The Rate of Cognitive Decline in Parkinson Disease

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Objectives: To measure the rate and predictors of change on the Mini-Mental State Examination in patients with Parkinson disease (PD) and to compare that change with the Mini-Mental State Examination changes of patients with Alzheimer disease and nondemented subjects.

Patients: Patients with PD were drawn from a community-based cohort in Rogaland County, Norway. Those who were without cognitive impairment at disease onset and participated in 1 or more assessments after visit 1 were included and examined after 4 years (visit 2) and 8 years (visit 3). Motor, cognitive, and psychiatric symptoms were rated using standardized scales at visit 1. Two population-based cohorts of patients with Alzheimer disease and nondemented control subjects were included for comparison. Data were analyzed using a mixed-effects model.

Results: One hundred twenty-nine PD patients (57% women) were included. The mean (SD) Mini-Mental State Examination score at visit 1 was 27.3 (5.7). The mean annual decline in score from visit 1 to visit 3 was 1.1 (95% confidence interval, 0.8 to 1.3; 3.9% change from visit 1). Patients with PD and dementia (n=49) had an annual decline from visit 1 to visit 2 of 2.3 (95% confidence interval, 2.1 to 2.5; 9.1% change from visit 1), compared with 2.6 (95% confidence interval, 2.3 to 2.8; 10.6% change from visit 1) in the patients with Alzheimer disease (n=34) (mean annual decline among patients with PD and dementia vs patients with Alzheimer disease, not significant). The change in score for nondemented PD patients (n=80) was small and similar to that for nondemented control subjects (n=1621). Old age, hallucinations, and more severe motor symptoms (rigidity and motor scores mediated by nondopaminergic lesions) at visit 1 were significantly associated with a more rapid cognitive decline in patients with PD.

Conclusions: The mean annual decline on the Mini-Mental State Examination for PD patients was 1 point. However, a marked variation was found. In patients with PD and dementia, the mean annual decline was 2.3, which was similar to the decline observed in patients with Alzheimer disease.
METHODS

VISIT 1

PD Patients

Details of the case-finding procedure have been published elsewhere. We attempted a total ascertainment of patients with recognized idiopathic PD in 9 municipalities with 220 000 inhabitants in the southern part of Rogaland County in western Norway. Parkinson disease was diagnosed in 245 subjects (visit 1), with a prevalence of 102 per 100 000, which is comparable to other prevalence studies. Patients were invited by letter to participate in the follow-up evaluations 4 years (visit 2) and 8 years (visit 3) after visit 1 (Figure 1).

Control Subjects

For comparison, we included subjects from a randomly drawn sample aged between 65 and 84 years in the municipality of Odense, Denmark, who underwent the MMSE at visit 1 and at a follow-up evaluation 5 years later (visit 2). At visit 1 and visit 2, 1621 normal control subjects were without dementia, and 34 subjects had AD and underwent the MMSE at both visits and were included as the AD control group (Figure 2).

Diagnosis and Clinical Assessments: PD Patients

Details of the diagnostic and clinical assessments have been published elsewhere. Information on disease history, drug therapy, and demographic variables was collected by means of a structured clinical interview. The clinical examination included a general physical examination, laboratory tests, assessment of motor symptoms (Unified Parkinson’s Disease Rating Scale [UPDRS]), and the Hoehn and Yahr scale. To independently assess the potential contribution of motor impairment mediated by dopaminergic (subscore A) and nondopaminergic (subscore B) systems, 2 subscores were calculated based on the UPDRS scores, as previously suggested. To achieve high diagnostic specificity as well as high sensitivity, a diagnostic classification of clinically definite, probable, and possible PD was used. Structural brain imaging (computed tomography or magnetic resonance imaging) was performed in most cases. We included in this study only patients who fulfilled the diagnostic criteria for clinically definite, probable, or possible PD at all examinations and who, according to the history, were without cognitive impairment at disease onset. A subgroup of PD patients (n=16) were assessed neuropathologically after they provided written informed consent. All patients had neuron loss and -synuclein–positive Lewy bodies in the surviving neurons of the substantia nigra, thus confirming the diagnosis of PD. The neurologist administered the MMSE and the Montgomery and Asberg Depression Rating Scale, and hallucinations were rated using the UPDRS thought-disorder item.

VISIT 2 AND VISIT 3

PD Patients

Patients were reassessed 4 years (visit 2) and 8 years (visit 3) after visit 1 by the same neurologist, a geriatric psychiatrist, and...
a research nurse trained for cognitive evaluation of PD patients. Patients with an MMSE score of 16 or higher underwent a neuropsychological battery. The Dementia Rating Scale, which also assesses executive functions and has been shown to be a valid measure of cognition in PD,23 was administered to all patients. The cognitive assessments were performed blind to the neurological evaluation.

For a patient to qualify for a diagnosis of dementia, the interview, the rating scales, and the neuropsychological tests had to be compatible with a diagnosis of dementia according to the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R),24 (See Aarsland et al17 for more details of the diagnosis of dementia.) For the purpose of this study, the PD patients with dementia at visit 2 were chosen as the PD and dementia (PDD) group. The study was approved by the ethical committee at the University of Bergen.

Control Subjects

Control subjects underwent a 2-phased diagnostic procedure as described elsewhere17 and were evaluated according to NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association) criteria for probable AD25 and NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association) criteria for vascular dementia and dementia of other types.

STATISTICS

For PD subjects, annual change (mean and 95% confidence interval [CI]) and annual percentage change on the MMSE from visit 1 to visit 2 (D1), from visit 2 to visit 3 (D2), and from visit 1 to visit 3 (D3) were calculated. Paired t tests were used to compare MMSE performance at the different time points. Simple regression analyses with D1 as the dependent variable were used to determine what visit-1 characteristics to include (P<.10) in separate multivariate analyses for the 2 UPDRS groupings (motor scores A and B, and tremor, bradykinesia, and rigidity). At consecutive visits, MMSE scores were analyzed in a mixed-effects model,26 with the time since visit 1 as the primary covariate. The square of the primary covariate was included to accommodate possibly accelerated cognitive decline, and a model with random effects in all coefficients was fitted. Visit-1 characteristics from the univariate analyses were included subsequently. Annual change in MMSE scores in normal control subjects and patients with PD, PDD, and AD was analyzed by analysis of covariance with adjustment for age. We further compared annual change in MMSE scores in PD and AD patients before they were diagnosed as having dementia for the first time.

RESULTS

One hundred twenty-nine PD patients (57% women) underwent the MMSE at visit 2 and were included in the study, and 83 completed all 3 visits (Figure 1). All PD patients except 1 were treated with levodopa at visit 1, 61 patients were treated with more than 1 antiparkinson agent, and only 2 were treated with an anticholinergic agent. Six patients received an antipsychotic agent, and 14 received a tricyclic antidepressant agent. The characteristics at visit 1 of the study population and of those who were not included are shown in Table 1.

COGNITIVE DECLINE IN PD

The mean (SD) MMSE score at visit 1 was 27.3 (3.7), 23.8 (8.0) at visit 2, and 19.2 (9.8) at visit 3 (all P values <.001; paired t tests) (Figure 3). The Pearson correlation between MMSE and Dementia Rating Scale scores at visit 2 was 0.87 (P <.001). The annual D1 was 0.9 (CI, 0.6 to 1.1; 3.3% change from visit 1), and the annual D3 was 1.1 (CI, 0.8 to 1.3; 3.9% change from visit 1).

Parkinson disease and dementia were diagnosed in 49 patients at visit 2. Patients with PDD had mean (SD) MMSE scores of 25.4 (4.9), 16.2 (8.0), and 7.2 (6.5) at

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics in Patients With Parkinson Disease and Control Subjects According to Completion of Follow-up*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Women, %</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Education &lt;8 y, %</td>
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<tr>
<td>Mini-Mental State Examination score</td>
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<tr>
<td>Duration of disease, y</td>
</tr>
<tr>
<td>Hoehn-Yahr stage</td>
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</tbody>
</table>

Abbreviation: NA, not applicable.

*Data are presented as mean (SD) unless otherwise indicated.
†P<.001.
‡P<.05.
visit 1, visit 2, and visit 3, respectively. The mean annual D1 was 2.3 (CI, 2.1 to 2.5; 9.1% change from visit 1), and the mean annual D3 was 2.4 (CI, 2.0 to 2.8; 9.4% change from visit 1) (Table 2) (Figure 3).

Table 2. Cognitive Decline in Patients With Parkinson Disease With and Without Dementia, Patients With Alzheimer Disease, and Nondemented Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With Parkinson Disease and Dementia at Visit 2</th>
<th>Patients With Alzheimer Disease</th>
<th>Patients With Parkinson Disease Without Dementia at Visit 2</th>
<th>Nondemented Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>49</td>
<td>34</td>
<td>80</td>
<td>1621</td>
</tr>
<tr>
<td>Age at visit 1, y</td>
<td>73.8 (6.0)</td>
<td>78.1 (3.9)*</td>
<td>67.6 (8.4)*</td>
<td>71.7 (4.9)†</td>
</tr>
<tr>
<td>Education &lt;8 y, %</td>
<td>49</td>
<td>74†</td>
<td>36</td>
<td>63†</td>
</tr>
<tr>
<td>MMSE score at visit 1, mean (SD)</td>
<td>25.4 (4.9)</td>
<td>24.5 (13.8)</td>
<td>28.4 (1.9)*</td>
<td>27.8 (1.8)*</td>
</tr>
<tr>
<td>MMSE score at visit 2, mean (SD)</td>
<td>16.2 (8.0)</td>
<td>11.4 (8.9)‡</td>
<td>28.5 (2.5)*</td>
<td>27.2 (2.1)*</td>
</tr>
<tr>
<td>Annual (95% confidence interval)</td>
<td>2.3 (2.1-2.5); 9.1 (2.1-2.5);</td>
<td>2.6 (2.3-2.8); -0.02 (-0.2-0.1);</td>
<td>0.1 (0.1-0.2);</td>
<td>0.4</td>
</tr>
<tr>
<td>Annual change on MMSE, No. (%) of patients§</td>
<td>9 (18)</td>
<td>10.6</td>
<td>9 (98.7)</td>
<td>1599 (98.5)</td>
</tr>
<tr>
<td>≤1</td>
<td>1.1-1.9</td>
<td>2-2.9</td>
<td>3-3.9</td>
<td>4+</td>
</tr>
<tr>
<td>9 (18)</td>
<td>13 (38)</td>
<td>9 (26)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>11 (22)</td>
<td>3 (9)</td>
<td>1 (1.3)</td>
<td>24 (1.5)</td>
<td></td>
</tr>
<tr>
<td>16 (33)</td>
<td>9 (26)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8 (16)</td>
<td>9 (26)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
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</table>

Abbreviation: MMSE, Mini-Mental State Examination.

*P<.001.
†P<.01.
‡P<.05.
§A positive value means a decline in score between the visits.

Thirty-six PD patients completed the 8-year follow-up without developing dementia. At the final visit (visit 3), the mean (SD) age was 72.8 (10.0) years, the duration of PD was 16.5 (5.3) years, and the MMSE score was 28.0 (2.0) in this group. The mean annual D3 was not significant (D3, 0.1; CI, -0.03 to 0.17; 0.3% change from visit 1; t3=1.4; P=.18), although a small but statistically significant decline occurred during the last 4 years (D2, 0.4; CI, 0.2 to 0.5; 1.3% change from visit 1; t5=4.5; P<.001) (Figure 3). Thus, 43% of those who survived the 8-year study period had no significant decline on the MMSE during the 8-year follow-up. This group comprises 28% of those who completed visit 2 and 15% of the population available for inclusion (ie, those who fulfilled inclusion criteria and completed visit 1; n=245).

PREDICTORS OF COGNITIVE DECLINE IN PD

The associations between D1 and the visit-1 demographic and clinical characteristics (age; age at onset; sex; years of education; duration of disease; UPDRS motor subscores A and B; tremor, rigidity, and bradykin-}

motor subscore B, higher Hoehn and Yahr stage, UPDRS rigidity and bradykinesia scores, and a trend toward an association with years of education (P=.10), and these variables were thus included in the mixed-effects models.

The UPDRS motor subscores A and B were included, and subsequently the alternative model using UPDRS rigidity and bradykinesia scores was used. In both models, there was a significant decline by time in MMSE (P<.001) at visit 2, and there was also a significant downward curvature (P<.001), implying accelerated cognitive decline. In the model including UPDRS motor subscores A and B, age (P<.001), motor score B (P<.001), and thought-disorder score (P<.01) were negatively related to MMSE score, with a negative curvature for age (P=.01) and motor score B (P<.001). Also, there were significant interactions of age by time (P<.01) and motor score B by time, implying more rapid cognitive decline with higher age and higher levels of motor score B. In the model including UPDRS scores of bradykinesia and rigidity, age (P<.001) and rigidity score (P<.01) were negatively related to MMSE score, with a negative curvature for age (P<.05) and rigidity score (P<.001). Also, there were negative age by time (P<.001) and rigidity score by time (P<.05) interactions, implying more rapid cognitive decline with higher age and higher levels of the rigidity score. Thus, higher age at visit 1 and higher scores on the UPDRS motor score B, rigidity subscore, and thought-disorder item predicted a more rapid cognitive decline.

COGNITIVE DECLINE IN PD COMPARED WITH AD AND CONTROLS

The AD patients were older and had a lower level of education than the PDD group, but visit-1 MMSE scores did not differ significantly (Table 2). The mean annual change of MMSE scores adjusted for age differed significantly be-
between the 4 groups ($F_{3,178} = 273; P < .001$). Sidak post-hoc tests based on estimated marginal means showed that the annual decline of AD patients (2.6; 95% CI, 2.3 to 2.8; 10.6% change from visit 1) was not significantly different from the annual decline from visit 1 and visit 2 in PDD patients (Table 2). Normal controls and nondemented PD patients had less decline than AD and PDD patients but did not differ from each other (Table 2). The proportion of patients with an annual decline of at least 4 points was 16.3% among PDD patients and 26.5% among AD patients (proportion with annual decline of at least 4 points among PDD patients vs AD patients, not significant).

We then compared the annual change on the MMSE in PD patients and control subjects who were nondemented at visit 1 but who at visit 2 completed the MMSE and were diagnosed as having AD (n=42) or PDD (n=41). Mean (SD) age at visit 1 was 76.0 (5.4) years in AD patients and 73.0 (5.9) years in PD patients ($P < .05$). Those who were diagnosed as having AD declined from a mean (SD) MMSE score of 25.4 (2.2) to 20.3 (3.6) during the 5 years prior to diagnosis, whereas PD patients declined from 26.9 (2.1) to 18.0 (6.8) during the 4 years prior to diagnosis. The annual decline in the PDD group was 2.2 (95% CI, 1.7 to 2.8; 8.3% change from visit 1), compared with a decline of only 1.0 (95% CI, 0.8 to 1.3; 4.1% change from visit 1) in the AD group. This difference was statistically significant even after controlling for age ($P < .001$). Thus, the initial cognitive decline in patients with PDD is more rapid than the initial cognitive decline in patients with AD.

### Comment

This study of 129 unselected community-based patients, observed prospectively for at least 4 years, constitutes the largest longitudinal study of cognitive functioning in patients with PD to date. The average annual decline on the MMSE was about 1 point. There was, however, a marked variation within the PD group. Patients with PD who developed dementia had an annual mean decline of 2.3 points, whereas the change in a small group who did not develop dementia was similar to that of nondemented elderly control subjects. Predictors of more rapid cognitive decline in PD were old age at study entry, hallucinations, and more severe motor symptoms, in particular symptoms not associated with dopaminergic motor systems, such as gait, speech, and postural disturbances.

Patients with PDD declined at about the same rate as AD patients. During the first 4 years of the dementia process, the decline was even more rapid in PD patients than in AD patients. Notably, the older age and fewer years of formal education in the AD patients would tend to be associated with an increased rate of cognitive decline in this group compared with PDD patients, thus strengthening the conclusion of similar rate of cognitive decline in PDD compared with AD.

Patients with hallucinations at visit 1 had a more rapid cognitive decline than those without hallucinations. Similarly, patients with AD and hallucinations decline more rapidly than those without hallucinations. Thus, hallucinations may either directly or through an as-yet-undefined underlying common etiologic factor contribute to a more rapid cognitive decline in patients with dementia. Alternatively, this association may be secondary to neuroleptic treatment. In this study, however, no relationship between the use of neuroleptics and the rate of cognitive decline was found. The association between hallucinations and cognitive decline found in the current study suggests that patients with DLB might erroneously have been included. This is unlikely, however, because none of the PD patients had cognitive impairment at disease onset. It is not known whether any of the 8 patients with dementia at visit 1 had developed dementia within the first year of PD and thus would fulfill the clinical criteria for DLB. However, when these patients were excluded from the analysis, a similar rate of cognitive decline was found, showing that the findings cannot be attributed to the inclusion of patients with DLB.

The methodological strengths of this study include the relatively large and community-based sample of patients with PD; the prospective design; the use of a comprehensive battery of standardized tests of motor, psychiatric, and cognitive functions to characterize the patients; the low attrition rate due to causes other than death; and the inclusion of 2 community-based control groups. Furthermore, the long duration of follow-up is important because this reduces the measurement error on the MMSE. Weaknesses of the study include the lack of autopsy data to corroborate the clinical diagnosis in the majority of patients, although the diagnosis was confirmed by autopsy in a subset of patients with PD. Furthermore, high diagnostic accuracy, up to 90%, can be achieved in expert groups, especially in patients assessed by the same neurologist in long-term clinical trials using accepted clinical criteria. The long intervals between tests resulted in a substantial attrition rate due to death. This attrition rate and the higher attrition rate among the control subjects, which may lead to a disproportionate contribution from comparatively high-functioning individuals, may bias the results. Because a prevalence PD sample was used, the disease duration at visit 1 was more than 8 years, and the findings may thus not be representative for early PD. Finally, the PD patients and control subjects lived in different countries; however, Denmark and Norway are ethnically, socially, and culturally similar, and urban and rural populations were included in both samples. Future studies should explore the evolution of different cognitive domains and their clinicopathologic relationship in incident samples of patients with PD and other dementia types, including DLB, as well as healthy subjects.

REFERENCES


