Lack of Familial Aggregation of Parkinson Disease and Alzheimer Disease

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Objective: To investigate the risk of Alzheimer disease (AD) in first-degree relatives of patients with Parkinson disease (PD) compared with first-degree relatives of controls.

Design: Case-control study, family history method, and reconstructed cohort approach.

Methods: Probands with PD without dementia and control probands, matched by age strata, sex, and ethnicity, were examined in person and enrolled without knowledge of family history of PD and other neurological disorders. Disease status in first-degree relatives of probands with PD and control probands was ascertained through a structured family history interview administered to the proband and a second informant (self-report or another informant). Cox proportional hazards models with double-censoring techniques for missing information on age of onset of AD were used to analyze the risk of AD in first-degree relatives of patients with PD compared with first-degree relatives of controls.

Results: Four hundred eighty-seven probands with PD and 409 control probands provided family history information on 4819 first-degree relatives older than 30 years (2534 relatives of probands with PD and 2285 relatives of control probands). One hundred thirteen first-degree relatives (2.3%; 61 relatives [2.4%] of probands with PD and 52 relatives [2.3%] of controls) were diagnosed with AD. The risk of AD was not increased in relatives of patients with PD compared with relatives of controls (hazard ratio, 1.1; 95% confidence interval, 0.7-1.6; P = .65). Similarly, no significantly increased risk of AD was observed when comparing relatives of patients with early-onset (<50 years) and late-onset (>50 years) PD with relatives of controls.

Conclusion: The lack of familial aggregation of PD and AD does not support the hypothesis of major shared genetic contributions to the etiology of the 2 most common neurodegenerative disorders.

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This study was designed as a case-control study using the family history method and reconstructed cohort approach. Probands with PD without dementia and control probands were examined in person and enrolled without knowledge of family history of PD and other neurological disorders. Disease status in first-degree relatives of probands with PD and control probands was ascertained through a structured interview. The primary aim of the study was to investigate the risk of PD in first-degree relatives of patients with PD compared with first-degree relatives of controls. We systematically collected family history information on essential tremor and AD, in addition to PD. In this analysis, we investigated the risk of AD in first-degree relatives of patients with PD compared with first-degree relatives of controls.

**METHODS**

**PROBANDS WITH PD AND CONTROL PROBANDS**

Probands with PD were recruited during a 4-year period from the Center for Parkinson's Disease and Other Movement Disorders of the Columbia Presbyterian Medical Center (a tertiary referral center in New York, NY) and a neurology clinic serving primarily individuals from the Washington Heights-Inwood community in northern Manhattan, NY. The protocol was approved by the Columbia Presbyterian Medical Center institutional review board.

Criteria for idiopathic PD included 2 of 4 neurological signs: bradykinesia, rest tremor, rigidity, and postural instability, 1 of which had to be either bradykinesia or rest tremor. Probands with PD were categorized by age of onset of PD (≤50 or >50 years), based on the patient's recall of the age of the first motor symptom of PD. Because the genetic contribution to PD was believed to be more important in early-onset disease and we wanted to assess the familial aggregation of PD in families of probands with early- and late-onset PD, this study deliberately oversampled probands with early-onset PD (≤50 years).

For the probands with PD from the Center for Parkinson's Disease and Other Movement Disorders, control probands were recruited by random-digit dialing during the same period and were frequency matched to the cases by 5-year age strata, sex, ethnicity, and telephone area code/exchange. For the probands with PD from the neurology clinic, most of the control probands were recruited from a 50% sample of names and addresses of Medicare recipients (provided by the Health Care Finance Association, Westchester, Ill) older than 65 years and living in the Washington Heights community. Potential controls from this sample were frequency matched to the cases by 5-year age strata, sex, and ethnicity. For 18 probands with PD from the neurology clinic who were younger than 65 years, controls were recruited from the control series of the Northern Manhattan Stroke Study in the Washington Heights community.

**EVALUATION OF PROBANDS WITH PD AND CONTROL PROBANDS**

Probands with PD and control probands were evaluated with a medical history, the Unified Parkinson's Disease Rating Scale (UPDRS), and a videotape assessment that included items from the UPDRS and an essential tremor rating scale. Probands with PD were classified as tremor-dominant and postural instability gait disorder (PIGD) subtypes of PD according to criteria from the DATATOP study. The last examination prior to the initiation of levodopa treatment was used to determine whether the individual had tremor-dominant or PIGD PD. When levodopa treatment was already initiated at the first examination, the earliest recorded examination was used.

To reduce the possibility of collecting inaccurate family history information, the modified Mini-Mental State Examination (MMSE) was administered to probands with PD and control probands. Those who screened positive for dementia were excluded. Because of concerns about the validity of the modified MMSE in screening for dementia in Spanish speakers, we also administered a core neuropsychological battery to Spanish speakers from the community of Washington Heights-Inwood. The Spanish-speaking probands with PD who screened positive for dementia but did not meet criteria for dementia based on the neuropsychological battery were not excluded.

**FAMILY HISTORY INTERVIEW**

To ascertain PD and other neurological disorders in first-degree relatives of probands with PD and control probands, a structured family history interview (FHI) was administered to the proband. To increase the sensitivity of the interview, we tried to obtain a second interview, by telephone, with the first-degree relative or with another informant if the first-degree relative had died or was unable to provide information. The FHI was administered in English or Spanish, either in person or over the telephone. First-degree relatives were considered the "subjects" of the FHI.

For ascertainment of PD in relatives, we used a set of 6 screening questions, which led to a set of follow-up questions when endorsed. Since PD is a cause of dementia and we have reported familial aggregation of PD in this sample, the inclusion of first-degree relatives with PD might introduce a confounding factor in this analysis. Therefore, first-degree relatives of probands with PD and control probands who were diagnosed with PD (n=96) were excluded from the present analysis.

For ascertainment of AD in relatives, we asked the informant 2 screening questions: (1) Does he/she have memory loss, senility, dementia, Alzheimer disease, hardening of the arteries or other mental changes? and (2) Has he/she ever been unable to care for him/herself? If the screening questions were not endorsed, no further questions were asked and the relative was assumed not to have AD. If either of the 2 screening questions was answered affirmatively, a set of follow-up questions was asked.

An algorithm was created to assign a level of certainty to the diagnosis of AD based on the follow-up questions. A definite diagnosis was reserved for autopsy-proven AD. Diagnoses were further stratified into probable, possible, uncertain, and unlikely AD. A liberal criterion for the diagnosis of AD included definite, probable, possible, and uncertain AD and required that at least 2 of 3 follow-up questions were answered affirmatively: (1) Did the person have a gradual and progressive loss of memory? (2) Was the person confused and disoriented most of the time? (3) Did the person have difficulty rec-
tremor-dominant nor PIGD, and 15 had missing information for motor subtype.

We performed analyses using the liberal and conservative criteria for the diagnosis of AD included definite, probable, and possible, all of which additionally required that a physician made the diagnosis of AD.

The validity of this questionnaire for the diagnosis of AD has been previously examined against direct evaluation of the subjects, including a structured medical and neurological examination and a neuropsychological battery, in 2 separate samples. In a sample of 180 siblings of 127 probands with AD, the sensitivity of the first screening question was 63% (33/56) and the specificity was 84% (104/124) (there were no cases in which the second screening question was endorsed without the first question being endorsed). When affirmative answers to the follow-up questions were taken into account, the specificity improved but the sensitivity diminished significantly. In a sample of 47 siblings of probands with AD, the specificity of the diagnosis of AD using the liberal criterion was 98% (44/45). Sensitivity (1/2 or 50%) was based on only 2 patients and therefore cannot be considered a reliable estimate. No evidence of differential misclassification in families of probands with AD and control probands (“reporting bias”) was found.

We performed analyses using the liberal and conservative criteria for the diagnosis of AD, as well as the first screening question only. For each analysis, relatives were considered to have AD if either the proband report or the second informant report (self-report or report from another informant) was positive. Results using the different definitions of AD were similar; hence for brevity, we will only report in detail the analysis using the liberal criterion.

STATISTICAL ANALYSIS

Differences in baseline demographic and clinical characteristics of probands with PD vs control probands and relatives of probands with PD vs relatives of control probands were investigated by using t tests and χ2 tests for continuous and categorical variables, respectively. The Kaplan-Meier method was used to plot the cumulative incidence of AD in first-degree relatives of probands with PD and control probands.

We used Cox proportional hazards models with double-censoring techniques for missing information to calculate the hazard ratio (HR) for AD in first-degree relatives of probands with PD and compared with first-degree relatives of control probands. The age of onset of AD was defined as the age of the first symptom of AD as reported by the proband or second informant. When age of onset was unknown, the age at AD diagnosis by a physician was used as an estimate of the age of onset of AD. Left-censoring was applied when a relative was deemed to have AD but information on age of onset was unavailable. Right-censoring was applied if a relative was not deemed to have AD, in which case years at risk were censored at current age (age at the time of the interview) for living relatives or age at death for deceased relatives.

The risk of AD was examined in (1) first-degree relatives of probands with PD compared with first-degree relatives of control probands, (2) first-degree relatives of probands with early-onset (≤50 years) and late-onset (>50 years) PD compared with first-degree relatives of control probands, and (3) first-degree relatives of probands with tremor-dominant and PIGD PD compared with first-degree relatives of control probands. We repeated the analyses after stratifying first-degree relatives into parents and siblings of probands. All models were adjusted for sex, years of education, and ethnicity of the relatives.

### RESULTS

#### DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PROBANDS AND RELATIVES

Table 1 summarizes the demographic and clinical characteristics of probands with PD and control probands and their first-degree relatives. There were 487 probands with
Of the probands with PD, 221 (45.4%) had early-onset PD (≤50 years). Probands with PD and control probands were similar in sex, years of education, and ethnicity. Probands with PD were significantly younger than control probands and had a higher frequency of family history of PD in first-degree relatives. Among probands with PD, the mean (SD) age of onset of PD was 54.4 (13.8) years, the mean (SD) disease duration was 8.4 (6.5) years, and the mean (SD) total UPDRS motor score was 23.1 (13.4).

Family history information on 4819 first-degree relatives whose current age was older than 30 years was included in this analysis (2534 relatives of probands with PD and 2285 relatives of control probands). Age, sex, and years of education of first-degree relatives of probands with PD and control probands were similar. There were significant differences between relatives of probands with PD and control probands in ethnicity, proportion alive, and relationship to probands (Table 1).

### Risk of AD in Relatives of Patients With PD

One hundred thirteen first-degree relatives (2.3%; 61 relatives [2.4%] of patients with PD and 52 relatives [2.3%] of controls) were diagnosed with AD according to the liberal criterion. One hundred (88.5%) of 113 had known age of onset of AD; hence, left-censoring was used for the other 13 patients. No increased risk of AD was observed in relatives of patients with PD compared with relatives of controls (HR, 1.1; 95% confidence interval [CI], 0.7-1.6; *P* = .65) (Figure). Similarly, no significantly increased risk was observed when comparing relatives of patients with early-onset and late-onset PD with relatives of controls, and relatives of patients with tremor-dominant and PIGD PD compared with relatives of controls. When we repeated the analyses stratifying relatives into parents and sibling of probands, no significant differences were observed (Table 2).

When we used the stricter conservative criterion for AD requiring a physician’s diagnosis, 58 first-degree relatives (1.2%; 30 relatives [1.2%] of patients with PD and 28 relatives [1.2%] of controls) were diagnosed with AD. No increased risk of AD for relatives of patients with PD compared with relatives of controls was observed (HR, 1.0; 95% CI, 0.6-1.7; *P* = .97). Two hundred sixty-seven relatives (5.5%) had an affirmative answer to the first screening question of the FHI (154 relatives [6.1%] of patients with PD and 113 relatives [4.9%] of controls). When the analysis was repeated using the screening question only, no significantly increased risk for relatives of patients with PD compared with relatives of controls was observed (HR, 1.2; 95% CI, 1.0-1.6; *P* = .09).

*Table 2. Risk of Alzheimer Disease (AD) in First-Degree Relatives of Patients With Parkinson Disease (PD) Compared With First-Degree Relatives of Controls*+

<table>
<thead>
<tr>
<th>Relative Type</th>
<th>No. of Relatives</th>
<th>No. (%) of Relatives Affected</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
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<tr>
<td>Relatives of patients with PD</td>
<td>2534</td>
<td>61 (2.4)</td>
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<td>Relatives of controls</td>
<td>2285</td>
<td>52 (2.3)</td>
<td>1.0 Referent</td>
<td></td>
</tr>
<tr>
<td>Relatives of patients with early-onset PD</td>
<td>1543</td>
<td>42 (2.7)</td>
<td>1.0 (0.6-1.7)</td>
<td>.93</td>
</tr>
<tr>
<td>Relatives of patients with late-onset PD</td>
<td>991</td>
<td>19 (1.9)</td>
<td>1.1 (0.7-1.7)</td>
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</tr>
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<tr>
<td>Relatives of patients with tremor-dominant PD</td>
<td>856</td>
<td>23 (2.7)</td>
<td>1.3 (0.8-2.1)</td>
<td>.37</td>
</tr>
<tr>
<td>Relatives of patients with PIGD PD</td>
<td>1300</td>
<td>28 (2.2)</td>
<td>1.0 (0.6-1.5)</td>
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<td>1.1 (0.5-2.8)</td>
<td>.76</td>
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<td>Siblings of controls</td>
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<tr>
<td>Parents of patients with PD</td>
<td>868</td>
<td>50 (5.8)</td>
<td>1.1 (0.7-1.6)</td>
<td>.74</td>
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<td>Parents of controls</td>
<td>762</td>
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Abbreviation: PIGD, postural instability gait disorder.

*Cox proportional hazards models with double censoring for missing information on age of onset of AD, adjusting for sex, years of education, and ethnicity, were used to analyze the risk of AD in first-degree relatives of patients with PD compared with first-degree relatives of controls.

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*Figure.* Cumulative incidence of Alzheimer disease in first-degree relatives of patients with Parkinson disease (PD) and controls according to the family history interview.

**Table 2** Risk of Alzheimer Disease (AD) in First-Degree Relatives of Patients With Parkinson Disease (PD) Compared With First-Degree Relatives of Controls**

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Abbreviation: PIGD, postural instability gait disorder.

*Cox proportional hazards models with double censoring for missing information on age of onset of AD, adjusting for sex, years of education, and ethnicity, were used to analyze the risk of AD in first-degree relatives of patients with PD compared with first-degree relatives of controls.*
In this study, we found no evidence of increased risk of AD in first-degree relatives of patients with PD compared with first-degree relatives of controls, regardless of the age of onset (≤50 or >50 years) or clinical phenotype (tremor-dominant vs PIGD) of the probands with PD and regardless of whether we analyzed siblings and parents separately.

Seven previous studies assessed the risk of PD in relatives of patients with PD compared with relatives of controls18-24 (Table 3). Only one of these studies found a significantly increased risk of PD in relatives of patients with PD, which was observed in men but not women.20 A collaborative reanalysis of data from this study20 pooled with the data from Amaducci et al18 yielded a relative risk of 2.4 (95% CI, 1.0-5.8).25

Two previous studies assessed the risk of AD in relatives of patients with PD compared with relatives of controls24,25 (Table 3). In the main analyses, no significantly increased risks were observed. In 1 of the 2 studies, we reported an increased risk of AD restricted to siblings of patients with PD with dementia.25 In a previous pilot study that did not include a control group, a family history of dementia was present more often in patients with PD with dementia than in patients with PD without dementia.46

One study assessed the risk of AD in relatives of patients with AD compared with relatives of patients with PD, who were considered the “control” group. Although the proportion of affected relatives was not significantly different between the AD and PD groups, relatives of patients with PD developed AD significantly later in life than relatives of patients with AD.47

The present study has several strengths. Case and control probands were enrolled without knowledge of family history of AD. Family history information on AD was collected through a structured and validated interview (FHI) and an algorithm was created to assign a level of certainty to the diagnosis of AD. Among all studies investigating the familial aggregation of PD and AD to date, this study had the largest sample size in terms of the number of relatives whose disease status was ascertained (Table 3).

Weaknesses of the study include the low sensitivity of the FHI-based diagnosis of AD (liberal criterion). We addressed this issue in 2 ways. First, we tried to maximize sensitivity by collecting a second informant report using the FHI (2768 [57.4%] of the relatives had information from a second FHI; 1584 relatives [62.5%] of cases and 1184 relatives [51.8%] of controls). Second, we repeated the analysis using a more sensitive (although less specific) screening question of the FHI. The proportions of affected relatives of probands with PD and control probands in this study (2.4% and 2.3%, respectively) were lower than in 2 previous studies using the same interview and diagnostic criteria for AD (4.5%-5.7%),16,30 However, only parents and siblings were included in these previous studies and the mean age of the relatives was higher than in the present sample. Our findings may not be generalizable to the PD population.

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**Table 3. Case-Control Studies Investigating the Familial Aggregation of Parkinson Disease (PD) and Alzheimer Disease (AD) Using the Family History Method**

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Case and Control Relatives</th>
<th>Relative Risk (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amaducci et al,18 1986</td>
<td>Not reported (first-degree relatives of 116 AD cases, 116 hospital controls, and 97 population controls)</td>
<td>Hospital control: OR, 6.00 (95% CI, 1.2-29.7)</td>
<td>95% CIs were not reported; P = .13 and .72 for the hospital and population control comparisons, respectively</td>
</tr>
<tr>
<td>Huff et al,19 1988</td>
<td>370 relatives of cases 339 relatives of controls</td>
<td>Not reported</td>
<td>Lifetime risk estimates: 1.0% (SE 1.0%) among relatives of patients with AD and 3.9% (SE 2.0%) among relatives of controls (P &gt; .05)</td>
</tr>
<tr>
<td>Hofman et al,20 1989</td>
<td>1302 relatives of cases 1227 relatives of controls</td>
<td>2.9 (1.1-8.5)</td>
<td>Among men, RR, 8.0 (95% CI, 1.0-66.9); among women, RR, 1.8 (95% CI, 0.5-6.4)</td>
</tr>
<tr>
<td>Li et al,21 1992</td>
<td>Not reported (first-degree relatives of 79 AD cases and 140 controls)</td>
<td>OR, 2.00 (0.13-31.89)</td>
<td></td>
</tr>
<tr>
<td>Fratigioni et al,22 1993</td>
<td>Not reported (first-degree relatives of 98 AD cases and 266 controls)</td>
<td>OR, 0.9 (0.3-2.7)</td>
<td></td>
</tr>
<tr>
<td>Silverman et al,23 1994</td>
<td>621 relatives of cases 640 relatives of controls</td>
<td></td>
<td>6 (1.0%) of 621 patient relatives and 6 (0.9%) of 640 control relatives affected; 3 of the 6 relatives in each group had PDD</td>
</tr>
<tr>
<td>Mickel et al,24 1997</td>
<td>626 relatives of cases 644 relatives of controls</td>
<td>Not reported</td>
<td>5 (0.8%) of 628 patient relatives and 6 (0.9%) of 644 control relatives affected (log rank, P = .64)</td>
</tr>
</tbody>
</table>

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<tr>
<td>Mickel et al,24 1997</td>
<td>625 relatives of cases 675 relatives of controls</td>
<td>1.55 (0.88-2.74)</td>
<td>In relatives of 15 patients with PDD, risk of AD was not increased compared with relatives of patients with PDND (log rank, P = .32)</td>
</tr>
<tr>
<td>Marder et al,25 1999</td>
<td>583 relatives of PDND cases 547 relatives of PDD cases 2865 relatives of controls</td>
<td>PDND cases: 0.9 (0.6-1.3)</td>
<td>Risk of AD was increased in siblings of patients with PDND compared with siblings of controls (RR, 3.2; 95% CI, 1.1-9.4)</td>
</tr>
<tr>
<td>This study</td>
<td>2534 relatives of cases 2285 relatives of controls</td>
<td>1.1 (0.7-1.6)</td>
<td>Patients with PD excluded</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio; PDD, PD with dementia; PDND, PD without dementia; RR, relative risk.
because we oversampled probands with early-onset PD (<50 years), but results were similar when we analyzed separately probands with late-onset PD (>50 years) and probands with PD with age of onset of 67 years or older (upper quartile of the age of onset distribution in probands with PD, data not shown). Patients with PD with dementia who were not able to provide accurate information on their relatives were not included. Therefore, we cannot explore the incidence of AD in relatives of patients with PD with dementia. The exclusion of patients with PD with dementia might underlie the lack of familial aggregation observed in this study, based on the assumption that patients with PD with dementia are those most likely to have concomitant AD pathological changes. However, PD with dementia is a clinical diagnosis. Recent neuropathological studies using α-synuclein immunostaining have found that cortical Lewy bodies are more strongly associated with dementia in PD than are AD cortica\ntal changes.86-10

The lack of familial aggregation of PD and AD observed in this and other studies does not support the hypothesis of major shared genetic contributions to the etiology. This is also consistent with the lack of overlap in currently known genetic causes of PD and AD. Among the rare Mendelian causes of these neurodegenerative disorders, mutations in distinct genes specifically cause each disorder.51-54 However, it remains plausible that overlapping genetic factors involved in disease progression (modifying genes) and shared pathogenetic pathways occur in PD and AD.95

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Author contributions: Study concept and design (Drs Levy, Louis, Ottman, and Marder); acquisition of data (Drs Levy, Côté, Andrews, Harris, Waters, Frucht, Fahn, Ottman, and Marder and Ms Mejia-Santana); analysis and interpretation of data (Drs Levy, Louis, Ottman, and Marder); drafting of the manuscript (Dr Levy); critical revision of the manuscript for important intellectual content (Drs Louis, Côté, Andrews, Harris, Waters, Ford, Frucht, Fahn, Ottman, and Marder and Ms Mejia-Santana); statistical expertise (Drs Levy, Louis, Andrews, and Ottman); obtaining funding (Dr Marder); administrative, technical, and material support (Drs Côté, Harris, and Fahn and Ms Mejia-Santana); study supervision (Dr Marder).

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