Apathy, fatigue and quality of life in patients with Parkinson's disease

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Chapter 6

Apathy in elderly non-demented patients with Parkinson's disease: clinical determinants and relationship to quality of life

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Abstract

Objectives: To describe the prevalence and clinical determinants of apathy in elderly non-demented Parkinson's disease (PD) patients and their relationship to quality of life (QoL).

Methods: A total of 106 non-demented elderly PD patients were examined using the MDS-UPDRS, Starkstein AS, HADS, BDI-II and PDQ-39.

Results: Apathy was present in 54% of the studied population. Factors associated with apathy were higher depression scores and a lower daily L-dopa equivalent dose. Longer disease duration, higher motor MDS-UPDRS sub-score, higher depression and anxiety scores, but not apathy, were found to be associated with worse QoL.

Conclusions: Although apathy does not seem to be an independent predictor of worse QoL specifically in elderly PD patients, it remains very relevant, as its presence increases caregiver burden. Both depression and potential dopaminergic treatment underdosing can be properly managed, thus potentially reducing the prevalence and severity of apathy in a proportion of the apathetic PD patients.

Keywords: Parkinson's disease, apathy, depression, elderly, quality of life, caregiver burden

Introduction

Apathy is a common non-motor symptom of many neuropsychiatric disorders, such as Parkinson's disease (PD), Alzheimer's disease and stroke (1-5). Apathy has been characterized as a lack of motivation manifested by diminished goal-directed cognition and behavior, with decreased emotional involvement (6). Diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders have been published recently (7) and these criteria have been later validated for non-demented PD patients by Drijgers et al (3). The reported prevalence of apathy in PD varies from 17% to 72% depending on the diagnostic tools used and patient samples examined (3,8). Apathy is present in all stages of PD, including early and untreated disease, and a possible role of dopamine depletion has been suggested (9-12).

Thus far depression has been identified as one of the factors most commonly associated with apathy in PD, and a few studies have addressed the issue of whether apathy is an independent syndrome or is mostly a co-morbid condition of depression (13-15). In fact, depending on the studied population, up to 33.4% of patients were found to have "pure" apathy in the absence of depression and dementia (8), and it has been repeatedly reported that apathy and depression in PD can be clearly distinguished and present discrete constructs (13-15). Apathy has also been associated with worse cognitive performance, such as executive dysfunction (16,17). A longitudinal study of cognitive status in initially non-demented and non-depressed apathetic versus non-apathetic PD patients found a significantly higher rate of conversion to dementia later on in the apathetic group (16). Their findings, as well as those of others (18), suggest that apathy may be a predictive factor for developing dementia and cognitive decline. A recent study of Harris et al. found that clinically significant levels of apathy are much more likely to occur in patients with right-onset disease and these patients might be at greater risk of developing PD-related dementia (19). In the general population, the prevalence of cognitive dysfunction and dementia, which are significant predictors of higher morbidity and mortality (20), increases with age (21). Apathy in otherwise healthy community-dwelling individuals was also shown to increase with increasing age, especially at 65 years of age and over (22). Apathy is significantly associated with older age in PD as well (2,8). Therefore, determining the prevalence of "pure" apathy as a potential predictive factor for dementia in elderly PD population is important.

Apathy has repeatedly been associated with worse quality of life (QoL) (1,2,23). In a study of recently diagnosed PD patients, apathetic patients were 2.49-times more likely to have lower QoL compared with non-apathetic PD patients after adjusting for sociodemographic factors and disease variables (1). Apathy has been also previously associated

with a worse 39-item Parkinson's Disease Quality of Life Questionnaire (PDQ39) total score and the PDQ39 cognition and stigma subdomains (2). The impact of apathy on QoL in the elderly PD population, however, has not yet been studied.

To the best of our knowledge, there have been no studies dealing with apathy specifically in geriatric PD patients, i.e. subgroup of patients older than 65 years of age. Thus, the aim of our study was to describe the prevalence of apathy in an elderly population of non-demented PD patients and to assess the clinical determinants of apathy in this population and their relationship with quality of life.

Methods

Patients

The final study sample consisted of 106 non-demented elderly PD patients. Patients older than 65 years of age were recruited from 25 neurology outpatient clinics in the Eastern Slovakian region between June 2011 and August 2012. All patients were diagnosed according to the United Kingdom PD Society Brain Bank Clinical Criteria (24), and their mental abilities were assessed with the Mini-Mental State Examination (MMSE) (25). A total of 126 patients initially agreed to participate in the study. Patients with an MMSE score lower than 24 (N=12), other forms of parkinsonism than idiopathic Parkinson's disease (N=3) and patients who initially agreed to participate and who filled in the questionnaire but did not come for the oral interview (N=5) were excluded. A total of 106 patients (84.1%) remained for analysis.

Data collection

An invitation letter, written informed consent and test battery comprising questions on sociodemographic background, medical history, current medication and self-report questionnaires (described below) were sent by postal mail to patients diagnosed with PD one week before the interview. During the interview, a trained interviewer assessed the cognitive functioning of patients using the MMSE and reviewed the questionnaires together with the patient to ensure, that no values were missing.

After this, a single neurologist specialized in Movement Disorders (M.S.) assessed each patient's disease severity using the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (26), including Hoehn and Yahr staging (27). Information on the presence of hallucinations from MDS-UPDRS item 1.2 (Hallucinations and psychosis) were recorded. Patients who were unable to fill in the questionnaires by themselves due to motor impairment answered the questions during the oral interview. The study was approved by the Local Ethics Committee. All patients participated voluntarily and gave written informed consent prior to the interview.

Measures

Sociodemographic data, including age, gender and education, were obtained from the structured interview. Education level was classified as: low (primary school or unfinished high school), middle (high school finished with general certificate of secondary education or specialization after high school – not a college or university) or high (university undergraduate or postgraduate or higher academic degree achieved).

Disease and medication related data

Information on disease duration, antiparkinsonian medication and other treatment was obtained during the interview. The levodopa equivalent daily dosage (LEDD) was counted using a previously published formula (28). Motor symptoms were rated in the ON state with the MDS-UPDRS part III (motor examination). The MDS-UPDRS is a four-subscale combined scale (non-motor experiences of daily living, motor experiences of daily living, motor examination and motor complications) (26). This scale was recently translated into Slovak and approved as an official non-English translation of the MDS-UPDRS (29). Scores were obtained by a semi-structured interview and examination. The disease stage was assessed by the Hoehn & Yahr scale (HY), which is applied to gauge the course of the disease over time (27).

Screening for congitive dysfunction

The Mini-mental state examination (MMSE) is used to screen for cognitive impairment (25). It consist of 30 items assessing orientation in time and place, registration, attention and calculation, recall, language, repetition and complex commands. Each answer is scored as 0 (incorrect) or 1 (correct), more points meaning better cognitive status. A cut-off of <24 points has been repeatedly used in PD populations to exclude patients with cognitive impairment if administration of self-report questionnaires was a part of the study protocol (15,30).

Apathy, Depression, Anxiety and Quality of Life

The Apathy scale is a self-administered 14-item scale assessing apathy (31). Each answer is scored from 0 (not at all) to 3 (a lot), with a higher summary score meaning more apathy. A cut-off of ≥14 is used to define the presence of apathy. In the present study, Cronbach's alpha was 0.78. The Beck Depression Inventory-II (BDI-II) is a self-administered 21-item scale assessing depression (32). Each answer was scored as 0-3. Cutoff values used are 0–13: normal range; 14–19: mild depression; 20–28: moderate depression; and 29–63: severe depression. Higher total scores indicate more severe depressive symptoms. The Cronbach's alpha for BDI-II in our study was 0.91. The Hospital Anxiety and Depression

Scale (HADS) is a self-administered scale with two subscales capable of evaluating anxiety (HADS-A) and depression (HADS-D) (33). This 14-item scale consists of seven items for assessing anxiety and seven items for assessing depression, with scoring from 0 (no problem) to 3 (extreme problem). The cut-off values applied are as follows: ≤7 on each subscale is considered unimpaired; 8–10 on each subscale means possibly impaired and ≥11 on each subscale means probably impaired (33). In the present study, we found Cronbach's alpha of 0.83 for anxiety domain and 0.82 for depression domain. Quality of Life (QoL) was assessed using the Parkinson's Disease Quality of Life Questionnaire (PDQ-39) (34). It is a disease-specific self-administered questionnaire comprised of 39 questions, each of them using a five-point ordinal scoring system, from which a single summary index can be calculated. For the summary index the scores were standardized from 0 to 100, so that higher scores indicate poorer QoL. The PDQ-39 measures 8 dimensions of health-related QoL: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication and bodily discomfort. The PDQ-39 has been shown to be feasible, reliable, valid, and responsive to change in patients with PD and to have good internal consistency (35). Good internal consistency of this scale was found also in our study with Cronbach's alpha 0.96.

Statistical analyses

Statistical analyses were performed using the statistical software program PASW SPSS version 18.0 for Windows (SPSS Inc, Chicago IL). First, we described the demographic and clinical characteristics of our studied groups. Significant differences between the group characteristics were analyzed by independent sample t-test and chi-square tests. Then, multiple linear regression analyses were performed to study the relationship between sociodemographic factors, disease duration and disease severity, LEDD and mood disorders with apathy. Finally, the relationship between the aforementioned variables and apathy with quality of life were analyzed. The level of statistical significance was defined as $p < .05$.

Results

Apathy was present in 57 patients (54% of the study sample) and depression in 65 patients (61%). Apathy without the presence of depression was present in 12 patients (11%), both apathy and depression in 45 patients (43%), depression only in 20 patients (19%) and neither apathy nor depression in 29 patients (27%). Further clinical characteristics of the study population can be found in Table 6.1. There were no significant differences in age, gender, education, disease duration, disease stage, total MMSE score, presence of motor complications and treatment

used between patients with or without apathy. The group of patients with apathy had significantly higher scores on MDS-UPDRS parts I-III, BDI-II, HADS-A, PDQ-39 total and all PDQ-39 subscales, and a higher prevalence of hallucinations was also recorded in this group.

Table 6.1 Sociodemographic and clinical characteristics of the study sample (N=106)

	Non-apathetic	Apathetic	Significant difference
Number of patients	49	57	
Gender (male/female)	22/27	28/29	P=ns
Age	73.8±4.5	74.8±5.2	P=ns
Disease duration	7.06±5.2	6.6±4.9	P=ns
Education level			
Low	20 (40%)	25 (44%)	P=ns
Middle	18 (37%)	19 (33%)	
High	11 (22%)	13(23%)	
Hoehn&Yahr stage	2.3±0.9	2.4±1.0	P=ns
H&Y 0	2 (4%)	2 (4%)	
H&Y 1	4 (8%)	8 (14%)	
H&Y 2	23 (47%)	19 (33%)	
H&Y 3	17 (35%)	22 (38%)	
H&Y 4	3 (6%)	6 (11%)	
MDS-UPDRS part I	10.7±5.5	15.6±6.5	p<0.001
MDS-UPDRS part II	11.0±8.0	15.8±9.4	p<0.01
MDS-UPDRS part III	33.7±13.0	39±14.2	p<0.05
MDS-UPDRS part IV	2.9±3.7	2.5±3.6	P=ns
Apathy scale	8.65±2.7	18.0±3.6	p<0.001
BDI-II	12.2±6.5	21.2±11.2	p<0.001
HADS anxiety	5.1±3.6	8.1±4.5	p<0.001
PDQ39 total	28.5±17.0	37.2±19.4	p<0.02
Hallucinations	1 (2%)	8 (14%)	p<0.05
LEDD (mg/day)	476 (0-2065)	440 (0-1335)	P=ns
L-dopa	32 (65%)	36 (63%)	P=ns
L-dopa +COMT inhibitor	15 (31%)	22 (39%)	P=ns
Dopamine agonists	33 (67%)	34 (60%)	P=ns
L-dopa + dopamine agonists	21 (43%)	20 (35%)	P=ns
No dopaminergic treatment	5 (10%)	8 (14%)	P=ns
Rasagiline	15 (31%)	15 (26%)	P=ns
Amantadine	6 (12%)	15 (26%)	P=ns
Antidepressants	5 (10%)	10 (18%)	P=ns

MDS-UPDRS – Movement Disorder Society - Unified PD Rating Scale, BDI-II – Beck Depression Inventory, HADS – Hospital Anxiety and Depression Scale, PDQ39 – Parkinson's Disease quality of life questionnaire, LEDD – levodopa daily dosage equivalent, ns – not significant

Linear regression analysis was performed to explore the variables associated with apathy (Table 6.2). Our adjusted model explained 37%

of the variance of apathy. We found a significant relationship between higher apathy and higher BDI-II scores (Beta 0.59, P<0.001) and lower LEDD (Beta -0.17, p<0.05). Sociodemographic variables, disease duration, disease severity and anxiety were not associated with apathy in our model. Results did not change significantly after removing patients who are not receiving any dopaminergic treatment from the analysis or after including MMSE as a variable into the analysis (results not shown).

Table 6.2 Multiple linear regression analysis: factors associated with apathy

	Beta	Significance
Age	.14	p=0.09
Gender	.17	P=0.06
Education level	-.13	P=0.12
Disease duration	-.06	P=0.50
MDS-UPDRS III	.00	P=0.96
LEDD	**-.17**	**P<0.05[a]**
BDI-II	**.59**	**P<0.001[a]**
HADS anxiety	.08	P=0.48
R^2 / Adjusted R^2	**0.42 / 0.37**	

MDS-UPDRS-III – Movement Disorder Society - Unified PD Rating Scale part III (motor examination), BDI-II – Beck Depression Inventory, HADS – Hospital Anxiety and Depression Scale, LEDD – levodopa daily dosage equivalent, ns – not significant
ap<0.05

In the regression analysis model without depression and anxiety, higher apathy, MDS-UPDRS III scores and higher LEDD were significantly associated with worse QoL as measured by the PDQ-39 summary index score (Table 6.3). In the next model, with depression and anxiety, apathy and LEDD did not play a further role in explaining QoL, and variables significantly related with worse QoL were lower education level, longer disease duration and higher BDI-II, HADS-A and MDS-UPDRS III scores. Similarly, in a regression analysis using the model with depression and anxiety, apathy was not associated with any of the PDQ-39 subscales (results not shown).

Table 6.3 Multiple linear regression analyses: sociodemographics, clinical variables and apathy on QoL (PDQ-39); models without and with controlling for depression and anxiety

	Model without depression and anxiety		Model with depression and anxiety	
	Beta	significance	Beta	significance
Age	.00	P=ns	.07	P=ns
Gender	-.03	P=ns	.12	P=ns
Education level	-.14	P=ns	-.18[a]	p<0.02
Disease duration	.17	p=ns	.18[a]	p<0.02
MDS-UPDRS III	.34c	p<0.001	.24[b]	p=0.001
LEDD	.31c	p<0.001	.13	P=ns
Apathy scale	.27b	P=0.001	-.03	P=ns
BDI-II			.21[a]	p<0.02
HADS anxiety			.36[c]	p<0.001
R^2 / Adjusted R^2	0.41 / 0.36		0.59 / 0.55	

Abbreviations: MDS-UPDRS-III – Movement Disorder Society - Unified PD Rating Scale motor part, BDI-II – Beck Depression Inventory, HADS – Hospital Anxiety and Depression Scale, PDQ39 – Parkinson's Disease quality of life questionnaire, LEDD – levodopa daily dosage equivalent, ns – not significant
ap<0.05; bp<0.01; cp<0.001

Discussion

To the best of our knowledge, this is the first study to specifically assess the prevalence of apathy in geriatric non-demented PD patients, the clinical determinants of apathy and their relationship with quality of life in this population. Both apathy and depression were a common finding in our population of elderly PD patients: apathy was present in 54% of the sample and depression in 61%. When comparing our results with previous studies which used the Starkstein Apathy Scale (AS) and Beck Depression Inventory-II (BDI-II) as outcome measures in a general non-demented PD population (2,13,14,36), the prevalence of apathy found in our study was similar (54% vs. 33.5-57%). The prevalence of depression, however, was slightly higher in our sample (61% vs. 22-56%) (2,13,14,36). Also, the prevalence of apathy in the absence of depression was the lowest in our study sample (11% vs. 17-34%), and the proportion of all apathetic patients vs. apathetic patients without depression was the lowest as well (20% vs. 30-63%). Depression was the most important determinant of apathy in the regression analysis model performed in our study. Depression and apathy share common features, and in fact major depression according to DSM-IV criteria may be diagnosed based on the presence of loss of motivation/anhedonia even in the absence of low mood. This might lead to a misdiagnosis of apathy as depression and vice versa in clinical practice. This issue has been addressed by several studies, which found

that apathy and depression can be clearly dissociated in PD and present discrete constructs (2,13-15).

Apathetic patients had worse functional status as measured by the MDS-UPDRS part III. Similar findings have been reported in some previous studies (2,8,37). However, lower daily L-dopa dosage and not worse motor status were significantly associated with apathy in a regression analysis model. These findings are supported by some previous studies, which suggest that a dopaminergic deficit could contribute to the pathogenesis of apathy in PD (9-12). In fact, apathy is a common finding in early untreated PD (9), and some previous reports suggest that dopamine agonists as well as levodopa may improve apathy (38). Apathy as a consequence of a dopamine withdrawal syndrome was suggested in some previous studies (10,12), including a study of 63 patients with PD after subthalamic deep brain stimulation, where 34 patients became apathetic after the dopaminergic medication was reduced by 82% within 2 weeks after surgery (12). In this study a subgroup of patients underwent a [11C]-raclopride positron emission tomography (PET) study, and patients with apathy showed increased binding bilaterally in the orbitofrontal cortex, the posterior cingulate cortex, the left dorsolateral prefrontal cortex, the bilateral striatum, the left thalamus and the right amygdala, suggesting that an increase of D2/D3 receptors or a reduction of synaptic dopamine levels might be related to subthalamic nucleus deep brain stimulation (STN-DBS) induced apathy. These findings suggest that in selected patients with PD displaying no cognitive deterioration, postoperative apathy can be seen as a model of a pure mesolimbic hypodopaminergic syndrome, which is unmasked by postoperative drug withdrawal (12). The pathophysiology of apathy is, however, clearly multifactorial, as not all patients with Parkinson's disease or dopaminergic depletion develop apathy. Apathy is often present after direct lesions of the prefrontal cortex (PFC) and also focal lesions of specific structures of the basal ganglia, such as the caudate nuclei, the internal pallidum and the medial-dorsal thalamic nuclei. Apathy is therefore clearly a clinical consequence of the disruption of the PFC-basal ganglia axis (39). The proposed prefrontal-basal ganglia circuits responsible for apathy according to its underlying mechanism are further discussed in a paper previously published by Levy and Dubois (39). Dopamine is associated with reward processing (39-41). The reward processing circuit involves the orbital-prefrontal-ventral striatum circuit, and therefore the influence of dopamine on reward processing and also apathy may act through modulation of this circuit via this mesocorticolimbic pathway (39).

Apathy has been repeatedly associated with worse QoL in PD (1,2,23). Apathy has also been previously associated with a higher PDQ39 summary score index and the PDQ39 cognition and stigma subdomains (2). In our study the PDQ39 total score as well as all PDQ39 subscores were

higher in apathetic patients, and apathy was significantly associated with worse QoL in a regression analysis model without depression and anxiety. When depression and anxiety were added to the model, worse QoL was associated with higher anxiety, depression and MDS-UPDRS III scores as well as longer disease duration and lower education, but not apathy. Although apathy in our sample was not a predictor of worse quality of life after controlling for depression, we suggest that apathy belongs to a more severe PD phenotype, as apathetic patients were repeatedly found to have higher motor and depression scores, as well as worse cognitive status, all of which significantly contribute to worse quality of life in the general PD population (1,2,15,16,37). Moreover, in a recent study Leroi et al. found a significantly greater caregiver burden in carers of PD patients with apathy compared with carers of patients without apathy (30).

Strengths and limitations

To the best of our knowledge, this is the first study to specifically assess apathy in a geriatric population of non-demented PD patients. Patients were enrolled from the primary care neurologists; therefore, they reflect the "typical" PD patient coming to a specialized center. However, all patients were examined by a single movement disorder neurologist, which ensured exclusion of the non-PD subjects and a uniform evaluation of their functional status. There were some limitations of our study. The sample consisted of more motivated patients who agreed to participate in the study and who were able to attend the examination. Also, the cross-sectional design of the study does not allow us to further explore the causal pathways between the studied variables. One of the limitations is also, that side of onset was not recorded in all patients, therefore our results cannot be compared with the recently published study of Harris et al. which suggested, that patients with right-onset disease are more likely to have higher apathy scores. Another limitation of the study is that depression and apathy were assessed through self-report questionnaires only, although all instruments used have been validated and repeatedly utilized for this purpose in PD patients. Assessment of the diagnostic criteria for apathy in PD, which have been proposed by Robert et al. (7) and later validated for PD patients by Drijgers et al. (3), would have enabled us to better describe the subtypes of apathy present in elderly non-demented PD patients and their clinical determinants in this population.

Implications for future research and clinical practice

Although apathy does not seem to be an independent predictor of worse quality of life, specifically in elderly non-demented PD patients, we suggest in line with some previous studies (1,2,15,16,37) that its presence belongs to a more severe phenotype of PD, and since it may significantly increase the caregiver burden (30), it is important in the clinical management of elderly

PD patients. Apathy is common in elderly non-demented PD patients and is often associated with depression. However, as repeatedly shown by previous studies, depression and apathy can be clearly dissociated and present discrete constructs (2,13-15). Therefore, recognizing that apathy can be present even without depression is important in order to prevent an incorrect diagnosis and unnecessary treatment as a depressive disorder. The absence of a significant association between apathy and QoL in our sample compared to some previous studies (2,42) could be also potentially explained by the higher prevalence of depression and the higher coincidence of depression with apathy in our sample. However, as these studies enrolled different patient samples, further research should be performed to distinguish the impact of older age versus depression on the relationship between apathy and QoL in elderly PD patients. Dopaminergic deficit is one of the possible pathways leading to apathy in PD; therefore, optimization of dopaminergic treatment should lead to improvement of apathy in selected PD patients. As apathy and cognitive dysfunction are common in elderly PD patients and since apathy was previously reported to be a potential predictor of dementia and cognitive decline, further longitudinal studies in elderly apathetic PD patients should be conducted in order to better understand the time frame and frequency of the potential conversion of apathy to dementia.

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