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-aphatic patients. Dementia at baseline and a stage of Parkinson disease (PD) 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 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) that is attributed to basal ganglia pathology and disturbances in fronto-subcortical connections. Cross-sectional studies have shown that apathy is associated with depression, cognitive deficits, a decrease in performing activities of daily living and possibly motor severity. 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, 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. 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. 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 and the Hoehn and Yahr stage 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. 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. Due to the variety of dopaminergic treatment, a daily levodopa equivalent dose was estimated, as previously described.

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

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

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) 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)\textsuperscript{20} in addition to at least one other symptom of depression (with cut-off score ≥2).\textsuperscript{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 \( \chi^2 \) 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

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Apathy</th>
<th>No apathy</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>(n = 79)</td>
<td>(n = 11)</td>
<td>(n = 68)</td>
<td></td>
</tr>
<tr>
<td>Age in years (SD)</td>
<td>72.0 (8.3)</td>
<td>73.4 (8.4)</td>
<td>71.8 (8.3)</td>
<td>0.533</td>
</tr>
<tr>
<td>Education in years (SD)</td>
<td>9.3 (3.3)</td>
<td>9.0 (2.7)</td>
<td>9.3 (3.4)</td>
<td>0.733</td>
</tr>
<tr>
<td>Disease duration in years (SD)</td>
<td>13.0 (4.7)</td>
<td>14.2 (4.4)</td>
<td>12.8 (4.8)</td>
<td>0.297</td>
</tr>
<tr>
<td>Total UPDRS motor score (SD)</td>
<td>28.5 (17.6)</td>
<td>23.8 (10.2)</td>
<td>29.3 (18.5)</td>
<td>0.0504</td>
</tr>
<tr>
<td>UPDRS motor subscore A (SD)</td>
<td>18.4 (12.3)</td>
<td>14.5 (6.9)</td>
<td>19.0 (12.9)</td>
<td>0.436</td>
</tr>
<tr>
<td>UPDRS motor subscore B (SD)</td>
<td>7.2 (4.5)</td>
<td>7.5 (3.7)</td>
<td>7.2 (4.7)</td>
<td>0.594</td>
</tr>
<tr>
<td>Hoehn and Yahr stage Mean (SD)</td>
<td>3.0 (0.9)</td>
<td>3.2 (0.6)</td>
<td>3.0 (1.0)</td>
<td>0.306</td>
</tr>
<tr>
<td>Range</td>
<td>1.0–5.0</td>
<td>2.5–4.0</td>
<td>1.0–5.0</td>
<td></td>
</tr>
<tr>
<td>Montgomery and Aasberg Depression Rating Scale score (SD)</td>
<td>5.4 (6.7)</td>
<td>13.3 (7.3)</td>
<td>4.2 (5.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mini-Mental State Examination score (SD)</td>
<td>25.5 (6.4)</td>
<td>21.1 (6.7)</td>
<td>26.2 (6.1)</td>
<td>0.011</td>
</tr>
<tr>
<td>Neuropsychiatric Inventory apathy score (SD)</td>
<td>1.2 (2.9)</td>
<td>7.9 (2.6)</td>
<td>0.1 (0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depression, n (%)</td>
<td>16 (20.3)</td>
<td>6 (54.5)</td>
<td>10 (14.7)</td>
<td>0.007</td>
</tr>
<tr>
<td>Dementia, n (%)</td>
<td>23 (29.1)</td>
<td>7 (63.6)</td>
<td>16 (23.5)</td>
<td>0.012</td>
</tr>
<tr>
<td>Levodopa equivalent dose, mg daily (SD)</td>
<td>658 (387)</td>
<td>630 (415)</td>
<td>663 (386)</td>
<td>0.456</td>
</tr>
<tr>
<td>Antidepressants, n (%)</td>
<td>14 (17.7)</td>
<td>3 (27.3)</td>
<td>11 (16.2)</td>
<td>0.370</td>
</tr>
<tr>
<td>Anxiolytics, n (%)</td>
<td>7 (8.9)</td>
<td>1 (9.1)</td>
<td>6 (8.8)</td>
<td>0.999</td>
</tr>
<tr>
<td>Antipsychotics, n (%)</td>
<td>9 (11.4)</td>
<td>3 (27.3)</td>
<td>6 (8.8)</td>
<td>0.084</td>
</tr>
</tbody>
</table>

Data are expressed as mean (SD) or number (percentage of assessed patients); all available data included. Comparisons between patients with and without apathy: \( \chi^2 \) 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.
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 serotoninergic systems have been found to be involved in apathy. These deficits are also thought to relate to depression and dementia associated with PD (PDD). This may explain 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. 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, with a cut-off ≧4 being recommended as indicating clinically significant apathy in PD.

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.
REFERENCES