

## Memory and Executive Function Impairment Predict Dementia in Parkinson's Disease

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**Abstract** We analyzed the association of neuropsychological test impairment at baseline with the development of dementia in idiopathic Parkinson's disease (PD) patients. A cohort of nondemented PD patients from northern Manhattan, NY was followed annually with neurological and neuropsychological evaluations. The neuropsychological battery included tests of verbal and nonverbal memory, orientation, visuospatial ability, language, and abstract reasoning. The association of baseline neuropsychological test scores with incident dementia was analyzed using Cox proportional hazards models. The analysis controlled for age, gender, education, duration of PD, and the total Unified Parkinson's Disease Rating Scale motor score at baseline. Forty-five out of 164 patients (27%) became demented during a mean follow-up of  $3.7 \pm 2.3$  years. Four neuropsychological test scores were significantly associated with in-

cident dementia in the Cox model: total immediate recall (RR: 0.92, 95% CI: 0.87–0.97,  $P = 0.001$ ) and delayed recall (RR: 0.73, 95% CI: 0.59–0.91,  $P = 0.005$ ) of the Selective Reminding Test (SRT), letter fluency (RR: 0.87, 95% CI: 0.77–0.99,  $P = 0.03$ ), and Identities and Oddities of the Mattis Dementia Rating Scale (RR: 0.85, 95% CI: 0.73–0.98,  $P = 0.03$ ). When the analysis was performed excluding patients with a clinical dementia rating of 0.5 (questionable dementia) at baseline evaluation, total immediate recall and delayed recall were still predictive of dementia in PD. Our results indicate that impairment in verbal memory and executive function are associated with the development of dementia in patients with PD. © 2002 Movement Disorder Society

**Key words:** Parkinson's disease; dementia; cognition; neuropsychological predictors

Although most patients with idiopathic Parkinson's disease (PD) have circumscribed cognitive impairment, only a proportion of them develops dementia.<sup>1</sup> Determining which neuropsychological tests are most predictive of incident dementia in PD may provide useful prognostic information. Because the pathological substrate underlying dementia in PD has not been clearly defined and some studies have suggested that the presence of concomitant Alzheimer's disease (AD) cortical changes is

etiologically related to dementia in PD,<sup>2–4</sup> the early cognitive impairment associated with the development of dementia may also provide insight into the biological basis of PD dementia.

In longitudinal studies, age and severity of extrapyramidal signs have been associated most consistently with incident dementia in PD.<sup>5–11</sup> We reported previously that verbal fluency tests were predictive of dementia in a community-based sample of PD patients followed for a mean of 2.7 years (maximum follow-up: 4 years).<sup>12</sup> Only one other longitudinal study of neuropsychological predictors of incident dementia in PD has been published.<sup>13</sup> We reexamined the pattern of cognitive impairment associated with incident dementia in an expanded cohort of PD patients with a longer duration of follow-up, including twice the number of incident dementia cases.

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## PATIENTS AND METHODS

### Patients and Procedures

A cohort of nondemented PD patients from the Washington Heights community in northern Manhattan, NY was followed annually with neurological and neuropsychological evaluations. The ascertainment procedure and inclusion and exclusion criteria for the cohort have been described previously.<sup>1</sup> We attempted complete case ascertainment through the development of a "registry" in the community for all individuals considered to have PD living within four zip codes in Washington Heights–Inwood. Patients were identified from many sources including admission and discharge lists from the Columbia Presbyterian Medical Center, lists from various ambulatory care sites, and practitioners both in the hospital and in the community. Idiopathic PD was defined by established research criteria.<sup>14–16</sup> Patients with postencephalitic and drug-induced parkinsonism or a parkinson-plus syndrome were excluded, as were patients who presented memory loss or dementia before the motor manifestations of PD. No patient became demented within 1 year of onset of motor manifestations (minimum disease duration until dementia, 2.5 years), therefore clinical criteria for dementia with Lewy bodies were not met.<sup>17</sup>

Of 319 patients with idiopathic PD, 105 considered to be demented at baseline evaluation were excluded. Of 214 nondemented patients, 31 had no follow-up visit. These 31 patients with no follow-up were less likely to be white/non-Hispanic (25.8% vs. 54.6%,  $P < 0.05$ ) than the patients with follow-up ( $n = 183$ ). No statistically significant differences were observed for age, gender, education, duration of PD, or severity of extrapyramidal signs. Three additional patients were excluded because they had signs or symptoms of stroke at baseline, leaving 180 patients with at least two visits for the present analysis.

Duration of PD was defined as the time period between the first symptom of PD and the baseline evaluation. The annual clinical evaluation included the Unified Parkinson's Disease Rating Scale (UPDRS)<sup>18</sup> on all patients, and the Hamilton Depression Rating Scale (HDRS)<sup>19</sup> on a subset of the patients. Functional status was assessed by a physician blind to the neuropsychological examination using the Blessed Dementia Rating Scale (part I),<sup>20</sup> and functional impairment was necessary for a diagnosis of dementia.

The neuropsychological battery, described in detail elsewhere,<sup>12,21</sup> included the following measures: total immediate recall, delayed recall, and delayed recognition memory of the Selective Reminding Test (SRT),<sup>22</sup> Benton Visual Retention Test matching and recognition,<sup>23</sup>

the Similarities subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R),<sup>24</sup> category fluency, letter fluency,<sup>25</sup> the Identities and Oddities subtest of the Mattis Dementia Rating Scale (MDRS),<sup>26</sup> Rosen Drawing Test,<sup>27</sup> Boston Naming Test,<sup>28</sup> repetition and auditory comprehension from the Boston Diagnostic Aphasia Examination,<sup>29</sup> and the orientation items of the Mini-Mental State Examination.<sup>30</sup> Neuropsychological test scores were evaluated using a fixed paradigm<sup>21</sup> and dementia was diagnosed based on Diagnostic and Statistical Manual of Mental Disorders, revised third edition (DSM-III-R)<sup>31</sup> criteria.

Each patient was assigned a Clinical Dementia Rating (CDR)<sup>32</sup> at each study visit. Nondemented patients had either CDR 0 (no dementia) or CDR 0.5 (questionable dementia). CDR 0.5 was assigned to patients who did not meet criteria for dementia according to a fixed paradigm<sup>21</sup> but whose test performance was believed to have functional significance.

### Data Analysis

Baseline characteristics of patients with and without incident dementia were compared using Student's  $t$  tests for continuous variables and  $\chi^2$  tests for categorical variables. The association of baseline cognitive impairment with incident dementia was studied using Cox proportional hazards models. Baseline scores on 14 neuropsychological tests were entered in the Cox model using a forward stepwise procedure for the selection of predictor variables (entry criterion:  $P < 0.05$ , removal criterion:  $P > 0.1$ ). These same neuropsychological test scores, in addition to functional impairment, were taken into account when diagnosing dementia. Duration of follow-up until the diagnosis of dementia or until the last visit for those patients who did not become demented was used as the timing variable in the Cox models. All analyses controlled for age, gender, years of education, duration of PD, and the total UPDRS motor score (Part III) at baseline. Analyses were performed both for the entire cohort and for the cohort excluding patients with CDR 0.5 at baseline evaluation.

## RESULTS

### Entire Cohort

Of 180 patients, 52 (29%) became demented during a mean follow-up period of  $3.6 \pm 2.2$  years (maximum follow-up: 8 years). Baseline characteristics of the cohort are summarized in Table 1. Patients who became demented subsequently were older, less educated, and had more severe motor signs at baseline than those who did not become demented. No significant differences were seen in gender, ethnicity, language in which the neuro-

**TABLE 1.** Baseline demographic and clinical characteristics of Parkinson's disease patients who did and did not become demented

Variable	Incident dementia (n = 52)	No incident dementia (n = 128)	Total (n = 180)
Age, yr (S.D.)	74.6 (8.2)	69.5 (10.7) <sup>a</sup>	71.0 (10.3)
Gender (% male)	55.8	42.2	46.1
Education, yr (S.D.)	9.4 (4.6)	11.8 (4.7) <sup>a</sup>	11.1 (4.8)
Ethnicity (% white/non-Hispanic)	55.8	54.7	55.0
Primary language (% English)	52.9	65.4	61.8
Duration of PD, yr (S.D.)	7.3 (5.8)	5.9 (7.2)	6.3 (6.9)
Total UPDRS motor score, range 0–100 (S.D.)	32.0 (13.6)	22.2 (11.4) <sup>a</sup>	25.0 (12.8)
Total 17-item HDRS score, range 0–53 (S.D.)	6.8 (5.6)	5.8 (5.0)	6.1 (5.1)
Use of dopaminergic agents (%) <sup>b</sup>	76.9	75.8	76.1
Use of anticholinergics (%)	17.6	15.2	15.9
Levodopa dosage, mg/day (S.D.)	326.7 (325.3)	364.2 (373.6)	354.1 (360.6)

Values are expressed as mean (S.D.) or percent.

Total n: 178 for language, 177 for UPDRS score, 154 for HDRS score, 176 for use of anticholinergics, and 159 for levodopa dosage.

<sup>a</sup>*P* < 0.05.

<sup>b</sup>Includes levodopa and dopaminergic agonists.

HDRS, Hamilton Depression Rating Scale; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale.

psychological tests were administered (English or Spanish), duration of PD, total HDRS score, use of dopaminergic and anticholinergic medications, and levodopa dosage.

In addition to age at baseline and the total UPDRS motor score, four neuropsychological tests were associated with incident dementia in the Cox regression model with forward stepwise procedure for the selection of predictor variables: total immediate recall and delayed recall of the SRT, letter fluency, and Identities and Oddities of the MDRS (Table 2). Sixteen patients, 7 of whom developed dementia during follow-up, were excluded due to missing data for one or more variables initially entered in the model. The excluded patients were older ( $78.2 \pm 5.7$  vs.  $70.3 \pm 10.3$  years, *P* < 0.001), less educated ( $8.2 \pm 5.6$  vs.  $11.4 \pm 4.6$  years, *P* = 0.009), and more often female (81.3% vs. 51.2%, *P* = 0.02) than those patients with complete data. Of the remaining 164 patients, 45 (27%) became demented during a mean follow-up of  $3.7 \pm 2.3$  years.

To aid in the clinical interpretation of the risk ratios of the neuropsychological variables retained in the Cox model, we dichotomized baseline performance into scores above and below the median. The median scores were 36 for total immediate recall (maximum possible score, 72), 5 for delayed recall (maximum possible score, 12), 9 for letter fluency (no maximum score), and 15 for Identities and Oddities (maximum possible score, 16). The four dichotomous neuropsychological variables were included in a Cox model controlling for age, gen-

der, education, duration of PD, and total UPDRS motor score at baseline. In this analysis (total N = 164; incident dementia N = 45), the risk ratio for dementia associated with obtaining a score <median vs.  $\geq$ median (reference) was 6.5 (95% CI: 2.0–21.6, *P* = 0.002) for total immediate recall, 4.4 (95% CI: 1.7–11.3, *P* = 0.002) for delayed recall, 1.6 (95% CI: 0.7–3.5, *P* = 0.2) for letter fluency, and 1.3 (95% CI: 0.6–2.7, *O* = 0.5) for Identities and Oddities.

**TABLE 2.** Risk ratios for incident dementia derived from a Cox proportional hazards model

Variable	Risk ratio	95% CI	<i>P</i>
Age at baseline (yr)	1.06	1.02–1.11	0.001
Gender (male)	1.69	0.89–3.22	0.1
Education	1.05	0.97–1.14	0.2
Duration of PD (yr)	0.98	0.93–1.04	0.5
Total UPDRS motor score	1.06	1.03–1.10	0.0001
Total immediate recall of the SRT	0.92	0.87–0.97	0.001
Delayed recall of the SRT	0.73	0.59–0.91	0.005
Letter fluency	0.87	0.77–0.99	0.03
Identities and oddities of the MDRS	0.85	0.73–0.98	0.03

Neuropsychological variables were selected using a forward stepwise procedure; all of the above variables are simultaneously included in the Cox model.

Total N = 164, incident dementia N = 45.

MDRS, Mattis Dementia Rating Scale; PD, Parkinson's disease; SRT, Selective Reminding Test; UPDRS, Unified Parkinson's Disease Rating Scale.

The initial Cox model analysis was repeated including the total HDRS score at baseline. Twenty cases had missing information for the total HDRS score, leaving 144 patients for this analysis. Results were similar except for the Identities and Oddities test, which was no longer included in the final model.

### Cohort Excluding CDR 0.5

Twenty-eight of 164 patients (17.1%) had a CDR of 0.5 (questionable dementia) at baseline. We performed the analysis after excluding these patients, and the final model retained total immediate recall, delayed recall, and Identities and Oddities as predictors of incident dementia, but letter fluency was not included in this model (Table 3).

We recalculated the median scores of the three neuropsychological test scores that were predictive of incident dementia in this subgroup (total N = 136, incident dementia N = 25) and compared those with scores <median to those with scores  $\geq$ median (reference). The median scores were 39 for total immediate recall, 6 for delayed recall, and 15 for Identities and Oddities. In a Cox model controlling for age, gender, education, duration of PD, and total UPDRS motor score at baseline, risk ratios were 7.3 (95% CI: 0.8–62.8,  $P = 0.07$ ) for total immediate recall, 12.2 (95% CI: 1.5–101.6,  $P = 0.02$ ) for delayed recall, and 1.7 (95% CI: 0.6–5.2,  $P = 0.3$ ) for Identities and Oddities.

## DISCUSSION

In this cohort, baseline impairment in verbal memory (total immediate and delayed recall) was associated with

**TABLE 3.** Risk ratios for incident dementia derived from a Cox proportional hazards model, excluding cases with questionable dementia (CDR 0.5) at baseline evaluation

Variable	Risk ratio	95% CI	P
Age at baseline	1.06	1.01–1.12	0.03
Gender (male)	1.14	0.47–2.76	0.8
Education	1.04	0.92–1.17	0.6
Duration of PD	0.97	0.91–1.02	0.2
Total UPDRS motor score	1.08	1.03–1.13	0.002
Total immediate recall of the SRT	0.89	0.83–0.95	0.0005
Delayed recall of the SRT	0.70	0.52–0.93	0.01
Identities and oddities of the MDRS	0.62	0.43–0.90	0.01

Neuropsychological variables were selected using a forward stepwise procedure; all of the above variables are simultaneously included in the Cox model.

Total N = 136, incident dementia N = 25.

CDR, Clinical Dementia Rating; MDRS, Mattis Dementia Rating Scale; PD, Parkinson's disease; SRT, Selective Reminding Test; UPDRS, Unified Parkinson's Disease Rating Scale.

incident dementia in PD, in addition to impairment in tests suggestive of executive dysfunction (letter fluency and Identities and Oddities). In the analysis including the total HDRS score as a covariate, the Identities and Oddities was not a significant predictor of dementia in PD, which may imply that depressive symptoms accounted for the association of the Identities and Oddities with incident dementia in PD. Alternatively, this may have been due to lower statistical power because of the loss of patients with missing data in this analysis. In the analysis excluding patients with CDR 0.5 at baseline evaluation, both memory tests were still predictive of dementia in PD, but letter fluency was not included in the model, which may be due to the smaller sample size in this analysis (Table 3).

In our previous study,<sup>12</sup> baseline performance on two verbal fluency tasks (letter fluency and category fluency) predicted incident dementia in PD patients. Sixty-one of 164 patients who were included in the stepwise Cox regression model were not included in the previous analysis.<sup>12</sup> Eight patients from the original cohort were not included in the current analysis because they were subsequently deemed not to have PD, or because different criteria for the exclusion of stroke cases were employed. The demographic characteristics of the present cohort, however, were similar to the previous cohort. Of 45 patients with incident dementia in the present analysis, 21 were included as incident dementia cases in the previous analysis, 9 became demented during the additional follow-up, and 15 were new patients not included in the previous analysis. The duration of follow-up until the diagnosis of dementia of these 15 patients was not significantly different from the group of 45 patients as a whole ( $2.5 \pm 1.4$  vs.  $2.7 \pm 1.7$  years,  $P = 0.7$ ). Thus, we believe that the additional findings in the present study are attributable to the statistical power gained from larger sample size and increased duration of follow-up.

In the only other published prospective study of neuropsychological predictors of dementia in PD,<sup>13</sup> 81 initially nondemented PD patients were reassessed after a mean of 3.5 years and 19 were diagnosed as demented. The Picture Completion subtest of the WAIS-R, the interference section of the Stroop test, and letter fluency were considered to be independent predictors of incident dementia. Three memory subtests of the Wechsler Memory Scale (Logical Memory, Visual Memory, and Associate Learning) were not predictors of incident dementia. Compared to our community-based cohort, the clinic sample used in this study was younger ( $66.9 \pm 10.0$  years), had a longer duration of PD ( $8.3 \pm 6.5$  years), and lower total UPDRS motor score ( $17.9 \pm 14.4$ ).

Previous studies of cognitive impairment in early PD

have demonstrated impaired performance in memory tests.<sup>33–36</sup> Yet, as stated by Levin and Katzen, “More research is needed to examine whether early memory impairment is a marker or precursor for a more widespread dementia that will develop in the later stages of the disease.”<sup>37</sup> In this cohort, memory impairment in nondemented PD patients predicted dementia in the later stages of PD. This finding, however, may not be applicable to a cohort of patients with a shorter duration of PD. Some studies have suggested that involvement of frontal lobe function accounts for memory impairment in early nondemented PD patients.<sup>35,38–41</sup> In a previous cross-sectional analysis, we observed a qualitative difference in memory performance between nondemented and demented PD patients, as compared to matched AD groups.<sup>42</sup> This finding was supported in a prospective study of the rate of cognitive decline in AD and PD dementia.<sup>43</sup>

In longitudinal studies of healthy elders, in addition to impairment in delayed and immediate recall, impairment in naming, category fluency, and Digit Symbol and Similarities subtests of the WAIS-R have been shown to be predictive of AD.<sup>44–46</sup> Although our study evidenced memory impairment as a precursor of dementia in PD, the neuropsychological impairment associated with incident PD dementia in this and other studies does not overlap completely with that of the preclinical phase of AD. Moreover, impairment in delayed recall reflects deficient encoding in AD as opposed to retrieval failure in PD.<sup>47</sup> Category fluency impairment is attributed to early deterioration of semantic knowledge in AD<sup>48</sup> and a deficit in semantic retrieval in PD.<sup>49</sup>

Our study has limitations. The cohort consisted of individuals with a mean age at baseline of  $71.0 \pm 10.3$  years (median: 71.8 years) and mean disease duration at baseline of  $6.3 \pm 6.9$  years (median: 4.2 years). Therefore, the findings may not be applicable to younger patients or patients with earlier PD. Although there were no statistically significant differences in medications use at baseline evaluation between incident dementia and no incident dementia patients, changes in medications use during follow-up are likely to have occurred and might have an effect in our analysis. Because cognitive impairment is part of the definition of dementia, worse performance on neuropsychological tests is expected to increase the risk of dementia in PD. The association of memory impairment with dementia in our study is not unexpected, because DSM-III-R criteria for dementia require memory impairment. The finding that memory impairment at baseline was predictive of incident dementia might denote that patients who developed dementia during follow-up were already in the early stages of the

dementing process. Even in the analysis that excluded cases with questionable dementia (CDR 0.5), however, both immediate and delayed recall predicted incident dementia in PD (Table 3).

In summary, our results indicate that verbal memory impairment and executive dysfunction predict the development of dementia in PD. Prospective longitudinal studies involving a cohort of younger patients or patients with earlier PD are needed before these findings can be generalized.

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