Prognosis of Parkinson Disease

Risk of Dementia and Mortality: The Rotterdam Study

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Background: Most prognostic studies on Parkinson disease have been hospital based or have applied register-based case-finding methods. Potential underrepresentation of mild cases may have given biased results.

Objective: To evaluate whether Parkinson disease is associated with an increased risk of dementia and death.


Setting: General population.

Participants: A total of 6969 participants, including 99 prevalent and 67 incident cases of Parkinson disease.

Main Outcome Measures: Incident dementia and death. Adjusted hazard ratios were calculated through Cox proportional hazards regression analysis.

Results: Patients with Parkinson disease had an increased risk of dementia (hazard ratio, 2.8; 95% confidence interval, 1.8-4.4), which was especially pronounced in participants carrying at least 1 apolipoprotein E gene (APOE) ε2 allele (13.5; 4.5-40.6). Parkinson disease was associated with an increased mortality risk (1.8; 1.5-2.3). The association consistently diminished when analyses were sequentially restricted to patients with shorter disease duration and after adjustment for the occurrence of dementia.

Conclusions: Especially patients with Parkinson disease who carry an APOE ε2 allele have an increased risk of developing dementia. Increased mortality risk in Parkinson disease is dependent on disease duration and is only modest in the absence of dementia.

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Parkinson disease; plus sign, plus any other allele.1,7-9 Briefly, all participants were screened for dementia, both of which have been described extensively to identify subjects with PD and a 3-stage protocol to assess evidence outcomes and mortality through computerized linkage to the cohort was continuously monitored for major dis-

2 follow-ups visits (1993-1994 and 1997-1999), participants were interviewed and underwent extensive physical examination. In addition, the cohort was continuously monitored for major disease outcomes and mortality through computerized linkage to general practitioners’ medical files. All participants gave their informed consent, and the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, the Netherlands, approved the study.

ASSESSMENT OF PD AND DEMENTIA

At baseline and follow-up, we used a 2-stage protocol to identify subjects with PD and a 3-stage protocol to assess dementia, both of which have been described extensively elsewhere.1,3,4 Briefly, all participants were screened for symptoms of parkinsonism, and those who screened positive received a structural diagnostic workup using the Unified Parkinson’s Disease Rating Scale. Persons suspected of having PD were examined by a neurologist. Parkinson disease was diagnosed if at least 2 parkinsonian signs were present or if at least 1 sign had improved through medication and all causes of secondary parkinsonism had been excluded. Age at diagnosis of PD and Hoehn and Yahr scale score for disease severity were assessed in the diagnostic workup and verified from medical records if possible. Cognitive screening of all participants was performed with the Mini-Mental State Examination and Geriatric Mental State schedule. Subjects in whom screening was positive were examined with the Cambridge Examination of Mental Disorders in the Elderly. If the result of this examination was inconclusive, a neuropsychologist performed further examination and, if possible, magnetic resonance imaging was done. Final diagnosis was made according to Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition criteria.10

The computerized surveillance system continuously provided additional information on both PD and dementia.

ASSOCIATION OF MORTALITY AND COVARIATES

Mortality until January 1, 2000, was assessed through continuous monitoring of the municipal address files and computerized reports from general practitioners on the deaths of participants. Information on highest attained educational level, smoking behaviors, medication use, and living situation was obtained during the baseline interview. APOE genotyping was performed on baseline samples.2

STUDY POPULATION

At baseline, 6969 participants underwent neurologic screening. Parkinson disease was diagnosed in 99 participants (prevalent PD). During follow-up, another 67 patients were identified (incident PD). All 6969 participants were followed up to study mortality risk.

To examine the risk of incident dementia, we excluded participants with incomplete baseline cognitive screening (n=6) and those diagnosed as having dementia at baseline (n=312). The resulting study sample of 6631 nondemented participants comprised 72 prevalent and 67 incident PD cases.

DATA ANALYSIS

Hazard ratios (HRs) for incident dementia and mortality were computed by means of Cox proportional hazards regression analysis allowing for delayed entry, with age as the time scale and PD as a time-dependent covariate. Models were initially adjusted for age and sex. Potential confounders we additionally adjusted for were smoking (ever vs never), nursing home residency, antiparkinsonian medication use, and educational level (primary education only vs more than primary education). Because of the wide range of disease duration of prevalent PD cases at the time of inclusion in the study, we performed separate analyses for cases with disease duration of 5 years or more and less than 5 years. Within the latter group, we further looked separately into those with less than 2 years’ duration (hence including incident PD cases) and incident PD cases only. To evaluate whether and to what extent reduced survival in patients with PD is explained by an increased risk of dementia, we adjusted for occurrence of dementia in a time-dependent fashion. All analyses were stratified on APOE genotype (ε3/ε3, ε4+, and ε2+; ε2/ε4 excluded) to examine potential modifying effects on prognosis. Median survival from diagnosis was calculated by the Kaplan-Meier method. All analyses were performed with SAS software (version 8.2; SAS Institute Inc, Cary, NC).

Table 1 displays baseline characteristics of the study population. Follow-up was virtually complete (99%) until January 1, 2000. The total follow-up time was 48,606 person-years (overall mean, 6.9 years; mean of incident PD cases after disease onset, 4.3 years). The mean Hoehn and Yahr scale score of patients with prevalent PD (2.3) and especially of patients with incident PD (1.8) was relatively low compared with previous studies.
RISK OF DEMENTIA

At baseline, 22% of the participants with PD and 4% of those without PD were diagnosed as having dementia. Demented patients with PD were significantly older than those without dementia. Of the cohort free of dementia at baseline, 21 (15.1%) of the 139 patients with PD and 318 (4.9%) of the 6512 participants without PD developed dementia during follow-up. The presence of PD was associated with a significantly increased risk of dementia (HR, 2.80; 95% CI, 1.79-4.38; Table 2). Results were similar after additional adjustments and for subgroups of disease duration at baseline. However, restricting analyses to only incident PD cases resulted in a higher estimate of disease duration at baseline, which may have led us to underestimate the risk. The strengths of this study are its population-based nature, size, and almost complete follow-up. In addition, thorough case ascertainment for PD and dementia was ensured through in-person instead of record-based screening methods. The use of strict diagnostic criteria enhanced diagnostic accuracy, and continuous monitoring of participants after diagnosis enabled us to revise diagnoses on the basis of additional information. Furthermore, because we followed up prevalent as well as incident PD cases, we could evaluate the effect of disease duration on prognosis and potential bias in prevalent cohorts.

An increased risk of dementia associated with PD has repeatedly been reported, with relative risks varying from 1.7 to 5.9.1,2,11-14 Our estimate of a 2.8-times increased risk is relatively low. A possible explanation is the low average disease severity in our study, which resulted from our relatively broad, nonselective recruitment methods. The use of strict diagnostic criteria enhanced diagnostic accuracy, and continuous monitoring of participants after diagnosis enabled us to revise diagnoses on the basis of additional information.

Table 3. PD and Mortality Risk According to Disease Duration at Time of Enrollment

<table>
<thead>
<tr>
<th>Genotype</th>
<th>All Cases (N = 166)</th>
<th>≤5 y (n = 52)</th>
<th>&lt;5 y (n = 114)</th>
<th>&lt;2 y (n = 87)</th>
<th>Incident Cases Only (n = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOE ε2+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.80 (1.79-4.38)</td>
<td>13.46 (4.46-40.64)</td>
<td>1.74 (0.77-3.97)</td>
<td>6.27 (3.07-12.82)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2</td>
<td>2.82 (1.80-4.42)</td>
<td>14.26 (4.68-45.50)</td>
<td>1.82 (0.80-4.16)</td>
<td>6.49 (3.17-13.31)</td>
<td>.024</td>
</tr>
</tbody>
</table>

Abbreviations: APOE, apolipoprotein E gene; CI, confidence interval; NA, not applicable; HR, hazard ratio; PD, Parkinson disease; plus sign, plus any other allele.

Table 2. PD and the Risk of Incident Dementia by Strata of APOE Genotype

<table>
<thead>
<tr>
<th>Model*</th>
<th>Overall</th>
<th>APOE ε2+</th>
<th>APOE ε3/ε3</th>
<th>APOE ε4+</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.80</td>
<td>13.46</td>
<td>1.74</td>
<td>6.27</td>
<td>2.11</td>
</tr>
<tr>
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<td>2.82</td>
<td>14.26</td>
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<td>6.49</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: APOE, apolipoprotein E gene; CI, confidence interval; NA, not applicable; HR, hazard ratio; PD, Parkinson disease.

†Model 1 was adjusted for age and sex; model 2 was adjusted for age, sex, and occurrence of dementia (time dependent).

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MORTALITY RISK

During follow-up, 90 (54.2%) of the 166 patients with PD and 1623 (23.9%) of the 6803 participants without PD died. Median survival after diagnosis of PD was 9.1 years (95% CI, 7.4-10.9 years). Overall, PD was associated with a significantly increased mortality risk (HR, 1.83; 95% CI, 1.47-2.26) (Table 3). However, HRs consistently decreased when the analyses were sequentially restricted to patients in whom PD was diagnosed more recently. Additional adjustments did not substantially change the results, but adjusting for occurrence of dementia yielded lower mortality HRs. The effect of PD on survival was not different for men and women, or by strata of APOE genotype (data not shown). Within PD cases, mortality risk was influenced by disease duration (HR increase per year, 1.03; 95% CI, 0.99-1.07) and by occurrence of dementia (HR, 2.85; 95% CI, 1.77-4.62).

Comment

The strengths of this study are its population-based nature, size, and almost complete follow-up. In addition, thorough case ascertainment for PD and dementia was ensured through in-person instead of record-based screening methods. The use of strict diagnostic criteria enhanced diagnostic accuracy, and continuous monitoring of participants after diagnosis enabled us to revise diagnoses on the basis of additional information. Furthermore, because we followed up prevalent as well as incident PD cases, we could evaluate the effect of disease duration on prognosis and potential bias in prevalent cohorts.

An increased risk of dementia associated with PD has repeatedly been reported, with relative risks varying from 1.7 to 5.9.1,2,11-14 Our estimate of a 2.8-times increased risk is relatively low. A possible explanation is the low average disease severity in our study, which resulted from our screening methods, through which we identified a large number of previously unrecognized patients with mild PD.1,2 Moreover, we consider it likely that patients with PD who agreed to participate at baseline had fewer cognitive complaints and thus a lower risk of future dementia than nonresponders, which may have led us to un-
deremestrate the risk for prevalent cases. The HR for incident cases was notably higher (4.7), despite lower disease severity, and presumably reflects the actual situation more accurately.

We found that the effect of PD on dementia risk was more pronounced in participants carrying at least 1 APOE ε4 allele and remarkably strong in those carrying at least 1 APOE ε2 allele. Apolipoprotein E, coded for by the APOE gene, is a polymorphic protein abundant in the brain that is involved in lipid transport, immunoregulation, and modulation of cell growth. For Alzheimer disease, the APOE ε4 allele is an established risk factor, whereas the ε2 allele is considered protective. In contrast, a recent meta-analysis confirmed the repeatedly observed association of the ε2 allele with an increased risk of PD, while results for the ε4 allele were inconsistent. A significant positive association with occurrence of dementia in patients with PD has been observed for both the ε4 allele and the ε2 allele, which suggests that the APOE gene might modify the risk of dementia associated with PD. However, the exact mechanism by which APOE genotype or apolipoprotein E isoforms influence the risk and course of PD is still unclear.

The overall mortality HR of 1.8 we observed is in line with figures from other studies, ranging from 1.5 to 2.7. We found that the mortality HR was higher for patients with longer disease duration and relatively low for newly diagnosed incident cases. This fits previous observations that mortality rates in patients with PD were not increased compared with those in controls in the first years of follow-up and differed more as time since diagnosis increased. Apart from the effect of aging, disease duration thus seems to influence mortality risk in PD, and differences in the composition of study populations with respect to mean and range of duration of PD may lead to different estimates of mortality risk. From studies in prevalent cohorts, in fact, only prognosis after enrollment can be derived, which is different from prognosis after diagnosis of PD, especially in cases of a long delay between diagnosis and inclusion in the study. Since we observed that mean Hoehn and Yahr scale scores were consistently higher in categories of longer disease duration, the effect of disease duration on mortality risk might reflect the effect of disease severity. Independent effects of disease severity on mortality have been described previously. To correctly evaluate prognosis after PD diagnosis, prospective studies of incident cases are required. These are difficult, given the low incidence rate of PD, and were conducted only twice previously. Both studies found a mortality HR somewhat higher than our figure for incident cases. This may be accounted for by the relatively high proportion of patients with mild PD and the fact that follow-up of incident PD cases was relatively short in our study.

Although both PD and dementia have separately been associated with increased mortality, few studies have investigated to what extent dementia contributes to the observed shorter survival in patients with PD. We tried to evaluate this by adjusting in a time-dependent fashion for the occurrence of dementia, which led to lower estimates of the mortality HRs in all strata of disease duration. This suggests that part of the reduced life expectancy of patients with PD can be ascribed to their increased risk of becoming demented. In fact, mortality risk is only slightly increased in the absence of dementia.

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Author Contributions: Study concept and design: de Lau, Hofman, Koudstaal, and Breteler. Acquisition of data: de Lau, Koudstaal, and Breteler. Analysis and interpretation of data: de Lau, Schipper, Koudstaal, and Breteler. Drafting of the manuscript: de Lau and Breteler. Critical revision of the manuscript for important intellectual content: de Lau, Schipper, Hofman, Koudstaal, and Breteler. Statistical analysis: de Lau, Schipper, and Breteler. Obtained funding: Hofman and Breteler. Study supervision: Koudstaal and Breteler.

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REFERENCES


**Correction**

**Error in Table.** In the Original Contribution by Galvin et al titled “Predictors of Preclinical Alzheimer Disease and Dementia: A Clinicopathologic Study,” published in the May issue of the *ARCHIVES* (2005;62:758-765), the number of patients with dementia in Table 1 should have been 39.