Minor Hallucinations Occur in Drug-Naive Parkinson’s Disease Patients, Even From the Premotor Phase

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ABSTRACT: Objectives: The description of minor hallucinatory phenomena (presence, passage hallucinations) has widened the spectrum of psychosis in Parkinson’s disease (PD). Minor hallucinatory phenomena seem to antedate the development of more severe hallucinations. Early detection of minor hallucinations may be useful for screening patients with more severe endophenotypes. Motivated by the observation of “de novo,” drug-naive PD patients reporting minor hallucinations, we aimed to prospectively identify “de novo” untreated PD patients experiencing hallucinatory phenomena, and to compare their clinico-demographic characteristics with those of untreated PD patients without hallucinations and healthy controls.

Methods: Screening and description of psychosis was assessed by the Movement Disorders Society Unified Parkinson’s Disease Rating Scale—Part I and a structured interview covering all types of psychotic phenomena reported in PD. Clinical, neuropsychological, and demographic data of PD patients with and without psychotic phenomena were compared with those of age- and education-matched healthy controls.

Results: Fifty drug-naive, “de novo” PD patients and 100 controls were prospectively included. Minor hallucinations were experienced in 42% (21 of 50) PD patients and 5% controls (P < 0.0001). Coexistence of passage and presence hallucinations was the most common finding. Unexpectedly, 33.3% of patients with minor hallucinations manifested these as a pre-motor symptom, starting 7 months to 8 years before first parkinsonian motor symptoms. The presence of minor hallucinations was significantly associated with presence of rapid eye movement sleep behavior disorder.

Conclusions: In this first study to prospectively analyze the frequency of minor hallucinatory phenomena in incident, untreated PD patients, hallucinations appeared as a frequent early non-motor symptom that may even predate the onset of parkinsonism.

Key Words: Parkinson’s disease; hallucinations; premotor; REM sleep behavior disorder; early untreated; drug-naive

Hallucinations are significantly more common in Lewy body disorders than in other neurodegenerative diseases.1-3 In parkinsonian disorders, visual hallucinations differentiate Parkinson’s disease (PD) from other non-Lewy-body causes of parkinsonism, predicting postmortem Lewy pathology with 93% accuracy.3 Hallucinations in PD have been considered a mental complication that appears within the second half of the disease.4 Nevertheless, minor hallucinatory phenomena, such as presence and passage hallucinations, have been described in up to 30% of patients in early stages of PD.2,5,6 Minor hallucinatory phenomena include presence hallucinations (or feeling of presence), passage hallucinations, and visual illusions. A presence hallucination is the vivid sensation that somebody (distinct from oneself) is present nearby, in the absence of sensory clues revealing a presence. Passage

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Funding agencies: The present research was funded by CIBERNED (Fundación CIEN, Instituto de Salud Carlos III, Spain).

Relevant conflicts of interest/financial disclosures: Nothing to report.

Received: 9 July 2015; Revised: 22 August 2015; Accepted: 1 September 2015

Published online 00 Month 2015 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.26432
hallucinations consists of a brief vision of a person, animal, or object passing sideways. Visual illusions are brief misperceptions of objects or living beings that differ from objective reality.7 Well-structured visual hallucinations tend to progress in frequency and severity,8 are a risk factor for dementia,9 and are linked to a higher mortality rate.10 Whether minor hallucinatory phenomena are an early marker of future disruptive psychosis or cognitive deterioration is unknown. Other nonmotor symptoms—such as rapid eye movement (REM) sleep behavior disorder (RBD), hyposmia, and depression—have been associated with higher risk of dementia11,12 and can help to detect more severe endophenotypes from the early stages of the disease. Such symptoms may even predate the appearance of parkinsonian motor symptoms and identify subjects at risk for PD.5,13

Epidemiological studies have linked dopaminergic agents (especially dopamine agonists, amantadine, and monoamine oxidase B inhibitors) with development of hallucinations,4,14 but the role of dopaminergic stimulation to elicit hallucinations is enhanced by progressive dysfunction of the amygdala and limbic structures.15,16 Cortical areas of visual processing17,18 and frontal areas involved in reality monitoring19,20 in fact, persistent visual hallucinations are associated with the spread of Lewy bodies in PD16 and dementia with Lewy bodies (DLB).21 Interestingly, historical descriptions of PD predate the appearance of parkinsonian motor symptoms and identify subjects at risk for PD.2,29

Motivated by our observation of “de novo,” drug-naive PD patients presenting minor hallucinations before any dopaminergic treatment was started, we aimed to prospectively identify “de novo” untreated PD patients experiencing hallucinatory phenomena. We compared their clinical, neuropsychological, and demographic data with “de novo” untreated PD patients without hallucinations, and age- and education-matched healthy controls.

## Methods

A prospective, longitudinal study was done of 50 “de novo,” drug-naive PD patients with a definite clinical diagnosis according to UK Parkinson’s Disease Society Brain Bank (UKPDSBB) criteria.23 All included patients accomplished steps 1 and 2 of UKPDSBB criteria, and three or more of the four first supportive positive criteria of step 3. All participants were recruited from a sample of outpatients attending the Movement Disorders Clinic at Hospital de la Santa Creu i Sant Pau in Barcelona. Because nonclinical auditory and visual hallucinations have been described in “healthy” elderly people,24,25 the presence of minor hallucinations was explored in 100 age-, sex- and education-matched healthy subjects that were recruited from volunteers, spouses, or friends of the patients.

The 1-year rule was used to distinguish DLB from PD with dementia.26 No patients with cognitive defects interfering with daily activities were included. Other exclusion criteria were history of major psychiatric disorders, cerebrovascular disease, and conditions known to impair mental status other than PD. We excluded patients with focal abnormalities in neuroimaging studies (magnetic resonance imaging was done on everyone within the past 18 months) or uncompensated systemic diseases (ie, diabetes, hypertension).

Each PD patient was interviewed regarding time from onset of parkinsonian motor symptoms, and disease duration was measured from onset of motor symptoms. Using the Movement Disorders Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) Part I,27 we assessed nonmotor aspects of experiences of daily living: cognitive impairment, hallucinations and psychosis, depressed mood, anxious mood, apathy, sleep problems, and daytime sleepiness. These symptoms were categorized as present whenever the score was 1 or higher. Patients were asked about the presence of hyposmia. The RBD screening questionnaire was administered to all patients, with a cutoff of 5 or higher indicating RBD.28

The Hallucinations and Psychosis item of the MDS-UPDRS is a clinical scale, rated on a 0 to 4 spectrum: 0 corresponds to absence of hallucinations; 1, illusions or nonformed hallucinations (presence and passage hallucinations, visual illusions); 2, formed hallucinations independent of environmental stimuli without loss of insight; 3, formed hallucinations with loss of insight; and 4, patients with delusions.27 The current version of the Hallucinations and Psychosis item of the MDS-UPDRS categorizes “illusions or nonformed hallucinations” as an early and slight (or minor) type of hallucination, known to be characteristic in PD.2,29

After a semistructured interview with patients and their relatives or caregivers, we further characterized psychotic phenomena. We assessed presence and passage hallucinations, visual illusions, well-structured hallucinations in various sensory modalities (visual, auditory, tactile, olfactory), and delusions (paranoid, jealousy, theft, self-referential) (see Supplemental Data). We collected information about when hallucinations started and how they evolved during the follow-up period after dopaminergic treatment was started.

During the follow-up, we collected information concerning current medications and drug dose (levodopa [l-dopa daily dose, and dopaminergic agonists−l-dopa equivalent daily dose]).30,31 Motor status and PD stage were assessed by the UPDRS and Hoehn & Yahr.32 Cognition was assessed in more detail in PD patients using the Parkinson’s Disease-Cognitive Rating Scale (PD-CRS)33 and the Mattis Dementia Rating Scale-2 (MDRS-2).34,35 The Snellen chart was used to assess visual acuity, and all PD patients and healthy controls had normal or corrected-to-normal vision.
Healthy controls were assessed using the Hallucinations and Psychosis item of the MDS-UPDRS, the semi-structured interview for psychosis, and the PD-CRS.

Student’s t tests and Mann-Whitney U tests were performed for clinical and demographic comparisons between drug-naive PD patients with and without hallucinations, and between PD patients and healthy controls. Significance was set at \( P < 0.05 \) for all analyses, performed using SPSS 19.0 (SPSS, Chicago, IL).

Informed consent to participate in the study was obtained from all participants or caregivers as appropriate. The study was approved by the Local Ethics Committee.

## Results

### Sample

Fifty drug-naive “de novo” PD patients (aged 68.8 ± 10 years [range, 41-82]; disease duration, 19.5 ± 15 months [3-48]), and 100 healthy controls (HC; aged 66.8 ± 8 years [50-84]) were included. The groups did not differ in terms of age, education, or sex (Table 1). Mean PD-CRS and MDRS total scores were within the range of preserved cognition in newly diagnosed, drug-naive PD patients and HC (Table 1).

According to published PD-CRS cutoff scores for mild cognitive impairment (MCI) and dementia, 34% of PD patients scored within the MCI range, and no patient scored within the dementia range. Using the same cutoffs for the control group, 25% scored within the MCI range, and no control scored within the dementia range. Parkinson’s disease patients showed significant impairment in global cognitive function compared with healthy controls (PD-CRS total score, 84.2 ± 17 vs 94.2 ± 16; \( t, P = 0.001 \)).

### Frequency and Phenomenology of Hallucinations

We found that 21 of 50 (42%) newly diagnosed drug-naive PD patients (PD-mH) had minor hallucinations within the last 3 months. Only four of these 21 patients spontaneously reported this phenomenon. In the other 17 patients, minor hallucinations became apparent only after the structured interview. Healthy controls presented significantly fewer minor hallucinations (5/100; 5%) than PD patients (\( \chi^2; P < 0.0001 \)).

Phenomenology of the experienced hallucinations fits the clinical features described in the literature. Parkinson’s disease patients reported mainly passage and presence hallucinations, and visual illusions. Passage hallucinations were described as the fleeting and poorly defined vision of a shadow (10/21, 47.6%), a person (mostly anonymous people) (8/21, 38.1%), animals (running cats, rats, or dogs) (6/21, 28%), or undefined objects (6/21, 28%) passing sideways in the periphery of the visual field, and moving forward from behind the shoulder (see Video—Supplemental Data). Presence hallucinations were explained as the feeling of the presence of a person, in close proximity to and behind the shoulder, while sitting or engrossed in household tasks. In the case of presence hallucinations, and contrary to passage hallucinations, patients were more likely to “feel the presence” of a known person (partner, siblings, caregiver, deceased spouse). All PD-mH patients with either passage or presence hallucinations turned their head to try to see that person, animal, or object. Additionally, seven patients, always in association with passage or presence hallucinations, reported visual illusions (eg, movement of doorknobs or curtains, undefined images emerging from a patterned sofa or wallpaper); two patients had olfactory hallucinations (smells of burning wood and plastic); two patients had transient and simple visual hallucinations (insects crawling on the kitchen table, vision of faces through the bedroom window); and one patient had auditory hallucinations (someone knocking on the door, and footsteps inside the apartment). Insight about the hallucinatory nature of the phenomenon was preserved in all patients. Regarding their frequency, 57.1% PD-mH patients had both presence and passage hallucinations, 28.6% had isolated passage hallucinations, and 14.3% had isolated presence hallucinations. Hallucinations were present more than once per week in 57.1% of hallucinators. Patients with combined passage and presence hallucinations had minor hallucinations more than once per week, whereas those with isolated passage or presence hallucinations had hallucinations less than once per week but more than once per month.

At baseline, the 21 PD-mH patients reported that hallucinations started 19 ± 23 months (3 months to 9 years) before a diagnosis of PD was given, and before
any dopaminergic drug was initiated. In 7 of 21 (33.3%), the hallucinations manifested as a premotor symptom, starting 20.8 ± 28 months (7 months to 8 years) before the onset of the first parkinsonian motor symptoms.

The hallucinations found in HC were very similar to those explained by PD patients, although they reported mostly presence hallucinations. The five healthy subjects with hallucinations reported presence hallucinations very occasionally (once to three times per year), and one of them also experienced passage hallucinations during the last year. In healthy subjects, establishing when hallucinations began was not possible, but none of them remembered to have experienced these phenomena when they were young.

The PD-mH patients were followed up for 4.4 ± 1.5 (range, 2-8) years. Only three patients were lost to follow-up. Two patients died of diseases unrelated to PD (cancer), and one patient moved to another city. Both PD-mH and PD-NH patients were treated with l-dopa or dopamine agonists. At last follow-up visit, total l-dopa equivalent doses did not differ between groups (PD-mH 364 ± 248 mg/d vs PD-NH 260 ± 56 mg; P = 0.33). During the follow-up, hallucinations disappeared in 2 of 21 (9.6%) patients, remained stable in 11 of 21 (52.3%), and worsened in 8 of 21 (38.1%). In this latter group, the frequency of minor hallucinations increased, and six patients developed well-structured visual hallucinations. Stable PD-mH patients described periods in which they had isolated presence hallucinations, isolated passage hallucinations, or both phenomena, but they did not develop well-structured hallucinations. Stable PD-mH patients recalled the hallucinations to be weekly or monthly.

Only three of 21 (14.2%) PD-mH patients, aged 78, 81, and 82 years, progressed to dementia. These three patients were part of those PD patients whose hallucinations worsened during the follow-up, and among those six patients who developed well-structured visual hallucinations. Dementia was diagnosed at 3, 4, and 6 years of follow-up, and all three were receiving monotherapy with l-dopa. In these patients, minor hallucinations progressed in severity and frequency, and well-structured vivid visual hallucinations with loss of insight emerged. One patient also developed reduplicative paramnesia.

Presence of delusions in this study was assessed by the Hallucinations and Psychosis item of the MDS-UPDRS part I, but no structured questions were designed for screening paranoid, jealousy, theft, or self-referential delusional thoughts. We did not find delusions in “de novo” PD patients or controls.

**Comparison of “De Novo” Drug-Naive PD Patients With and Without Hallucinations**

Table 2 compares demographic, clinical, and neuropsychological data between PD-mH and PD-NH patients. The only difference between PD-mH and PD-NH patients was age and the presence of RBD. Patients with hallucinations were older (71.1 ± 7 vs 65.8 ± 12 years; P = 0.062), and RBD was significantly more frequent in PD-mH patients at baseline (37.8% vs 10.3%; P = 0.03). No differences were observed regarding the presence of hyposmia, depression, anxiety, apathy, insomnia, or daytime sleepiness. Global cognitive function and performance on the cognitive domains covered by the PD-CRS and the MDRS did not differ between groups (Table 3).

Compared with HC, PD-mH patients had significantly more cognitive impairment (PD-CRS 85.0 ± 18 vs 95.1 ± 16; P = 0.001), higher age (71.1 ± 7 vs 66.3 ± 10 years; P = 0.053), and higher frequency of anxiety, depression, and apathy (χ²; P = 0.01), but did not differ in educational level (P = 0.12).

**Discussion**

This prospective analysis of hallucinatory phenomena in incident, untreated patients characterizes minor hallucinations in PD as a frequent and very early non-motor symptom that may even predate the onset of parkinsonian motor symptoms.

The frequency of 42% of minor hallucinatory phenomena in newly diagnosed drug-naive PD patients is higher than in previous studies. Because clinical and demographic data of our patients are comparable to previous series, the difference can be explained by the systematic use of a specific interview that emphasized...
in early PD searched only for the presence of well-formed visual hallucinations, which may occur independently of medications. In a recent cross-sectional study of untreated PD patients, the prevalence of psychosis with the MDS-UPDRS Part I was 3% at baseline, increasing to 10% after 24 months. Notably, if we had used similar diagnostic tools and searched only for structured hallucinations, we would have identified only five patients (10%) with hallucinations.

The phenomenology of hallucinations found in this study fits prior descriptions. Both presence and passage hallucinations were more frequent than visual illusions or misinterpretations, and coexistence of passage and presence hallucinations was the most common finding. The mild evolution of cognitive dysfunction through a mean follow-up of 4 years rules out the diagnosis of DLB, and the significant difference in the frequency of minor hallucinatory phenomena in matched HC suggests that minor hallucinations are phenomena linked to PD.

In our series, the presence of minor hallucinations in “de novo” untreated patients was significantly associated with the presence of possible RBD, with a trend for older age. Patients with or without hallucinations, however, did not differ in depression, anxiety, apathy, daytime sleepiness, or cognitive performance. Well-formed hallucinations in nondemented PD patients have been associated with older age, depression, cognitive impairment, daytime sleepiness, and RBD. Two recent studies have not shown a significant correlation of cognitive dysfunction with measures of global cognitive performance or delusions. Regression analyses have shown well-structured hallucinations to be independently associated with RBD in advanced PD patients, and Lee et al showed that severity of RBD symptoms correlated with psychosis in early PD patients without cognitive impairment. These data suggest that screening for RBD could be useful for selecting patients with a more aggressive form of PD and higher risk of psychosis or dementia.

The association of cognitive impairment with development of visual hallucinations remains controversial. In a previous study that described the neuropsychological features of different types of hallucinations in PD, patients with minor hallucinations did not differ significantly from healthy controls in neuropsychological performance, whereas patients with well-formed visual hallucinations and insight retained had more executive dysfunction. Two recent studies have not shown a significant correlation of psychosis with measures of global cognitive dysfunction, although Morgante et al observed that decline in cognitive performance after 24 months of follow-up correlated with a higher cumulative prevalence of well-structured hallucinations. These studies suggest that neural systems other than those involved in cognitive performance contribute to the genesis of milder hallucinations. They also could indicate that tools more sensitive for specific cognitive functions (ie,
visuospatial processing, limbic system dysfunction) should be used to screen for the earliest cognitive systems involved in psychosis development. In the current study, the lack of association between hallucinations and neuropsychological performance could be attributable to the lack of a systematic assessment of visuospatial and visuoperceptual functions in the neuropsychological battery used.

Likewise, the lack of a relationship of minor hallucinations with depression, anxiety, or apathy, which have been previously and clearly related to visual hallucinations, suggests that dysfunction at different neural systems may be necessary for minor hallucinatory phenomena to become more structured and severe. Different brain structural alterations have been associated with minor and formed hallucinations. We recently reported minor hallucinations in early PD to be associated with a restricted decrease of gray matter volume in areas of the dorsal visual stream. Well-structured hallucinations, however, have been associated with more extensive loss of gray matter in the ventral and dorsal visual stream, prefrontal cortex, limbic system, and anteromedial temporal areas.

The description of visual illusions and minor hallucinations in early PD is not novel. However, a novel finding of this study is the observation that minor hallucinatory phenomena may appear not only before starting dopaminergic treatment, but long in advance of the onset of parkinsonian motor symptoms. One third of patients with minor hallucinations manifested hallucinations between 7 months and 8 years before the onset of motor symptoms. As far as we know, this is the first series to specifically report minor hallucinations as a premotor symptom. In a recent pathological study, 33% (2 of 6) of living subjects without Parkinsonism but with α-synuclein aggregates in epicardial fat tissue reported visual hallucinations, compared with 4% (2 of 49) of those without incidental Lewy bodies. We have not found other contemporary studies in which hallucinations have been described as a premotor phenomenon.

As previously reported, the frequency of olfactory and auditory hallucinations in our series was lower than that of minor hallucinations. However, these nonvisual hallucinations were present in incident drug-naïve patients, which reinforces the concept that hallucinations in all sensory modalities may be taken into account in the assessment of psychosis in PD.

Only few subjects in the control group were found to experience minor hallucinations. The frequency of nonclinical auditory hallucinations in the general population is higher (up to 15%), whereas the prevalence of Charles Bonnet syndrome in healthy elderly people is much lower (1%). However, no previous studies describe the presence of minor hallucinatory phenomena in elderly people, with the exception of the development of psychotic phenomena in conditions of bereavement. Different studies have observed that 50% to 60% of widowed people have hallucinatory experiences, either feeling the presence of, seeing, hearing, or talking to the deceased spouse. In our series, only eight of 50 PD patients were widowed, and only two of them had presence hallucinations concerning the deceased spouse.

With the present protocol, we cannot rule out the possibility that healthy participants with minor hallucinations suffer a subclinical form of a synucleinopathy. Long-term follow-up in these individuals, and epidemiological studies in larger populations of healthy controls and subjects at risk of developing PD, will further clarify whether minor hallucinations constitute a confident premotor marker of PD.

Some limitations of our study must be considered. We acknowledge that one of the potential weaknesses in this study is that evaluations were not blinded, so there was chance for biasing patients’ response. Patients and caregivers may be more likely to give more importance to uncommon perceptions or events than healthy subjects, and researchers may be more prone to find hallucinations in the PD group. In addition, given that the recruitment of the sample was carried out in a specialized movement disorders unit using a nonvalidated structured interview, generalizability of the high prevalence of minor hallucinations in drug-naïve PD patients should await replication in community-based patients. Third, using a screening questionnaire instead of formal sleep studies limits the confidence of RBD diagnosis, and because hyposmia was evaluated subjectively and no specific smell testing was performed, an association with olfactory impairments cannot be excluded. It is also a limitation that we did not include a formal hearing evaluation. Finally, the development of hallucinations was not systematically collected during the follow-up in PD patients without hallucinations at baseline, which does not allow making comparisons on the evolution of psychosis between drug-naïve PD patients with or without hallucinations.

In summary, we have observed minor hallucinatory phenomena in incident, untreated PD patients to be frequent and significantly higher than in well-matched healthy controls, to correlate mainly with the presence of RBD, and to manifest even in premotor stages. In addition, these results reinforce the hypothesis that the use of dopaminergic drugs is not mandatory for hallucinations to appear in PD.

A systematic search of minor hallucinatory phenomena in PD and analysis of their neuropsychological, behavioral, and imaging characteristics would help to early identify patients with more widespread disease and to establish their clinical implications and neurobiological correlates.
**Video legend**

Description of the passage and presence hallucinations experienced by a “de novo” PD patient before any dopaminergic treatment was started.

**Acknowledgements:** The authors are grateful to the patients and their families, and to healthy volunteers for their participation in this study and continued support of our research.

**References**


Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.