Parkinsonianlike Signs and Risk of Incident Alzheimer Disease in Older Persons

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Background: Parkinsonianlike signs are common in older persons, but little is known about how their severity or rate of progression is related to the development of Alzheimer disease (AD) or decline in cognition.

Objective: To examine the association of progression of parkinsonianlike signs with incident AD and cognitive decline.

Design: Longitudinal cohort study.

Participants and Setting: For up to 8 years, 824 older Catholic clergy members without clinical evidence of AD or Parkinson disease at baseline underwent annual clinical evaluations that included a modified version of the Unified Parkinson’s Disease Rating Scale (UPDRS), detailed cognitive function testing, and clinical classification of AD.

Main Outcome Measures: Clinically diagnosed AD and change in global and specific measures of cognitive function.

Results: During an average of 4.6 years of observation, 114 persons developed AD. The global UPDRS score increased in 79% of participants, who were divided into tertiles with the least, moderate, or most rapid progression. We examined the relationship of progression to disease risk in a proportional hazards model that controlled for baseline global UPDRS and demographic variables. Compared with the 21% without progression, risk of AD more than doubled in the subgroup with the least progression (P=.08), more than tripled in the moderate subgroup (P=.02), and increased more than 8-fold in the subgroup with the most rapid progression (P<.001). This effect was mainly due to worsening gait and rigidity. Rate of change on the global UPDRS measure was inversely correlated with rate of change on a global measure of cognitive function (r=−0.64).

Conclusion: Progression of parkinsonianlike signs in old age is associated with decline in cognitive function and the development of AD.

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Parkinsonianlike signs are common in older persons with and without Alzheimer disease (AD). Literature suggests that the presence of these signs may be associated with an increased risk of developing AD. However, recent data suggest that parkinsonianlike signs in older persons are multidimensional (ie, gait disturbance, bradykinesia, rigidity, tremor) and often progressive. Furthermore, the severity of parkinsonianlike signs assessed at one point in time is not strongly predictive of the rate at which the signs progress. This suggests that understanding the relationship of these signs to AD will require information about how progression in different signs is related to the development of AD and its principal manifestation, cognitive decline.

We used data from the Religious Orders Study, a longitudinal clinicopathologic investigation of aging and AD, to assess the relationship of parkinsonianlike signs to the development of incident AD. For up to 8 years, participants had annual evaluations that included clinical classification of dementia and AD, administration of a modified Unified Parkinson’s Disease Rating Scale (UPDRS), and detailed assessment of cognitive function. We examined the association of baseline level of and rate of change in UPDRS scores with disease incidence and with decline in global and specific measures of cognitive function.

Methods

Subjects

Participants were from the Religious Orders Study, a longitudinal clinicopathologic study of aging and AD in older Catholic nuns, priests,
and brothers recruited from across the United States (see the acknowledgments). They agreed to annual clinical evaluations and brain donation at death. The study was approved by the institutional review board of Rush-Presbyterian-St Luke’s Medical Center, Chicago, Ill.

At the time of these analyses, 905 persons had completed the baseline evaluation. We excluded 70 with dementia and 11 with Parkinson disease, leaving 824 persons. At baseline, their mean age was 75.4 years (SD, 6.9 years); mean education was 18.2 years (SD, 3.4 years); and mean score on the Mini-Mental State Examination was 28.4 (SD, 1.7). There were 257 men and 567 women; 740 were white and non-Hispanic, 53 were black and non-Hispanic, and 31 were Hispanic or belonged to another ethnic group.

CLINICAL EVALUATION

At baseline, participants had a uniform, structured clinical evaluation that was repeated annually with examiners blinded to previously collected data. The evaluation, which has been previously described, included a medical history, neurologic examination, cognitive function testing, and review of brain scan when available. On the basis of this evaluation, a study physician classified persons with respect to AD and other common conditions of old age. The diagnosis of dementia and AD was based on the criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association. A history of cognitive decline and evidence of impairment in at least 2 cognitive domains are required for dementia, and one of the impaired domains must be memory to meet AD criteria. Persons who met these criteria and also had another condition believed to contribute to cognitive impairment (ie, possible AD) were included in all analyses because exclusion of this subgroup did not change results.

MOTOR PORTION OF THE UPDRS

A modified version of the motor portion of the UPDRS was administered at each evaluation by trained nurse clinicians. The modifications were minor and meant to make the scale more applicable to persons without Parkinson disease and easier to use by nonphysicians. Four previously established UPDRS sign scores were derived: bradykinesia (based on 4 UPDRS items), gait disorder–postural reflex impairment (based on 6 items), rigidity (based on 5 items), and tremor (based on 2 items). A global UPDRS score was formed by averaging the 4 sign scores. Scores on each measure range from 0 to 100 and denote the percentage of the total possible item score obtained. In previous research, these measures have been shown to have high interrater reliability and short-term temporal stability and to be strongly related to progression of AD.

ASSESSMENT OF COGNITIVE FUNCTION

Nineteen cognitive tests were administered at each evaluation. There were 7 episodic memory measures: Word List Memory, Recall, and Recognition and immediate and delayed recall of the East Boston Story and Story A from Logical Memory. Semantic memory was assessed with a 20-item version of the Boston Naming Test and 15-item form of Extended Range Vocabulary, and a 20-item form of the National Adult Reading Test. Working memory was assessed with Digits Forward and Digits Backward, Digit Ordering, and Alpha Span. The Symbol Digit Modalities Test and Number Comparison were used to assess perceptual speed, and visuospatial ability was assessed with a 15-item form of Judge-ment of Line Orientation and a 17-item form of Standard Progressive Matrices.

Composites of 2 or more tests were used in analyses to reduce measurement error in general and floor and ceiling artifacts in particular. We used a global measure of cognition based on all 19 tests and specific measures of episodic memory (based on 7 tests), semantic memory (4 tests), working memory (4 tests), perceptual speed (2 tests), and visuospatial ability (2 tests). Raw scores on each component test were converted to z scores, using the baseline mean and SD, and averaged to form the composite measures. Further information on the individual tests and on the psychometric properties of these composite measures is contained in previous publications.

APOLIPOPROTEIN E GENOTYPING

Blood was collected with acid citrate dextrose anticoagulant and kept at room temperature until undergoing lymphocyte separation within 24 hours of collection. DNA was extracted from about 2 to 3 million cells and amplified. Apolipoprotein genotype was available in 715 participants.

FOLLOW-UP PARTICIPATION

Of 824 eligible persons at baseline, 25 died before the first follow-up and 29 had not yet reached the date of their first follow-up at the time of data analysis. Of the remaining 770 persons, follow-up information on AD was available in 746 (97%), with an average of 3.6 annual evaluations per individual (including the baseline); 750 (97%) had at least 2 valid global cognitive scores and 753 (98%) had at least 2 valid global UPDRS scores, with an average of 5.6 valid cognitive and UPDRS scores per person.

DATA ANALYSIS

Annual rates of change in cognitive and UPDRS measures were assessed with random effects regression models with a term for time, in years, since baseline. In this approach, variation is assumed to arise from people following different underlying paths of change and from the observed data deviating from the true underlying paths. Each person’s path was assumed to follow the mean path except for random effects, which caused the initial level of function to be higher or lower and the rate of change to be faster or slower. The models provided estimates of each person’s annual rate of change, controlling for baseline level of function. Models were validated graphically and analytically for assumptions of linearity, normality, and independence and homoscedasticity of errors. Further information about the application of these models to longitudinal UPDRS and cognitive data is published elsewhere.

Cox proportional hazards models were used to see how baseline UPDRS score and annual rate of change were associated with risk of developing incident AD on follow-up. All models included terms for the potentially confounding effects of age, sex, and education. An initial model included a term for the global UPDRS score at baseline. A second model added a term for annual change in global UPDRS score estimated from a random effects model with a term for time. To further examine the association, we formed 4 subgroups: the 21% without evidence of progression on the UPDRS served as a reference group and the remaining 79% were divided into tertiles based on rate of UPDRS progression. We plotted the unadjusted cumulative hazard of developing AD in the UPDRS subgroups. We then analyzed the association in a proportional hazards model, with the group without progression on the UPDRS serving as a reference group that was contrasted with each of the remaining 3 subgroups, controlling for baseline UPDRS. We
repeated the analysis with a term added for possession of at least 1 apolipoprotein E ε4 allele. A final model included terms for the global UPDRS score at baseline and for annual rates of change in bradykinesia, gait/posture, rigidity, and tremor. We found no graphic or analytic evidence of nonlinearity or nonproportionality.

Pearson correlation coefficients were used to estimate the correlations of the UPDRS and cognitive scores at baseline, of baseline UPDRS with change in cognition, and of change in UPDRS with change in cognition. To portray the association between rates of cognitive and UPDRS change, we used a locally weighted regression smooth function that is based on weighted locally linear fits, thereby reducing the influence of outliers on the regression line. All analyses were carried out in SAS statistical software.

RESULTS

UPDRS MOTOR SIGNS AND INCIDENT AD

At baseline, the global UPDRS score ranged from 0 to 36.3, with higher scores indicating more dysfunction; 74% had scores less than 10, 20% had scores from 10 to 19, and 6% had scores of 20 or more. The global UPDRS score increased an average of 0.73 points per year (95% confidence interval, 0.61-0.85), as estimated from a random effects model, but there were substantial individual differences, with no progression in 21% and annual increases of 0.001 to 7.797 points in the remaining 79%.

During an average of 4.6 years of follow-up, 114 persons developed AD. Five persons developed other forms of dementia, and they were excluded from analyses of incident AD. In an initial proportional hazards model that contrasted each tertile with the reference group, the remaining 79% were divided into tertiles, and each tertile was contrasted with the reference group.

To assess the association of change on the UPDRS with incident AD, we constructed a proportional hazards model with terms for baseline UPDRS score, annual rate of UPDRS change, age, sex, and education. In this model, more rapid progression on the UPDRS was associated with increased risk of AD ($P < .001$).

To portray the association of UPDRS progression with disease risk more clearly, we formed 4 subgroups:

![Figure 1. Cumulative hazard of developing incident Alzheimer disease (AD) during the study in those without progression on the Unified Parkinson’s Disease Rating Scale and in tertiles with the least, moderate, and most rapid progression.

Table 1. Baseline Characteristics of Subgroups Differing in Rate of Progression on the UPDRS*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No UPDRS Progression (n = 124)</th>
<th>Least UPDRS Progression (n = 208)</th>
<th>Moderate UPDRS Progression (n = 201)</th>
<th>Most UPDRS Progression (n = 202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71.2 (4.8)</td>
<td>72.4 (5.2)</td>
<td>75.8 (6.2)</td>
<td>80.2 (6.5)</td>
</tr>
<tr>
<td>Sex, % women</td>
<td>46.0</td>
<td>68.8</td>
<td>72.1</td>
<td>76.7</td>
</tr>
<tr>
<td>Years of education</td>
<td>18.3 (3.4)</td>
<td>18.6 (3.2)</td>
<td>18.0 (3.0)</td>
<td>17.6 (3.6)</td>
</tr>
<tr>
<td>Global UPDRS</td>
<td>5.1 (4.6)</td>
<td>3.9 (3.6)</td>
<td>7.0 (5.8)</td>
<td>14.8 (9.3)</td>
</tr>
<tr>
<td>Global cognition</td>
<td>0.24 (0.50)</td>
<td>0.24 (0.49)</td>
<td>0.04 (0.54)</td>
<td>-0.43 (0.80)</td>
</tr>
</tbody>
</table>

Abbreviation: UPDRS, Unified Parkinson’s Disease Rating Scale.

*All data are presented as mean (SD) unless otherwise indicated.

Table 2. Relative Risk of Incident AD Associated With Global UPDRS at Baseline and Change in UPDRS*

<table>
<thead>
<tr>
<th>Model Terms</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global UPDRS at baseline</td>
<td>1.03</td>
<td>1.00-1.06</td>
</tr>
<tr>
<td>Change in global UPDRS†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertile 1</td>
<td>2.73</td>
<td>0.89-8.42</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>3.52</td>
<td>1.19-10.43</td>
</tr>
<tr>
<td>Tertile 3</td>
<td>8.50</td>
<td>2.97-24.34</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; UPDRS, Unified Parkinson’s Disease Rating Scale.

†Estimated from a proportional hazards model that also included terms for age, sex, and education.

The 21% without progression on the UPDRS and the remaining 79% divided into tertiles according to rate of progression (Table 1). A plot of the unadjusted cumulative hazard of developing AD in the subgroups (Figure 1) suggested that more rapid progression on the UPDRS was associated with increased disease risk. To analyze this association, we constructed a proportional hazards model that contrasted each tertile with the 21% without progression. The model also included terms for age, sex, education, and baseline UPDRS (Table 2). Compared with those without progression, risk of AD more than doubled in those with the least progression (although $P = .08$), more than tripled in those with more rapid progression ($P = .02$),...
and increased more than 8-fold in the subgroup with the most rapid progression ($P<.001$).

Because the apolipoprotein E ε4 allele is an established risk factor for AD, we repeated the analysis with a term added for possession of 1 or more ε4 alleles (present in 26%). The results of this analysis were comparable to the original model.

To see which UPDRS domains were contributing to risk of incident disease, we constructed another model with terms for annual rate of change in each UPDRS sign score, global UPDRS at baseline, age, sex, and education (Table 3). More rapid progression of gait/posture and rigidity, but not bradykinesia or tremor, was associated with increased risk of AD.

**UPDRS MOTOR SIGNS AND COGNITIVE FUNCTION**

Because AD arises by minute degrees, separating normality from disease can be difficult. Therefore, to ensure that our results were not due to imprecise clinical classification of disease, we examined the relationship of UPDRS scores to cognitive decline, a continuous outcome that reflects the progressive nature of the disease. To make use of all available data, the global measure of cognitive function was used in initial analyses. It ranged from −1.69 to 1.37 at baseline, with higher scores indicating better cognitive function. Cognition declined an average of 0.04 unit per year (95% confidence interval, −0.05 to 0.03), but wide individual differences were observed (SD, 0.12).

Those with higher global UPDRS scores at baseline tended to have lower global cognition at baseline ($r=-0.32, P<.001$) and more rapid cognitive decline ($r=-0.25, P<.001$), but much heterogeneity was evident. By contrast, annual rates of change on the global UPDRS and cognitive measures, estimated from separate random effects models, were strongly correlated ($r=-0.64, P<.001$). Figure 2 shows that more rapid progression on the UPDRS was associated with more rapid decline in global cognition.

To determine whether the association of progression on the UPDRS with declining cognition varied across specific UPDRS signs or cognitive domains, we calculated rates of change in UPDRS signs and in specific cognitive functions and computed the correlations among them (Table 4). Progression of each UPDRS sign was associated with decline in each cognitive domain (all $P<.001$). These correlations were relatively stronger for gait/posture (median $r=0.51$) and rigidity (median $r=0.44$) than for bradykinesia (median $r=0.34$) or tremor (median $r=0.16$), but the correlations did not vary substantially across cognitive domains.

**Table 3. Relative Risk of Incident AD Associated With Global UPDRS Score at Baseline and Change in UPDRS Signs**

<table>
<thead>
<tr>
<th>Model Terms</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global UPDRS at baseline</td>
<td>1.03</td>
<td>1.00-1.06</td>
</tr>
<tr>
<td>Change in bradykinesia</td>
<td>1.16</td>
<td>0.92-1.46</td>
</tr>
<tr>
<td>Change in gait/posture</td>
<td>1.24</td>
<td>1.12-1.37</td>
</tr>
<tr>
<td>Change in rigidity</td>
<td>1.12</td>
<td>1.01-1.24</td>
</tr>
<tr>
<td>Change in tremor</td>
<td>1.28</td>
<td>0.68-2.42</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; UPDRS, Unified Parkinson’s Disease Rating Scale.

*Estimated from a proportional hazards model that also included terms for age, sex, and education.

In a cohort of more than 700 older persons examined annually for up to 8 years, evidence of parkinsonianlike signs at baseline, as assessed on the UPDRS, was associated with increased risk of incident AD. After controlling for baseline UPDRS, annual rate of progression on the UPDRS was related to disease incidence. Compared with those without progression on the UPDRS, risk of developing AD was increased more than 8-fold in those with the most rapid progression. The results suggest that progression of parkinsonianlike signs in older persons is related to the development of AD.

One previous study reported that the presence of parkinsonianlike signs on a short form of the UPDRS was associated with an increased risk of incident dementia. We observed a similar association, and after controlling for it, we observed a considerably stronger association of progression on the UPDRS with disease incidence. We are unaware of any previous study that has examined change in parkinsonianlike signs and risk of AD. Overall, these results suggest a strong link between progressive motor impairment, as assessed on the UPDRS, and the development of AD.

Because AD develops by minute degrees during several years, the diagnosis can be difficult. To ensure that our findings were not due to diagnostic imprecision or bias, we also examined the association of UPDRS motor signs with cognitive decline, the principal manifestation of AD, and obtained comparable results. Thus, baseline UPDRS score was associated with baseline level of cognition, consistent with previous research, and with annual rate of change, but it accounted for less than 10% of the variation in each. By contrast, the rate of progression on the UPDRS accounted for more than 40% of the variation in rate of global cognitive decline.
Table 4. Correlations Between Change in UPDRS Sign Scores and Change in Cognitive Measures

<table>
<thead>
<tr>
<th>UPDRS Signs</th>
<th>Episodic Memory</th>
<th>Semantic Memory</th>
<th>Working Memory</th>
<th>Perceptual Speed</th>
<th>Visuospatial Ability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradykinesia</td>
<td>-0.34</td>
<td>-0.33</td>
<td>-0.33</td>
<td>-0.36</td>
<td>-0.34</td>
</tr>
<tr>
<td>Gait/posture</td>
<td>-0.54</td>
<td>-0.51</td>
<td>-0.48</td>
<td>-0.56</td>
<td>-0.49</td>
</tr>
<tr>
<td>Rigidity</td>
<td>-0.47</td>
<td>-0.46</td>
<td>-0.41</td>
<td>-0.44</td>
<td>-0.44</td>
</tr>
<tr>
<td>Tremor</td>
<td>-0.13</td>
<td>-0.14</td>
<td>-0.16</td>
<td>-0.16</td>
<td>-0.18</td>
</tr>
</tbody>
</table>

Abbreviation: UPDRS, Unified Parkinson’s Disease Rating Scale.
*Estimated from separate random effects models. All P < .001.

To our knowledge, the association of specific UPDRS motor signs with risk of incident AD or rate of cognitive decline has not been previously described. We found that progression of gait disorder and rigidity but not of bradykinesia or tremor was related to disease incidence. Progression of each sign was associated with cognitive decline, but the association was substantially stronger for gait disorder and rigidity than for bradykinesia or tremor. A similarly strong association between progression of these 4 UPDRS signs, especially gait disorder and rigidity, on the one hand and cognitive decline on the other has been described in a cohort of persons with AD examined at an AD referral center.13,14

Previous cross-sectional research in older persons with and without AD has suggested that parkinsonian-like signs may be more strongly related to some forms of cognition than others.4,34,35 In this study, progression on the UPDRS was associated with decline in all cognitive domains, and these associations did not substantially vary across cognitive domains, consistent with a previous longitudinal study of persons with AD.14

The bases of the association of parkinsonian-like signs with AD are uncertain. One possibility is that pathologic changes of AD in the substantia nigra, and perhaps elsewhere, are strongly contributing to these signs. This would explain the progressive nature of the signs as well as their association with AD. Among persons with AD, neurofibrillary pathologic findings in the substantia nigra have been associated with parkinsonian-like signs, further suggesting a direct link between AD pathologic features and these signs. Other possibilities, not mutually exclusive, are that other forms of pathologic findings, like Lewy bodies or cerebrovascular disease, are contributing to both parkinsonian-like signs and dementia. Large-scale clinicopathologic studies will be needed to investigate these and other possibilities.

Confidence in these findings is enhanced by several factors. Participants were examined annually for up to 8 years, with more than 95% follow-up participation in survivors. The diagnosis of AD was based on a uniform, structured evaluation and widely used criteria, and has been confirmed pathologically in a high proportion of those who have undergone brain autopsy.9

Previously established UPDRS and cognitive measures were used in analyses. The UPDRS measures had similar associations with incident AD and cognitive decline. The main limitation is that the findings are based on a selected cohort that differs in important ways from older persons in the general US population. It will be important to investigate the associations among parkinsonian-like signs, AD, and cognitive decline in more diverse cohorts.

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Author contributions: Study concept and design (Drs Wilson, Evans, and Bennett); acquisition of data (Drs Wilson, Evans, and Bennett); analysis and interpretation of data (Drs Wilson, Schneider, Bienias, Evans, and Bennett); drafting of the manuscript (Dr Wilson); critical revision of the manuscript for important intellectual content (Drs Wilson, Schneider, Bienias, Evans, and Bennett); statistical expertise (Drs Bienias and Bennett); obtained funding (Drs Evans and Bennett); administrative, technical, and material support (Drs Wilson, Schneider, Evans, and Bennett); study supervision (Dr Evans).

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