale (NMSS) total score, Beck Depression Inventory (BDI) score, and Parkinson's Disease Questionnaire-8 (PDQ-8) score. Clinical variables independently associated with the Apathy Evaluation Scale (AES) score were NMSS domain 3 score and BDI score. The univariate regression analysis revealed that the PDQ-8 score was significantly associated with age; disease duration; formal education duration; and UPDRS-III, UPDRS-II, NMSS total, Mini-Mental Status Examination, BDI, Beck Anxiety Inventory, and AES scores. Independent predictors of the PDQ-8 score in the multivariate regression analysis were UPDRS-III, UPDRS-II, NMSS total, NMSS domain 3, Beck Anxiety Inventory, and AES scores.

In the present study, apathy was an independent predictor of HRQoL in patients with early PD. Therefore, identifying and managing apathy could help improve HRQoL in patients with early PD.

Abbreviations: ADL = activities of daily living, AES = Apathy Evaluation Scale, BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, HRQoL = health-related quality of life, mHY = modified Hoehn–Yahr, MMSE = Mini-Mental Status Examination, NMSS = Non-Motor Symptoms Scale, PD = Parkinson disease, PDQ-8 = Parkinson's Disease Questionnaire-8, UPDRS = Unified Parkinson's Disease Rating Scale.

Keywords: anxiety, apathy, Parkinson disease (PD), quality of life (QoL)

1. Introduction

Apathy is a syndrome of primary motivational loss not attributable to cognitive impairment, emotional stress, or diminished level of consciousness.[1] It is a common neuropsychiatric symptom that can occur in patients with various neurodegenerative disorders. The prevalence of apathy is more common in neurodegenerative diseases, such as progressive supranuclear palsy, frontotemporal dementia, and Huntington disease, which prominently involve the prefrontal cortex and caudate nuclei.[2] Apathy is associated with caregiver burden, decreased response to treatment, and poor long-term prognosis in various neurological diseases.[3] Therefore, recognition of apathy associated with neurological disease may be important for patient care.

Apathy is a common non-motor symptom of Parkinson disease (PD), but its prevalence and clinical correlates in PD vary across studies. It is found in patients with de novo PD, with a higher prevalence in patients with advanced PD.[2] It can precede the onset of motor symptoms of PD and be considered as a premotor symptom suggestive of PD development.[4] Apathy caused by PD is associated with motor dysfunction and various non-motor symptoms, particularly depression and cognitive dysfunction.[5] It can affect the health-related quality of life (HRQoL) of patients with PD and their caregivers,[2,6] however, some studies have shown that apathy was not an independent predictor of poor HRQoL in patients with PD.[7] Therefore, the aim of this study was to describe the prevalence of apathy in

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Table 1

Clinical characteristics of patients with early apathetic and non-apathetic Parkinson disease.

	No apathy (n = 214)	Apathy (n = 110)	*P* value	ANCOVA *P* value	Corrected *P* value
Age (yr)	67.0 ± 9.4	68.2 ± 9.6	.284		
Sex (male:female)	91: 123	43: 67	.634		
Disease duration (mo)	16.9 ± 16.5	19.8 ± 17.4	.140		
Formal education (yr)	9.1 ± 4.6	8.3 ± 4.9	.140		
mHY stage	1.8 ± 0.6	2.0 ± 0.7	**.003**		
UPDRS-III score	21.1 ± 10.0	23.2 ± 10.4	.082		
UPDRS-II score	5.4 ± 4.5	9.9 ± 7.8	**<.001**		
NMSS total score	38.2 ± 26.4	67.4 ± 38.5	**<.001**	**<.001**	**<.001**
MMSE score	26.3 ± 3.2	25.8 ± 3.5	.152	.744	1.000
BDI score	8.4 ± 7.4	18.05 ± 12.0	**<.001**	**<.001**	**<.001**
BAI score	7.5 ± 6.3	14.9 ± 10.8	**<.001**	**<.001**	**<.001**
AES score	30.4 ± 6.0	46.4 ± 6.1	**<.001**	**<.001**	**<.001**
PDQ-8 score	3.9 ± 3.8	8.9 ± 6.5	**<.001**	**<.001**	**<.001**

Data are presented as mean ± standard deviation. Covariates of ANCOVA were the mHY stage and UPDRS-III and UPDRS-II scores. The corrected *P* values were Bonferroni corrected for multiple comparisons. Bold font indicates statistical significance.

AES = Apathy Evaluation Scale, ANCOVA = analysis of covariance, BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, mHY = modified Hoehn and Yahr scale, MMSE = Mini-Mental State Examination, NMSS = Non-Motor Symptoms Scale, PDQ-8 = Parkinson's Disease Questionnaire-8, UPDRS = Unified Parkinson's Disease Rating Scale.

patients with early PD and to investigate the clinical determinants of apathy and its impact on HRQoL.

2. Subjects and Methods

We consecutively enrolled patients with PD from the outpatient clinic of our hospital. Inclusion criteria were as follows: a diagnosis of PD according to the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria,[8] modified Hoehn–Yahr (mHY) stages 1 to 3, and a disease duration ≤5 years. Exclusion criteria were as follows: neurodegenerative disorders other than PD, dementia, and any clinically significant lesion on brain magnetic resonance imaging. This study was approved by the Institutional Review Board of our hospital and conducted in accordance with the ethical standards laid down by the Declaration of Helsinki.

Demographic information, such as age, sex, disease duration, and formal education duration, were obtained. Severity of motor symptoms and activities of daily living (ADL) were assessed according to the mHY stage[9] and parts III and II of the Unified Parkinson's Disease Rating Scale (UPDRS-III and UPDRS-II, respectively).[10] The Non-Motor Symptoms Scale (NMSS) was used to evaluate non-motor symptoms of PD,[11] the Mini-Mental Status Examination (MMSE) to evaluate global cognitive functioning,[12] Beck Depression Inventory (BDI) to evaluate depression,[13] the Beck Anxiety Inventory (BAI) to evaluate anxiety,[14] the Apathy Evaluation Scale (AES) to evaluate apathy,[15] and the Parkinson's Disease Questionnaire-8 (PDQ-8) to evaluate HRQoL.[16,17] Apathy was assessed using the self-report version of the AES (AES-S), and a cutoff score of 38/39 was used to distinguish apathetic from non-apathetic PD.[15,18]

To compare clinical characteristics of patients with apathetic and non-apathetic PD, the independent-sample *t* test was performed for continuous variables, and chi-square test was performed for categorical variables. The analysis of covariance was performed to compare non-motor variables between the 2 groups after controlling for the mHY stage and UPDRS-III and UPDRS-II scores, which were significantly different in the *t* test. The *P* values were then Bonferroni-corrected for multiple comparisons. The univariate linear regression analysis was performed to explore potential factors affecting the PDQ-8 score. The multivariate linear regression analysis was performed to identify independent factors associated with AES and explore independent clinical variables to predict the PDQ-8 score. Data were analyzed using Statistical Package for the Social Sciences version 27.0 for Windows (IBM Corp.; Armonk, NY), and a *P* value <.05 was considered to be statistically significant.

3. Results

We enrolled 324 patients, including 134 men and 190 women, with a mean age of 67.4 ± 9.5 years. The mean disease duration was 17.9 ± 16.8 months, and mean duration of formal education was 8.8 ± 4.7 years. Apathy was found in 110 (33.9%) patients with PD. There were no significant differences in age, sex, disease duration, or formal education duration between patients with apathetic and non-apathetic PD. Compared with patients with non-apathetic PD, those with apathetic PD had significantly higher mHY stage and UPDRS-II score. There was no significant difference in the UPDRS-III score between the 2 groups. Among non-motor variables, compared with patients with non-apathetic PD, those with apathetic PD had significantly higher NMSS total, BDI, BAI, AES, and PDQ-8 scores, which were statistically significant after controlling for the mHY stage and UPDRS-III and UPDRS-II scores. There was no significant difference in the MMSE score between the 2 groups (Table 1).

In the multivariate regression analysis, NMSS domain 3 score and BDI score were significantly correlated with the AES score. However, age, sex, disease duration, formal education duration, and UPDRS-III; UPDRS-II; NMSS total; MMSE; and BAI scores were not correlated with the AES score (Table 2).

The univariate linear regression analysis was performed to explore potential factors affecting the PDQ-8 score. There were statistically significant associations between the PDQ-8 score and age, disease duration, formal education duration, and UPDRS-III; UPDRS-II; NMSS total; MMSE; BDI; BAI; and AES scores. Sex was not associated with the PDQ-8 score (Table 3).

In the final multivariate linear regression analysis to explore the independent predictors of the PDQ-8 score, we included all variables associated with the AES or PDQ-8 score in the aforementioned analysis. AES score as well as UPDRS-III; UPDRS-II; NMSS total; NMSS domain 3; and BAI scores were significant independent predictors of the PDQ-8 score (Table 4).

4. Discussion

In this study on apathy and its impact on HRQoL in patients with early PD, we observed that the clinical determinants of apathy were NMSS domain 3 score and BDI score; apathy was an independent predictor of HRQoL; other significant predictors of HRQoL were motor dysfunction, the ADL status, global non-motor symptoms, and anxiety.

Apathy is a common non-motor symptom that can occur in all stages of PD.[2] The prevalence of apathy in PD is variable, ranging from 15 to 70%, depending on the stage of PD and

Table 2

Factors associated with the Apathy Evaluation Scale score.

	β	*P* value
Age (yr)	−0.052	.974
Sex (male:female)	−0.001	.985
Disease duration (mo)	0.060	.992
Formal education (yr)	−0.015	.947
UPDRS-III score	0.064	.980
UPDRS-II score	0.097	.680
NMSS total score	0.032	.444
NMSS domain 3 score	0.432	**<.001**
MMSE score	0.005	.948
BDI score	0.317	**<.001**
BAI score	0.056	.534

Bold font indicates statistical significance.

BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, MMSE = Mini-Mental State Examination, NMSS = Non-Motor Symptoms Scale, UPDRS = Unified Parkinson's Disease Rating Scale.

Table 3

Univariate regression analysis to explore potential factors affecting the PDQ-8 score in patients with early Parkinson disease.

	B (SE)	*P* value
Age (yr)	0.078 (0.032)	**.015**
Sex	0.390 (0.620)	.529
Disease duration (mo)	0.073 (0.018)	**.005**
Formal education (yr)	−0.184 (0.066)	**<.001**
UPDRS-III score	0.163 (0.028)	**<.001**
UPDRS-II score	0.616 (0.035)	**<.001**
NMSS total score	0.124 (0.006)	**<.001**
MMSE score	−0.234 (0.092)	**.011**
BDI score	0.338 (0.024)	**<.001**
BAI score	0.380 (0.027)	**<.001**
AES score	0.319 (0.026)	**<.001**

Bold font indicates statistical significance.

AES = Apathy Evaluation Scale, BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, MMSE = Mini-Mental State Examination, NMSS = Non-Motor Symptoms Scale, PDQ-8 = Parkinson's Disease Questionnaire-8, UPDRS = Unified Parkinson's Disease Rating Scale.

Table 4

Multivariate regression analysis to explore predictors of the PDQ-8 score in patients with early Parkinson disease.

	β	*P* value
Age (yr)	−0.060	.817
Disease duration (mo)	−0.005	.877
Formal education (yr)	0.019	.942
UPDRS-III score	0.114	**.001**
UPDRS-II score	0.190	**<.001**
NMSS total score	0.355	**<.001**
NMSS domain 3 score	0.206	**<.001**
MMSE score	0.040	.941
BDI score	0.054	.408
BAI score	0.162	**<.001**
AES score	0.083	**<.044**

Bold font indicates statistical significance.

AES = Apathy Evaluation Scale, BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, MMSE = Mini-Mental State Examination, NMSS = Non-Motor Symptoms Scale, PDQ-8 = Parkinson's Disease Questionnaire-8, UPDRS = Unified Parkinson's Disease Rating Scale.

diagnostic methods used.[2,18,19] In a previous study, apathy was found in 20 to 36% of patients with new-onset PD, 40% of those with PD without dementia, and 60% of those of PD with dementia.[2] In our PD cohort, the prevalence of apathy was 33.9%, similar to that of new-onset PD in the previous study, probably because we enrolled patients with early PD with a short disease duration of 17.9 months.[2,18]

In a previous study, apathy in PD was associated with older age, higher motor scores, more severe disability, depression, and cognitive dysfunction.[5,19] In the present study, NMSS domain 3 score and BDI score were independent factors affecting the AES score, consistent with previous reports. The relationship between apathy and higher mHY stage suggests that nigrostriatal pathway dysfunction might play a role in the development of apathy.[20] However, UPDRS motor and ADL scores were not related to the AES score in our study, indicating that apathy in PD should not be considered an entirely dopamine-dependent symptom.[5,20] We also found that the BDI score was significantly associated with the AES score. The association between depression and apathy in patients with PD has been reported in many studies.[5,7,20] However, apathy and depression share several clinical characteristics and are, therefore, difficult to differentiate clinically.[2] Scales to evaluate apathy that are devoid of depression-related items are required. Contrary to previous studies, our study showed that the MMSE score was not significantly associated with the AES scores, probably because patients with dementia were excluded while those with relatively low education were included in our study.

HRQoL in PD is affected by various demographic and clinical factors.[21,22] Activity limitation, which is significantly related to motor impairment, is the strongest predictor of HRQoL in PD.[23] Similarly, the UPDRS motor and ADL scores were independent predictors of HRQoL in this study. Including patients with early PD who do not have significant activity limitations might have provided an advantage in investigating non-motor symptoms affecting HRQoL. Non-motor symptoms affecting HRQoL in patients with PD include cognitive impairment, neuropsychiatric symptoms, autonomic disorders, and sleep disturbance.[22,24,25] Among neuropsychiatric symptoms, depression is the most frequently identified determinant of HRQoL in patients with PD.[21,24] However, depression was not an independent determinant of HRQoL in our PD cohort. Cognitive dysfunction is also a potential factor determining HRQoL in patients with PD,[23,26] however, the MMSE score was not an independent factor determining HRQoL in our study. These discrepancies occurred probably because we enrolled patients with early PD patients in our study with a relatively low prevalence of depression and cognitive dysfunction. In contrast, apathy and anxiety were significant factors affecting HRQoL in our PD cohort. Some studies have reported apathy as a predictor of HRQoL in patients with PD, whereas other have not.[7,24,25,27,28] This discrepancy of the results regarding relationship between apathy and HRQoL in patients with PD might be related to the differences in the patients group, the disease severity, and the apathy scale used. This should be considered when investigating apathy affecting HRQoL in patients with PD.

This study has several limitations. First, no control group was included. Therefore, the prevalence of apathy could not be compared between patients with PD and controls. Second, we did not differentiate apathy from depression. It remains unclear whether apathy is a symptom of depression or an independent syndrome.[20] Therefore, depression and apathy rating scales without items related to overlapping symptoms are necessary, when considering depression and apathy as distinct syndromes.

5. Conclusions

In the present study, depression was a clinical determinant of apathy, and apathy and anxiety were independent non-motor symptoms that determined poor HRQoL in patients with

early PD. Therefore, identifying and managing these non-motor symptoms in patients with early PD could help improve patients' HRQoL.

Author contributions

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References

[1] Marin RS. Apathy: a neuropsychiatric syndrome. J Neuropsychiatry Clin Neurosci. 1991;3:243–54.
[2] Pagonabarraga J, Kulisevsky J, Strafella AP, et al. Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment. Lancet Neurol. 2015;14:518–31.
[3] van Reekum R, Stuss DT, Ostrander L. Apathy: why care? J Neuropsychiatry Clin Neurosci. 2005;17:7–19.
[4] Pont-Sunyer C, Hotter A, Gaig C, et al. The onset of nonmotor symptoms in Parkinson's disease (the ONSET PD study). Mov Disord. 2015;30:229–37.
[5] Pedersen KF, Larsen JP, Alves G, et al. Prevalence and clinical correlates of apathy in Parkinson's disease: a community-based study. Parkinsonism Relat Disord. 2009;15:295–9.
[6] Benito-León J, Cubo E, Coronell C. Impact of apathy on health-related quality of life in recently diagnosed Parkinson's disease: the ANIMO study. Mov Disord. 2012;27:211–8.
[7] Skorvanek M, Rosenberger J, Gdovinova Z, et al. Apathy in elderly nondemented patients with Parkinson's disease: clinical determinants and relationship to quality of life. J Geriatr Psychiatry Neurol. 2013;26:237–43.
[8] Hughes AJ, Daniel SE, Kilford L, et al. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry. 1992;55:181–4.
[9] Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology. 1967;17:427–42.
[10] Fahn S, Elton R, Marsden C. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden C, Goldstein M, Calne D. (Eds.), Recent Developments in Parkinson's Disease. Florham Park, NJ: McMillan Healthcare Information. 1987;153–63.
[11] Chaudhuri KR, Martinez-Martin P, Brown RG, et al. The metric properties of a novel Non-Motor Symptoms Scale for Parkinson's disease: results from an international pilot study. Mov Disord. 2007;22:1901–11.
[12] Kang Y, Na DL, Hahn S. A validity study on the Korean mini-mental state examination (K-MMSE) in dementia patients. J Korean Neurol Assoc. 1997;15:300–8.
[13] Beck AT, Beamesderfer A. Assessment of depression: the depression inventory. Mod Probl Pharmacopsychiatry. 1974;7:151–69.
[14] Beck AT, Epstein N, Brown G, et al. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 1988;56:893–7.
[15] Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. Psychiatry Res. 1991;38:143–62.
[16] Peto V, Jenkinson C, Fitzpatrick R, et al. The development and validation of a short measure of functioning and well-being for individuals with Parkinson's disease. Qual Life Res. 1995;4:241–8.
[17] Jenkinson C, Fitzpatric, R, Peto V. The Parkinson's Disease Questionnaire: User Manual for the PDQ-39, PDQ-8 and PDQ Summary Index. Oxford: University of Oxford Health Services Research Unit. 1998.
[18] Santangelo G, Barone P, Cuoco S, et al. Apathy in untreated, de novo patients with Parkinson's disease: validation study of Apathy Evaluation Scale. J Neurol. 2014;261:2319–28.
[19] den Brok MG, van Dalen JW, van Gool WA, et al. Apathy in Parkinson's disease: a systematic review and meta-analysis. Mov Disord. 2015;30:759–69.
[20] Levy R, Czernecki V. Apathy and the basal ganglia. J Neurol. 2006;253(Suppl 7):vii54–vii61.
[21] Soh SE, Morris ME, McGinley JL. Determinants of health-related quality of life in Parkinson's disease: a systematic review. Parkinsonism Relat Disord. 2011;17:1–9.
[22] Hinnell C, Hurt CS, Landau S, et al. Nonmotor versus motor symptoms: how much do they matter to health status in Parkinson's disease? Mov Disord. 2012;27:236–41.
[23] Soh SE, McGinley JL, Watts JJ, et al. Determinants of health-related quality of life in people with Parkinson's disease: a path analysis. Qual Life Res. 2013;22:1543–53.
[24] Balestrino R, Martinez-Martin P. Neuropsychiatric symptoms, behavioural disorders, and quality of life in Parkinson's disease. J Neurol Sci. 2017;373:173–8.
[25] Barone P, Antonini A, Colosimo C, et al. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord. 2009;24:1641–9.
[26] van Uem JM, Marinus J, Canning C, et al. Health-related quality of life in patients with Parkinson's disease--a systematic review based on the ICF model. Neurosci Biobehav Rev. 2016;61:26–34.
[27] Kuhlman GD, Flanigan JL, Sperling SA, et al. Predictors of health-related quality of life in Parkinson's disease. Parkinsonism Relat Disord. 2019;65:86–90.
[28] D'Iorio A, Vitale C, Piscopo F, et al. Impact of anxiety, apathy and reduced functional autonomy on perceived quality of life in Parkinson's disease. Parkinsonism Relat Disord. 2017;43:114–7.