

Prevalence and Characteristics of Dementia in Parkinson Disease

An 8-Year Prospective Study

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Background: Few longitudinal studies of dementia in Parkinson disease (PD) have been reported, and the proportion of patients with PD who eventually develop dementia is unknown.

Objective: To examine the 8-year prevalence, characteristics, and risk factors of dementia in patients with PD.

Methods: Patients were recruited from an epidemiological study of PD in the county of Rogaland, Norway, using explicit criteria for PD. Subjects with cognitive impairment at disease onset were excluded. A semistructured caregiver-based interview, cognitive rating scales, and neuropsychological tests were used to diagnose dementia according to criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* at baseline and 4 and 8 years later. A population-based sample of 3295 subjects in the municipality of Odense, Denmark, was used as a comparison group and examined at baseline and after 2 and 5 years.

Results: We included 224 patients with PD (116 women). At baseline, 51 patients (26%) had dementia. Fifty-five patients died, and 10 refused follow-up without their dementia status known. Forty-three and 28 new cases of dementia were identified at the 4- and 8-year evaluations, respectively. The 4-year prevalence of dementia in PD was nearly 3 times higher than in the non-PD group. The 8-year prevalence in PD was 78.2% (95% confidence interval [CI], 71.1-84.0). Risk factors for dementia were hallucinations before baseline (odds ratio [OR]=3.1; 95% CI, 1.6-6.2) and akinetic-dominant or mixed tremor/akinetic PD (OR=3.3; 95% CI, 1.2-8.5).

Conclusions: More than three quarters of this representative PD cohort developed dementia during the 8-year study period. Early hallucinations and akinetic-dominant PD were associated with an increased risk of dementia.

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PREVALENCE STUDIES of dementia in PD have focused on point prevalence, and wide variations have been reported.¹⁻⁴ Because survival time is shorter in patients who have PD with dementia compared with those without dementia,⁵ and development of dementia is associated with longer disease duration,² longitudinal studies are needed to explore the frequency of dementia in PD.

Although longitudinal studies of dementia in PD are few and have usually reported an incidence of new cases,⁶⁻¹⁰ little is known regarding the proportion of patients with PD who will eventually develop dementia. Recently, the cumulative proportion of patients who developed dementia after a mean observation period of 5.5 years was found to be 0.38.⁶ However, because the patients were referrals to a neurological clinic at a teaching

hospital, were markedly younger (mean age, 57 years), and had a shorter duration of disease (4.0 years) compared with other population-based PD samples,¹¹ that cohort may not be fully representative of the PD population in general.

Information about which patients will eventually develop dementia may be useful for the patient, caregiver, and physician to plan future treatment.^{12,13} Although prospective studies of the period prevalence of dementia in PD exist, no studies have implemented methodological requirements such as a representative patient sample, adequate observation time, and modern criteria for dementia. Therefore, we performed a prospective study of the 8-year prevalence of dementia in PD using standard criteria for the diagnosis of PD and dementia in a community-based cohort and compared our findings with those in a non-PD population. We also ex-

plored risk factors for developing dementia and characteristics of the patients with PD who developed dementia at the time of diagnosis.

METHODS

ASCERTAINMENT OF PATIENTS WITH PD

Total ascertainment of patients with recognized idiopathic PD in 9 municipalities with 220 000 inhabitants in the southern part of Rogaland County, western Norway, was attempted. Details of the case-finding procedure have been published elsewhere¹¹ and are described briefly as follows. Clinical information on all patients with suspected parkinsonism was collected from the general physicians, nursing homes, district nurses, and home health care workers in the study area. After a screening procedure, 400 patients were invited to participate and were interviewed and examined by 1 of the neurologists in the study group. Parkinson disease was diagnosed in 245 subjects, yielding a prevalence rate of 111 per 100 000 inhabitants on January 1, 1993.¹¹ During follow-up, 7 subjects were rediagnosed as not having PD (multiple system atrophy in 3, progressive supranuclear palsy in 1, and other neurodegenerative diseases in 3), leaving 238 patients eligible for our study.

DIAGNOSIS AND MOTOR EVALUATION

All patients were interviewed and examined by a neurologist in an evaluation program consisting of two 1-hour consultations held within 1 month between September 1992 and May 1993. A semistructured interview was administered to both the patient and a caregiver to obtain information on disease history, from disease onset to the baseline evaluation. Patients were classified, based on this history and baseline evaluation, as having an akinetic-dominant, tremor-dominant, or mixed tremor/akinetic clinical subtype and symmetrical or asymmetrical symptom onset and progression. In addition, information regarding drug therapy, response to levodopa, and demographic variables was collected including whether patients had previously experienced hallucinations while taking anti-PD medication. The clinical examination included a general physical examination and laboratory tests. Assessment of motor symptoms was carried out according to the Unified Parkinson's Disease Rating Scale (UPDRS)¹⁴ and the Hoehn and Yahr scale.¹⁵ The diagnostic evaluation was based on clinical information, disease development, and response to levodopa as elicited at the baseline interview and from the hospital record.

To achieve high diagnostic specificity as well as high sensitivity, a clinical classification of definite, probable, and possible PD was used.¹⁶ Definite PD required that a patient had resting tremor and at least 2 more cardinal signs: akinesia, rigidity, or postural abnormalities. The disease has a unilateral onset and asymmetrical development, and the response to a dopaminergic agent is good to excellent. For a diagnosis of probable PD, the patient must have fulfilled at least 2 of the 4 clinical criteria. Resting tremor was not mandatory, and a maximum of 1 of the following atypical clinical features could be present: (1) mild cognitive impairment or clinically relevant autonomic failure at disease onset; (2) symmetrical disease development; or (3) a moderate response to a dopaminergic agent. For a diagnosis of possible PD, the patient must have had at least 2 of the 4 cardinal signs. The response to a dopaminergic agent must have been at least moderate. Mild to moderate cognitive impairment and autonomic failure at disease onset were allowed. Patients with other neurological diagnoses or the presence of radiologic structural brain abnormalities compatible with

a diagnosis other than PD were excluded. During a follow-up evaluation 4 years later, a diagnostic reevaluation was performed. To avoid the inclusion of patients with other diagnoses such as dementia with Lewy bodies (DLB),¹⁷ only those who fulfilled the diagnostic criteria for PD at all examinations and were without cognitive impairment at disease onset were included.

DIAGNOSIS OF DEMENTIA AND NEUROPSYCHIATRIC EVALUATION AT BASELINE

The diagnosis of dementia at baseline was made by the same neurologist based on an interview with the patient and a caregiver using the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*¹⁸ (DSM-III-R) as a guide, as well as the administration of 3 cognitive rating scales: the Mini-Mental State Examination (MMSE),¹⁹ the mentation item from the mental subscale of the UPDRS, and the Gottfries-Bråne-Steen scale.²⁰ The latter rates the severity of 4 dementia domains (cognition, activities of daily living, emotional symptoms, and other behavioral symptoms) based on observation of the patient and interview of the caregiver. To qualify for a diagnosis of dementia, the patient had to meet the DSM-III-R criteria for dementia at the interview and at least 1 of the following 3 criteria: (1) MMSE score lower than for the corresponding quartile based on age and education²¹; (2) a score of 2 or higher on at least 3 items on the Gottfries-Bråne-Steen scale other than the items "wakefulness" and "ability to concentrate"; and (3) a score of 2 or higher on the UPDRS intellectual impairment item. Presence and severity of hallucinations during the last 2 weeks before the baseline evaluation were assessed using the thought disorder item of the UPDRS, and severity of depression during the last week was rated using the Montgomery-Åsberg Depression Rating Scale.²²

FOLLOW-UP EVALUATION OF PATIENTS WITH PD

Survivors were invited by letter to participate in the follow-up evaluations 4 and 8 years after baseline. The final evaluation was conducted from November 2000 to April 2001. The follow-up evaluations included the neurological and neuropsychiatric evaluation performed at baseline, with 1 change: the Dementia Rating Scale (DRS)²³ was administered instead of the Gottfries-Bråne-Steen scale. In addition, patients with an MMSE score of 16 or higher underwent a neuropsychological battery assessing executive functioning, visual memory, and visuospatial functioning. A group of healthy elderly controls with a similar age and sex distribution as the patients with PD performed the cognitive test battery to obtain normative data. Independent raters who were blind to the diagnostic and motor evaluations performed the neuropsychiatric and neuropsychological assessments.

The diagnosis of dementia was made by 2 of us (D.A. and J.P.L.) based on the clinical interview, the cognitive screening, and the neuropsychological tests. To qualify for this diagnosis, the results of the interview, rating scales, and neuropsychological tests had to be compatible with a diagnosis of dementia. Population-based, age- and education-corrected normative data for the MMSE²¹ and DRS²⁴ were used, and scores lower than the lowest quartile (MMSE) or lower than the 19th percentile (DRS) were considered to indicate cognitive impairment. For the neuropsychological tests, a score 2 SDs or more lower than the mean of the control group was considered to indicate impairment. In cases of inconsistencies between these measures, all of the available material was reviewed, and both raters made an independent diagnosis of dementia or no dementia according to DSM-III-R criteria. In cases of disagreement, a consensus diagnosis was made. If a

definite diagnosis of dementia or no dementia could not be made after this procedure, patients were classified as having possible dementia and were included in the no-dementia group. The data for this cohort in 1993 and 1997 have previously been reported.^{2,9}

ASCERTAINMENT AND EVALUATION OF CONTROL SUBJECTS

To calculate the relative risk of developing dementia in patients who have PD compared with subjects without PD, we used a population-based study of dementia based on a randomly drawn sample of 5237 subjects aged 65 to 84 years in the municipality of Odense, Denmark.²⁵ A total of 3346 subjects participated in the baseline examination, conducted between February 1992 and March 1994; 3295 did not have PD. The diagnosis of PD was based on self-report during an interview at baseline. Furthermore, the participants underwent a 2-phased diagnostic procedure in which the first phase was a screening for dementia with the cognitive section of the Cambridge Mental Disorders of the Elderly Examination (CAMDEX).²⁶ Subjects with a positive result underwent the second phase, which consisted of the remainder of the CAMDEX and a neuropsychological test battery. The diagnosis of dementia was made by consensus between the participating physicians and a neuropsychologist according to criteria from the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association²⁷ for probable Alzheimer disease and the *DSM-III-R* for vascular dementia and dementia of other types. Participants were reexamined 2 and 5 years later.

STATISTICS

Four- and 8-year prevalence of dementia were calculated by adding the number of cases with dementia at baseline and all new cases divided by the mean population during the middle of the observation period.²⁸ Rates and confidence intervals (CIs) were also calculated. For the patients with PD, demographic and clinical characteristics that occurred before the initial evaluation were first identified as potential risk factors for developing dementia by using bivariate analyses (χ^2 test). Variables associated with dementia at a significance level of $P \leq .10$ were included in a multivariate logistic regression analysis.

RESULTS

Two subjects died between the baseline neurological and mental assessments, 1 patient refused to participate at the mental evaluation, and 11 patients had cognitive impairment at disease onset. Thus, 224 patients with PD were included. Baseline characteristics of patients with PD and control subjects are shown in **Table 1**. A total of 139 patients (mean \pm SD age, 74.3 \pm 8.1 years) were assessed at the 4-year follow-up visit, and 87 (mean \pm SD age, 76.1 \pm 8.4 years) at the 8-year follow-up. Among patients previously diagnosed as not having dementia, 7 (4.0%) and 3 (3.4%) refused to participate, and 36 (20.8%) and 19 (21.8%) had died, at the 4- and 8-year evaluations, respectively. Thus, a total of 65 patients (29%) dropped out without dementia being diagnosed, 55 (85%) of these because of death. A baseline comparison of patients with PD who dropped out of the study without being diagnosed as having dementia and the other patients is shown in **Table 2**.

Table 1. Baseline Characteristics*

	PD Group (n = 224)	Control Group (n = 3295)	P Value
Age, y	73.4 \pm 8.5	73.3 \pm 5.4	.86
Female, %	52	55	.29
Education, y	9.1 \pm 3.0	8.1 \pm 1.7	<.001
Age at onset of PD, y	64.3 \pm 9.8
Duration of disease, y	9.2 \pm 5.9
Hoehn and Yahr scale score	2.8 \pm 1.1
Montgomery-Åsberg Depression Rating Scale Score	7.9 \pm 6.3

Abbreviations: Ellipses, not applicable; PD, Parkinson disease.

*Data are expressed as mean \pm SD unless otherwise indicated. Groups were compared using the *t* test or χ^2 test.

Fifty-one patients with PD (26%) were diagnosed as having dementia at baseline. In this group, the mean \pm SD duration of PD at baseline was 11.5 \pm 7.3 years. Forty-three and 28 new cases of dementia were diagnosed at the 4- and 8-year evaluations, respectively. Thus, a total of 122 patients with dementia were identified. In no cases were patients with dementia later diagnosed as not having dementia. Reversible dementia was not observed. The average population in the middle of the observation period was (224+87)/2; so the 8-year prevalence rate was calculated to be 78.2% (95% CI, 71.1%-84.0%). The 4-year prevalence of dementia was 51.6% (95% CI, 44.4%-58.8%) compared with a 5-year prevalence of 18.5% (17.1%-20.0%) in the non-PD group. At the time they first fulfilled the dementia criteria, the mean \pm SD data for patients with PD were as follows: age, 78.4 \pm 5.7 years; duration of PD, 13.8 \pm 6.3 years; Hoehn and Yahr scale score, 3.8 \pm 0.9; MMSE score, 17.0 \pm 6.2 (n=105); Montgomery-Åsberg Depression Rating Scale score, 10.0 \pm 7.9; and daily levodopa dose, 572 \pm 375 mg.

Characteristics of patients with and without dementia are shown in **Table 3**. Forty-three (35%) of those who developed dementia had experienced hallucinations prior to the baseline evaluation compared with only 14 (14%) of those without ($P < .001$). Among the 199 patients with akinetic-dominant or a mixed tremor/akinetic pattern of PD, 115 (58%) developed dementia compared with 7 (28%) of 25 with tremor-dominant PD ($P = .005$). Seventeen (74%) of 23 patients with symmetrical PD developed dementia compared with 105 (53%) of 200 patients in whom PD symptoms were most severe on the left or right side ($P = .05$). Variables associated with dementia at the level of $P \leq .10$ were included in a logistic regression analysis using conditional forward stepping. Significant predictors of dementia were hallucinations before baseline (odds ratio [OR] = 3.1; 95% CI, 1.6-6.2) and mixed tremor/akinetic PD (OR = 3.3; 95% CI, 1.2-8.5), whereas symmetrical PD did not reach the statistical criterion of significance.

COMMENT

We found that 78% of a population-based and representative cohort of patients with PD developed dementia dur-

Table 2. Baseline Comparisons of Patients With PD Who Dropped Out of the Study Without Being Diagnosed as Having Dementia and the Remaining Patients*

	Completers (n = 159)	Noncompleters (n = 65)	t/ χ^2 Value	P Value
Female, %	56	43	3.1†	.08
Age, y	72.9 ± 9.1	74.8 ± 6.7	1.6	.11
Education, y	8.9 ± 2.8	9.7 ± 3.3	1.8	.07
Age at onset of PD, y	63.3 ± 10.2	66.8 ± 8.5	2.5	.01
Duration of disease, y	9.7 ± 6.0	7.8 ± 5.3	2.2	.03
Hoehn and Yahr scale score	2.9 ± 1.1	2.7 ± 0.8	1.4	.17
MMSE score	24.0 ± 6.9	27.6 ± 2.0	4.1	<.001

Abbreviations: MMSE, Mini-Mental State Examination; PD, Parkinson disease.

*Data are expressed as mean ± SD unless otherwise indicated. Groups were compared using the *t* test or χ^2 test.

†For this comparison the χ^2 test was used; all other values were compared using the *t* test.

Table 3. Characteristics of Patients With PD Who Did and Did Not Develop Dementia

	Dementia, No. (%) (n = 122)	No Dementia, No. (%) (n = 102)	χ^2 Value	P Value
Sex			0.8	.40
M	55 (51)	52 (49)		
F	67 (57)	50 (43)		
Age at onset, y			0.3	.60
≤65 (n = 112)	59 (53)	53 (47)		
>65 (n = 112)	63 (56)	49 (44)		
Education, y (n = 209)			2.5	.12
>8 (n = 88)	42 (48)	46 (52)		
≤8 (n = 121)	71 (59)	50 (41)		
Subdiagnosis			0.14	.90
Definite PD (n = 131)	70 (53)	61 (47)		
Probable PD (n = 68)	38 (56)	30 (44)		
Possible PD (n = 25)	14 (56)	11 (44)		
Side			4.1	.05
Symmetrical (n = 23)	17 (74)	6 (26)		
Asymmetrical (n = 200)	105 (53)	95 (47)		
Type			8.6	.01
Tremor-dominant (n = 25)	7 (28)	18 (72)		
Akinetic-dominant (n = 42)	22 (52)	20 (48)		
Hallucinations before baseline			13.3	<.001
Yes (n = 57)	43 (75)	14 (25)		
No (n = 164)	78 (48)	86 (52)		

Abbreviation: PD, Parkinson disease.

ing the 8-year study period. The 4-year prevalence was nearly 3 times higher in the PD compared with the non-PD group. Patients with akinetic-dominant PD and hallucinations prior to the baseline evaluation were at higher risk of developing dementia than those with tremor-dominant parkinsonism and without hallucinations. Our prevalence finding is consistent with those in previous longitudinal studies,⁸ although considerably lower results have been reported^{6,7,10} in studies using less rigorous methods than our investigation. In terms of caregiver burden,¹² nursing home admission,¹³ hallucinations,²⁹ and mortality,⁵ these findings underline the importance of cognitive impairment in addition to the motor symptoms of the disease.

The major methodological limitation of our study was the extended periods between assessments, and a degree of attrition in this group of elderly subjects was to be expected. Fifty-five patients died, and 10 refused to

participate at follow-up; thus, 65 patients were lost to follow-up without their dementia status known. Dementia may reduce survival in patients with PD,⁵ and patients might have developed dementia between the last evaluation and death, indicating that the prevalence observed is a conservative estimate. Neuropsychological assessment was not used at the baseline evaluation. Patients who had PD with mild dementia might therefore have been misclassified as not having dementia. If these subjects were not assessed at the 4-year evaluation, this would also have led to an underestimation of dementia prevalence.

The baseline population was a cross-sectional PD sample with a mean duration of disease at baseline of nearly 10 years. Therefore, our results may not be applicable to patients with early PD. An optimal design would be to include successive, recently diagnosed PD cases and assess them annually.

The patients with PD and control subjects lived in different countries and were assessed by physicians from different research groups using slightly different diagnostic procedures to identify dementia. However, Denmark and Norway are socially and culturally similar, and urban and rural populations were included in both samples. Dementia was diagnosed according to *DSM-III-R* criteria in both groups. A standardized interview (CAMDEX) was used in the control group, whereas a semi-structured interview based on the *DSM-III-R* criteria was administered to the patients with PD and their caregivers. We have previously found that the accuracy of these 2 diagnostic procedures is comparable.⁹ Minor variations may exist in the Norwegian and North American norms for the MMSE, which might have influenced the findings.

The Danish non-PD group was based on self-report, and whether this might cause an underestimation or an overestimation of the risk of dementia in this group cannot be further examined. However, the non-PD group was less educated than the PD group, and the data were based on a 5-year observation period compared with only 4 years in the PD group, which suggests that the 3-fold higher risk among patients with PD is a minimal difference.

The strengths of the study include the large and representative community-based PD population, standardized diagnostic criteria for the diagnosis of PD and dementia, comprehensive evaluation battery, independent evaluation of motor and mental symptoms, inclusion of a large and representative control group, a long follow-up period, and the low attrition rate due to causes other than death. Most previous studies have used smaller and less representative PD samples^{6,7,10} and a shorter follow-up time.^{7,8} Depression could potentially contribute to cognitive impairment and thus lead to an overestimate of dementia in the PD group. However, because the depression score at the time of dementia was only slightly higher than that of the total population at baseline, and no cases of reversible dementia were observed, it is unlikely that this effect would have influenced the prevalence of dementia in our study.

Clinical and neurobiological overlaps exist between PD and DLB.¹⁷ Patients with cognitive impairment at disease onset were not included in this study so that patients fulfilling DLB criteria were excluded. It is possible that a proportion of patients with dementia at the baseline evaluation developed this condition within the first year after disease onset, thereby fulfilling conventional DLB criteria. However, because these patients had had PD for 11.5 years at the baseline evaluation, we assumed that most of them would develop dementia after several years of motor symptoms and thus would not fulfill clinical DLB criteria. The prevalence of dementia did not differ among patients with definite, probable, and possible PD, indicating that even in patients with a highly specific type of PD, dementia will eventually develop in most cases. Recent studies have found nearly identical clinical symptoms in patients with DLB and PD with dementia.³⁰⁻³³ Clinicopathologic studies suggest that cortical Lewy bodies are associated with dementia in PD³⁴⁻³⁶; therefore, we hypothesize that most patients with PD develop DLB after a de-

cade of pure motor disease. The overlap with DLB is underlined by the finding that akinetic-dominant PD and early hallucinations, features typical of DLB,¹⁷ predicted the subsequent development of dementia. Furthermore, there was a trend toward a higher risk of dementia in patients with symmetrical PD (more common in DLB than PD)³² compared with patients who had right- or left-sided parkinsonism. Prospective clinicopathologic studies with representative populations of patients with DLB and PD are needed to explore the clinical, pathologic, and nosologic relationship between DLB and PD and the causes of dementia in PD.

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