PATIENT'S CHOICE

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

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ABSTRACT

Background: Apathy is a common but under-recognised behavioural disorder associated with depression and cognitive impairment in patients with Parkinson 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 standardised rating scales for parkinsonism, depression and cognitive impairment. A follow-up evaluation was carried out in 79 patients (78.2% of the survivors) 4 years later.

Results: Of the 79 patients included in this study, 29 patients (36.7%) had never had apathy, 11 (13.9%) had persistent apathy, and a 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 a high incidence and prevalence over time. Progression of motor signs predominantly mediated by non-dopaminergic systems may be a useful preclinical marker for incident apathy in PD.

Apathy is a common but frequently under-recognised neuropsychiatric disorder in patients with Parkinson 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, 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 and 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 reassessed 4 years later using the same evaluations as those performed at baseline (50 patients had died, and 10 refused to participate). There were no significant differences in age, gender or education between non-participants 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 Disease Rating Scale (UPDRS) motor part[9] and the Hoehn and Yahr stage[10] were administered when patients were in their best on state. The total UPDRS motor score (range 0–108) was divided into six motor domains (speech, facial expression, tremor, rigidity, bradykinesia and axial impairment) based on the cardinal clinical manifestations of PD.[11] These six motor domains were grouped into two subscores that represented predominantly dopaminergic (subscore A: tremor, rigidity, bradykinesia and facial expression; range 0–88) and non-dopaminergic (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) criteria[13] based on a care-giver-based interview, cognitive rating scales including Mattis Dementia Rating Scale[14] 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] A high inter-rater 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 a 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, Kruskal–Wallis tests and χ^2 tests or Fisher 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.

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 a 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.

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 with those who remained non-apathetic during the study period, patients with incident apathy were more frequently demented at baseline, and more frequently depressed and demented at follow-up. Compared with patients free from apathy during the study period, patients with incident apathy at follow-up had a significantly more rapid increase in the UPDRS motor score, motor subscore B and MADRS score, as well as a 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. An increase in motor subscore B was the only independent predictor of incident apathy in the model (odds ratio 1.345, 95% CI 1.067 to 1.696, p = 0.012). Because a 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 to 32.898, p = 0.024) and an increase in motor subscore B (odds ratio 1.268, 95% CI 1.055 to 1.524, p = 0.011) had a significant effect. Both the Omnibus tests of

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 Value
Female, n (%)	44 (55.7)	7 (63.6)	37 (54.4)	0.746
Age in years (SD)	72.0 (8.3)	73.4 (8.4)	71.8 (8.3)	0.533
Education in years (SD)	9.3 (3.3)	9.0 (2.7)	9.3 (3.4)	0.733
Disease duration in years (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	
Montgomery and Aasberg Depression Rating Scale score (SD)	5.4 (6.7)	13.3 (7.3)	4.2 (5.6)	<0.001
Mini-Mental State Examination score (SD)	25.5 (6.4)	21.1 (6.7)	26.2 (6.1)	0.011
Neuropsychiatric Inventory 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 expressed as mean (SD) or number (percentage of assessed patients); all available data included. Comparisons between patients with and without apathy: χ^2 tests or Fisher exact tests when appropriate for categorical variables, Mann–Whitney tests for continuous variables. All p values are two-tailed.
UPDRS, Unified Parkinson Disease Rating Scale.

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 Value*
Change in total Unified Parkinson Disease Rating Scale motor score† (SD)	12.9 (13.7)	21.5 (15.6)	36.8 (18.1)	0.001
Change in motor subscore A‡ (SD)	8.8 (10.8)	14.4 (12.0)	24.7 (12.9)	0.003
Change in motor subscore B§ (SD)	2.6 (2.6)	5.2 (3.7)	7.2 (5.3)	0.004
Change in MADRS score¶ (SD)	−0.2 (3.9)	4.3 (8.9)	−1.0 (1.6)	0.042
Change in MMSE score§ (SD)	−3.4 (4.8)	−8.3 (6.6)	−12.2 (6.4)	<0.001
Change in NPI apathy score† (SD)	−0.10 (0.90)	8.3 (2.8)	1.2 (3.1)	<0.001
Depression				
Baseline‡, n (%)	5 (17.2)	5 (12.8)	6 (54.5)	0.055
Follow-up§, n (%)	3 (10.3)	11 (28.2)	5 (45.5)	0.004
Dementia				
Baseline§, n (%)	2 (6.9)	14 (35.9)	7 (63.6)	<0.001
Follow-up§, n (%)	6 (20.7)	34 (87.2)	10 (90.9)	<0.001

Data are expressed as mean (SD) or number (percentage 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 Montgomery and Aasberg Depression Rating Scale (MADRS) and Neuropsychiatric Inventory (NPI) apathy score changes represent improvement of depressive and apathetic symptoms, whereas negative Mini-Mental State Examination (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.
†Comparisons: Never apathy versus Incident apathy & Never apathy versus Persistent apathy & Incident apathy versus Persistent apathy: $p<0.05$.
‡Comparisons: Never apathy versus Persistent apathy & Incident apathy versus Persistent apathy: $p<0.05$.
§Comparisons: Never apathy versus Incident apathy & Never apathy versus Persistent apathy: $p<0.05$ for motor subscore B and depression at follow-up, $p\leqslant 0.01$ for MMSE, $p\leqslant 0.005$ for dementia at baseline, and $p<0.001$ for dementia at follow-up.
¶Comparison: Never apathy versus Incident apathy: $p<0.05$.

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 found 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 previous[5] 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 $\geqslant$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 care givers 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 non-dopaminergic subcortical structures, independently predicted incident apathy. Other studies have reported that progression of these motor symptoms is associated with incident dementia and ageing,[11 25] and so the high incidence of apathy in our cohort may have been caused by brain changes related to both normal ageing 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 characterised 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 emphasised 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 as having 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 standardised 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 $\geqslant$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.

Ethics approval: Ethics approval was provided by the Regional Committee for Medical Research Ethics at the University of Bergen, Norway.

Patient consent: Obtained.

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Information for patients from JNNP

Apathy is a common sign of worsening Parkinson's disease

The development of apathy is a sign of worsening Parkinson's disease, a study has found. The study suggests that apathy is due to changes in the brain, caused by the disease and by ageing.

What do we know already?

Apathy, generally defined as a lack of interest or concern about life, is relatively common among people with Parkinson's disease. A previous study found that about 38 in 100 people with Parkinson's disease exhibit apathy at any one time.

We also know that it's more common in people with Parkinson's disease who are showing signs of dementia, such as memory loss and confusion. It's also more common among people with Parkinson's disease who've become depressed. But doctors aren't sure how these things are related, or in what order they tend to happen.

This new study followed a group of 79 patients with Parkinson's disease over a 4-year period. It measured their levels of apathy, depression and mental skills at the start of the study, and again at the end.

What does the new study say?

The study showed that people were likely to become apathetic during the four years of the study, and that this was linked to depression and dementia.

Only 14 per cent of patients were apathetic at the start of the study. They were also more likely to have been diagnosed with depression and dementia at this time. During the study, another 40 per cent of patients developed apathy, and they too were more likely to have depression and dementia by the end of the study. No-one with apathy at the start of the study had recovered from it by the end of the study.

Mostly, depression and dementia seemed to happen before apathy. People who had been depressed or showed signs of dementia at the start of the study were more likely to be apathetic by the end of the study. But people who were apathetic at the start of the study were not especially likely to develop depression or dementia, if they didn't already have them.

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How reliable are the findings?

This is a fairly small study, so the findings should be treated with some caution. The results might have been different in a bigger group of patients.

Where does the study come from?

The researchers were from Stavanger University Hospital and the University of Bergen, both in Norway.

What does this mean for me?

If you have Parkinson's disease or you care for someone with Parkinson's disease, it's important to know that symptoms like depression and apathy are part of the disease process. Although the figures in the study seem quite bleak, not everyone in the study developed these conditions. More than a third had not become apathetic by the end of the study. Remember these are just statistics, and they can't predict what will happen to you or your loved one.

What should I do now?

It's not easy caring for someone with Parkinson's disease. If you are struggling, your doctor should be able to help you find out about local support for carers. If you've noticed the person you care for seems to be losing interest in life, it may help to know that this is a symptom of the disease. It's not anything personal, and it hasn't been caused by anything that you have or haven't done. Talking to other carers for people with Parkinson's disease may also help.

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