ORIGINAL CONTRIBUTION

A 12-Year Population-Based Study of Psychosis in Parkinson Disease

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Objective: To investigate the prevalence, incidence, risk factors, and concomitants of Parkinson disease (PD)–associated psychosis (PDP) in a population-based prevalent cohort.

Design: Prospective longitudinal cohort study.

Setting: Community-based study in southwestern Norway.

Participants: Two hundred thirty community-based PD patients were followed up prospectively for 12 years. Reassessments were conducted at 4 and 8 years and then annually.

Main Outcome Measures: Severity of PDP was measured by the Unified Parkinson Disease Rating Scale thought disorder (UPDRS-TD) item. Patients with a UPDRS-TD score of 2 or more or those taking antipsychotic drugs owing to psychotic symptoms were categorized at each visit as having PDP. Generalized estimating equations were applied to investigate baseline risk factors for incident PDP and clinical and demographic concomitants of PDP during 12 years.

Results: By study's end, 137 patients (60%) had developed hallucinations or delusions. The incidence rate of PDP was 79.7 per 1000 person-years. Higher age at onset, higher baseline levodopa-equivalent doses, probable rapid eye movement (REM) sleep behavior disorder at baseline, and follow-up time were independent risk factors of incident PDP. Significant concomitant features of patients with PDP during the 12-year study period were low activities of daily living function (UPDRS II), dementia, high levodopa-equivalent dose, and probable REM sleep behavior disorder.

Conclusions: Psychotic symptoms affect most patients with PD, with increased risk in those with higher age at onset, need for high doses of dopaminergic drugs, and probable REM sleep behavior disorder. This risk factor pattern and the observed associations with increased disability and dementia place PDP within a symptom complex signaling a malignant disease course.

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PSYCHOTIC SYMPTOMS SUBSTANTIALLY contribute to the burden of Parkinson disease (PD), as they are associated with increased caregiver distress,[1] risk of hospitalization and nursing home placement,[2,3] and consequently health care costs. Although psychotic symptoms associated with PD (PDP) may be heterogeneous, they are predominated by visual hallucinations with retained insight, which may progress into more complex and severe psychotic symptoms with loss of insight, including delusions.[4,5] Reported prevalence rates of hallucinations vary, most likely because of differences in patient selection and study design, ranging from 16% to 75% in prospective cross-sectional studies.[6] Delusions affect 1% to 35% of subjects with PD.[6] Longitudinal studies of PDP are few and usually relatively short and not population-based.[7-9] The incidence rates as well as risk factors for emergence of PDP in the general PD population remain unclear. We therefore prospectively observed a population-based prevalence cohort of patients with PD for 12 years to explore the long-term course and associated risk factors and concomitant features of PDP.

METHODS

STUDY POPULATION

The Stavanger Parkinson Project is a population-based prevalence study conducted in Rogaland County, Western Norway, in 1993, composed of about 220 000 inhabitants. The study is approved by the Regional Committee for Medical Research Ethics, Western Norway. Details on patient recruitment have been previously published.[10] In brief, approximately 400 subjects were identified through hospital files and information obtained from available sources in the community (general practitioners, nursing homes, district nurses, and pa-

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tient organizations) and evaluated clinically by experienced movement-disorder specialists. Two hundred forty-five of the subjects were diagnosed with PD according to published diagnostic criteria,[11] whereas the remaining individuals were excluded because they were identified as having other parkinsonian syndromes or as not having parkinsonism.[10] Of the 245 PD patients, 239 consented to participation in a baseline examination of various motor and nonmotor features including PDP, as part of a prospective, longitudinal, clinical observation study of PD. To date, a subgroup (n = 27) of the enrolled patients have undergone autopsy. In all of these subjects, the clinical diagnosis of PD was confirmed neuropathologically.

STUDY DESIGN AND EXAMINATION PROGRAM

The cohort was followed up prospectively for 12 years, with reassessments conducted in survivors after 4 and 8 years and thereafter annually. Patients were examined at baseline and each follow-up visit using standardized examination programs. Motor and nonmotor symptoms were assessed by semistructured interviews and clinical examination at each study visit. Neuropsychiatric assessments were conducted by a psychiatrist or trained psychiatric nurse of the study group, separate from and blinded to the formal ratings of motor symptoms. Subjects not able to be transported to the outpatient clinic were examined at their homes or nursing homes.

Motor Examination

Severity of parkinsonism and disability was assessed by study neurologists with experience in movement disorders, using the Unified Parkinson Disease Rating Scale (UPDRS)[12] activities of daily living (ADL) (part II) and motor (part III) subscores and Hoehn and Yahr staging.[13]

Psychotic Symptoms

At each study visit, information on presence and severity of hallucinations was derived from the UPDRS I subscore, item 2 (thought disorder [TD]). The TD item allocates stages from 0 to 4 as follows: no symptoms = 0; vivid dreaming = 1; "benign" hallucinations with insight retained = 2; occasional to frequent hallucinations or delusions without insight (could interfere with daily activities) = 3; and persistent hallucinations, delusions, or florid psychosis = 4. Psychosis associated with PD was defined as a UPDRS-TD score of 2 or more or use of antipsychotics owing to symptomatic treatment for previous PDP. Baseline assessments included a standardized questionnaire, identical to the UPDRS-TD item, that assessed the history of the presence and severity of psychotic symptoms before study start for each patient.

Nonmotor Examination

The Mini-Mental State Examination (MMSE) was used to assess cognitive impairment,[14] and a diagnosis of dementia was made according to *Diagnostic and Statistical Manual of Mental Disorders (Third Edition Revised)* criteria, including interviews with patient and caregiver, clinical examination, and a comprehensive neuropsychiatric test battery, as described more thoroughly in previous publications.[15] For clinical evaluation of rapid eye movement (REM) sleep behavior disorder (RBD), patients and their caregivers or close relatives rated the severity of motor and vocal activity during sleep on a 4-point (0-3) scale that is part of the Stavanger Sleepiness Questionnaire.[16] Probable RBD was diagnosed when the score was 2 (very active during sleep, tends to wake up spouse) or 3 (very active physically and verbally, hitting or hurting herself or caregiver while sleeping).

Medications

Treatment of motor and nonmotor symptoms including PDP was based on best clinical judgment. Use of antiparkinson and antipsychotic drugs was recorded at each visit. Levodopa-equivalent dose (LED) was calculated according to previously published recommendations[17,18] using the following formula: LED = [regular levodopa dose × 1] + [levodopa-controlled release dose × 0.75] + [pramipexole dose × 67] + [ropinirole dose × 16.67] + [(pergolide dose + cabergoline dose) × 67] + [bromocriptine dose × 10] + [(regular levodopa dose + levodopa controlled-release dose × 0.75) × 0.25] if taking tolcapone or entacapone.

STATISTICAL ANALYSIS

Medians of continuous variables were compared using Mann-Whitney tests. Proportions of categorical variables were compared by Pearson χ^2 tests.

The annual incidence rate of PDP was estimated as the number of patients with new-onset PDP during the study period divided by the number of person-years at risk. Person-years at risk were estimated as the total follow-up time until incident PDP, death, dropout, or study's end for those ever free from PDP at or before baseline. Time of onset of PDP or dropout was assumed to be the midpoint between the study visits.

Population-averaged regression models for correlated data, generalized estimating equations, were applied to investigate risk factors for development of PDP (model 1) and to explore concomitant features of PDP during the study period (model 2). In both models, the independence correlation structure was run. Model 1 included patients without PDP before or at baseline who had at least 1 follow-up observation. Predictor variables in this model were sex, age at motor onset, education, follow-up time, and baseline values for disease duration, UPDRS ADL score, UPDRS motor score, Hoehn and Yahr stage, LED, MMSE, dementia (present or absent), and probable RBD (present or absent). Model 2 was based on all patients in the cohort and included the following independent variables at each study visit: sex, age at motor onset, education, follow-up time, disease duration, UPDRS ADL score, UPDRS motor score, Hoehn and Yahr stage, LED, MMSE score, dementia (present or absent), and RBD (present or absent).

Statistical analyses were performed using the statistical software programs SPSS, version 15.0, and R, version 2.7.0 (University of Auckland). Two-tailed $P < .05$ was considered statistically significant.

RESULTS

Of the 239 patients assessed at baseline, 2 subjects were excluded from the study owing to psychosis prior to PD and 7 were excluded because they were rediagnosed as not having PD later during follow-up. Therefore, 230 patients were eligible for this study of PDP. Demographic and clinical baseline characteristics of these are given in **Table 1**. The numbers of patients who were reassessed or had died, respectively, during follow-up were 142 and 81 at 4 years, 88 and 135 at 8 years, 67 and 153 at 9 years, 50 and 171 at 10 years, 37 and 180 at 11 years, and 25 and 192 at 12 years, generating a total of 639 observa-

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Table 1. Demographic and Clinical Baseline Characteristics of Patients With and Without a History of PDP

Characteristic	Mean (SD) Overall (N = 230)	No PDP (n = 160)	PDP (n = 70)	*P* Value
Male sex, No. (%)	113 (49.1)	76 (47.5)	37 (52.9)	.55
Age at onset, y	64.9 (9.9)	64.8 (9.7)	65.2 (10.4)	.95
Disease duration, y	8.6 (5.8)	7.8 (5.3)	10.5 (6.4)	.001
Age at baseline, y	73.5 (8.5)	72.6 (8.2)	75.7 (8.8)	<.001
Education, y	9.1 (2.9)	9.5 (3.1)	8.3 (2.1)	.002
UPDRS ADL score	14.8 (9.0)	12.3 (6.9)	20.6 (10.6)	<.001
UPDRS motor score	28.7 (16.1)	24.3 (12.8)	38.7 (18.3)	<.001
Hoehn and Yahr stage	2.8 (1.1)	2.5 (0.9)	3.5 (1.1)	<.001
Hoehn and Yahr stage, No. (%)				
I and I.5	35 (15.2)	31 (19.4)	4 (5.7)	
II and II.5	79 (34.3)	67 (41.9)	12 (17.1)	
III	58 (25.2)	38 (23.8)	20 (28.6)	
IV	37 (16.1)	20 (12.5)	17 (24.3)	
V	21 (9.1)	4 (2.5)	17 (24.3)	
LED, mg	476 (256)	463 (226)	507 (313)	.34
MMSE score	24.7 (6.0)	26.5 (4.5)	20.4 (7.2)	<.001
Dementia, %	26.5	15.0	52.9	<.001
RBD, %	14.8	10.0	25.7	.003
Taking neuroleptic drugs, %	5.2	0	17.1	<.001

Abbreviations: ADL, activities of daily living; LED, levodopa-equivalent dose; MMSE, Mini-Mental State Examination; PDP, psychotic symptoms associated with Parkinson disease; RBD, rapid eye movement sleep behavior disorder; UPDRS, Unified Parkinson Disease Rating Scale.

Table 2. Baseline Risk Factors for Incident PDP During the 12-Year Follow-up Period

Characteristic	OR (95% CI)	Wald χ^2	*P* Value
Age at onset, y	1.07 (1.02-1.12)	8.75	.003
Disease duration, y	1.04 (0.94-1.16)	0.57	.45
Female sex	1.64 (0.82-3.27)	1.96	.16
Education, y	1.05 (0.95-1.17)	0.96	.33
UPDRS ADL score	0.94 (0.83-1.06)	0.90	.34
UPDRS motor score	1.04 (0.99-1.09)	2.15	.14
Hoehn and Yahr stage	1.29 (0.60-2.76)	0.43	.51
LED	1.26[a] (1.06-1.50)	6.65	.01
MMSE score	1.10 (0.93-1.30)	1.26	.26
Dementia	2.52 (0.35-17.91)	0.85	.36
RBD	3.52 (1.27-9.79)	5.83	.02
Follow-up time	1.19 (1.08-1.32)	10.59	.001

Abbreviations: ADL, activities of daily living; CI, confidence interval; LED, levodopa-equivalent dose; MMSE, Mini-Mental State Examination; OR, odds ratio; PDP, psychotic symptoms associated with Parkinson disease; RBD, rapid eye movement sleep behavior disorder; UPDRS, Unified Parkinson Disease Rating Scale.

[a] Per 100-mg difference in LED.

tions. Dropouts for reasons other than death were rare (3.0%-5.7%; mean, 4.3%).

PREVALENCE AND INCIDENCE OF PDP

Twenty-nine of 230 subjects had a history of PDP before the study but were free from PDP at baseline. The point prevalence of PDP was 17.8% (41 of 230) at baseline, 35.9% (51 of 142) at the 4-year visit, 51.1% (45 of 88) at 8 years, 46.3% (31 of 67) at 9 years, 46.0% (23 of 50) at 10 years, 48.6% (18 of 37) at 11 years, and 48.0% (12 of 25) at the 12-year visit.

By the end of the study period, 137 of 230 patients (59.5%) had developed PDP during the course of their disease. Of the 160 patients without PDP before or at baseline, 67 subjects (41.9%) developed incident PDP during the 12-year study, an average of 13.0 years (median, 13.1 years) after motor onset, but with considerable interindividual variation (2.2-25.1 years). The incidence rate of PDP was 79.7 per 1000 person-years.

RISK FACTORS OF PDP

Independent risk factors (generalized estimating equations model 1, **Table 2**) for new-onset PDP during the 12-year follow-up period were higher LED at baseline (odds ratio [OR], 1.26 per 100 mg; $P=.01$), probable RBD at baseline (OR, 3.52; $P=.02$), higher age at motor onset (OR, 1.07; $P=.003$), and follow-up time (OR, 1.19; $P=.001$).

CONCOMITANT FEATURES OF PDP DURING STUDY FOLLOW-UP

Clinical variables significantly associated with PDP (generalized estimating equation model 2, **Table 3**) during the 12-year study period were higher LED (OR, 1.11 per 100 mg; $P=.03$), probable RBD (OR, 4.07; $P<.001$), dementia (OR, 5.18; $P<.001$), and worse ADL function (UPDRS II) (OR, 1.10; $P=.002$) compared with subjects without PDP.

COMMENT

This prospective 12-year longitudinal study enabled us to explore the long-term course of psychosis, associated baseline risk factors, and concomitant features of PDP in a population-based prevalence cohort with PD. Psy-

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chotic symptoms increased with time, and 60% of patients had developed visual hallucinations or delusions during the course of their disease. Higher age at onset, higher LED, and presence of probable RBD at study entry independently predicted new-onset PDP during long-term follow-up. This risk factor pattern and the observed associations with increased disability and dementia over time place PDP within a symptom complex that signals a more malignant disease course. Our study emphasizes psychotic symptoms as key neuropsychiatric disability in PD.

The observed increase in point prevalence rates of PDP from about 18% to approximately 50% during long-term follow-up corroborates the results from recent longitudinal studies. In a 6-year clinic-based prospective study of 89 PD patients, the prevalence of hallucinations increased from 33% to 55%.[8] The corresponding values in patients originally included in a clinical trial were 21% at 15 years vs 74% at 20 years of follow-up.[19] While these studies were relatively small or clinic-based, another community-based study of 125 PD patients reported an increase of hallucinations from 23% to 56% during 4 years of follow-up, similar to our estimates.[20]

Forty-two percent of patients without any history of PDP at baseline developed visual hallucinations or delusions during the 12-year prospective study period, yielding an annual incidence rate of 80 per 1000 person-years. In comparison, the 4-year Kaplan-Meier incidence estimate of visual and auditory hallucinations in patients with PD participating in the Comparison of the Agonist Pramipexole With Levodopa on Motor Complications of Parkinson's Disease (CALM-PD) trial was 17%,[21] but no annual incidence rates were provided. By study's end, about 60% in our cohort had developed visual hallucinations or delusions during the course of their disease. Although some of our patients were still alive and at risk of new-onset PDP at study's end, this value and that of another long-term study[19] exceed the lifetime prevalence estimate of 50% for visual hallucinations reported from a large retrospective, but probably highly selected, cohort of patients with autopsy-verified PD.[22] Of note, we did not assess milder forms such as illusions and false sense of presence, which have been included as characteristic symptoms in recently proposed consensus criteria of PDP,[23] nor did we capture nonvisual hallucinations. In addition, owing to the long-time intervals between study visits during the first 8 years of follow-up, some patients may have developed new-onset PDP close to their deaths. For these reasons, we consider our estimates to be conservative.

Our analytic methods allowed us to explore risk factors and concomitant features of PDP separately. Our finding of a 5-fold increased prevalence of PDP over time in demented compared with nondemented patients is consistent with previous studies.[6,24] Common underlying neurochemical and pathological mechanisms, including neurotransmitter imbalance and increased cortical Lewy body burden,[6,24] have long been suggested for psychosis and dementia in PD. It is, however, remarkable but in agreement with a previous 4-year longitudinal study[7] that states that lower MMSE scores per se were neither associated with nor predicted future development of PDP in multivariate models. This finding indicates that there is no simple linear association between performance on this widely used cognitive screening tool and risk of or cooccurrence of PDP. Furthermore, dementia did not predict future development of PDP in our cohort, suggesting that psychotic symptoms in PD tend to develop prior or in parallel to severe cognitive impairment. This extends clinic-based longitudinal studies that found visual hallucinations to be a risk factor of cognitive decline[25] and progression to dementia.[26,27] However, both psychotic symptoms and cognitive impairment occur across a clinical continuum and thus it is possible that less severe cognitive deficits, ie, attentional-executive and visuospatial impairments, which are not adequately measured by MMSE, may precede the onset of PDP. Mild cognitive impairment is common even in early PD, whereas PDP usually develops during later stages of the disease. In support of this, in a community-based cohort of nondemented patients with newly diagnosed PD, 20% of subjects exhibited sufficient neuropsychological deficits to be classified with mild cognitive impairment,[28] but only 1.5% reported PDP.[29]

An association between sleep-related phenomena and PDP has been demonstrated in hospital-based cross-sectional[4,6] and longitudinal[8,9] studies in PD. Our finding of an almost 4-fold higher prevalence of clinical RBD features over time in patients with PDP extends these previous observations and is in line with polysomnographic studies that have demonstrated an association between REM sleep abnormalities and visual hallucinations/delusions in PD.[30-32] Moreover, probable RBD in nonpsychotic patients predicted a 3-fold increased risk of incident PDP during the 12-year follow-up period. Rapid eye movement sleep behavior disorder is increasingly recognized as a common feature in PD and precedes the motor onset in about 20% of PD patients with this parasomnia.[33] Thus, our observation of probable RBD being a risk factor for PDP during long-term follow-up highlights this parasomnia as a potential early marker of psychosis and, given the close as-

Table 3. Clinical Correlates of PDP During the 12-Year Study Period

Characteristic	OR (95% CI)	Wald χ^2	*P* Value
Age at onset, y	1.02 (0.99-1.06)	1.55	.21
Disease duration, y	1.04 (0.98-1.11)	2.02	.16
Female sex	1.28 (0.75-2.16)	0.82	.36
Education, y	1.00 (0.90-1.11)	<0.01	>.99
UPDRS ADL score	1.10 (1.03-1.16)	9.27	.002
UPDRS motor score	0.98 (0.95-1.01)	1.90	.17
Hoehn and Yahr stage	1.12 (0.72-1.75)	0.26	.61
Dementia	5.18 (2.55-10.51)	20.79	<.001
MMSE	1.00 (0.98-1.01)	0.21	.64
LED	1.11[a] (1.01-1.21)	5.05	.03
RBD	4.07 (2.33-7.12)	24.26	<.001
Follow-up time	1.06 (0.98-1.14)	2.09	.15

Abbreviations: ADL, activities of daily living; CI, confidence interval; LED, levodopa-equivalent dose; MMSE, Mini-Mental State Examination; OR, odds ratio; PDP, psychotic symptoms associated with Parkinson disease; RBD, rapid eye movement sleep behavior disorder; UPDRS, Unified Parkinson Disease Rating Scale.
[a] Per 100-mg difference in LED.

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sociation of psychosis and cognitive impairment, probably dementia in PD.[34] Additional longitudinal studies with repeated polysomnographic and detailed cognitive assessments are needed to clarify the temporal relationship between psychosis, RBD, and cognition in PD.

Although psychotic symptoms were rarely observed in the prelevodopa era[35] and clinical experience suggests a role of dopaminergic drugs in the etiology of PDP,[6,24] most epidemiological studies found no association between antiparkinsonian drug dosages and PDP.[6] Potential explanations for this paradox include nonconsideration of dopaminergic drugs other than levodopa and that, in naturalistic studies, dose reductions may occur in patients with PDP as a reflection of attempted treatment of PDP. While such symptomatic interventions often lead to an intermittent (short-term) relief of psychosis, they do not affect the underlying pathological processes or the long-term progression of PDP. In half of patients with PDP observed in a recent longitudinal study, psychotic symptoms reemerged within less than 1 year after dose reduction or initiation of antipsychotic drugs.[36] Our observation that LED was independently associated with PDP over time during long-term follow-up, whereas objective motor severity and disease stage were not, supports the concept that extrinsic dopaminergic stimulation is an important contributor to psychotic symptoms in PD.

Multivariate analyses also revealed that higher LED was a strong predictor of new-onset PDP in a dose-dependent manner, with a 26% increased risk of incident PDP during the 12-year follow-up period for a 100-mg increase in baseline LED. Thus, when high antiparkinsonian doses are needed to achieve sufficient motor control, or when drug response is low, this signals significantly increased risk of future PDP. There is consistent evidence that drug response as assessed by standardized levodopa challenge is less marked in older than younger patients with PD.[37] In addition, older age in PD is shown to be associated with more rapid motor decline[38] and higher risk of gait/balance problems and dementia.[39] Our finding that higher age at PD onset also predicts future emergence of PDP expands on these observations of a more malignant disease course in PD patients with older age and may reflect a more extensive or different topographical spread of the underlying neurodegenerative processes in later-onset PD.[37]

Follow-up time was a risk factor of incident PDP in multivariate analysis, suggesting that additional features not captured by our study may be associated with increased risk of PDP. These may include comorbid illnesses[21] or disease-related complications such as dysautonomia[22] or visual impairment,[9] which were not systematically assessed in our study. Further limitations of this study include the clinical rather than polysomnographic diagnosis of RBD and the long intervals between study visits during the first 8 years of follow-up. In addition, the UPDRS-TD item does not assess minor and nonvisual psychotic symptoms, whose predictors and concomitants may differ from those of visual hallucinations and delusions. Strengths of this study include the size and population-based nature of our cohort, the prospective long-term follow-up with multiple assessments over time, the low attrition rate for reasons other than death, and the use of robust statistical methods in the setting of repeated measurements.

Our study demonstrates that in the general PD population, most patients develop hallucinations or more severe psychotic symptoms during the course of their disease and that these features are associated with significantly increased disability in these subjects. In a clinical setting, particular awareness should be given to patients who develop PD at an older age, are in need of high doses of dopaminergic medication, or present clinical symptoms suspicious for RBD, as each feature independently signaled increased risk of PDP. In a research context, patients with these risk factors may be considered most suitable for inclusion in future clinical trials of agents for the prevention of psychosis in PD.

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