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Psychotic and compulsive symptoms in Parkinson's disease

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Movement Disorders in press

Abstract

Objective: To evaluate psychiatric symptoms in Parkinson's disease (PD) patients and assess their relation with other clinical aspects of PD.

Methods: Psychotic symptoms (PS) and compulsive symptoms (CS) as well as other non-motor and motor features were evaluated in 353 PD patients.

Results: Psychotic and compulsive symptom scores did not correlate significantly. PS occurred in 65% of patients, with item frequencies ranging from 10% (paranoid ideation) to 55% (altered dream phenomena). Regression analysis showed that autonomic impairment accounted for 20% of the 32% explained variance of PS, whereas cognitive problems, depression, daytime sleepiness, and dopamine agonist (DA) dose explained the rest. CS occurred in 19%, with item frequencies of 10% for both sexual preoccupation and compulsive shopping/gambling. Patients with more severe CS (score ≥ 2 on one or both items) were significantly more often men, had a younger age at onset, a higher DA dose and experienced more motor fluctuations compared to the other patients.

Conclusions: PS and CS are common but unrelated psychiatric symptoms in PD. The relations found between PS and cognitive problems, depression, daytime sleepiness, and autonomic impairment suggest a resemblance with Dementia with Lewy Bodies. The prominent association between PS and autonomic impairment may be explained by a shared underlying mechanism. Our results confirm previous reports on the profile of patients developing CS, and mechanisms underlying motor fluctuations may also play a role in the development of CS in PD.

Introduction

Parkinson's disease (PD) is a multisystem disorder, encompassing both well-known motor as well as many non-motor features, including psychotic symptoms (PS).[1] PS range from comparatively subtle symptoms such as occasional, non-disturbing hallucinations, mild illusions and vivid dreams, to a psychotic state with disturbing hallucinations and paranoid delusions.[2] PS are common in PD, with prevalence estimates ranging from 6% for specific symptoms[3] to 80% for more general symptoms in advanced PD patients.[4] More recently, the spectrum of psychiatric symptoms in PD has broadened with compulsive symptoms (CS), which may include hypersexuality, pathological gambling, and compulsive shopping. CS are incentive- or reward-based with a repetitive nature and prevalences of CS in PD range from 0.4% to 8%.[5]

Both PS and CS can have major psychosocial consequences and negatively influence quality of life of patient and caregiver.[2,5] The mechanisms underlying both PS and CS in PD are not well understood but in the literature PS are generally related to the underlying disease process[2] whereas CS are generally associated with antiparkinsonian medication.[5]

Major differences exist between studies that evaluated PS and CS in PD, and concern study design, data collection methods and study populations. Additionally, in most studies non-validated scales or arbitrary definitions of symptoms have been used.[1,5] Recently, a disease-specific instrument for the assessment of the severity of psychiatric symptoms in PD, the SCOPA-Psychiatric Complications (SCOPA-PC) was developed and found to be reliable and valid.[6] The first aim of this study was to evaluate the occurrence of both PS and CS in a large population of PD patients. The second aim of this study was to assess if the relations between PS and the disease process (such as motor impairment, cognitive impairment, and autonomic dysfunction) and between CS and antiparkinsonian medication could be confirmed.

Methods

Design

The study is part of the "PROfiling PARKinson's disease" (PROPARK) study, a longitudinal cohort study of patients with PD (start baseline assessment May 2003, n=420), who are profiled on phenotype, genotype, disability, and global outcomes of health, using valid and reliable assessment instruments for PD. Patients from this longitudinal cohort with their annual appointment between July 2005 and February 2007 (n=353) were used for analysis.

Participants

All patients fulfilled the United Kingdom Parkinson's Disease Society Brain Bank criteria for idiopathic PD.[7] Recruitment of patients was based on age at onset (AO) and disease duration, which are important determinants of disease course in PD.[8] The recruitment procedure has been described elsewhere.[9] The majority of patients were assessed at the Leiden University Medical Center (LUMC). To avoid bias towards recruiting less severely affected patients, patients who were unable to come to the hospital were assessed at home. This study was approved by the medical ethical committee of the LUMC and all patients gave informed consent.

Measurement instruments

Within PROPARK, all patients received standardized assessments, including evaluation of demographic and clinical characteristics, family history of PD, and medication use. Measurement instruments for the different clinical domains of PD were derived from a prior project (SCales for Outcomes in PArkinson's disease: SCOPA).[10]
For the current study, data obtained for psychiatric complications (SCOPA-PC))[6], disease severity (Hoehn & Yahr (H&Y))[11], motor functioning (SPES/SCOPA-motor, range 0-42)[12], dyskinesias and motor fluctuations (SPES/SCOPA-motor complications, range 0-6 for both subscales), autonomic functioning (SCOPA-AUT, range 0-69)[13], depressive symptoms (Beck Depression Inventory (BDI), range 0-63)[14], cognitive functioning (Mini Mental State Examination (MMSE), range 0-30[15]; SCOPA-COG,

range 0-43)[16], nighttime sleep (SCOPA-SLEEP NS, range 0-15), and daytime sleepiness (SCOPA-SLEEP DS, range 0-18)[17] were used. Except for the SCOPA-COG, higher scores indicate more severe impairment. Patients with MMSE scores < 24 were considered as having cognitive impairment.

The SCOPA-PC is a semi-structured interview-based scale consisting of seven items (hallucinations, illusions, paranoid ideation, altered dream phenomena, confusion, sexual preoccupation and compulsive behavior (shopping or gambling)). All items except for compulsive behavior, which was based on DSM-IV-criteria[18], were modified items from the Parkinson Psychosis Rating Scale.[19] All items address the occurrence of problems in the past month and has four response options ranging from 0 (no problems) to 3 (severe problems). The total SCOPA-PC score ranges from 0-21.[6]

In this study a psychotic symptom score and a compulsive symptom score were calculated. The psychotic symptom score ranges from 0-12 and is calculated by adding up scores from the items hallucinations, illusions, paranoid ideation, and altered dream phenomena. Possibly because of the confounding influence of cognitive decline, the item addressing confusion was found to be too sensitive in an earlier study.[6] Therefore, in this study the item confusion is not included in the psychotic symptom score and frequencies of psychotic symptoms are presented with and without the item addressing confusion. The compulsive symptom score ranges from 0-6 and is calculated by adding up the items sexual preoccupation and compulsive behavior (shopping or gambling). All instruments were either self-administered (SCOPA-AUT, BDI, and SCOPA-SLEEP), or administered by trained research associates (SCOPA-PC, H&Y, SPES/SCOPA-motor, SPES/SCOPA-motor complications, and SCOPA-COG). For reasons of comparability, all patients who used levodopa or dopamine agonists and experienced motor fluctuations, were assessed during 'on'-state. For each patient, a levodopa equivalent (LDE) for the dose of levodopa (LDE-Dopa) and dopamine agonists (LDE-DA) was calculated, and a total LDE was calculated by adding up these equivalents.[20]

Statistical Analysis

If 25% or more of the data from a questionnaire or scale was missing, data from this scale for this patient was excluded from statistical analyses. Differences between groups of patients were analyzed with Chi-square tests (χ^2) or student's T-tests for independent samples. Pearson's correlation coefficient or Spearman's rho were used to assess relations between the psychotic symptom score and other features. Correlation coefficients were defined as very weak (r=0-0.19), weak (r=0.20-0.39), moderate (r=0.40-0.59), strong (r=0.60-0.79), or very strong (r=0.80-1.00).[21] Multiple forward linear regression analyses were used to explore the contribution of different variables to the psychotic symptom score. A p-value < 0.05 was considered significant. All analyses were performed with Statistical Package for the Social Sciences 14.0 Software (SPSS 14.0).

Results

A total of 353 PD patients (64% men) with a mean (SD) age of 62.0 (11.1) years participated in the study (Table 1). The percentage of patients with too many missing values ranged from 0% (SPES/SCOPA-motor) to 6% (SCOPA-AUT). Psychotic and compulsive symptom scores did not correlate significantly (r=0.100, p=0.060). Patients using antipsychotics (clozapine or quetiapine) (n=27) had a higher mean psychotic symptom score (mean scores 1.9 versus 1.0 (mean difference 0.9, 95% CI 0.5 to 1.3)) and a lower mean compulsive symptom score (mean scores 0.0 versus 0.3 (mean difference -0.3, 95% CI -0.4 to -0.2)) compared to patients not on antipsychotics. Patients using antipsychotics were significantly older, had a higher LDE-Dopa, more severe PD (H&Y), worse motor, cognitive and autonomic function, and more depressive symptoms and daytime sleepiness compared to the other patients.

Patients using antidepressants (n=46) had a comparable mean psychotic symptom score (mean difference 0.2, 95% CI -0.1 to 0.5) and mean compulsive symptom score (mean difference -0.1, 95% CI -0.3 to 0.1) to patients not on antidepressants. Patients using antidepressants had significantly more severe PD (H&Y), worse

motor and cognitive function, more motor fluctuations, and more depressive symptoms compared to the other patients. The group of patients using rivastigmine (n=8) was too small, therefore a group comparison was not feasible.

Table 1. Characteristics of patients with PD

Characteristics	Patients
Patients, n	353
Age, mean (SD), y	62.0 (11.1)
Sex, m/w (% men)	226/127 (64%)
Disease duration, mean (SD), y	12.7 (6.5)
AO, mean (SD), y	49.3 (11.5)
Hoehn and Yahr stage, %*	
1/2/3/4/5/missing	3/37/31/24/6/0
Cognitive impairment, n (%)	40 (11%)
No dopaminergic medication, n (%)	22 (6%)
Total LDE, mean (SD), mg/day	736.5 (514.1)
Levodopa therapy, n (%)	277 (79%)
LDE-Dopa, mean (SD), mg/day	491.7 (427.4)
DA therapy, n (%)	245 (69%)
LDE-DA, mean (SD), mg/day	245.1 (228.2)
Anticholinergics, n (%)	50 (14%)
Antipsychotics, n (%)	27 (8%)
Antidepressants, n (%)	46 (13%)
Rivastigmine, n (%)	8 (2%)

*: sum of percentages does not equal 100 due to rounding off

PD: Parkinson's disease; AO: age at onset; LDE: levodopa equivalent; DA: dopamine agonists

Psychotic symptoms

Frequencies of psychotic symptoms

Because the item addressing confusion was found to be too sensitive in an earlier study[6], frequencies of psychotic symptoms are presented with and without the item addressing confusion and the psychotic symptom score does not include confusion.

Including confusion, eighty-seven percent of all patients (n=306) had PS (one or more item score(s) ≥ 1), with confusion (76%) being reported most frequent. Twenty-seven percent of the patients (n=96) had a score ≥ 2 on one or more of the items, with 15% of the patients reporting confusion.
Without confusion, sixty-five percent of all patients (n=230) had PS. Altered dream phenomena (55%) were reported most frequent. Nineteen percent of the patients (n=68) had a score ≥ 2 on one or more of the items, with 11% of the patients reporting hallucinations (Table 2).

Table 2. Mean scores and frequencies of psychotic and compulsive symptoms in patients with PD

Characteristics	Mean (SD)	N (% ≥1)	N (% ≥2)
Psychotic symptom score	1.07 (1.02)	-	-
Psychotic symptoms	-	230 (65%)	68 (19%)
Hallucinations	-	85 (24%)	37 (11%)
Illusions	-	64 (18%)	25 (7%)
Paranoid ideation	-	34 (10%)	6 (2%)
Altered dream phenomena	-	195 (55%)	20 (6%)
Compulsive symptom score	0.27 (0.62)	-	-
Compulsive symptoms	-	68 (19%)	24 (7%)
Sexual preoccupation	-	36 (10%)	21 (6%)
Compulsive behavior	-	35 (10%)	4 (1%)
Shopping	-	26 (7%)	3 (1%)
Gambling	-	7 (2%)	1 (0%)
Both	-	2 (1%)	0 (0%)

≥1: one or more item score(s) greater or equal to 1

≥2: one or more item score(s) greater or equal to 2

Determinants of psychotic symptoms

Moderate correlations were found between the psychotic symptom score and autonomic impairment (r=0.47) and depressive symptoms (r=0.44) (all p-values <0.001). Weak correlations were found between the psychotic symptom score and cognitive functioning (r=-0.36), H&Y-stage (Spearman's rho: 0.31), daytime sleepiness (r=0.31), age (r=0.27), LDE-Dopa (r=0.24), nighttime sleep problems (r=0.24), and total LDE (r=0.22) (all p-values <0.001). The multiple forward linear regression analysis revealed that autonomic impairment accounted for 20% of the 32% total explained variance of the psychotic symptom score. Worse cognitive function, depressive symptoms, daytime sleepiness, and a higher LDE-DA additionally explained the rest (total regression model; p<0.001) (Table 3).

Table 3. Regression analysis of the psychotic symptom score of the SCOPA-PC in patients with PD

SCOPA-PC	Variable[2]	R square	Standardized β
Psychotic symptom score[1]	Autonomic functioning	0.20	0.209
	Cognitive functioning	0.06	-0.217
	Depressive symptoms	0.03	0.213
	Daytime sleepiness	0.02	0.139
	LDE-DA	0.01	0.100
	Total	0.32	-

LDE: levodopa equivalent; DA: dopamine agonists

[1]: multiple forward linear regression analysis was used with the variables: Age, sex, disease duration, LDE-Dopa, LDE-DA, motor functioning, dyskinesias, motor fluctuations, cognitive functioning, autonomic functioning, depressive symptoms, nighttime sleep, and daytime sleepiness

[2]: variables are ordered in the table as they appeared in the model

The regression analysis was also performed in patients not on antipsychotics (n=324), which showed largely similar results as the aforementioned analysis. The total explained variance of this model was 33% with 20% accounted for by autonomic impairment. Furthermore, worse cognitive functioning, depressive symptoms, and daytime sleepiness also remained in the model and explained the rest of the variance of the psychotic symptom score together with more dyskinesias, better motor functioning, and higher age (total regression model; $p<0.001$).

Relation between psychotic and autonomic symptoms

To evaluate if a particular autonomic subdomain determined the relation with the psychotic symptom score, the multiple forward regression analysis was repeated with each separate autonomic subdomain score (gastrointestinal, urinary, cardiovascular, thermoregulatory, pupillomotor, and sexual functioning) as independent variable. These analyses revealed that gastrointestinal, urinary, and cardiovascular impairment remained in the regression models. All these autonomic domains had a similar contribution to the model, suggesting that the relation between PS and autonomic dysfunction is not determined by one particular subdomain. To examine if the relation between PS and autonomic impairment could be explained through their relation with disease severity, the correlation between H&Y and SCOPA-AUT was also determined, which was moderate (0.42; Spearman's rho: $p<0.001$).

Compulsive symptoms

Nineteen percent (n=68) of all patients reported CS (one or both item score(s) ≥ 1). In total, 7% (n=24) of the patients had a score ≥ 2 on one (n=23) or both (n=1) of the items, with 6% of patients reporting sexual preoccupation (Table 2). Compared to all other patients, these 24 patients were significantly more often men, had a younger AO, higher LDE-DA, and experienced more motor fluctuations (Table 4).

Table 4. Comparison of patients with moderate or severe compulsive symptoms and patients with no or mild compulsive symptoms

Characteristics	Moderate or severe CS (one or both of the item score(s) ≥ 2)	No or mild CS (both item scores ≤ 1)	p-value
Patients, n	24	329	-
Age, mean (SD), y	58.6 (10.1)	62.3 (11.2)	p=0.124[1]
Sex, m/w (% men)	20/4 (83%)	206/123 (63%)	p=0.041[2]
AO, mean (SD), y	44.9 (11.0)	49.6 (11.4)	p=0.048[1]
Disease duration, mean (SD), y	13.8 (7.3)	12.6 (6.5)	p=0.402[1]
Total LDE, mean (SD), mg/day	873.4 (465.5)	726.5 (516.7)	p=0.177[1]
LDE-Dopa, mean (SD), mg/day	524.9 (359.2)	489.3 (432.3)	p=0.694[1]
LDE-DA, mean (SD), mg/day	348.4 (259.4)	237.6 (224.4)	p=0.021[1]
Hoehn and Yahr stage, %*			
1/2/3/4/5/missing	8/33/29/21/8/0	2/37/31/24/5/0	p=0.421[2]
SPES/SCOPA-motor score, mean (SD)	14.3 (5.7)	16.2 (6.5)	p=0.171[1]
Dyskinesias score, mean (SD)	1.0 (1.6)	1.1 (1.7)	p=0.706[1]
Motor fluctuations score, mean (SD)	1.9 (1.8)	1.0 (1.5)	p=0.019[1]
SCOPA-AUT score, mean (SD)	21.3 (6.8)	18.5 (8.5)	p=0.117[1]
BDI score, mean (SD)	9.5 (7.0)	10.3 (6.7)	p=0.548[1]
SCOPA-COG score, mean (SD)	28.4 (5.7)	26.3 (7.3)	p=0.160[1]
SCOPA-SLEEP NS score, mean (SD)	5.4 (3.6)	4.4 (3.4)	p=0.161[1]
SCOPA-SLEEP DS score, mean (SD)	4.8 (3.2)	5.3 (4.0)	p=0.565[1]

*: sum of percentages does not equal 100 due to rounding off

[1]: student's T-test for independent samples; [2]: χ^2 test

CS: compulsive symptoms; AO: age at onset; LDE: levodopa dosage equivalent; DA: dopamine agonists; BDI: Beck Depression Inventory; NS: nighttime sleep; DS: daytime sleepiness

Discussion

In this study, a large population of PD patients was assessed for both PS and CS, which emerged as common but unrelated psychiatric symptoms in PD. Frequencies of PS and patients on antipsychotic treatment are within the frequencies found by

others, with a slightly higher percentage of patients with PS compared to the literature when including the item addressing confusion.[3,4,22] The use of antipsychotics may mask the presence of PS. However, patients on antipsychotics still had significantly more PS compared to patients not on antipsychotics. Assuming that antipsychotics are at least partly efficacious, the mean PS score in this study possibly reflects an underestimation. Furthermore, several case reports describe a positive effect of antidepressants in resolving PS.[23-25] We found comparable mean psychotic scores for patients on antidepressants and patients not on antidepressants.

Forward regression analysis in which interrelations of factors in the analysis are taken into account, revealed strong relations between PS and autonomic impairment, cognitive impairment, depressive symptoms, and daytime sleepiness. These relations correspond with the notion that PS are mainly associated with the disease process.[2] PS (especially visual hallucinations), autonomic dysfunction, depression, and daytime sleepiness are well recognized features of a related disorder, Dementia with Lewy Bodies (DLB).[26] In PD, cognitive impairment, depressive symptoms, and daytime sleepiness have been found to be related to PS.[1] The relation between PS and autonomic impairment, however, has hardly been addressed. One study reported greater cardiac and vasomotor sympathetic dysfunction in PD patients with visual hallucinations compared to those without hallucinations.[27] In this study, we found that autonomic impairment was strongly associated with PS. This association was not determined by a particular autonomic domain, and was also present in patients not on antipsychotics. The question which factors underlie the association between PS and autonomic impairment remains open.

One possibility is that this association may be due to mechanisms induced by antiparkinsonian drug treatment. Weak relations were found between PS and dosages of antiparkinsonian medication. However, a relation with medication can only correctly be evaluated using the cumulative drug exposure over the disease course. Since this information was not available in our study, firm conclusions can not be drawn. In DLB, both PS and autonomic dysfunction are present early in the disease course[26,28], which makes exposure to antiparkinsonian drugs an unlikely cause for

this association, at least in DLB.

Another potential explanation is that PS and autonomic impairment coincide as the disease progresses. The results of this study suggest that disease severity may not play an important role in this association, however, the possibility that there is a non-linear relation between disease severity and both non-motor symptoms can not be excluded. Other non-motor features were also related to PS, suggesting more advanced disease in patients experiencing more PS. In DLB, a more widespread form of α-synucleinopathy, these non-motor features also tend to occur together.[26] In terms of underlying pathology, co-occurrence of these features may be explained by the Braak staging, in which the upper brainstem, midbrain and limbic system are involved at a certain stage in the disease process of PD.[29]

Finally, the same pathophysiological mechanism, which is unrelated to disease severity and drug exposure per se, may be responsible for the association between PS and autonomic impairment. One such potential mechanism is postsynaptic dopaminergic receptor hypersensitivity.[30] In PD, this occurs as a compensatory mechanism for presynaptic dopaminergic neuron loss[31], and has been documented in the striatum, mesolimbic system and hypothalamus.[31-33] Hypersensitivity of the dopamine receptors in the mesolimbic system has been proposed to underlie PS in PD.[33] Given that the hypothalamus is involved in autonomic functions, dopamine receptor hypersensitivity in this region may underlie some of the autonomic dysfunction. Hence postsynaptic dopaminergic hypersensitivity may be the common mechanism underlying these symptoms and may explain their strong association.

CS occurred in 19% of the patients. A limitation of this study is that not all compulsive behaviors such as compulsive eating, hobbyism and punding were assessed within the SCOPA-PC, which may have resulted in an underestimation of CS in our study. This was due to the fact that during the time the SCOPA-PC was developed, the nature and relevance of other compulsive behaviors were not well established.[6] However, frequencies of sexual preoccupation (10%) and compulsive shopping (8%) were higher than those found by others.[5] This may be due to the stratification procedure, which makes our study population not representative of the general PD

population. This procedure resulted in a population with a relatively young mean AO and, therefore, a large proportion (69%) of patients using dopamine agonists, both of which are known risk factors for CS.[5] In our cohort patients with more severe CS (score ≥ 2 on one or both of the compulsive items) were more often men, had a younger AO, higher LDE-DA, and experienced more motor fluctuations compared to patients without CS or with a mild CS score. These findings are largely in line with those of others[34-39] and partly supports the concept of antiparkinsonian medication as most important factor underlying the development of CS in PD.[5]

The relation between motor fluctuations and CS has not been formally addressed in previous studies, although motor fluctuations are frequently mentioned in case reports.[40-43] In two small case series, patients almost exclusively exhibited compulsive behavior or showed an increase of compulsive behavior during "on time", although it remained unclear whether these behaviors were specifically related to "on time" or whether they could not be carried out during "off time".[40,43] In the first study they proposed that the mechanisms underlying the onset of motor fluctuations may also play a role in the onset of repetitive behaviors[40], whereas the authors of the second study suggest that compulsive behavior during "on time" could represent a behavioral manifestation of pharmacological treatment. Another possibility is that CS and motor fluctuations are associated through their relation with AO, as a younger AO is not only related to CS, as found in our study, but also to motor fluctuations.[44] We emphasize, in agreement with others, that awareness for the risk of CS is important in patient management.[45] Our findings point out that caution is particularly important in younger PD patients, mostly men, with motor fluctuations receiving dopamine agonists.

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