Combined Effect of Age and Severity on the Risk of Dementia in Parkinson's Disease

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Age and severity of extrapyramidal signs have been consistently associated with incident dementia in Parkinson's disease. We evaluated the separate and combined effects of age and severity of extrapyramidal signs on the risk of incident dementia in Parkinson's disease in the setting of a population-based prospective cohort study. Age and the total Unified Parkinson's Disease Rating Scale motor score at baseline evaluation were dichotomized at the median. Four groups of Parkinson's disease patients were defined: younger age/low severity (reference), younger age/high severity, older age/low severity, and older age/high severity. Risk ratios for incident dementia were calculated with Cox proportional hazards models controlling for gender, education, ethnicity, and duration of Parkinson's disease. Of 180 patients, 52 (28.9%) became demented during a mean follow-up period of 3.6 ± 2.2 years. The median age at baseline of the Parkinson's disease patients was 71.8 years (range, 38.5–95.9 years), and the median total Unified Parkinson's Disease Rating Scale motor score was 24 (range, 2–65). The group with older age/high severity had a significantly increased risk of incident dementia (relative risk, 9.7; 95% confidence interval, 3.9–24.4) compared with the group with younger age/low severity (reference), whereas the groups with older age/low severity (relative risk, 1.6; 95% confidence interval, 0.5–4.8) and younger age/high severity (relative risk, 1.2; 95% confidence interval, 0.5–3.2) did not. These findings suggest that the increased risk of incident dementia in Parkinson's disease associated with age and severity of extrapyramidal signs is related primarily to their combined effect rather than separate effects.

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Dementia complicates the course of idiopathic Parkinson's disease (PD) in many patients. The development of dementia in patients with PD limits standard pharmacotherapy of PD,[1] affects quality of life,[2] contributes to caregiver distress,[3] and has been associated with nursing home placement.[4] The development of dementia also has been associated with reduced survival in patients with PD.[5–7] In community-based studies using *Diagnostic and Statistical Manual of Mental Disorders*, revised third edition (DSM-III-R)[8] criteria, dementia is present in approximately 20 to 40% of PD patients.[9–13] Incidence rates of dementia in PD, estimated in both hospital-based and community-based studies using DSM-III-R criteria, range from 42.6 to 112.5 per 1,000 person-years of observation.[12,14–18]

Age and severity of extrapyramidal signs (EPSs) have been consistently associated with incident dementia in PD in longitudinal studies.[12,15,17–21] Mayeux and colleages[14] showed that age-specific incidence rates for dementia in a clinic-based sample of PD increased with age; the cumulative incidence of dementia reached 65% by age 85 years. In a population-based sample, the same investigators found that the age-specific prevalence of dementia in PD ranged from 12.4% in the group 50 to 59 years old to 68.7% in the group older than 80 years old.[10] The pathological basis of dementia in PD has not been clearly established. Although some studies suggest that the presence of concomitant Alzheimer's disease (AD) cortical changes is causally related to dementia in PD,[22–24] the correlation of severity of EPSs with intellectual deficits has been seen as evidence in favor of the contribution of the subcortical pathology characteristic of PD to the development of dementia.[25–27]

No previous longitudinal study has investigated the combined effect of age and severity of EPSs on the risk of incident dementia in PD. Basing their statement on cross-sectional studies of the influence of age at onset of PD on neuropsychological performance,[28–30] Dubois and colleages[29] suggested that the cognitive

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disorder in the late-onset group might be related to "a potentiation between the effect of aging and the effect of PD-specific brain lesions." We hypothesized that the increased risk of dementia in PD associated with older age and increased severity of EPSs was primarily related to their combined effects. To test this hypothesis, we evaluated the separate and combined effects of age and severity of EPSs on the risk of incident dementia in PD by using a prospective cohort design. We also evaluated the effect of age and severity of EPSs on the relative risk (RR) of incident dementia in PD compared with the risk of dementia in a normal aging population from the same community.

Patients and Methods

Patients and Procedures

A cohort of nondemented PD patients from the Washington Heights–Inwood community in northern Manhattan in New York City was followed up annually with neurological and neuropsychological evaluations. The ascertainment procedure and inclusion and exclusion criteria for the cohort have been described previously.[10] Patients were ascertained through the development of a registry in the community for all individuals considered to have PD living within four zip codes in Washington Heights–Inwood. This registry included, but was not limited to, all patients living in the community who received their care at the Columbia Presbyterian Medical Center. Patients were identified from many sources, including admission and discharge lists from the hospital, lists from various ambulatory care sites, and practitioners both in the hospital and in the community.

Idiopathic PD was defined by established research criteria.[31–33] Patients with postencephalitic and drug-induced parkinsonism or a Parkinson-plus syndrome were excluded, as were patients who developed memory loss or dementia before the motor manifestations of PD. In this study of incident dementia in PD, of 319 patients with idiopathic PD, 105 considered to be demented at baseline evaluation were excluded. Of 214 nondemented PD patients, 30 had no follow-up visit, and 4 with signs or symptoms of stroke at baseline were excluded, leaving 180 patients for this analysis.

The annual clinical evaluation included the Unified Parkinson's Disease Rating Scale (UPDRS).[34] The duration of PD was defined as the time period between the first symptom of PD as reported by the patient/informant and the baseline evaluation. The neuropsychological battery consisted of tests of verbal and nonverbal memory, orientation, visuospatial ability, language, and abstract reasoning, and neuropsychological test scores were evaluated with a fixed paradigm.[35] Dementia was diagnosed according to the DSM-III-R criteria, which require memory impairment and impairment of abstract thinking, impaired judgment, disturbances of higher cortical function, or personality change, of sufficient severity to interfere with social or occupational functioning.[8]

For the second analysis, which was designed to calculate RRs of dementia in PD compared with a normal aging population, we selected a random sample of 180 controls participating in a longitudinal study of aging and dementia in the same community.[36] This control sample was frequency-matched to the PD patients by age at baseline, gender, education, and ethnicity as closely as possible. The annual neuropsychological evaluation and the criteria for the diagnosis of dementia for the controls were the same as for the PD patients.[35]

Data Analysis

Age and total UPDRS motor score at baseline evaluation were dichotomized at the median. We defined four PD groups based on these two dichotomous variables: younger age/low severity, younger age/high severity, older age/low severity, and older age/high severity. The group with younger age/low severity was used as the reference against which the risk ratios for incident dementia of the other three groups were calculated.

Each item of the motor examination (part III) of the UPDRS was rated from 0 (no impairment) to 4 (severe impairment).[34] The total UPDRS motor score (range, 0–100) was calculated by the summing of 25 items of the UPDRS (part III). In a previous analysis of the association of motor impairment with incident dementia in PD,[37] we divided the total UPDRS motor score into two subscores because of the clinical evidence that some motor signs (speech, gait, posture, and balance impairment) are relatively refractory to L-dopa therapy, especially in middle and late stages of the disease, whereas others (tremor, rigidity, and bradykinesia) are not.[38–41] Subscore A, representing predominantly dopaminergic deficiency, includes facial expression, tremor at rest, action or postural tremor, rigidity, body bradykinesia and hypokinesia, hand movement, rapid alternating movements of hands, and leg agility (range, 0–80). Subscore B, representing predominantly nondopaminergic deficiency, includes speech, rising from a chair, posture, gait, and postural stability (range, 0–20). When these two subscores were substituted for the total UPDRS motor score in the analysis, subscore B, but not subscore A, was significantly associated with incident dementia in PD.[37] Therefore, in this study we repeated the analyses using severity of motor impairment according to subscores A and B as the measures of disease severity.

Baseline characteristics of patients were compared with Student t tests and one-way analysis of variance for continuous variables and χ^2 tests for categorical variables. Post hoc pairwise comparisons for overall differences in the one-way analysis of variance were performed with Tukey-Kramer multiple-comparisons test. We used Cox proportional hazards models[42] to calculate risk ratios for incident dementia in PD patients stratified by age and severity of EPSs (reference group: younger age/low severity). The duration of follow-up from the baseline until the diagnosis of dementia (or until the last visit for those patients who did not become demented) was used as the timing variable in the Cox models. These analyses were adjusted for gender, education, ethnicity, and duration of PD. When the risk ratios were estimated for incident dementia in PD patients compared with controls, the age at time of development of dementia (or at the last visit for those patients and controls who did not become demented) was used as the timing variable in the Cox models, with adjustments made for gender, education, and eth-

nicity. The proportional hazards assumption of the Cox models was checked by an examination of the martingale residuals.[43]

Results

Of 180 PD patients, 52 (28.9%) became demented during a mean follow-up period of 3.6 ± 2.2 years (median, 3.1; range, 0.5–8.2 years), whereas of 180 controls, 19 (10.6%) became demented during a mean follow-up period of 3.9 ± 2.0 years (median, 3.5; range, 1.0–9.5 years). Baseline demographic and clinical characteristics of PD patients and controls are shown in Table 1. PD patients were not significantly different from controls in terms of education, gender, ethnicity, and primary language. However, age at baseline was slightly but significantly higher in controls (73.8 ± 6.3 vs 71.0 ± 10.3 years, $p = 0.002$). PD patients with incident dementia were significantly older and had fewer years of education than PD patients without incident dementia. At baseline, the total UPDRS motor score and subscores A and B were significantly higher in PD patients with incident dementia than in PD patients without incident dementia.

The median age at baseline of the PD patients was 71.8 years (range, 38.5–95.9 years), and the median total UPDRS motor score was 24 (range, 2–65). We created, using these median values, dichotomous variables for younger and older ages (<72 and ≥72 years) and low and high severities of EPSs (≤24 and >24). The demographic and clinical characteristics of the four groups defined by these two dichotomous variables are shown in Table 2. There were statistically significant differences among the four groups in education, ethnicity, primary language, duration of PD, and estrogen replacement therapy. No statistically significant differences were observed for gender, medication use, depressive symptoms, having at least one apolipoprotein E-ε4 allele, ever or currently smoking, or stroke signs or symptoms during follow-up. Approximately 60% of the older age/high severity group and 15 to 25% of the other three groups developed dementia during follow-up.

The risk ratios (95% confidence intervals [CIs]) for incident dementia in PD patients stratified by age and severity of EPSs are shown in Table 3. The group with older age/high severity had a significantly increased risk of incident dementia (RR, 9.7; 95% CI, 3.9–24.4) compared with the group with younger age/low severity (reference). The groups with older age/low severity (RR, 1.6; 95% CI, 0.5–4.8) and younger age/high severity (RR, 1.2; 95% CI, 0.5–3.2) did not have a significantly increased risk of incident dementia compared with the reference. When we repeated this analysis in females, adjusting for estrogen replacement therapy, in

Table 1. Baseline Demographic and Clinical Characteristics of PD Patients and Controls

	PD			
Variable	Incident Dementia (n = 52)	No Incident Dementia (n = 128)	Total (n = 180)	Control (n = 180)
Age (yr)	74.6 (8.2)	69.5 (10.7)[a]	71.0 (10.3)	73.8 (6.3)[b]
Education (yr)	9.4 (4.6)	11.8 (4.7)[a]	11.1 (4.8)	10.2 (4.9)
Gender (% male)	55.8	42.2	46.1	43.9
Ethnicity (%)				
White non-Hispanic	55.8	55.5	55.6	53.3
Black non-Hispanic	7.7	9.4	8.9	10.6
Hispanic	36.5	35.2	35.6	36.1
Primary language (% English)	52.9	65.4	61.8	64.2
Age at onset of PD (yr)	67.3 (10.3)	63.6 (12.8)	64.7 (12.2)	NA
Duration of PD (yr)	7.3 (5.8)	5.9 (7.2)	6.3 (6.9)	NA
Total UPDRS motor score (range, 0–100)	32.0 (13.6)	22.2 (11.4)[a]	25.0 (12.8)	NA
Subscore A (range, 0–80)	23.4 (11.7)	17.1 (9.2)[a]	18.9 (10.4)	NA
Subscore B (range, 0–20)	8.6 (3.2)	5.1 (3.5)[a]	6.1 (3.7)	NA
Use of L-dopa (%)	71.2	73.4	72.8	NA
Use of dopaminergic agonists (%)	34.0	25.8	28.1	NA
Use of anticholinergics (%)	17.6	15.2	15.9	NA
Use of selegiline (%)	5.8	11.7	10.0	NA
L-dopa dosage (mg/day)	326.7 (325.3)	364.2 (373.6)	354.1 (360.6)	NA

Values are given as mean (standard deviation) or percentage. Total: 178 for language, 177 for total UPDRS motor score and subscores A and B, 178 for use of dopaminergic agonists, 176 for use of anticholinergics, and 159 for L-dopa dosage.

[a] $p < 0.05$, PD patients with incident dementia vs PD patients without incident dementia; [b] $p < 0.05$, PD patients vs controls.

NA = not applicable; PD = Parkinson's disease; UPDRS = Unified Parkinson's Disease Rating Scale.

Table 2. Demographic and Clinical Characteristics of 4 Groups of Parkinson's Disease Patients (Total 177) Stratified by Age and Severity of Extrapyramidal Signs as Measured by the Total Unified Parkinson's Disease Rating Scale Motor Score at Baseline Evaluation

Variable	Age/Severity of EPS's			
	Younger/Low (n = 47)	Younger/High (n = 43)	Older/Low (n = 43)	Older/High (n = 44)
Age[a] (yr)	62.2 (8.5)[b]	63.7 (5.9)[b]	78.9 (5.4)	79.3 (4.7)
Education (yr)[a]	12.6 (4.4)[b]	9.7 (5.1)	12.5 (4.0)[b]	9.7 (4.7)
Gender (% male)	53.2	55.8	30.2	45.5
Ethnicity (%)[a]				
White non-Hispanic	57.4	25.6	81.4	56.8
Black non-Hispanic	8.5	7.0	7.0	11.4
Hispanic	34.0	67.4	11.6	31.8
Primary language (% English)[a]	71.7	32.6	73.8	65.9
Age at onset of PD[a] (yr)	56.9 (9.6)[b]	56.7 (8.7)[b]	75.1 (6.5)	70.2 (11.4)
Duration of PD (yr)*	5.3 (4.4)[b]	6.9 (6.7)	3.9 (3.2)[b]	9.1 (10.2)
Total UPDRS motor score (range, 0–100)[a]	14.6 (6.5)[b]	34.7 (9.6)	16.1 (5.9)[b]	35.4 (9.9)
Use of L-dopa (%)	80.9	76.7	58.1	72.7
Use of dopaminergic agonists (%)	31.9	32.6	20.9	26.2
Use of anticholinergics (%)	19.6	23.8	14.0	7.1
Use of selegiline (%)	17.0	2.3	11.6	9.1
L-dopa dosage (mg/day)	420.6 (340.8)	428.5 (455.6)	212.8 (258.4)	321.6 (326.5)
Total 17-item HDRS score (range, 0–53)	5.7 (5.0)	5.9 (4.7)	6.0 (5.3)	6.7 (5.8)
Estrogen replacement therapy (%)[a]	30.4	22.2	6.7	4.0
At least one APOE-ε4 allele (%)	23.1	19.4	32.0	21.9
Ever smoking (%)	46.8	41.9	36.6	51.2
Current smoking (%)	4.3	4.7	7.3	4.7
Stroke signs or symptoms during follow-up (%)	10.6	16.3	9.3	13.6
Incident dementia (%)[a]	14.9	23.3	18.6	59.1

Values are given as mean (standard deviation) or percentage. Total: 175 for language, 175 for dopaminergic agonists, 173 for use of anticholinergics, 157 for L-dopa dosage, 151 for total HDRS score, 96 for estrogen replacement therapy, 132 for apolipoprotein E genotype, and 174 for ever and current smoking.

[a]Overall statistically significant ($p < 0.05$) difference among the four groups (χ^2 test for categorical variables and one-way analysis of variance for continuous variables); [b]pairwise statistically significant difference (Tukey-Kramer multiple-comparisons test; $p < 0.05$) compared with the group with older age/high severity.

EPS = extrapyramidal sign; HDRS = Hamilton Depression Rating Scale; PD = Parkinson's disease; UPDRS = Unified Parkinson's Disease Rating Scale.

Table 3. Risk Ratios for Incident Dementia in Parkinson's Disease Patients Stratified by Age and Severity of Extrapyramidal Signs[a]

Age/Severity of EPSs	Total UPDRS Motor Score (95% CI)	Subscore A (95% CI)	Subscore B (95% CI)
Younger/low (reference)	1	1	1
Younger/high	1.2 (0.5–3.2)	1.0 (0.4–2.7)	3.7 (1.3–10.3)
Older/low	1.6 (0.5–4.8)	1.4 (0.5–4.3)	2.1 (0.6–8.0)
Older/high	9.7 (3.9–24.4)	9.3 (3.7–23.4)	16.1 (6.0–43.0)

[a]Cox proportional hazards model with duration of follow-up until dementia as the timing variable, adjusting for gender, education, ethnicity, and disease duration.

CI = confidence interval; EPS = extrapyramidal sign; PD = Parkinson's disease; UPDRS = Unified Parkinson's Disease Rating Scale.

addition to education, ethnicity, and disease duration, results were similar.

The median subscore A was 18 (range, 0–53), and the median subscore B was 6 (range, 0–18). Based on these median values, two dichotomous variables for low and high severities of EPSs according to subscore A (≤18 and >18) and subscore B (≤6 and >6) were created. When subscore A was used as the measure of disease severity, only the group with older age/high severity had a significantly increased risk of incident dementia (RR, 9.3; 95% CI, 3.7–23.4) compared with the group with younger age/low severity. In the analysis using subscore B as the measure of disease severity, both the groups with younger age/high severity (RR, 3.7; 95% CI, 1.3–10.3) and older age/high severity (RR, 16.1; 95% CI, 6.0–43.0) had a significantly increased risk of incident dementia compared with the group with younger age/low severity (see Table 3).

Table 4. Incidence Rates of Dementia for Controls and Parkinson's Disease Patients and Risk Ratios for Incident Dementia in Parkinson's Disease as Compared with Controls

	Incidence Rate of Dementia (per 1,000 Person-Years) (95% CI)	Risk Ratio (95% CI)[a]
Total (n = 360)		
Control (n=180)	27.0 (15.0–39.0)	1 (reference)
PD (n = 180)	79.9 (59.1–100.7)	3.7 (2.1–6.3)
Age at baseline (yr)		
<72 (n = 183)		
Control (n = 93)	16.8 (4.5–29.2)	1 (reference)
PD (n = 90)	44.3 (23.7–64.9)	5.6 (2.3–13.6)
≥72 (n = 177)		
Control (n = 87)	41.8 (18.7–65.0)	1 (reference)
PD (n = 90)	130.9 (90.4–171.3)	3.5 (1.7–6.9)
Gender		
F (n = 198)		
Control (n = 101)	29.5 (13.0–45.9)	1 (reference)
PD (n = 97)	65.7 (39.7–91.6)	2.5 (1.2–5.3)
M (n = 162)		
Control (n = 79)	23.7 (6.3–41.0)	1 (reference)
PD (n = 83)	96.4 (63.1–129.8)	5.5 (2.4–12.7)

[a]Cox proportional hazards model with age at dementia as the timing variable; analyses for the total PD patients and controls and stratified by age at baseline performed adjusting for gender, education, and ethnicity; analyses stratified by gender performed adjusting for education and ethnicity.

CI = confidence interval; PD = Parkinson's disease.

Risk ratios (95% CI) for incident dementia in PD compared with controls, as well as estimates of the incidence rates (95% CI) of dementia in PD patients and controls per 1,000 person-years of observation, are shown in Table 4. The risk ratio for incident dementia in the PD cohort compared with controls was 3.7 (95% CI, 2.1–6.3), with adjustments made for gender, education, and ethnicity (Fig, A). When we performed this analysis stratifying by age at baseline (<72 and ≥72 years), the RR of incident dementia in PD compared with controls was higher for the younger group (RR, 5.6; 95% CI, 2.3–13.6) than for the older group (RR, 3.5; 95% CI, 1.7–6.9). In the analysis stratified by gender, males (RR, 5.5; 95% CI, 2.4–12.7) had a higher RR of incident dementia in PD compared with controls than females (RR, 2.5; 95% CI, 1.2–5.3).

Table 5 shows the risk ratios (95% CI) for incident dementia in PD compared with controls according to severity of EPSs. The group with high EPS severity had a higher risk of incident dementia than the group with low EPS severity, but both groups had a significantly increased risk compared with controls (see Fig, B). We also repeated these analyses stratifying by gender. Males with low EPS severity and females with high EPS severity had a threefold significantly increased risk, whereas males with high EPS severity had a sevenfold significantly increased risk of incident dementia in PD compared with controls (see Table 5).

Discussion

Combined Effect of Age and Extrapyramidal Sign Severity on the Risk of Dementia in Parkinson's Disease

The main aim of this study was to evaluate the separate and combined effects of age and severity of EPSs on the risk of incident dementia in PD. Compared with PD patients with younger age/low severity of EPSs, only the group with older age/high severity had a sig-

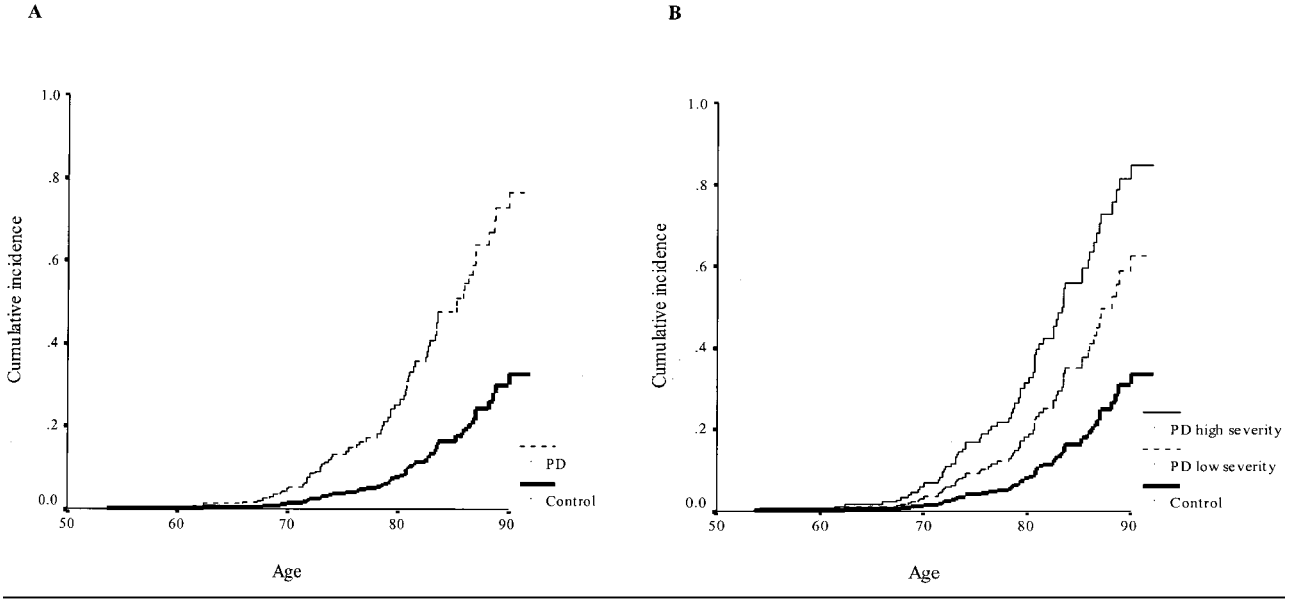

Fig. Cox proportional hazards model plots of the cumulative incidence of dementia in (A) Parkinson's disease (PD) patients and controls and (B) PD patients with high and low severity of extrapyramidal signs, as measured by the total Unified Parkinson's Disease Rating Scale motor score, and controls.

Table 5. Risk Ratios for Incident Dementia in PD as Compared with Controls According to Severity of EPSs as Measured by the Total UPDRS Motor Score, for the Total PD Patients and Controls and Stratified by Gender[a]

	Total (n = 357) (95% CI)	F (n = 196) (95% CI)	M (n = 161) (95% CI)
Control (reference)	1	1	1
PD low severity	2.4 (1.2–4.9)	1.9 (0.7–5.0)	3.0 (1.0–8.7)
PD high severity	4.6 (2.6–8.1)	3.0 (1.3–6.8)	7.2 (3.1–17.2)

[a]Cox proportional hazards model with age at dementia as the timing variable; analyses for the total PD patients and controls performed adjusting for gender, education, and ethnicity; analyses stratified by gender performed adjusting for education and ethnicity.

CI = confidence interval; EPS = extrapyramidal sign; PD = Parkinson's disease; UPDRS = Unified Parkinson's Disease Rating Scale.

nificantly increased risk of incident dementia in PD. This finding suggests that the increase in risk of incident dementia in PD associated with age and severity of EPSs is related primarily to their combined effects.

The combined effect of age and severity of EPSs on the risk of dementia in PD has possible implications for the understanding of the biological substrate of dementia in PD. Our findings suggest that dementia in PD may be caused by a PD and age-related pathological process, rather than concomitant AD. In principle, superimposed AD might account for the increased risk of dementia in PD compared with a normal aging population because a shared genetic susceptibility to both PD and AD would increase the risk of dementia in PD patients because of concomitant AD. In fact, we previously reported a threefold increased risk of AD in siblings of demented PD patients compared with siblings of controls, supporting this possibility.[44] The present data cannot address the question of whether there is a shared susceptibility to PD and AD. However, the finding that the older age/high severity group, but not the older age/low severity group, is at a significantly increased risk of dementia compared with the younger age/low severity group supports a role of the pathological process intrinsic to PD in the development of dementia. This is consistent with recent neuropathological studies using α-synuclein immunostaining that found a stronger association of the presence of Lewy bodies in cortical areas than AD cortical changes with dementia in PD.[45–47]

It has been proposed that PD patients with older age at onset have increased motor disability because of more widespread subcortical involvement including nondopaminergic structures.[48–50] In a previous study, we suggested that gait and postural impairment (subscore B), especially late in the disease course, resulted from a combined effect of the disease and aging process in nondopaminergic brainstem structures (ie, locus ceruleus and pedunculopontine nucleus).[37] In this study, using subscore A as the measure of disease severity, we found that only the group with older age/high severity had a significantly increased risk of dementia. In the analysis using subscore B as the measure of disease severity, both the group with younger age/high severity and the group with older age/high severity had a significantly increased risk of dementia (see Table 3). This is consistent with the previous finding that subscore B, representing predominantly nondopaminergic deficiency, is more closely related to dementia in PD.[37] It also suggests that subscore A may represent a more specific measure of the disease process.

Incidence of Dementia in Parkinson's Disease Compared with Controls

The risk ratio for incident dementia in PD compared with controls was 3.7 (95% CI, 2.1–6.3). In previous studies, estimates of the RR of incident dementia in PD compared with controls have ranged from 1.7-fold to 5.9-fold.[12,18,51,52] In a previous analysis of a 2-year follow-up of 140 patients,[12] we reported a lower risk ratio of incident dementia in PD compared with controls (RR, 1.7; 95% CI, 1.1–2.7) than in this study because of a higher incidence rate of dementia in the control group than in this study. A total of 27 PD patients became demented during the 2-year period, resulting in an incidence rate of 112.5 per 1,000 person years, whereas 87 of 572 controls became demented during the same period (approximately 80/1,000 person years). However, in a recent study in the same community over a 7-year period,[53] the incidence rate of AD in the elderly (30/1,000 person years) was close to that observed in the control sample in this study.

Breteler and colleagues[52] evaluated the risk of developing dementia in PD patients aged 50 to 75 years compared with a control group in a study based on Dutch nationwide morbidity registers. Because the age-specific risk differences or attributive risks (excess absolute risk with respect to the reference group) were constant in 5-year age groups, these authors suggested that the increase in the incidence of dementia in PD with age was due to the increasing background risk of dementia. In our study, the risk differences did increase with increasing age, as can be estimated from the differences in the incidence rates of dementia in PD and controls stratified by age at baseline (see Table 4) and from the curves of cumulative incidence of dementia in PD and controls (see Fig, A). The differences in the

age distributions between studies may have influenced the findings; the 75-year upper limit of age at entry in the cohort in the study by Breteler and colleagues contrasted with the median age at baseline of 71.8 years (range, 38.5–95.9 years) in our PD cohort. Increases in the risk difference of dementia in PD compared with controls with age may be observed only in cohorts including patients older than 75 years.

The risk ratio for incident dementia in PD compared with controls was higher for males than females (see Tables 4 and 5). Many studies have reported a higher frequency of dementia in PD in males,[17,52,54–56] but this association has not been demonstrated in other studies.[10,18,20,57] To our knowledge, no study has reported a higher frequency of dementia in females with PD.

Methodological Considerations

There are some methodological limitations to this study. The median age at baseline of our PD cohort was 71.8 years, and the group with older age included patients aged 72 years and older. Our results to a great extent may depend on the overall old age of patients in this cohort and may not be applicable to a younger cohort of PD patients. Although age at baseline evaluation rather than age at onset of PD was used in our analysis, the analysis adjusted for the duration of PD from onset to baseline evaluation. Moreover, these two age variables were highly correlated ($r = 0.83$, $p < 0.001$), and results were similar when the analysis was repeated after the groups with younger and older ages were defined by the median age at onset of PD (65.7 years; range, 25.8–87.5 years). Most patients were taking L-dopa (72.8%), 28.1% were taking a dopaminergic agonist, and 15.9% were taking anticholinergics when evaluated. However, there were no statistically significant differences in the use of medications, or L-dopa dosage, among the four groups of PD patients (see Table 2), and we did not observe a relationship between medication regimen at baseline (eg, L-dopa alone vs L-dopa plus dopaminergic agonist and/or anticholinergics) and the development of dementia (data not shown).

In the analysis of the incidence of dementia in PD patients compared with a normal aging population, the control group was not completely comparable because it was selected from an aging study including patients 60 years and older, whereas 15% of our PD cohort were younger than 60 years at baseline. However, this control group was representative of the risk of dementia in the population of patients because controls were drawn from the same community, were submitted to similar annual clinical and neuropsychological evaluations, were diagnosed as demented according to the same criteria, and were closely matched to our PD cohort in gender, education, and ethnicity.

In summary, PD patients were three to four times as likely as controls to develop dementia in this study, and the risk was highest for men with severe EPSs. Our findings suggest that the association of age and EPS severity with incident dementia in PD consistently demonstrated in previous studies is related primarily to their combined effect rather than separate effects.

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