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Occurrence and risk factors for apathy in Parkinson's disease: a 4-year prospective longitudinal study

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ABSTRACT

Background: Apathy is a common but underrecognized behavioural disorder associated with depression and cognitive impairment in patients with Parkinson's disease (PD). However, the longitudinal course of apathy in PD has not been studied.

Objective: To examine the occurrence of and risk factors for apathy over time in a representative sample of patients with PD.

Methods: A sample of 139 patients was drawn from a population-based prevalence study of PD in Rogaland County, Western Norway. Apathy was measured with the Neuropsychiatric Inventory, using a composite score ≥ 4 to indicate clinically significant apathy. Additional measurements included standardized rating scales for parkinsonism, depression and cognitive impairment. A follow-up evaluation was carried out in 79 patients (78.2% of the survivors) four years later.

Results: Of the 79 patients included in this study, 29 patients (36.7%) had never apathy, 11 (13.9%) had persistent apathy, and further 39 (49.4%) developed apathy during follow-up. At follow-up, patients with apathy were more frequently depressed and demented than never-apathetic patients. Dementia at baseline and a more rapid decline in speech and axial impairment during follow-up were independent risk factors for incident apathy.

Conclusions: Apathy is a persistent behavioural feature in PD with high incidence and prevalence over time. Progression of motor signs predominantly mediated by nondopaminergic systems may be a useful preclinical marker for incident apathy in PD.

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INTRODUCTION

Apathy is a common but frequently underrecognized neuropsychiatric disorder in patients with Parkinson's disease (PD)¹ that is attributed to basal ganglia pathology and disturbances in frontal-subcortical connections.² Cross-sectional studies have shown that apathy is associated with depression, cognitive deficits, and a decrease in performing activities of daily living,³⁻⁵ and possibly motor severity.⁶ However, the frequency and clinical correlates of apathy in PD over time have not yet been studied.

Here we report on the occurrence and risk for apathy with emphasis on motor, depressive and cognitive symptoms in a 4-year prospective population-based longitudinal cohort study of patients with prevalent PD.

METHODS

Subjects

One-hundred thirty-nine patients with PD from an ongoing prospective community-based study of PD in Rogaland County, Western Norway,⁷ were invited during 1996 and 1997 to participate in the baseline evaluation of the present study and completed a comprehensive neurological, psychiatric and neuropsychological assessment after having provided written informed consent.⁴ A total of 79 patients (78.2% of the survivors with PD) were re-assessed 4 years later using the same evaluations as performed at baseline (50 patients had died and 10 refused to participate). There were no significant differences on age, gender or education between nonparticipants and patients included at follow-up. In 22 cases from the study cohort who have come to autopsy so far, the findings were compatible with PD in all cases.⁸ The study was approved by the Regional Committee for Medical Research Ethics at the University of Bergen, Norway.

Assessment

The Unified Parkinson's Disease Rating Scale (UPDRS) motor part⁹ and the Hoehn and Yahr stage¹⁰ were administered when patients were in their best *on* state. The total UPDRS motor score (range 0-108) was divided into 6 motor domains (speech, facial expression, tremor, rigidity, bradykinesia, and axial impairment) based on the cardinal clinical manifestations of PD.¹¹ These 6 motor domains were grouped into 2 subscores that represented predominantly dopaminergic (subscore A: tremor, rigidity, bradykinesia, and facial expression; range 0-88) and nondopaminergic (subscore B: speech and axial impairment; range 0-20) deficiencies.¹¹ Due to the variety of dopaminergic treatment a daily levodopa equivalent dose was estimated, as previously described.¹²

Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) criteria¹³ based on a caregiver-based interview, cognitive rating scales including Mattis Dementia Rating Scale¹⁴ and Mini-Mental State Examination (MMSE),¹⁵ and neuropsychological tests, as described in detail previously.¹⁶

Apathy was measured with the Neuropsychiatric Inventory (NPI),¹⁷ using a composite apathy score (severity multiplied by frequency) of ≥ 4 indicating clinically significant apathy, as recommended in PD.¹⁸ High interrater reliability of the NPI apathy subsection has been demonstrated in PD.⁴

Major depression was diagnosed by a psychiatrist on the basis of a clinical interview according to DSM-III-R criteria. The Montgomery and Aasberg Depression Rating Scale (MADRS)¹⁹ was used to evaluate severity of depressive symptoms, and to diagnose minor depression when only sad mood was present (item 1 or 2 with cut-off score ≥ 2)²⁰ in addition to at least one other symptom of depression (with cut-off score ≥ 2).²¹ Both patients with major and minor depression were classified as being depressed. The NPI, dementia interview, cognitive and depression assessments were performed blind to the motor evaluation.

Statistical analysis

Mann-Whitney and Kruskal-Wallis tests and χ^2 tests or Fisher's exact tests were used for comparisons as appropriate. Wilcoxon signed rank tests were used to compare differences between paired groups over time. Binary logistic regression analyses with forward stepping (likelihood ratio method) were performed, with the presence or absence of apathy as the

dependent variable. SPSS version 15.0 was used for the analyses. Two-tailed p values < 0.05 were considered statistically significant.

RESULTS

Development of apathy

Demographic and clinical characteristics at study entry are provided in table 1.

Table 1. Baseline demographic and clinical findings in patients with and without apathy

	All patients (n = 79)	Apathy (n = 11)	No apathy (n = 68)	P
Female, n (%)	44 (55.7)	7 (63.6)	37 (54.4)	0.746
Age, yr (SD)	72.0 (8.3)	73.4 (8.4)	71.8 (8.3)	0.533
Education, yr (SD)	9.3 (3.3)	9.0 (2.7)	9.3 (3.4)	0.733
Disease duration, yr (SD)	13.0 (4.7)	14.2 (4.4)	12.8 (4.8)	0.297
Total UPDRS motor score (SD)	28.5 (17.6)	23.8 (10.2)	29.3 (18.5)	0.650
UPDRS motor subscore A (SD)	18.4 (12.3)	14.5 (6.9)	19.0 (12.9)	0.436
UPDRS motor subscore B (SD)	7.2 (4.5)	7.5 (3.7)	7.2 (4.7)	0.594
Hoehn and Yahr stage				
Mean (SD)	3.0 (0.9)	3.2 (0.6)	3.0 (1.0)	0.306
Range	1.0 – 5.0	2.5 – 4.0	1.0 – 5.0	
MADRS score (SD)	5.4 (6.7)	13.3 (7.3)	4.2 (5.6)	< 0.001
MMSE score (SD)	25.5 (6.4)	21.1 (6.7)	26.2 (6.1)	0.011
NPI apathy score (SD)	1.2 (2.9)	7.9 (2.6)	0.1 (0.6)	< 0.001
Depression, n (%)	16 (20.3)	6 (54.5)	10 (14.7)	0.007
Dementia, n (%)	23 (29.1)	7 (63.6)	16 (23.5)	0.012
Levodopa equivalent dose, mg daily (SD)	658 (387)	630 (415)	663 (386)	0.456
Antidepressants, n (%)	14 (17.7)	3 (27.3)	11 (16.2)	0.370
Anxiolytics, n (%)	7 (8.9)	1 (9.1)	6 (8.8)	0.999
Antipsychotics, n (%)	9 (11.4)	3 (27.3)	6 (8.8)	0.084

Data are mean (SD) or number (% of assessed patients); all available data included.

Comparisons between patients with and without apathy: χ^2 tests or Fisher's exact tests when appropriate for categorical variables, Mann-Whitney tests for continuous variables. All P values are two tailed.

PD = Parkinson's disease; UPDRS = Unified Parkinson's Disease Rating Scale; MADRS = Montgomery and Aasberg Depression Rating Scale; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory.

The majority of patients (93%) were in Hoehn and Yahr stage 2 or higher. At baseline, 11 of 79 patients (13.9%) were apathetic, whereas 68 (86.1%) were not. At the 4-year study visit, all patients with apathy at baseline remained apathetic, and further 39 subjects (49.4%) had developed apathy during the study period. Twenty-nine patients (36.7%) were without apathy at both baseline and follow-up.

Motor, cognitive and neuropsychiatric correlates of apathy

Patient characteristics according to apathy status are presented in table 2.

Table 2 Neurological and psychiatric changes in patients with never apathy, incident apathy, and persistent apathy during the 4-year observation period

	Never apathy (n = 29)	Incident apathy (n = 39)	Persistent apathy (n = 11)	P*
Change in total UPDRS motor score ^a (SD)	12.9 (13.7)	21.5 (15.6)	36.8 (18.1)	0.001
Change in motor subscore A ^b (SD)	8.8 (10.8)	14.4 (12.0)	24.7 (12.9)	0.003
Change in motor subscore B ^c (SD)	2.6 (2.6)	5.2 (3.7)	7.2 (5.3)	0.004
Change in MADRS score ^d (SD)	-0.2 (3.9)	4.3 (8.9)	-1.0 (1.6)	0.042
Change in MMSE score ^e (SD)	-3.4 (4.8)	-8.3 (6.6)	-12.2 (6.4)	< 0.001
Change in NPI apathy score ^a (SD)	-0.10 (0.90)	8.3 (2.8)	1.2 (3.1)	< 0.001
Depression				
Baseline ^b , n (%)	5 (17.2)	5 (12.8)	6 (54.5)	0.055
Follow-up ^c , n (%)	3 (10.3)	11 (28.2)	5 (45.5)	0.004
Dementia				
Baseline ^c , n (%)	2 (6.9)	14 (35.9)	7 (63.6)	<0.001
Follow-up ^c , n (%)	6 (20.7)	34 (87.2)	10 (90.9)	<0.001

Data are mean \pm SD or number (% of assessed patients); all available data included. All P values are two tailed. A positive change in total motor score and motor subscore A or B represents a worsening of motor performance, negative MADRS and NPI apathy score changes represent improvement of depressive and apathetic symptoms, whereas negative MMSE score changes represent a worsening of cognitive symptoms, compared with baseline values.

*P values computed using Kruskal-Wallis tests for continuous variables, linear-by-linear association test for categorical variables.

^aComparisons: Never apathy vs. Incident apathy & Never apathy vs. Persistent apathy & Incident apathy vs. Persistent apathy: $p < 0.05$.

^bComparisons: Never apathy vs. Persistent apathy & Incident apathy vs. Persistent apathy: $p < 0.05$.

^cComparisons: Never apathy vs. Incident apathy & Never apathy vs. Persistent apathy: $p < 0.05$ for motor subscore B and depression at follow-up, $p \leq 0.01$ for MMSE, $p \leq 0.005$ for dementia at baseline, and $p < 0.001$ for dementia at follow-up.

^dComparison: Never apathy vs. Incident apathy: $p < 0.05$.

PD = Parkinson's disease; UPDRS = Unified Parkinson's Disease Rating Scale; MADRS = Montgomery and Aasberg Depression Rating Scale; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory.

There were no significant differences between the three apathy groups regarding demographic (age, gender, education or disease duration) and treatment (dopaminergic, antidepressant, anxiolytic or antipsychotic medication) variables (data not shown). Compared to those who remained nonapathetic during the study period, patients with incident apathy were more frequently demented at baseline, and more frequently depressed and demented at follow-up. Compared to patients free from apathy during the study period, patients with incident apathy at follow-up had significantly more rapid increase in the UPDRS motor score, motor subscore B, and MADRS score, as well as more rapid decline in MMSE score.

Patients with persistent apathy during the observation period were more frequently depressed at baseline, and had a more pronounced increase in total UPDRS motor score and motor subscore A, than those with incident apathy at follow-up. Persistent apathy was not associated with incident depression or dementia at follow-up. There was no significant difference on NPI apathy scores between patients with persistent and incident apathy at follow-up.

Risk factors of apathy

In the regression analysis we first entered age at baseline, changes in motor subscore A and B, and changes in MADRS and MMSE scores as predictor variables for the presence or

absence of apathy. Increase in motor subscore B was the only independent predictor of incident apathy in the model (odds ratio 1.345, 95% CI: 1.067 - 1.696, $p = 0.012$). Because change in total UPDRS motor score was highly intercorrelated with changes in motor subscore A (Pearson $r = 0.980$) and B (Pearson $r = 0.767$), only changes in motor subscores were included in the multivariate analysis. In a second step, we exchanged changes in MADRS and MMSE scores with presence of depression and dementia at baseline, while all other covariates remained unchanged, and found that both dementia at baseline (odds ratio 6.492, 95% CI: 1.281 – 32.898, $p = 0.024$) and increase in motor subscore B (odds ratio 1.268, 95% CI: 1.055 – 1.524, $p = 0.011$) had significant effect. Both the Omnibus tests of model coefficients and the Hosmer-Lemeshow goodness of fit test supported our regression models as being valid.

DISCUSSION

In this longitudinal study of patients derived from a community-based cohort of prevalent PD, apathy was a frequent and persistent behavioural feature. Although the sample size was limited, this finding suggests that apathy may be caused by an irreversible biological deficiency in patients with more advanced PD. The biological basis of apathy is unclear, but neurotransmitter deficits in the dopaminergic, cholinergic, noradrenergic and serotonergic systems have been discussed to be involved in apathy.²² These deficits are also thought to relate to depression and dementia associated with PD (PDD).²³ This may explain our and previous⁵ observations of apathy being associated with more severe depressive symptoms and greater cognitive impairment.

The occurrence of apathy increased substantially and affected more than 60% at follow-up, yielding an annual incidence rate of 12.3%. In comparison, apathy (NPI \geq 4) was present in 38% of a clinic-based sample of patients with PDD drawn from an international cross-sectional multicentre study published recently.²⁴ These figures, and previous reports of increased distress in caregivers of PD patients with apathy,²⁴ highlight apathy as a frequent and important feature in advancing PD.

Dementia and a more rapid decline in speech and axial impairment, features predominately associated with dysfunction in nondopaminergic subcortical structures, independently predicted incident apathy. Other studies have reported that progression of these motor symptoms are associated with incident dementia and aging,^{11,25} and thus the high incidence of apathy in our cohort may have been caused by brain changes related to both normal aging and the neurodegenerative process of dementia in PD. Although previous studies have shown that dopaminergic treatment may decrease apathy in patients with PD without dementia and major

depression,²⁶ our findings suggest that dopaminergic dysfunction does not play a major role in the pathophysiology of apathy in more advanced PD with comorbid depression and dementia. It is generally accepted that cognitive impairment in PD is characterized by subcortical and eventually cortical cholinergic deficits and lewy body pathology.²⁷ Recent consensus criteria consider apathy a supporting feature of PDD,²⁸ which is clearly emphasized by our finding that nearly 90% of patients with PDD had clinically significant apathy.

The main strength of this study is the prospective longitudinal design that involved patients derived from a community-based cohort with prevalent PD. Patients were carefully diagnosed with PD according to published criteria, and in those who underwent autopsy all fulfilled neuropathological criteria for PD. Finally, the neuropsychiatric and neuropsychological assessments were performed blind to the motor evaluation. Limitations include the long time intervals between study visits, and that minor depression and clinical significant apathy were defined by cut-off scores rather than standardized diagnostic criteria. However, currently there are no generally accepted criteria and ad-hoc rating scales for apathy.¹ The NPI is frequently used to screen and assess the severity of neuropsychiatric symptoms, including apathy, in neurodegenerative disorders, and has recently been considered a “suggested” scale for apathy in PD,¹ with a cut-off ≥ 4 being recommended as indicating clinically significant apathy in PD.¹⁸

Our study demonstrates that apathy is a key neuropsychiatric disorder in more severe cases of PD, underlining the need for drug trials to improve motivation, cognition and emotional deficits in patients with PD. Further research in larger groups of patients with early PD and with more frequent evaluations over time is necessary to identify factors that may predict apathy at an earlier stage of the disease.

COMPETING INTERESTS

None declared.

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