Clinical Predictors of disease progression in Parkinson's disease

Zhu, K.

Chapter 2:

Risk Factors for Hallucinations in Parkinson's Disease: Results From a Large Prospective Cohort Study

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ABSTRACT

The aim of this study was to identify risk factors for the development of hallucinations in patients with Parkinson's disease (PD). A broad range of motor and nonmotor features was assessed at baseline and during the following 5 years in 386 PD patients. Cross-sectional analyses of baseline data and longitudinal analyses of follow-up data were performed to identify risk factors for hallucinations in PD. Twenty-one percent of the patients had hallucinations at baseline, whereas 46% of the patients without hallucinations at baseline developed this feature during follow-up. Univariate survival analysis showed that older age, female sex, less education, higher age at onset, and more severe motor and cognitive impairment, depression, daytimes sleepiness, autonomic dysfunction, and motor fluctuations and dyskinesias, as well as higher daily levodopa dose, were associated with the risk of developing hallucinations. This largely corresponds with the features that were associated with the presence of hallucinations at baseline. In a stepwise regression model, older age at onset, female sex, excessive daytime sleepiness, autonomic dysfunction, and dyskinesias emerged as independent risk factors for developing hallucinations. Female sex, autonomic dysfunction, motor fluctuations, and dyskinesias have not been reported as risk factors in previous studies. These findings lend support to the notion that hallucinations in PD are caused by a combination of risk factors that are associated with (the interaction between) older age and more advanced disease. The identification of female sex as a risk factor for developing of hallucinations in PD is a new finding and should be verified in future studies.

INTRODUCTION

Parkinson's disease (PD) is a progressive multisystem disorder that is associated with an increased risk of developing psychotic symptoms such as illusions and hallucinations. In PD, hallucinations may manifest in a variety of forms, with visual hallucinations the most prevalent.[1,2] Hallucinations can be benign with retained insight, but can also occur without insight and perceived as threatening.[1] The prevalence of hallucinations in PD may vary from 33% to 63%, with probability and severity increasing over the course of disease.[3] They are associated with abnormal behavior and increased probability of nursing home placement and mortality.[4,5] In view of these severe consequences, early identification of patients at risk of developing hallucinations is important, and thorough knowledge of potential factors that may predict future development of hallucinations is therefore indispensable and a prerequisite for adequate management. Previous studies identified various risk factors for developing hallucinations in PD, such as older age, older age at onset, longer disease duration, depression, sleep disturbances (insomnia, REM-sleep behavioural disorder [RBD], and excessive daytime sleepiness), cognitive impairment, severity of motor symptoms, and comorbidity.[1,3,6–14] Hallucinations have also long been considered a side effect of long-term levodopa treatment[2]; more recent studies, however, have questioned this assumption, as a relation with levodopa dosage level has not been consistently found.[3,13–17]

Previous studies on hallucinations in PD have often yielded inconsistent results. This may evidently be a result of differences in population characteristics and methodological issues. The latter include small sample size[6,7,9] and low prevalence of patients with hallucinations.[3,18] Another important aspect is the design of the study; most studies used a cross-sectional design, which obscures the time relation between potential risk factors and emergence of hallucinations. Longitudinal studies are therefore preferred. Unfortunately, large longitudinal studies with several years of follow-up are scarce in PD. The length of follow-up is important, though, because a sufficient number of patients must have developed hallucinations to obtain a solid notion of the robustness of the identified risk factors.

We found 3 prospective studies dealing with predictors of hallucinations in PD that followed more than 100 patients, with follow-up periods of 1, 4, and 12 years.[3,18,19] However, these studies only analysed a limited number of potential risk factors. For the purpose of the present study, data from the PROPARK cohort were used. This is a longitudinal study of more than 400 PD patients who are broadly characterized and have been examined annually and followed up for 5 years (i.e. 6 assessments).[20] These characteristics make this study very well suited for the purpose of identifying risk factors for the development of hallucinations in patients with PD. Analyses include a cross-sectional examination of baseline data as well as a longitudinal analysis of follow-up data.

PATIENTS AND METHODS

Study Design and Participants

Patients were recruited from neurology clinics of university and regional hospitals in the western part of the Netherlands, and all fulfilled the United Kingdom Parkinson's disease Society Brain Bank criteria for idiopathic PD.[21] Given that we intended to obtain information on the full spectrum of the disease, a recruitment strategy based on age at onset (≤50 years or >50 years) and disease duration (≤10 years or >10 years) was applied. We aimed to recruit at least 100 patients in each of the 4 strata. The majority of the patients were evaluated at the Leiden University Medical Center, but more severely affected patients were offered the possibility to be examined at their homes to prevent selective dropout as much as possible. More detail on the design of the PROPARK study can be found elsewhere.[20] The medical ethical committee of the Leiden University Medical Center approved the PROPARK study, and written informed consent was obtained from all patients.

Assessment of Hallucinations

Patients were considered to have hallucinations if a score≥1 was obtained on the hallucinations item of the SCOPA-Psychiatric Complications scale (SCOPA-PC).[22]
In the SCOPA-PC a semistructured interview is used to elicit information. The hallucination item of this instrument covers visual, auditory, tactile, and olfactory hallucinations. The items address the occurrence of these events in the past month and are rated as 0=absent, 1=mild, 2=moderate, or 3=severe. Mild hallucinations (score of 1) involved hallucinations with insight, whereas moderate hallucinations (score of 2) concerned hallucinations with partial insight for which patients could be convinced that their hallucinations were not real. Patients with severe hallucinations (score of 3) had no insight, and the hallucinations were often perceived as threatening.[22] In addition, patients were also considered to suffer from hallucinations if they used quetiapine or clozapine, because both drugs are specifically prescribed for hallucinations[23]; because rivastigmine is prescribed for both cognitive problems and hallucinations,[24,25] only patients who, according to the patients' records, received this drug because of hallucinations were counted as hallucinators.

Assessment of Baseline Variables

At baseline (2003–2005) and at the 5 following annual visits, all patients received standardized assessments. The assessments included an evaluation of demographic and clinical characteristics, family history of PD, and the use of antiparkinsonian medication. For each patient, a levodopa equivalent (LDE) of levodopa and dopamine agonist dose was calculated at baseline. Total LDE is the sum of levodopa dosage equivalent (LDE-dopa) and dopamine agonist dosage equivalent (LDE-

DA).[26] Hoehn & Yahr (H&Y) stages of the patients were ascertained at every assessment.[27] Measurement instruments for the different clinical domains of PD were derived from the SCOPA project and have all been found valid and reliable. The following instruments were administered by a qualified examiner: the SPES/SCOPA (including sections on motor examination, activities of daily living, and motor complications),[28] the SCOPA-COG (cognitive function),[20] and the SCOPA-PC.[22] Patients completed the following instruments: the SCOPA-AUT(autonomic complaints),[29] the SCOPA-SLEEP (with sections on nighttime sleep problems and daytime sleepiness),[30] and the Beck Depression Inventory.[31] For all instruments except the SCOPA-COG, higher scores reflect poorer functioning.

Clinical Subtypes of PD

Recently, van Rooden et al identified 4 clinical subtypes of PD using a data-driven approach.[32] The numbers of patients with subtypes 1, 2, 3, and 4 were 169, 45, 101, and 26, respectively, and subtype data were missing for 45 patients who were included at baseline. With increasing subtype number, patients are clinically characterized by more severe symptoms of the nondopaminergic domains especially. In addition, patients with subtypes 2 and 4 have more severe motor complications than those with subtypes 1 and 3, whereas patients with subtypes 1 and 2 are younger and have a younger age at onset than those with subtypes 3 and 4. For more detail, see the publication by van Rooden et al.[32]

Inclusion and Exclusion Criteria

Patients who underwent deep brain stimulation (DBS) before the start of the study were excluded from the cross-sectional baseline analysis; patients who underwent DBS during follow-up contributed time up to the last annual assessment before DBS. Only patients who had no hallucinations at baseline were included in the longitudinal analysis. In addition, patients who were only assessed in year 1 and did not show up for later annual assessments were excluded from the longitudinal analysis.

Statistical Analysis

Cross-sectional analyses to assess differences at baseline between PD patients with and without hallucinations were performed as appropriate. In the longitudinal analyses we first performed univariate analyses to evaluate which baseline variables were associated with the later development of hallucinations. The following baseline variables were taken from the literature and were included if they had been shown to contribute significantly to the

development of hallucinations in 1 or more studies: age, age at onset of PD, disease duration, Hoehn & Yahr stage, cognitive function, comorbidity, excessive daytime sleepiness, depression, hypokinesia, rigidity, postural instability and gait disorder, and the use of antiparkinsonian medication.[1,3,6–14] Furthermore, a few other baseline variables were added because a relation with development of hallucinations could be presumed: sex, education, tremor, motor fluctuations, number of falls in the past year, dyskinesias, autonomic dysfunction, and nighttime sleep problems. Education is closely related to cognitive disorders and may therefore be considered a risk factor. Motor fluctuations and dyskinesias are associated with the use of antiparkinsonian medication, which in turn are related to the development of hallucinations. Autonomic symptoms and falling are related to comorbidity, but may also serve as indicators of disease severity. All baseline variables with a $P<.10$ in the univariate analysis were subsequently included in the multivariate Cox proportional hazards model with a backward-selection approach. In addition, in a separate Cox regression analysis, the differences in the probability of developing hallucinations among the 4 clinical subtypes were examined while the influence of confounders was taken into account. Kaplan–Meier curves (i.e., unadjusted) were also used to illustrate the differences in survival times. The associations between baseline variables and the development of hallucinations were calculated as hazard ratios (HRs) with 95% confidence intervals (CIs). An $HR>1$ indicates that the variable is associated with a higher risk of developing hallucinations during follow-up. $P<.05$ was considered significant.

Calculation of Survival Time

Follow-up ended at the date of the final follow-up visit (for those still without hallucinations), the date of the last examination before loss to follow-up, or the date of the examination at which hallucinations were observed, whichever came first. Survival time was calculated as the difference between these dates and the date of the patient's baseline assessment. Patients were considered to have an event ("uncensored") if they scored≥1 on the hallucinations item of the SCOPA-PC or if they used quetiapine, clozapine, or rivastigmine for hallucinations. If a patient did not have an event during the complete follow-up, he or she was withdrawn alive and classified as "censored." In addition, if a patient underwent DBS or died during follow-up, survival time was calculated as the difference between the date of the last assessment before DBS or death and the date of the baseline assessment. If a patient had missed 1 year and had no hallucinations in the previous and following years, we assumed that the patient did not have hallucinations in that particular year. All analyses were performed with Statistical Package for the Social Sciences (SPSS) version 18.0.

RESULTS

Hallucinations

A total of 386 patients were included at baseline, of whom 81 (21.0%) had hallucinations and/or used medication for hallucinations (Figure 2.1, Table 2.1). Twenty-five of these patients also suffered from paranoid ideation. Patients without hallucinations at baseline (n=305) were followed for a maximum of 5 years; of these, 28 patients (9.2%) were lost to follow-up during the first year because they died (n=5), lost interest in the study (n=13), or considered the study too demanding (n=10). Thus, a total of 277 patients remained for inclusion in the longitudinal analysis. Patients with hallucinations at baseline were older, had longer disease duration, and had higher H&Y scores (Table 2.1). In addition, patients with hallucinations had more severe cognitive impairment, depression, daytime sleepiness, and dyskinesias. Patients with hallucinations also had more postural instability and gait disorder (PIGD), fell more often, and used higher daily doses of levodopa and dopamine agonists. The 28 patients who stopped after the baseline assessment were older (65.4±14.3 vs 59.4±11.0 years, P=.048) and were more severely affected by the disease as measured by H&Y (median, 3.00 vs 2.00;U=4508; z=2.029; P=.042). Patients without hallucinations at baseline (n=277) were followed up for a maximum of 5 years, and 126 of them (45%) developed hallucinations. Univariate analyses showed that older age at examination, older age at onset, female sex, and fewer years of education were associated with an increased risk of hallucinations (Table 2.2). Of the motor symptoms, PIGD, dyskinesias, and motor fluctuations predicted future onset of hallucinations. Other baseline characteristics that were associated with an increased probability of developing hallucinations were higher H&Y score, lower cognition, more severe daytime sleepiness, autonomic dysfunction, and depression, as well as higher daily levodopa dose. All baseline variables that showed univariate associations (P<.10) with hallucinations were entered in the multivariate analysis, after which older age at onset, female sex, excessive daytime sleepiness, autonomic dysfunction, and dyskinesias emerged as independent risk factors in the Cox proportional hazards regression analysis (Table 2.3).

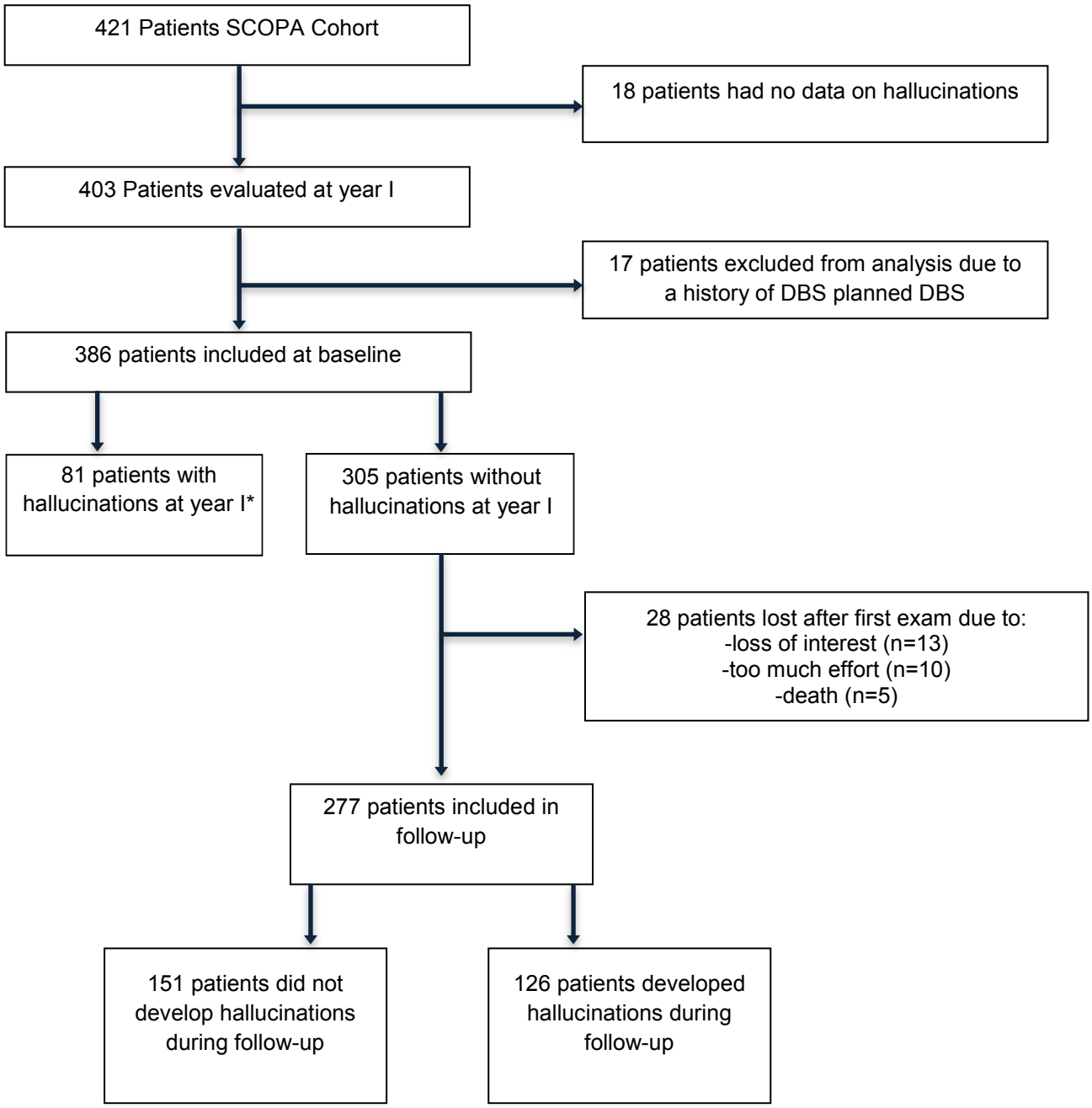
Table 2.1: Baseline data of patients with and without hallucinations

	Total	With hallucinations	Without hallucinations	p-values
N	386	81	305	
Age, y	61.06 (11.46)	65.38 (10.62)	59.91 (11.41)	<0.001
Sex, % male	63.5	59.3	64.6	0.376[a]
Education, y	11.98 (4.11)	11.34 (4.43)	12.14 (4.01)	0.118
Age at onset, y	50.93 (11.82)	52.32 (10.96)	50.56 (12.03)	0.232
Disease duration, y	10.13 (6.19)	13.05 (6.15)	9.36 (5.97)	<0.001
Hoehn & Yahr, stage	2 (2,3)	3 (2,4)	2 (2,3)	0.001[b]
Tremor score	3.71 (2.04)	3.49 (2.28)	3.77 (1.98)	0.296
Bradykinesia/rigidity score	5.06 (2.02)	5.36 (2.26)	4.99 (1.96)	0.157
PIGD	2.3 (1.92)	3.04 (2.21)	2.11 (1.79)	0.001
Dyskinesia score	0.86 (1.57)	1.51 (1.81)	0.7 (1.45)	<0.001
Motor Fluctuations	0.73 (1.23)	0.97 (1.34)	0.67 (1.19)	0.070
Number of falls past year	0 (0-2)	1 (0-5)	0 (0-1)	<0.001[b]
SCOPA-COG	25.55 (6.67)	20.9 (7.83)	26.79 (5.74)	<0.001
Beck Depression Inventory	10.09 (6.55)	13.3 (7.29)	9.25 (6.08)	<0.001
SCOPA-SLEEP - nighttime	4.45 (3.75)	5.18 (3.84)	4.25 (3.71)	0.051
SCOPA-SLEEP - EDS	4.88 (3.73)	6.73 (4.14)	4.39 (3.46)	<0.001
SCOPA-AUT, total score	10.44 (5.67)	13.03 (5.95)	9.78 (5.41)	<0.001
Total LDE	577 (437)	771 (452)	525 (419)	<0.001
Daily levodopa dose, mg	349 (365)	493 (370)	311 (331)	<0.001
Daily DA dose, mg	227 (224)	278 (232)	214 (220)	0.022

Variables are expressed as means (standard deviations (SD)), except for gender (percentages), and Hoehn and Yahr stage and number of falls past year (median (interquartile range)). All differences are calculated with the independent-samples t-tests, except for [a] Chi-square test and [b] Mann-Whitney U test.

SCOPA-COG: cognitive function, higher scores reflect better functioning; SCOPA-SLEEP, nighttime: nighttime sleep problems; SCOPA-SLEEP, EDS: daytime sleepiness; SCOPA-AUT, total score: sumscore autonomic functioning including items from the sections on gastrointestinal, cardiovascular and urinary tract; LDE: Total levodopa dosage equivalent; DA: Dopamine agonists; PIGD: Postural instability gait disorder.

Figure 2.1: Flow Chart of follow-up for hallucinations



*15 used medication, 54 had hallucinations, 12 had both

Table 2.2: Univariate associations between baseline characteristics and risk of hallucinations

	Hazard Ratio (95% CI)	P-values
Age, y	1.039 (1.022-1.057)	<0.001
Sex, HR for females[a]	1.656 (1.164-2.355)	0.005
Education, y	0.953 (0.909-0.999)	0.044
Age at onset, y	1.029 (1.012-1.045)	0.001
Disease duration, y	1.016 (0.988-1.045)	0.272
Hoehn & Yahr stage	1.426 (1.152-1.766)	0.001
Tremor score	1.041(0.955-1.134)	0.360
Bradykinesia/rigidity score	1.070(0.978-1.171)	0.138
PIGD score	1.220(1.111-1.340)	<0.001
Dyskinesia score	1.201(1.080-1.336)	0.001
Motor Fluctuations	1.200(1.050-1.371)	0.008
Number of falls past year	1.004(0.998-1.006)	0.402
SCOPA-COG	0.938(0.908-0.969)	<0.001
Beck Depression Inventory	1.045(1.021-1.070)	<0.001
SCOPA-SLEEP - nighttime	0.992(0.946-1.040)	0.740
SCOPA-SLEEP - EDS	1.079(1.030-1.130)	0.001
SCOPA-AUT, total score	1.103(1.069-1.138)	<0.001
Total LDE	1.000(1.000-1.001)	0.070
Daily Levodopa Dose, mg	1.001(1.000-1.001)	0.001
Daily DA Dose, mg	0.999(0.999-1.000)	0.159

All variables are expressed with hazard ratio (HR) with 95% confidence interval.
[a]Fifty-five of 97 women (56.7%) developed hallucinations during follow-up vs 71/180 (39.4%) men.
EDS: Excessive Daytime Sleepiness; PIGD: Postural-instability-gait disorder; LDE: Levodopa dosage equivalent; DA: Dopamine agonists.

Table 2.3: Summary of Cox Proportional hazards model for hallucinations in Parkinson's Disease

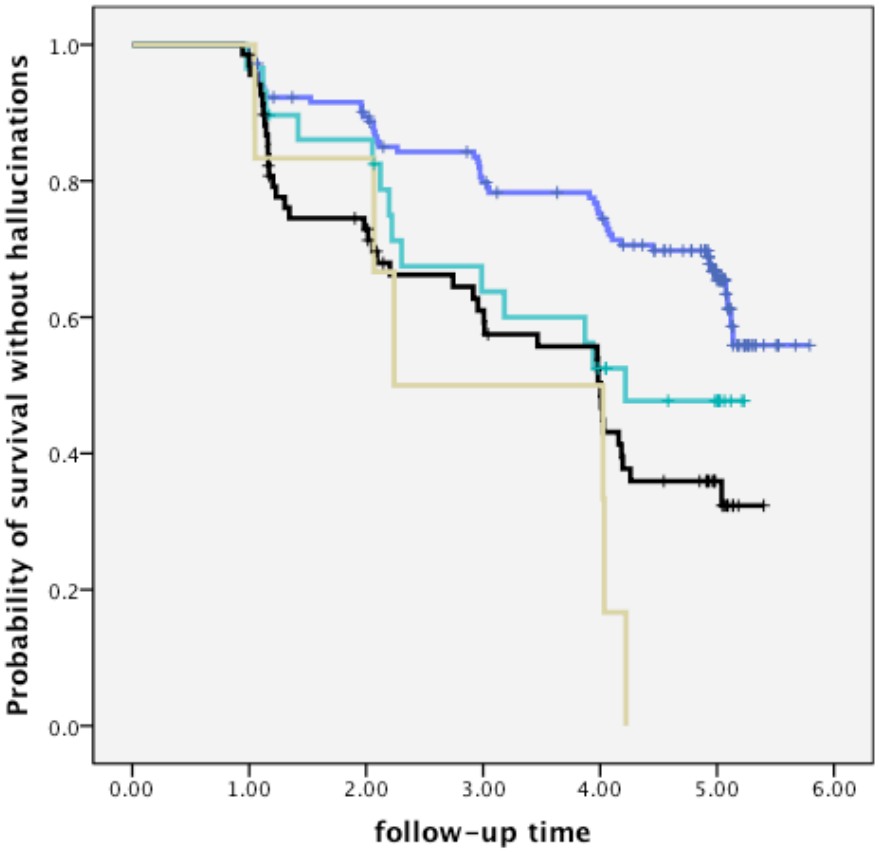
	Hazard Ratio (95% CI)	P-values
Sex, HR for females	1.619 (1.099-2.383)	0.015
Age at onset, yr	1.030 (1.011-1.049)	0.002
Dyskinesia score	1.164 (1.023-1.324)	0.021
SCOPA-SLEEP - EDS	1.087 (1.030-1.147)	0.003
SCOPA-AUT, total score	1.062 (1.019-1.106)	0.004
Age, yr	0.985(0.941-1.031)	0.803
Education, yr	1.008(0.955-1.063)	0.781
SCOPA-COG	0.994(0.955-1.035)	0.760
Beck Depression Inventory	1.005(0.969-1.041)	0.803
PIGD score	1.024(0.870-1.204)	0.778
Hoehn & Yahr stage	1.125(0.868-1.459)	0.372
Motor Fluctuations	1.166(0.972-1.400)	0.099
Total LDE	1.000(0.999-1.000)	0.238
Daily Levodopa Dose, mg	1.001(1.000-1.002)	0.156

All variables are expressed with hazard ratio (HR) with 95% confidence interval.
EDS: Excessive Daytime Sleepiness; PIGD: Postural-instability-gait disorder; LDE: Levodopa dosage equivalent; DA: Dopamine agonists.

Influence of Clinical Subtypes

Information on subtype classification was available for 247 of the 277 patients (89.2%) without hallucinations at baseline. Clinical subtypes could not be determined in the other patients because some values required for the correct classification were missing. In the model with adjustment for differences in age, sex, and disease duration, we found that patients with more severe disease and stronger progression (subtypes 3 and 4) had a significantly increased risk of developing hallucinations compared with those with subtype 1 (reference category). Compared with subtype 1 (HR=1), patients with subtype 2 had an HR of 1.40 (95% CI, 0.78–2.52), whereas patients with subtypes 3 and 4 had an HR of 1.80 (95% CI, 1.22–2.68) and 3.70 (95% CI, 1.60–8.57), respectively. Post hoc analyses showed no further differences in risks among subtypes 2, 3, and 4. Figure 2 shows the Kaplan–Meier curves of the 4 clinical subtypes. The log-rank test, a test that does not account for baseline differences between the subtypes, was significant at P<.001.

Figure 2.2: Kaplan-Meier curves displaying unadjusted risk for developing hallucinations for 4 clinical subtypes of PD.



1. mild symptoms

2. motor complications

3. non-dopaminergic symptoms

4. severe symptoms

DISCUSSION

The cross-sectional analysis showed that approximately 20% of the patients had hallucinations at baseline, whereas the longitudinal analysis showed that almost half the patients without hallucinations at baseline developed this symptom during the 5-year follow-up period. Variables that showed significant associations in the cross-sectional analyses largely corresponded to the risk factors that emerged as significant predictors by the longitudinal analyses, with the exception of disease duration, daily dopamine agonist dose, number of falls in the past year (significant only in the cross-sectional analyses), age at onset of PD symptoms, female sex, years of education, and presence of motor fluctuations (significant only in the longitudinal analyses). Risk factors reported in earlier studies that were confirmed by our longitudinal analyses were older age at examination, older age at onset, fewer years of education, higher H&Y stage, postural problems, impaired cognition, depression, excessive daytime sleepiness, and higher dose of levodopa.[3,7,13-15,33-35] With the exception of education, these factors all reflect to some extent the intricate relation between older age and advanced disease that underlies so many late complications of PD. Risk factors identified in the longitudinal analysis that have not been reported earlier as risk factors for hallucinations are female sex, autonomic dysfunction, motor fluctuations, and dyskinesias, and these risk factors will therefore be discussed in greater detail.

That female sex emerged as a risk factor neither in previous studies nor in our analysis of baseline data evidently leaves open the possibility that we are dealing here with a chance finding. However, the numbers on which the longitudinal analysis was based are quite robust: 55 of the 97 women (57%) versus 71 of the 180 men (39%) without hallucinations at baseline developed this symptom during follow-up. Because levodopa treatment was found to be associated with increased risk of developing hallucinations, one explanation might be that female PD patients have a higher sensitivity to dopaminergic medication.[36] This is partly supported by the finding that levodopa-induced dyskinesias, which also emerged as a risk factor in the longitudinal analysis, occur earlier in female patients[37] and by the observation that they were associated with hallucination scores in our study (r_s=0.227, P<.001). A possible explanation for the increased sensitivity to levodopa could be the greater amount of levodopa per kilogram, but our data did not support this assumption (4.06±4.72 mg/kg for women vs 3.93±4.53 mg/kg for men, P=.823). However, this does not rule out a potential effect of higher bioavailability and lower clearance of medication in female patients, possibly mediated by estrogen.[38] A difference in Lewy body deposition or amyloid-β plaques between men and women would also explain our findings,[39] although, to our knowledge, such a difference between male and female patients with PD has not been reported. A final possibility is that disease progression in women is faster, and given that disease

severity is associated with the risk of hallucinations, this could explain the observed result. This assumption is supported by findings from the Sydney Multicenter Study,[40] in which it was observed that women progressed at a similar rate to men until 8 years, when the severity of their disease as measured by Hoehn and Yahr stage became greater. Given the relatively long disease duration in our cohort (10.1±6.2 years for the total population at baseline, 13.1±6.2 years for those with hallucinations at baseline), this possibility should be explored. When we looked at the baseline data, we indeed found that men and women had similar disease duration (9.91±7.58 years for women vs 9.95±6.59 years for men, P=.959), but that women had a significantly higher mean H&Y score (2.75±0.93 for women vs 2.44±0.76 for men, P=.005). In addition to the arguments mentioned above, it should be considered that community-based studies on the occurrence of hallucinations in the general population have shown that women are at higher risk of experiencing hallucinations at some time during their lives than are men.[41] Therefore, future studies are needed to examine the main effect of sex and the possible interaction between sex and levodopa on the risk of developing hallucinations in PD.

That autonomic dysfunction has not been reported in earlier studies may largely be because to date its role in predicting hallucinations in PD has hardly been investigated. We found only 1 study, by Biglan et al,[3] who examined the role of comorbidity in PD and found that disturbances in more than 5 organ systems was a risk factor for hallucinations. In the present study we used the items of the SCOPA-AUT that pertained to 3 organ systems: the gastrointestinal tract, the urinary tract, and the cardiovascular system. We found that not only the total score but also the 3 separate scores were independently associated with future development of hallucinations (data not shown). This relation may be explained by more severe autonomic dysfunction reflecting more advanced disease; autonomic dysfunction has been identified before as 1 of a set of variables—together with axial, psychotic, and depressive symptoms, daytime sleepiness, and cognitive impairment—that form a strong independent factor (factor 1 in the study by van Rooden et al)[42] that is associated with disease severity (as measured by H&Y) and disease duration. It is not surprising that dyskinesias and motor fluctuations emerged as risk factors for hallucinations, because these complications are well documented side effects of long-term levodopa treatment.[43] That total LDE was not identified as an independent risk factor could have been because of the close relation between levodopa treatment and dyskinesias. To examine this, we removed dyskinesias from the multivariate model, after which the contribution of total LDE was found to be significant. Hence, long-term levodopa treatment may lead to dyskinesias, and both are associated with the occurrence of hallucinations. Subtype classifications were not available for 30 of the 277 patients (10.8%) without hallucinations at baseline. No significant differences in age, sex, disease duration, and H&Y stage were found between these 30

patients and the patients who were included in the analysis, which indicates that it is unlikely that the absence of information on subtype allocation poses a threat to the validity of our findings. Patients who were mildly affected by the disease (subtype 1) were less likely to develop hallucinations at any time during follow-up compared with patients with subtypes 3 and 4. Patients who were severely affected on all domains (subtype 4) eventually all developed hallucinations at some point during follow-up, although it should be noted that this involved only 6 patients. This further supports the notion that hallucinations are a symptom of more severe disease.

A limitation of our study is that we were not able to verify the relationship between some potential risk factors and the development of hallucinations because these variables were not evaluated at baseline. For example, visual disturbances and RBD are well-documented risk factors of visual hallucinations in PD reported in earlier studies[3,6,9,18] but were not included here. That the 28 patients who dropped out of the study in the first year had older age at onset and more advanced disease may have led to an underestimation of the HRs, but this did not affect the validity of our findings. Strong points of this study are the large number of patients, the longitudinal design, the broad characterization of the patients, and the long follow-up duration.

To summarize, hallucinations in PD are caused by a combination of risk factors that are associated with (the interaction between) older age and more advanced disease. Older age, older age at onset, longer disease duration, and more advanced motor symptoms, as well as more severe depressive and autonomic symptoms, cognitive impairment, sleep disturbances and higher levodopa dose are associated with development of these symptoms. This indicates that patients with these characteristics must be examined carefully for the presence of hallucinations, and more frequent follow-up should be considered. If symptoms are present, the medication regimen should be adjusted. The identification of female sex as a risk factor for developing of hallucinations in PD is a new finding and should be verified in future studies.

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