Progression of Parkinsonism and Loss of Cognitive Function in Alzheimer Disease

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Objective: To assess the relation between parkinsonism and cognitive function in Alzheimer disease from cross-sectional and longitudinal perspectives.

Design: Prospective cohort study with annual clinical evaluations during a 4-year period.

Setting: Alzheimer disease clinic in an urban medical center.

Participants: Four hundred ten persons with clinically diagnosed Alzheimer disease.

Main Outcome Measures: Global and specific measures of cognitive function and parkinsonism.

Results: Higher levels of parkinsonism at baseline were reliably associated with lower levels of cognitive function at baseline and with more rapid cognitive decline during the 4-year study period. However, the associations were small, with baseline parkinsonism accounting for less than 10% of the variation either in baseline cognitive function or in the rate of cognitive decline. By contrast, rates of change in parkinsonism and cognitive function were strongly correlated, with 70% or more shared variance in the rates of change in many models. The association was observed with diverse measures of cognition and parkinsonism and was not explained by demographic variables or use of neuroleptic medications.

Conclusion: In Alzheimer disease, progressive worsening of parkinsonism is more strongly associated with cognitive decline than previously recognized.

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SUBJECTS AND METHODS

SUBJECTS

Participants were recruited from the Rush Alzheimer’s Disease Center, Chicago, Ill. Eligibility required a diagnosis of AD,25 a Mini-Mental State Examination26 score of 11 or more, and community residence at baseline; 410 people met these criteria and agreed to participate (83% of those eligible). Their mean (SD) age at baseline was 75.5 years (7.3 years), mean (SD) educational level was 12.0 years (3.4 years), and mean (SD) baseline Mini-Mental State Examination score was 18.7 (4.3); 274 were women; 61 were African American and the remainder were white. Informed consent was obtained from participants and their family members, following procedures approved by the Institutional Review Board of Rush-Presbyterian-St Luke’s Medical Center.

CLINICAL EVALUATION

A structured clinical evaluation was administered at baseline and repeated annually with examiners blinded to previously collected data. The evaluation, which has been described elsewhere,23,24 included a medical history, neurological examination, cognitive testing, and interview with a knowledgeable informant. Laboratory tests and brain scans were done at baseline. Medications were inspected, identified, and coded using the Medi-Span Drug Data Base system.27 Neuroleptic medications with the potential to cause parkinsonism were being taken by 44 persons at baseline and by 151 persons at 1 or more study evaluations.

The diagnosis of AD required a history of cognitive decline and evidence of impairment in memory and cognition, as specified by the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association.25 At baseline, 380 people met National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria for probable AD and 30 met criteria for possible AD. Because exclusion of the possible subgroup did not substantially change analytic results, it is included in all analyses reported in this article. Pathological criteria for AD28 were met by 52 of the 54 study participants who underwent brain autopsy.24

Assessment of Parkinsonism

At each evaluation, the entire motor portion of the Unified Parkinson’s Disease Rating Scale29 plus a turning item3 was administered. These data yielded summary measures of 4 parkinsonian signs—bradykinesia, gait disorder/postural reflex impairment, rigidity, and tremor—and a global measure of parkinsonism. Scores on each measure range from 0 to 100 and represent the percentage of the total possible item score obtained. Information on the derivation and psychometric properties of these summary scores and their patterns of change in this cohort has been published elsewhere.23,30,31

Assessment of Cognitive Function

Eighteen cognitive tests were administered as part of each evaluation. The Mini-Mental State Examination was used for descriptive purposes only. Information on the remaining 17 tests23,30 is provided in Table 1. To minimize floor-and-ceiling effects and other sources of measurement error that can bias estimates of change in a clinically heterogeneous

RESULTS

To capitalize on all available data, global measures of parkinsonism and cognitive function were used in primary analyses. At baseline, the global measure of parkinsonism ranged from 0 to 51 (mean [SD] = 9.9 [9.9]) and the composite measure of cognitive function ranged from −1.7 to 1.4 standard units (mean [SD] = 0.0 [0.6] standard units), with higher scores indicating more severe parkinsonism and better cognitive functioning.

At baseline, the correlation between the global measure of parkinsonism and the composite measure of cognitive function was −0.30 (P < 0.001). Persons with more severe parkinsonism tended to have lower cognitive function, but only about 9% of the variability in cognitive function at baseline was associated with severity of parkinsonism.

The relation of parkinsonism at baseline to subsequent rate of cognitive decline was assessed in a random effects model with terms for time, baseline parkinsonism, and their interaction (Table 2). There was an average annual decline of 0.51 standard units on the composite cognitive score (95% confidence interval, −0.44 to −0.58). With the association between baseline parkinsonism and cognitive function accounted for in the analysis, baseline parkinsonism was significantly related to rate of cognitive decline, as shown by the interaction term in the model. For each 1-point increase in baseline parkinsonism, rate of cognitive decline increased by an average of 0.01 standard units. Thus, the average annual rate of cognitive decline associated with a baseline parkinsonism score of 15 (75th percentile) was 0.66 standard units, an increase of about 29% compared with the average annual rate of decline (−0.51 standard units) associated with a parkinsonism score of 0 (10th percentile).

To further quantify this association, individual rates of cognitive decline were estimated from a model with a term for time. The correlation of baseline parkinsonism score with rate of decline was −0.24 (P < 0.001),
condition like AD, summary measures were used in analyses rather than individual test scores. The primary measure was a composite score based on all 17 tests. Summary measures of memory, visuconstruction, naming, and repetition, based on 6, 3, 4, and 4 tests, respectively, were used in some secondary analyses. Each measure was computed by converting raw scores on component tests to z scores, using the baseline means and SDs, and computing an average. An earlier publication provides further psychometric information on the summary measures of cognitive function, including the results of a factor analysis that guided formation of the specific cognitive measures.

Follow-up Participation

There were 141 deaths during the study period. Analyses required at least 2 valid scores on a given outcome measure. Of the 387 people who survived to the first follow-up evaluation, 354 (91.5%) met this criterion for the composite cognitive score (mean=3.8 observations per person), 365 (94.3%) met it for the global parkinsonism score (mean=4.0 observations per person), and 353 (91.2%) met it for both. Among survivors, the overall rate of missing data was 18.2% for the composite cognitive score and 11.1% for the global measure of parkinsonism. The specific cognitive scores and parkinsonian sign scores had similar rates of missing data. Further information about participation is published elsewhere.

DATA ANALYSIS

The association of baseline level of parkinsonism with baseline level of cognitive function was assessed with product moment correlation coefficients. The association between baseline parkinsonism and rate of change in cognitive function was assessed in repeated measures regression models with random effects error structures. These models included estimates of the mean overall level of cognitive function at the baseline and the mean rate of decline per year during the follow-up. The models assumed that each person’s individual path then followed the mean path, except for random effects, which modified the overall level to be higher or lower, and the rate of change to be faster or slower. Each model had terms for (1) study time, which indicated the annual rate of cognitive change; (2) baseline parkinsonism, to control for the correlation of parkinsonism and cognition at baseline; and (3) the interaction of parkinsonism with time, which tested whether rate of cognitive change was correlated with baseline level of parkinsonism.

A second group of random effects models included repeated measures of both cognitive function and parkinsonism as outcomes, and characterized simultaneously the rate of change in each, individual differences in rates of change, and the associations between change in parkinsonism and change in cognitive function. Each model provided a correlation coefficient between the estimated individual rates of change.

Secondary analyses addressed 3 issues. To see if neuroleptic medications affected results, analyses were repeated excluding those with neuroleptic use. To see if demographic variables influenced the correlation of parkinsonism and cognition, terms for age, education, sex, race, and their interactions with time were added to models. Finally, to see if the association of parkinsonism and cognition varied across individual parkinsonian signs or specific cognitive domains, analyses were repeated using specific measures of parkinsonism and cognition rather than global ones.

All models were validated both graphically and analytically for assumptions of linearity, multivariate normality, and homoscedasticity. Analyses were carried out in SAS.

indicating that about 6% of the variation in the rate of cognitive decline was associated with baseline severity of parkinsonism.

The association between change in parkinsonism and change in cognitive function was assessed by fitting random effects models to both outcomes simultaneously. The resulting correlation between rates of change in the global measure of parkinsonism and the composite cognitive score was −0.83. This means that more than two thirds of the variation in rate of cognitive decline could be predicted from knowledge of the rate of progression of parkinsonism alone.

The Figure is a 2-dimensional histogram of rates of change in the global measures of parkinsonism and cognition estimated by the model. The points cluster along the full range of the diagonal, indicating a strong linear association between change in these 2 domains of function.

Because neuroleptic medications can contribute to parkinsonism and may impair cognitive function, analyses were repeated excluding persons with neuroleptic use. Among those who were not using neuroleptic medications at baseline, the correlation between parkinsonism and cognition at baseline was −0.26 (P<.001). In those who were not using neuroleptic medications at any evaluation, the association between baseline parkinsonism and rate of cognitive decline was unchanged from the primary model (for interaction of baseline parkinsonism and time, mean [SE]=−0.01 [0.003]). In this same subset, the correlation between the rates of change in parkinsonism and cognition was −0.88.

Secondary analyses also addressed whether demographic variables, by virtue of an association with cognitive function, affected results. First, terms for age, education, sex, race, and their interactions with time were added to the model assessing the relation of baseline parkinsonism to rate of cognitive decline. Results were identical to those from the primary analysis (for interaction of baseline parkinsonism and time, mean [SE]=−0.01, [0.003]). Second, the simultaneous random effects analysis was repeated with terms added for age, then with terms for education, then with terms for sex, and then with terms for race. In these models, the correlations between rates of change in parkinsonism and cognition ranged from −0.82 to −0.85.

To see if the association between parkinsonism and cognitive function varied across specific subdomains of either, simultaneous random effects models were run with each parkinsonian sign score paired with each cognitive measure. Table 3 shows the correlations from these analyses in the full cohort and in the subset not receiving neuroleptic medications. Progression of each par-
kinsonian sign was related to more rapid decline in each cognitive domain. The correlations were largest for rigidity and smallest for tremor. In general, the size of the correlations did not strongly depend on the cognitive domain being measured. Correlations were somewhat larger for memory and smaller for naming, with visuconstruction and repetition occupying intermediate positions. Exclusion of those on neuroleptic medications resulted in substantial increases in correlations involving tremor; correlations involving other signs were comparable or slightly increased.

**COMMENT**

In this cohort of people with AD evaluated annually during a 4-year period, severity of parkinsonism at the baseline evaluation was related to both baseline level of cognitive function and rate of cognitive decline. The size of these correlations was small, however, with baseline parkinsonism accounting for less than 10% of the variation in either baseline level of cognitive function or rate of cognitive decline. As noted above, a similar association has been reported in many cross-sectional and longitudinal studies, but other studies have yielded mixed or negative results. The inconsistency in prior studies is probably owing to the small effect size, differing methods of assessing parkinsonism, and, in longitudinal studies, the complexities involved in securely characterizing individual rates of cognitive decline in this disease.

A novel feature of this study is that parkinsonism was assessed longitudinally. In contrast with the modest association of baseline parkinsonism with both baseline cognitive function and rate of cognitive decline, we observed a remarkably strong association between rate of progression of parkinsonism and rate of cognitive decline. The shared variance between rates of change in these outcomes was 70% or greater in some models. The association was not explained by demographic variables; it was slightly greater in the subset that was never treated with neuroleptic medications; and it was seen with both global and specific measures of parkinsonism and cognitive function.

The disparity between results obtained with assessment of parkinsonism at one point in time vs assessment of its rate of progression is striking. The strong effect ob-

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**Table 1. Descriptive Information on Cognitive Function Tests**

<table>
<thead>
<tr>
<th>Test*</th>
<th>Function</th>
<th>Performance Measure</th>
<th>Range</th>
</tr>
</thead>
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<tr>
<td>Immediate Story Recall32</td>
<td>Memory</td>
<td>Ideas recalled</td>
<td>0-6</td>
</tr>
<tr>
<td>Delayed Story Recall32</td>
<td>Memory</td>
<td>Ideas recalled</td>
<td>0-6</td>
</tr>
<tr>
<td>Figural Memory</td>
<td>Memory</td>
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<td>0-8</td>
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<tr>
<td>1 (24)</td>
<td>Memory</td>
<td>Figures recognized</td>
<td>0-8</td>
</tr>
<tr>
<td>2 (24)</td>
<td>Memory</td>
<td>Figures recognized</td>
<td>0-8</td>
</tr>
<tr>
<td>3 (24)</td>
<td>Memory</td>
<td>Figures recognized</td>
<td>0-8</td>
</tr>
<tr>
<td>Boston Naming Recognition34</td>
<td>Memory</td>
<td>Pictures recognized</td>
<td>0-15</td>
</tr>
<tr>
<td>Constructional Praxis33</td>
<td>Visuconstruction</td>
<td>Design features copied</td>
<td>0-11</td>
</tr>
<tr>
<td>Facial Recognition34</td>
<td>Visuconstruction</td>
<td>Faces matched</td>
<td>0-27</td>
</tr>
<tr>
<td>Figural Recognition34</td>
<td>Visuconstruction</td>
<td>Figures matched</td>
<td>0-8</td>
</tr>
<tr>
<td>Body Part Identification35</td>
<td>Naming</td>
<td>Parts identified</td>
<td>0-18</td>
</tr>
<tr>
<td>Responsive Naming35</td>
<td>Naming</td>
<td>Items named</td>
<td>0-10</td>
</tr>
<tr>
<td>Boston Naming35</td>
<td>Naming</td>
<td>Pictures named</td>
<td>0-15</td>
</tr>
<tr>
<td>Verbal Fluency33</td>
<td>Naming</td>
<td>Animals named</td>
<td>NA†</td>
</tr>
<tr>
<td>Word Repetition35</td>
<td>Repetition</td>
<td>Words repeated</td>
<td>0-10</td>
</tr>
<tr>
<td>High Probability Phrase Repetition35</td>
<td>Repetition</td>
<td>Phrases repeated</td>
<td>0-8</td>
</tr>
<tr>
<td>Low Probability Phrase Repetition35</td>
<td>Repetition</td>
<td>Phrases repeated</td>
<td>0-8</td>
</tr>
<tr>
<td>Commands35</td>
<td>Repetition</td>
<td>Commands followed</td>
<td>0-15</td>
</tr>
</tbody>
</table>

*Number in parentheses indicates the total number of patients tested.
†Score is number of unique animal names produced in 1 minute. NA indicates not applicable.

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**Table 2. Relation of Time, Global Parkinsonism at Baseline, and Their Interaction to the Composite Measure of Cognitive Function**

<table>
<thead>
<tr>
<th>Model Terms</th>
<th>Mean</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>−0.51*</td>
<td>0.038</td>
</tr>
<tr>
<td>Global parkinsonism</td>
<td>−0.02*</td>
<td>0.004</td>
</tr>
<tr>
<td>Global parkinsonism × time</td>
<td>−0.01 †</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*P < .001.
†P < .05.

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**Figure.** Two-dimensional histogram of annual rates of change in global measures of parkinsonism and cognitive function estimated by simultaneous random effects model.
tained with the fully longitudinal design indicates that knowledge of how a person is changing in one functional domain (ie, parkinsonism or cognition) provides a strong prediction of how that person is changing in the other domain. However, because individuals are changing at widely varying rates, assessment of function at a single point in time, in parkinsonian or cognitive domains, is of limited value in predicting change within domains or across them.

These data suggest that worsening parkinsonism and declining cognition are strongly linked in persons with AD. This could be owing to a single pathological feature of AD affecting different brain regions that contribute to parkinsonism and cognitive impairment. For example, in the neocortex, neurofibrillary tangles are related to cognitive impairment, and in the substantia nigra, they are related to parkinsonism. In addition, impairment of the dopamine system could contribute to cognitive impairment. For example, severity of Parkinson disease, presumably an index of striatal dopamine depletion, has been related to cognitive performance. Finally, it has long been speculated that degeneration of neurons throughout the neureka could share an etiopathogenesis such as oxidative stress.

Because global measures of parkinsonism have been used in most previous longitudinal studies, little is known about correlations of specific parkinsonian signs with cognitive decline in AD. In this study, the rates of change in bradykinesia, gait disorder/postural reflex impairment, and especially rigidity were strongly related to rate of cognitive decline. A significant but substantially weaker association was observed for tremor. In cross-sectional research on Parkinson disease, a somewhat similar pattern has been described with motor signs other than tremor showing modest correlations with cognitive function.

Several factors increase confidence in the findings. First, the clinical diagnosis of AD was based on uniform application of widely accepted criteria and has agreed with pathological diagnosis in more than 90% of those who have come to autopsy. Second, there was a high rate of follow-up participation among survivors, limiting possible bias owing to selective attrition. Third, the growth curve approach permitted characterization of individual paths of change in cognitive function, of how parkinsonism and other covariates were related to initial level of cognition and rate of change, and of how change in parkinsonism was associated with change in cognitive function. Fourth, previously established indexes of global and specific aspects of parkinsonism and cognitive function were used and yielded generally consistent results. Fifth, because of the large number of study participants, there was sufficient statistical power to evaluate demographic and clinical variables that might have affected results.

This study also has important limitations. First, participants were selected from a specialized diagnostic and treatment center and are unlikely to represent the full spectrum of AD in the general population. Longitudinal studies of population-based samples are needed. Second, observation over a period of more than 3 to 4 years would probably improve estimation of individual patterns of functional decline in this disease.

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REFERENCES


### Table 3. Correlations Between Change in Parkinsonian Sign Scores and Change in Cognitive Function Measures Estimated From Simultaneous Random Effects Models

<table>
<thead>
<tr>
<th>Parkinsonian Signs</th>
<th>Memory Medication</th>
<th>Visuoconstruction Medication</th>
<th>Naming Medication</th>
<th>Repetition Medication</th>
<th>Composite Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
<td>−0.51</td>
<td>−0.81</td>
<td>−0.16</td>
<td>−0.82</td>
<td>−0.14</td>
</tr>
<tr>
<td>Rigidity</td>
<td>−0.93</td>
<td>−0.94</td>
<td>−0.83</td>
<td>−0.89</td>
<td>−0.14</td>
</tr>
<tr>
<td>Gait/posture</td>
<td>−0.79</td>
<td>−0.84</td>
<td>−0.73</td>
<td>−0.81</td>
<td>−0.14</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>−0.86</td>
<td>−0.82</td>
<td>−0.71</td>
<td>−0.70</td>
<td>−0.14</td>
</tr>
<tr>
<td>Medication</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
</tbody>
</table>
| *P = .05; all other P < .01.*