Risk of Cognitive Impairment or Dementia in Relatives of Patients With Parkinson Disease

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Background: The evidence for increased risk of dementia in relatives of patients with Parkinson disease (PD) remains conflicting.

Objective: To study the risk of cognitive impairment or dementia in first-degree relatives of patients with PD.

Design, Setting, and Participants: We conducted a historical cohort study of 1019 first-degree relatives of 162 patients with PD and of 858 relatives of 147 matched controls representative of the population of Olmsted County, Minnesota. In addition, we studied 2716 first-degree relatives of 411 patients with PD referred to Mayo Clinic.

Main Outcome Measures: We administered via telephone a cognitive test directly to relatives or a dementia questionnaire to proxies. For relatives reported by proxies to have dementia, we obtained copies of their medical records to confirm the diagnosis. We also obtained dementia information from a medical records-linkage system.

Results: In the overall population-based sample, the risk of cognitive impairment or dementia was increased in relatives of patients with PD compared with relatives of controls (hazard ratio, 1.37; 95% confidence interval, 1.03-1.81; P = .03) and was particularly increased in relatives of patients with onset of PD at age 66 years or younger (youngest tertile; hazard ratio, 1.73; 95% confidence interval, 1.21-2.46; P = .003). The findings were consistent in several sensitivity analyses. In the referral-based sample, the risk of cognitive impairment or dementia in relatives increased with younger age at onset of PD but did not vary by other clinical characteristics.

Conclusion: Cognitive impairment or dementia may share familial susceptibility factors with PD (genetic or nongenetic).

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Several clinical or epidemiologic studies have shown an increased risk of dementia in first-degree relatives of patients with Parkinson disease (PD). However, other studies did not confirm the association. The co-occurrence of Alzheimer disease and PD in families and in individuals may be due to the sharing of susceptibility genetic variants (eg, the apolipoprotein E gene). In addition, Alzheimer disease brain lesions (plaques and tangles) and PD brain lesions (Lewy bodies) may share risk factors or could be reciprocally causal. Thus, as part of the Mayo Clinic Family Study of Parkinson Disease, we studied the risk of cognitive impairment or dementia in first-degree relatives of patients with PD.

METHODS

STUDY DESIGN

The study included 4 cohorts of relatives: (1) first-degree relatives of patients with incident PD from Olmsted County; (2) first-degree relatives of matched controls from the same Olmsted County population; (3) first-degree relatives of patients with PD referred to Mayo Clinic from a 120-mile radius centered in Rochester; and (4) first-degree relatives of patients with PD referred to Mayo Clinic from a broader 5-state region (Minnesota, Iowa, Wisconsin, and North and South Dakota). Members of all 4 cohorts were followed up historically through interviews and review of medical records to ascertain cognitive impairment or dementia. Details about the overall study design were reported elsewhere. Only the methods specific for cognitive impairment or dementia are reported herein. All aspects of the study involving participant contact were approved by the institutional review boards of Mayo Clinic and Olmsted Medical Center.

PATIENTS WITH PD AND CONTROLS

The medical records-linkage system of the Rochester Epidemiology Project was used to identify all individuals residing in Olmsted County who developed PD between January 1, 1976, and December 31, 1995, as reported elsewhere. The clinical classification of pa-
tients with PD through medical record review was found to be valid compared with direct examination by a movement disorders specialist. Each patient with PD was individually matched by age (±1 year) and sex to a general population control residing in Olmsted County and free of PD, other parkinsonism, or tremor of any type in the index year (year of onset of PD in the matched case). Records of potential controls were reviewed by a neurologist (D.M.M.) to confirm their eligibility. The exclusion of parkinsonism in controls through medical record review was found to be valid compared with direct examination by a movement disorders specialist. The presence of dementia or other neurologic diseases was not an exclusion criterion. Extensive additional details about the selection of controls have been reported elsewhere. In addition, we recruited a series of sequential new patients with PD referred to the Department of Neurology at Mayo Clinic between July 1, 1996, and October 31, 2000. All the patients were examined by a movement disorders specialist (J.H.B., J.E.A., or D.M.M.) following a standardized clinical assessment form. This referral sample was divided into 2 strata: (1) patients residing within a 120-mile radius centered in Rochester and (2) patients residing in a broader 5-state region. The diagnostic criteria for PD have been reported elsewhere.

CONSTRUCTION OF PEDIGREES
We asked patients with PD and controls (or their proxies) to provide a full listing and contact information for all first-degree relatives. For some of the families who resided in Olmsted County and who had no available informant, the pedigree composition was obtained using the obituaries archived at the Olmsted County Historical Society and the medical records-linkage system, as described elsewhere. Because this study was originally designed to investigate the risk of parkinsonism in relatives and because parkinsonism is rare before age 40 years, we excluded relatives who were younger than 40 years at the time of the study. In addition, we excluded stepparents, stepsiblings, and adopted relatives (because they were not blood related) and half-siblings.

ASCERTAINMENT OF COGNITIVE IMPAIRMENT OR DEMENTIA IN RELATIVES
Cognitive impairment or dementia was ascertained using a combination of 2 methods: (1) telephone interviews and (2) review of medical records from a records-linkage system. The telephone contact was made by 1 of 3 specifically trained research assistants and involved the Telephone Interview for Cognitive Status–Modified (TICS-m) (12 items; maximum score of 50 points). For deceased or incapacitated (eg, deaf, cognitively impaired, or terminally ill) relatives, we administered to the most knowledgeable person in the family the brief dementia questionnaire reported in Table 1 (8 questions). For relatives interviewed directly, we did not perform any additional proxy interviews.

Independent of the interview, relatives of patients with PD and controls who resided in Olmsted County for part or all of their life were studied passively through review of the inpatient and outpatient medical records archived in the local records-linkage system. In addition, for relatives who resided outside of Olmsted County and for whom proxies reported dementia, we obtained written authorization and requested copies of their pertinent medical records. All medical records from within or outside the records-linkage system were abstracted by a specifically trained nurse abstractor following a specified protocol, and all diagnoses of dementia were validated by a neurologist (J.H.B.). Telephone interviewers and all research team members involved in the ascertainment of cognitive impairment or dementia were kept uninformed of the relation of relatives to patients with PD or controls to prevent bias.

Table 1. Proxy Dementia Questionnaire

<table>
<thead>
<tr>
<th>Memory Questions</th>
<th>Activities of Daily Living Question</th>
<th>Diagnosis Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did or does he or she have trouble remembering things like a short shopping list, things to do, or events that happened recently?</td>
<td>Did or does he or she need help to dress, eat, or bathe because of confusion, poor judgment, or other thinking problems?</td>
<td>Did or does he or she have dementia or senility?</td>
</tr>
<tr>
<td>Did or does he or she have trouble finding his or her way even in familiar places?</td>
<td>Did or does he or she have trouble recognizing family members?</td>
<td>Did or does he or she have trouble remembering the exact day or year?</td>
</tr>
<tr>
<td>Did or does he or she have trouble remembering his or her past?</td>
<td>Did or does he or she have problems with his or her memory?</td>
<td>Did or does he or she have dementia or senility?</td>
</tr>
</tbody>
</table>

a Eight questions derived and modified from a more detailed dementia questionnaire are reported elsewhere. b If at least 1 answer was positive, we asked additional details about age at onset of symptoms, type of onset (sudden vs gradual), and follow-up (improved vs worsened across time). In addition, we asked whether the cause of the symptoms was known. c If at least 1 answer was positive, we asked about confirmation of the diagnosis by a physician or medical institution, age at diagnosis, and the name and address of the physician or medical institution. In addition, we obtained written authorization and requested a copy of the pertinent medical record.

DIAGNOSTIC CRITERIA FOR COGNITIVE IMPAIRMENT OR DEMENTIA
Relatives were considered to be affected by cognitive impairment or dementia if they met 1 or more of the following 4 criteria: (1) they scored 27 or less on the TICS-m at direct interview (improved vs worsened across time). (2) A proxy respondent reported a previous diagnosis of dementia, senility, or Alzheimer disease; (3) a proxy respondent reported impairment in activities of daily living (dressing, eating, or bathing) caused by cognitive problems; and (4) there was medical record documentation of signs or symptoms meeting the criteria for dementia of the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition). For relatives with multiple sources of information, the final diagnosis was based on the best available information in hierarchical order.

Consistent with these 4 criteria, age at onset was defined as the age at administration of the TICS-m (direct contact only), the age at onset of dementia reported by a proxy, the age at onset of impaired activities of daily living reported by a proxy, or the age at onset of dementia as documented in medical records. For relatives with more than 1 reported age at onset of cognitive symptoms, we used the earliest.

STATISTICAL ANALYSIS
First-degree relatives were included in the analyses from birth through the onset of cognitive impairment or dementia, contact for the study (or time of last medical record information), or death. For 11 relatives of population-based patients with PD, 12 relatives of population-based controls, and 20 relatives of referral patients with PD with unknown age at onset of cognitive impairment or dementia, we used age at contact for the study or age at death (carry-forward imputation).
We obtained cumulative incidence curves of cognitive impairment or dementia using the Kaplan-Meier method and estimated hazard ratios (HRs) and their 93% confidence intervals (CIs) using Cox proportional hazards models.23 The proportionality assumption was tested graphically and by introducing a time-dependent coefficient in the Cox models.23

For each analysis, we obtained unadjusted HRs using age as the time scale and HRs adjusted for educational level, tertiles of age (14-16, or 17-19 years) and type of interview (direct, proxy, or medical record only) to prevent possible confounding effects.

Analyses were conducted separately on the population-based and referral samples. In addition to overall analyses, we performed analyses stratified by age at onset of PD (youngest, middle, and oldest tertiles), clinical characteristics of patients with PD, type of relatives, and sex of relatives. We also performed additional analyses accounting for the clustering of relatives within families24 and several sets of sensitivity analyses. Data were analyzed using a software program (SAS version 8.2; SAS Institute Inc, Cary, North Carolina), and all statistical testing was performed at the conventional 2-tailed α = .05.

### RESULTS

#### VALIDITY

The TICS-m was previously validated by other researchers,16,20,21 and the cutoff score of 27 or less was previously established.20,21 In addition, we studied the convergent validity of the TICS-m with the Mini-Mental State Examination in a sample of 397 individuals with both measures (Spearman correlation, 0.48; P < .001).23 These 397 relatives were examined independently of the TICS-m score as part of a validation study described elsewhere.10

The brief dementia questionnaire was derived and modified from a more detailed instrument published by other researchers.19 We investigated its validity by comparing 265 proxy administrations of the questionnaire via telephone with the independent documentation of dementia in medical records from the records-linkage system. The brief dementia questionnaire had 73.3% sensitivity and 85.6% specificity for Alzheimer disease and 44.6% sensitivity and 92.2% specificity for all types of dementia. The sensitivity for all types of dementia was increased by also including in the dementia category relatives for whom the proxy informant reported a positive response to 3 or more of 5 memory questions (sensitivity, 48.7%). More important, sensitivity and specificity were similar in relatives of patients with PD and relatives of controls.

In addition, for 2125 relatives assessed via proxy in this study, we studied the internal consistency of the brief dementia questionnaire (Table 1). Agreement between the 2 questions about previous diagnoses and the question about impaired activities of daily living was 93.4% (κ = 0.58; 95% CI, 0.52-0.64). More important, the agreement...
per the diagnostic criteria for PD, all 162 patients were interviewed. Using the TICS-m, and 39.0% had a proxy dementia. Of the 546 relatives with clinical information obtained for relatives affected by developed dementia at some point during follow-up. elsewhere, approximately 52% of the patients developed dementia at some point during follow-up. The HRs are estimated using age as a time scale but with no additional adjustments. Analyses stratified by type of interview yielded an unadjusted HR of 1.24 (95% CI, 0.92-1.67; P = .18) for direct interview or medical record only combined (difference, 0.002). Tertiles are presented from the youngest to the oldest. Analyses for offspring were not reported separately because of the small number of outcomes.

DESCRIPTION OF THE SAMPLE

Details about the participation of the 162 patients with PD and the 147 matched controls from Olmsted County in the construction of pedigrees and the identification of first-degree relatives have been reported elsewhere. As per the diagnostic criteria for PD, all 162 patients were free of dementia preceding onset or within 1 year of onset of the motor symptoms of PD. However, as reported elsewhere, approximately 52% of the patients developed dementia at some point during follow-up.

Table 2 provides details about the recruitment of first-degree relatives and the type of interview or other source of follow-up information. Overall, we interviewed 82.4% of all relatives, and an additional 4.0% were studied through medical records information (total participation, 86.4%). Table 3 gives the degree of clinical information obtained for relatives affected by cognitive decline or dementia. Of the 546 relatives with cognitive impairment or dementia, 34.1% had medical record information, 26.9% had direct cognitive assessment using the TICS-m, and 39.0% had a proxy dementia interview.

PRIMARY ANALYSES

Table 4 and Figure 1 provide the results in the population-based sample. Overall, the relatives of patients with PD had an increased risk of cognitive impairment or dementia compared with relatives of controls. However, relatives of patients with onset of PD in the youngest tertile had a particularly increased risk, and there was a trend

Table 4. Risk of Cognitive Impairment or Dementia in First-degree Relatives of Population-Based Patients With PD and Controls

<table>
<thead>
<tr>
<th>Type of Relative</th>
<th>Relatives at Risk, No.</th>
<th>Relatives With Cognitive Impairment or Dementia, No. (%)</th>
<th>Unadjusted HR (95% CI)a</th>
<th>P Value</th>
<th>Adjusted HR (95% CI)b</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relatives of controls</td>
<td>858</td>
<td>119 (13.9)</td>
<td>1 [Reference]</td>
<td>...</td>
<td>1 [Reference]</td>
<td>...</td>
</tr>
<tr>
<td>Relatives of all patients with PD</td>
<td>1019</td>
<td>146 (14.3)</td>
<td>1.24 (0.97-1.58)c</td>
<td>.08</td>
<td>1.37 (1.03-1.81)c</td>
<td>.03</td>
</tr>
<tr>
<td>Onset ≤66 y (youngest)d</td>
<td>349</td>
<td>52 (14.9)</td>
<td>1.70 (1.23-2.36)</td>
<td>.002</td>
<td>1.73 (1.21-2.46)</td>
<td>.003</td>
</tr>
<tr>
<td>Onset &gt;75 y (oldest)</td>
<td>339</td>
<td>43 (12.7)</td>
<td>0.86 (0.60-1.22)</td>
<td>.39</td>
<td>1.01 (0.66-1.55)</td>
<td>.96</td>
</tr>
<tr>
<td>Parents of controls</td>
<td>176</td>
<td>28 (15.9)</td>
<td>1 [Reference]</td>
<td>...</td>
<td>1 [Reference]</td>
<td>...</td>
</tr>
<tr>
<td>Parents of all patients with PD</td>
<td>226</td>
<td>57 (25.2)</td>
<td>1.94 (1.23-3.06)</td>
<td>.004</td>
<td>2.84 (1.62-5.00)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Parents of patients with PD ≤66 y</td>
<td>94</td>
<td>24 (25.5)</td>
<td>1.98 (1.15-3.42)</td>
<td>.01</td>
<td>3.04 (1.51-6.11)</td>
<td>.002</td>
</tr>
<tr>
<td>Siblings of patients with PD</td>
<td>463</td>
<td>83 (17.9)</td>
<td>1.03 (0.76-1.39)</td>
<td>.85</td>
<td>1.07 (0.76-1.52)</td>
<td>.70</td>
</tr>
<tr>
<td>Siblings of patients with PD ≤66 y</td>
<td>158</td>
<td>27 (17.1)</td>
<td>2.23 (1.43-3.48)</td>
<td>&lt;.001</td>
<td>1.91 (1.19-3.07)</td>
<td>.007</td>
</tr>
<tr>
<td>Male relatives of patients with PD</td>
<td>414</td>
<td>48 (11.6)</td>
<td>1 [Reference]</td>
<td>...</td>
<td>1 [Reference]</td>
<td>...</td>
</tr>
<tr>
<td>Male relatives of patients with PD ≤66 y</td>
<td>471</td>
<td>52 (11.0)</td>
<td>1.15 (0.78-1.71)</td>
<td>.49</td>
<td>1.55 (0.99-2.43)</td>
<td>.05</td>
</tr>
<tr>
<td>Male relatives of patients with PD &gt;75 y (oldest)</td>
<td>152</td>
<td>21 (13.8)</td>
<td>1.93 (1.15-3.23)</td>
<td>.01</td>
<td>2.05 (1.17-3.58)</td>
<td>.01</td>
</tr>
<tr>
<td>Female relatives of patients with PD</td>
<td>444</td>
<td>71 (16.0)</td>
<td>1 [Reference]</td>
<td>...</td>
<td>1 [Reference]</td>
<td>...</td>
</tr>
<tr>
<td>Female relatives of patients with PD ≤66 y</td>
<td>548</td>
<td>94 (17.2)</td>
<td>1.32 (0.97-1.80)</td>
<td>.08</td>
<td>1.28 (0.89-1.85)</td>
<td>.16</td>
</tr>
<tr>
<td>Female relatives of patients with PD &gt;75 y (oldest)</td>
<td>197</td>
<td>31 (15.7)</td>
<td>1.63 (1.07-2.50)</td>
<td>.02</td>
<td>1.66 (1.04-2.64)</td>
<td>.03</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; PD, Parkinson disease.

a The HRs are estimated using age as a time scale but with no additional adjustments.

b Analyses are adjusted for educational level (<9, 9-12, 13-16, or >16 years) and type of interview (proxy interview, direct interview, or medical record only). Educational level was missing for 203 relatives of controls (23.7%) (of whom 34 had cognitive impairment or dementia) and 247 relatives of patients with PD (24.2%) (of whom 51 had cognitive impairment or dementia).

c Accounting for the clustering of relatives within families, the 95% CIs were 0.92 to 1.66 (P = .15) for unadjusted analyses and 0.99 to 1.88 (P = .06) for adjusted analyses. Analyses stratified by type of interview yielded an unadjusted HR of 1.24 (95% CI, 0.92-1.67; P = .17) for proxy interview and 1.33 (95% CI, 0.87-2.03; P = .18) for direct interview or medical record only combined (difference, P = .97).

data Tests of a linear trend of the log HRs across age tertiles were significant (adjusted P = .002). Tertiles are presented from the youngest to the oldest.

e Analyses for offspring were not reported separately because of the small number of outcomes.

Figure 1. Results in the Olmsted County, Minnesota, population-based sample. Cumulative incidence of cognitive impairment or dementia in first-degree relatives of patients with Parkinson disease with onset in the youngest tertile (age ≤66 years), the middle tertile (age 67-75 years), and the oldest tertile (age >75 years) and in first-degree relatives of controls.
Table 5. Risk of Cognitive Impairment or Dementia in First-degree Relatives of Referral Patients With PD

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Relatives at Risk, No.</th>
<th>Relatives With Cognitive Impairment or Dementia, No. (%)</th>
<th>Unadjusted HR (95% CI)</th>
<th>P Value</th>
<th>Adjusted HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All relatives</td>
<td>1094</td>
<td>108 (9.9)</td>
<td>1 [Reference]</td>
<td>...</td>
<td>1 [Reference]</td>
<td>...</td>
</tr>
<tr>
<td>Onset &gt;68 y (oldest)</td>
<td>1094</td>
<td>108 (9.9)</td>
<td>1 [Reference]</td>
<td>...</td>
<td>1 [Reference]</td>
<td>...</td>
</tr>
<tr>
<td>Onset 58-68 y (middle)</td>
<td>887</td>
<td>94 (10.6)</td>
<td>1.24 (0.94-1.63)</td>
<td>.13</td>
<td>1.21 (0.90-1.62)</td>
<td>.21</td>
</tr>
<tr>
<td>Onset &lt;57 y (youngest)</td>
<td>735</td>
<td>79 (10.8)</td>
<td>1.88 (1.40-2.53)</td>
<td>&lt;.001</td>
<td>1.86 (1.37-2.52)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Parents of patients with PDd</td>
<td>760</td>
<td>165 (21.7)</td>
<td>1 [Reference]</td>
<td>...</td>
<td>1 [Reference]</td>
<td>...</td>
</tr>
<tr>
<td>Siblings of patients with PD</td>
<td>1339</td>
<td>108 (8.1)</td>
<td>1.39 (1.07-1.80)</td>
<td>.01</td>
<td>1.12 (0.82-1.52)</td>
<td>.47</td>
</tr>
<tr>
<td>Female relatives of patients with PD</td>
<td>1330</td>
<td>154 (11.6)</td>
<td>1 [Reference]</td>
<td>...</td>
<td>1 [Reference]</td>
<td>...</td>
</tr>
<tr>
<td>Male relatives of patients with PD</td>
<td>1386</td>
<td>127 (9.2)</td>
<td>1.01 (0.80-1.28)</td>
<td>.93</td>
<td>1.08 (0.85-1.39)</td>
<td>.50</td>
</tr>
<tr>
<td>Other first symptom</td>
<td>1129</td>
<td>113 (10.0)</td>
<td>1 [Reference]</td>
<td>...</td>
<td>1 [Reference]</td>
<td>...</td>
</tr>
<tr>
<td>Tremor as first symptom</td>
<td>1559</td>
<td>165 (10.6)</td>
<td>1.13 (0.89-1.44)</td>
<td>.32</td>
<td>1.00 (0.85-1.40)</td>
<td>.90</td>
</tr>
<tr>
<td>Akinetic-rigid</td>
<td>850</td>
<td>75 (8.8)</td>
<td>1 [Reference]</td>
<td>...</td>
<td>1 [Reference]</td>
<td>...</td>
</tr>
<tr>
<td>Tremor-predominant or mixed</td>
<td>1859</td>
<td>203 (10.9)</td>
<td>1.36 (1.04-1.77)</td>
<td>.02</td>
<td>1.29 (0.98-1.70)</td>
<td>.07</td>
</tr>
</tbody>
</table>

| Relatives of patients with PD onset <57 y    | 269                    | 55 (20.5)                                                | 1 [Reference]          | ...     | 1 [Reference]        | ...     |
| Parents of patients with PDd                 | 409                    | 21 (5.1)                                                 | 1.23 (2.09-6.92)       | <.001   | 3.56 (1.78-7.14)     | <.001   |
| Siblings of patients with PD                 | 362                    | 39 (10.8)                                                | 1 [Reference]          | ...     | 1 [Reference]        | ...     |
| Male relatives of patients with PD            | 373                    | 40 (10.7)                                                | 1.02 (0.65-1.58)       | .95     | 1.18 (0.74-1.88)     | .48     |
| Other first symptom                           | 328                    | 36 (11.0)                                                | 1 [Reference]          | ...     | 1 [Reference]        | ...     |
| Tremor as first symptom                       | 392                    | 41 (10.5)                                                | 1.08 (0.69-1.69)       | .74     | 1.05 (0.66-1.66)     | .84     |
| Akinetic-rigid                                | 198                    | 21 (10.6)                                                | 1 [Reference]          | ...     | 1 [Reference]        | ...     |
| Tremor-predominant or mixed                   | 530                    | 55 (10.4)                                                | 1.04 (0.63-1.72)       | .88     | 1.00 (0.60-1.67)     | .99     |

Abbreviations: CI, confidence interval; HR, hazard ratio; PD, Parkinson disease.

a The HRs are estimated using age as a time scale but with no additional adjustments.

b Analyses are adjusted for educational level (<9, 9-12, 13-16, or >16 years) and type of interview (proxy interview, direct interview, or medical record only).

Educational level was missing for 138 relatives (5.1%) (of whom 20 had cognitive impairment or dementia).

Because an adequate group of controls was not available for referral patients with PD, we compared the risk of cognitive impairment or dementia in first-degree relatives of patients with PD onset in the middle and youngest tertile with the risk in relatives of patients with PD onset in the oldest tertile (reference).

Tertiles are presented from the oldest to the youngest to keep the reference stratum on top. Results of a test of linear trend of the log HRs across age tertiles were significant (adjusted P < .001).

d Analyses for offspring were not reported because of the small number of outcomes.

Table 5 and Figure 2 provide the results of the analyses comparing the risk of cognitive impairment or dementia across strata of patients with PD with specific clinical characteristics in the Mayo Clinic referral sample. Patients from the 120-mile radius and from the 5-state region were pooled because the results were similar (data not shown). Again, we observed a trend of increasing risk in relatives of patients with younger age at onset of PD (test for linear trend, P < .001). However, none of the strata defined by clinical characteristics were significantly different in adjusted analyses.

SENSITIVITY ANALYSES

Because the presence of cognitive impairment or dementia could be documented only through administration of the TICS-m for 55 relatives in the population-based sample (Table 3), we cannot exclude some degree of misclassification. Therefore, we conducted a series of sensitivity analyses that excluded these 55 relatives. The adjusted HRs were 1.37 (95% CI, 0.99-1.90; P = .06) overall and 1.66 (95% CI, 1.08-2.54; P = .02) for relatives of patients with younger age at onset of PD.

Sensitivity analyses that excluded the 23 relatives with unknown age at onset of cognitive impairment or dementia in the population-based sample yielded adjusted HRs of 1.39 (95% CI, 1.04-1.87; P = .03) overall and 1.78 (95% CI, 1.23-2.58; P = .002) for relatives of patients with age at onset of PD (younger tertile), we performed additional analyses restricted to that stratum.
younger age at onset of PD. Sensitivity analyses using a broader definition of dementia in the population-based sample (adding 14 relatives for whom a proxy reported positive responses to 3 or more of 5 memory questions) yielded adjusted HRs of 1.36 (95% CI, 1.04-1.79; P = .03) overall and 1.70 (95% CI, 1.20-2.41; P = .003) for relatives of patients with younger age at onset of PD.

Finally, sensitivity analyses removing the 43 relatives of patients with PD and the 29 relatives of controls in the population-based sample who developed PD or parkinsonism yielded adjusted HRs of 1.27 (95% CI, 0.94-1.72; P = .12) overall and 1.50 (95% CI, 1.01-2.22; P = .04) for relatives of patients with younger age at onset of PD. Only 11 relatives of patients with PD and 8 relatives of controls developed dementia after parkinsonism.

In this population-based sample, the risk of cognitive impairment or dementia was modestly increased overall but was sizably increased for relatives of patients with younger age at onset of PD. In the referral sample, we confirmed the increasing risk of cognitive impairment or dementia in relatives of patients with younger age at onset of PD; however, we did not observe significant differences in risk for relatives of patients with tremor-predominant or mixed PD compared with relatives of patients with akinetic-rigid PD in adjusted models. These findings in the population-based and referral samples remained consistent after adjustment for educational level and type of interview and in several sets of sensitivity analyses addressing possible biases.

This study has several strengths. First, it represents a major departure from most previous attempts to study the risk of cognitive impairment or dementia in relatives of patients with PD because we used the family study method (ie, we assessed each relative separately for cognitive status) rather than the family history method (ie, the proband or a single proxy provided information for the full family).8 Thus, we confirmed the presence of cognitive impairment or dementia through medical records for 34.1% of the relatives presumed to have cognitive impairment or dementia. In addition, for relatives who were reported to have dementia by proxies, we obtained medical records from physicians or medical institutions throughout the United States whenever possible.

Second, we enriched the documentation of cognitive impairment or dementia in family members who lived in Olmsted County by using medical record information from the unique records-linkage system serving the community.10,15 The system provided medical record documentation for 417 relatives of population-based patients with PD, 359 relatives of population-based controls, and 356 relatives of referral patients. In support of the completeness of the identification of cognitive impairment or dementia, we compared the number of relatives of controls who were found to be affected by dementia with the number expected using published incidence rates in the same Olmsted County population.27 We detected 119 relatives with cognitive impairment or dementia vs 103.4 expected (standardized incidence ratio, 1.15; 95% CI, 0.95-1.38). This higher yield was expected because we used a more inclusive definition of outcome.

Third, we included in the study a population-based series of patients with incident PD and a series of patients with PD referred to Mayo Clinic. The population-based sample avoided possible biases related to survival (incidence-prevalence bias) and to selection of patients with PD and controls for inclusion in the study (referral bias).28 However, the sample was somewhat limited by the size of the Olmsted County population. To investigate specific hypotheses in strata defined by clinical characteristics of PD, we performed additional analyses across strata of relatives from a larger sample of referral patients.

However, this study has several limitations, and not all potential biases could be controlled. As reported elsewhere,29 the participation rate was higher overall and involved more often a direct interview for first-degree relatives of patients with PD compared with first-degree relatives of controls in the population-based sample. In addition, living first-degree relatives of patients with PD and controls were included more often than deceased relatives.30 However, the overall mortality was similar for relatives of patients with PD and relatives of controls (HR, 1.04; 95% CI, 0.91-1.18). In addition, analyses adjusted by type of interview yielded consistent results. Finally, the frequency of cognitive impairment or dementia was similar for the 1683 relatives in the population-based sample studied via direct or proxy interview (13.8%) and for the 194 relatives who could be studied only via abstraction of medical records (17.0%; P = .22).

Second, the direct or proxy telephone assessments of cognitive impairment or dementia were imperfect. However, in addition to the published validity data for the TICS-m,16,20,21 we reported good convergent validity between the TICS-m and the Mini-Mental State Examination from our own experience.25 The brief dementia questionnaire had somewhat low sensitivity; however, it had similar internal consistency and validity for relatives of patients with PD and relatives of controls. Thus, any potential undercounting should be nondifferential in the 2 groups. Similar brief dementia questionnaires have been introduced and validated by other investigators.29,30 Finally, sensitivity analyses using a broader definition of cognitive impairment or dementia and analyses adjusted by the type of interview yielded consistent results.

Third, age at onset of cognitive impairment or dementia was not available for some of the relatives, and we used a carry-forward imputation method. However, sensitivity analyses removing all relatives with unknown age at onset yielded consistent results. Finally, because some of the stratified analyses conducted in this study were based on small numbers of events, they had limited power.

This study provides evidence that relatives of patients with PD have an increased risk of cognitive impairment or dementia. This association is primarily driven by families of patients with younger age at onset of PD, but the risk does not vary across relatives of patients with different clinical characteristics of PD. The observed associations suggest the action of shared familial susceptibility factors, genetic or nongenetic.
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