The changing face of Parkinson's disease-associated psychosis: a cross-sectional study based on the new NINDS-NIMH criteria.

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Abstract

New criteria for Parkinson's disease-associated psychosis (PDAP) were recently proposed by a NINDS-NIMH working group. We assessed 116 consecutive unselected outpatients with PD for the existence of psychotic symptoms during the previous month, using a structured questionnaire covering the whole spectrum of PDAP symptoms. Hallucinations occurred in 42% of the patients (visual: 16 %; non-visual: 35%), delusions in 4%, and minor symptoms in 45% (sense of presence, visual illusions, or passage hallucinations). The prevalence of PDAP was 43% when the usual definition was used (hallucinations and/or delusions) and 60% when the NINDS-NIHM criteria were used. Correlations between PDAP and patient characteristics varied with the definition of PDAP. These findings suggest that the epidemiology of PDAP should be re-evaluated with the new criteria. Minor symptoms and non-visual hallucinations are an important part of the PDAP spectrum, which has commonly been restricted to visual hallucinations and delusions.

In the context of Parkinson's disease (PD), the term psychosis usually refers to a mental state characterized by hallucinations and/or delusions. However, definitions have varied over the years, and the typical hallucinatory syndrome in PD encompasses other related phenomena.1 Recently, new criteria for PD-associated psychosis (PDAP) were proposed by an NIH-sponsored workshop (Table 1).2 According to these criteria, the diagnosis of PDAP requires at least one of the following features: hallucinations, delusions, sense of presence and visual illusions, occurring with a clear sensorium and a chronic course (thus excluding delirium). Most systematic studies of PDAP have focused on visual hallucinations, and few have included hallucinations in other sensory modalities, minor phenomena, or delusions. The main goal of this study was to document the full spectrum of psychotic symptoms in a population of consecutive PD outpatients, and to assess their prevalence based on two different definitions.

Patients and methods

The study population consisted of 116 consecutive outpatients seen in a movement disorder clinic. To be included, patients had to meet the UK Brain Bank criteria for probable PD,3 to be fluent in French, and if cognitively impaired, to be able to understand and answer the questionnaire. Demographic and clinical variables were recorded. The levodopa-equivalent daily dose was calculated using published equivalencies.4 The patients answered a structured questionnaire composed of ten qualitative items on hallucinations (visual, auditory, tactile, somatic, olfactory, and gustatory), minor phenomena (sense of presence, visual illusions, passage hallucinations), and delusions (see Appendix). The questionnaire was read verbatim to the patient. When necessary, precisions were added to check whether the answer was appropriate: for instance, patients reporting a sense of presence were asked if they actually saw an unreal person, which would have corresponded to a visual hallucination and not a sense of presence. Definitions of hallucinations and delusions were taken from the DSM–IV glossary.5 Minor phenomena were defined as previously described:6 illusions are misinterpretations of a real external stimulus (essentially visual), “sense of presence” refers to a vivid sensation that somebody is present nearby, when no one is there and no one is seen, and “passage hallucinations” consist of a brief vision of a person or an animal passing sideways. Passage hallucinations are not mentioned in the new NINDS-NIMH criteria and thus were not taken into account for the diagnosis of psychosis, Hereafter, hallucinations and/or delusions (excluding minor phenomena) are considered to correspond to the “usual definition” of PDAP. We also applied the NINDS-NIMH criteria (Table 1).

The data were analyzed with SPSS software version 14.0. Because most of the variables examined in this study had a skewed distribution, Spearman's rho correlation was used to study links between hallucinatory syndromes and demographic and clinical variables.

Results

The characteristics of the 116 patients are summarized in Table 2 .. None of the patients had delirium. The distribution of psychotic symptoms is shown in Figure 1 . Fifty patients (43%) had either hallucinations or delusions, thus fulfilling the usual definition of PDAP, while 70 patients (60%) fulfilled the NINDS-NIMH criteria for PDAP. Sixteen patients (14%) had at least two types of hallucination, 29

patients (25%) had at least two types of minor symptom, including 21 patients (18%) with both sense of presence and visual illusions. and 31 patients (27%) had at least one type of hallucination and one type of minor symptom. Only two patients had isolated passage hallucinations and were not considered “psychotic”. If passage hallucinations had been considered as a form of visual hallucinations, the prevalence of PDAP would have increased slightly (45% with the usual definition, 62% with the NINDS-NIMH criteria). The existence of visual and non visual hallucinations correlated with the presence of minor symptoms (respectively $r_s = 0.35$, $P < 0.001$, and $r_s = 0.22$, $P < 0.05$). The NINDS-NIMH and usual criteria for PDAP also correlated with one another ($r_s = 0.71$, $P < 0.001$).

The prevalence of PDAP, as defined with the usual and NINDS-NIMH criteria, correlated with the duration of PD ($r_s = 0.26$ and 0.25 respectively, $P < 0.01$), the Hoehn and Yahr stage while “on” ($r_s =$, 0.25 in both cases, $P < 0.01$) and the use of psychoactive drugs (rs = 0.18 and 0.23 respectively, $P < 0.05$). PDAP defined with the usual criteria also correlated with age ($r_s = 0.30$, $P < 0.01$), while PDAP defined with the NINDS-NIMH criteria correlated with the daily levodopa-equivalent dose ($r_s = 0.19$, $P < 0.05$). No significant correlation was found between PDAP and gender, manual laterality, age at onset, or the predominant side of parkinsonism.

Comments

The distribution of psychotic symptoms in this study was unexpected, non-visual hallucinations being about twice as frequent as visual hallucinations. Although auditory hallucinations are mentioned in some studies, with prevalence rates of between 0% and 22%,1 the frequency of hallucinations in other sensory modalities has rarely been systematically studied. As suggested by previous studies, tactile, and olfactory hallucinations, are not infrequent.7 –9 In a recent questionnaire-based study, 31 of 70 PD patients had hallucinations, including 24 patients (34%) with visual hallucinations, and 16 patients (23%) with non-visual hallucinations.9 Focusing on new-onset hallucinations, Goetz et al found that older patients were more likely to have nonvisual or mixed hallucinations than purely VH, suggesting that age may influence the distribution of the types of hallucinations.8 The high prevalence of non-visual hallucinations confirms that the use of detailed questionnaires is mandatory to capture the whole spectrum of hallucinatory symptoms.10 Another important implication of our findings is that explanatory models must integrate the polymodal nature of PDAP, whereas previous models have focused on visual hallucinations.11 ,12 Minor phenomena were present in 45% of our patients, compared to 25%,6 17%,13 and 72%14 of patients enrolled in prospective cross-sectional studies performed in movement disorder clinics. This discrepancy may be due to differences in the study populations, in the questionnaires, and in the time frame chosen to assess PDAP, which ranged from one to three months prior to the date of evaluation.

The prevalence rates found here should be interpreted with care, as outpatients attending a movement disorder clinic differ from unselected community-based patients. It is not clear in which direction this selection bias may influence the results, as both patients with mild uncomplicated PD (with a lower probability of PDAP) and institutionalized patients with more advanced PD (with a higher probability of PDAP) may be underrepresented in movement disorder clinics. We also acknowledge that the questionnaire we used has unknown psychometric properties.

Logically, we found differences in the prevalence of PDAP depending on the criteria used. Focusing on visual hallucinations, as in most studies, results in a truncated view of the spectrum of psychotic phenomena. Indeed, in our study only one-quarter of patients with PDAP had visual hallucinations. Moreover, the prevalence of PDAP differed depending on whether the “usual” or NINDS-NIMH criteria were used (43% and 60% respectively), because the latter encompass two frequent minor symptoms (sense of presence and visual illusions). The 60% prevalence is far higher than that found in previous cross-sectional studies, but most of these latter studies focused on a selection of psychotic symptoms, excluding visual illusions, sense of presence, and/or non-visual hallucinations, with the common exception of auditory hallucinations.1

Our aim was not to identify clinical factors associated with PDAP. Previous studies have repeatedly shown that several clinical factors are associated with visual hallucinations and PDAP, the most consistently found being dementia, a longer duration of PD, and/or an older age.1 However, we found that correlations with demographic and disease-related characteristics varied according to the criteria used to define PDAP and the psychotic symptom (Table 3). In other words, studies on associated factors may yield different results, and therefore different pathophysiological interpretations, depending on the chosen definition of psychosis. Interestingly, the use of psychoactive drugs (antidepressants, anxiolytics, and/or hypnotics) correlated with the presence of PDAP in our study, suggesting that polypharmacy, including the use of psychoactive drugs, should be taken into account in studies of facilitating factors and therapeutic strategies.15

In conclusion, this study suggests that the frequency of PDAP, and its associated clinical factors, should be revisited using the new NINDS-NIMH criteria. Minor phenomena and non-visual hallucinations are an important part of the PDAP spectrum, which has commonly been restricted to visual hallucinations and delusions.

APPENDIX

Parkinson's disease-associated psychotic symptoms questionnaire (questions relate to the past month).

Hallucinations

- Vous est-il arrivé de voir des personnes, des animaux ou des objets que les autres ne voyaient pas, qui n'étaient pas réellement là?

  Did you see any persons, animals, or objects that were not really there?

- Vous est-il arrivé d'entendre des sons, de la musique ou des bruits de voix que les autres n'entendaient pas?

  Did you hear any sounds, music or voices that others did not hear?

- Avez vous eu l'impression que quelque chose vous touchait ou bougeait sur votre peau sans explication apparente ?

  Did you have the feeling of something touching you or moving on your skin with no detectable cause?

- Avez-vous eu la sensation d'une transformation d'une partie du corps (plus grande, plus petite, déformée)?

  Did you have the feeling that part of your body was changing (larger, smaller, or distorted)

- Avez vous senti des odeurs sans raison apparente?

  Did you smell things with no detectable source?

- Avez-vous eu par moment un goût étrange dans la bouche sans raison apparente?

  Did you experience an unusual taste with no detectable cause?

Minor psychotic phenomena

- Avez-vous eu la sensation forte d'une présence, que quelqu'un était là, alors qu'il n'y avait en réalité personne?

  Did you have a vivid impression of a “presence”, of somebody being there, when in fact nobody was there?

- Vous est-il arrivé de voir autre chose à la place d'un objet réel, par exemple de voir une personne ou un animal à la place d'un buisson ou d'un arbre, ou encore un insecte à la place d'une tache sur le sol?

  Did you see something else instead of a real object, for example a person or an animal instead of a bush or a tree, or an insect instead of a spot on the floor?

- Avez-vous eu la sensation de voir un animal ou une personne passer brièvement sur le côté, alors qu'il n'y avait rien?

  Did you have the impression of seeing an animal or a person passing briefly sideways across your field of view, when in fact there was nothing there?

Delusions

- Avez-vous eu parfois des idées bizarres, par exemple le sentiment qu'on cherchait à vous nuire, à vous voler, ou que des personnes de votre entourage vous trompaient?

  Did you have any unusual ideas, for example the impression that somebody wanted to harm you, or steal from you, or that someone close was trying to deceive you?

Footnotes:

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References:

- 1 . Fénelon G . Psychosis in Parkinson's disease: Phenomenology, frequency, risk factors, and current understanding of the pathophysiologic mechanisms . CNS Spectrums . 2008 ; 13 : (suppl 4) 18 - 25
- 2 . Ravina B , Marder K , Fernandez HH . Diagnostic Criteria for Psychosis in Parkinson's disease: Report of an NINDS/NIMH Work Group . Mov Disord . 2007 ; 22 : 1061 - 1068
- 3 . Gibb WRG , Lees AJ . The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease . J Neurol Neurosurg Psychiatry . 1988 ; 51 : 745 - 752

- 4 . Thobois S . Proposed dose equivalence for rapid switch between dopamine receptor agonists in Parkinson's disease: a review of the literature . Clin Ther . 2006 ; 28 : 1 - 12
- 5 . American Psychiatric Association . Diagnostic and statistical manual of mental disorders . 4 (DSM IV) Washington, DC American Psychiatric Association ; 1994 ;
- 6 . Fénelon G , Mahieux F , Huon R , Ziégler M . Hallucinations in Parkinson's disease. Prevalence, phenomenology and risk factors . Brain . 2000 ; 123 : 733 - 745
- 7 . Chou K , Messing S , Oakes D . Drug-induced psychosis in Parkinson disease: phenomenology and correlations among psychosis rating instruments . Clin Neuropharmacol . 2005 ; 28 : 215 - 219
- 8 . Goetz CG , Wuu J , Curgian L , leurgans S . Age-related influences on the clinical characteristics of new-onset hallucinations in Parkinson's disease patients . Mov Disord . 2006 ; 21 : 267 - 270
- 9 . Papapetropoulos S , Katzen H , Schrag A . A questionnaire-based (UM-PDHQ) study of hallucinations in Parkinson's disease . BMC Neurol . 2008 ; 8 : 21 -
- 10 . Fernandez HH , Aarsland D , Fénelon G . Scales to Assess Psychosis in Parkinson's disease: Critique and Recommendations . Mov Disord . 2008 ; 23 : 484 - 500
- 11 . Diederich NJ , Goetz CG , Stebbins GT . Repeated visual hallucinations in Parkinson's disease as disturbed external/internal perceptions: focused review and a new integrative model . Mov Disord . 2005 ; 20 : 130 - 140
- 12 . Collerton D , Perry E , McKeith I . Why people see things that are not there: a novel Perception and Attention Deficit model for recurrent complex visual hallucinations . Behav Brain Sci . 2005 ; 28 : 737 - 57
- 13 . Pacchetti C , Manni R , Zangaglia R . Relationship between hallucinations, delusions and REM behavior disorder in Parkinson's disease . Mov Disord . 2005 ; 20 : 1439 - 48
- 14 . Williams DR , Warren JD , Lees AJ . Using the presence of visual hallucinations to differentiate Parkinson's disease from atypical parkinsonism . J Neurol Neurosurg Psychiatry . 2008 ; 79 : 652 - 655
- 15 . Poewe W . When a Parkinson's disease patient starts to hallucinate . Pract Neurol . 2008 ; 8 : 238 - 241

FIG. 1

Distribution of psychotic symptoms in 116 consecutive PD outpatients

Psychotic symptoms include hallucinations and delusions (white bars) and minor phenomena (grey bars). The proportion of patients with psychosis (black bars) is shown, based on the usual definitions (hallucinations or delusions) and the new NINDS-NIMH criteria (hallucinations, delusions, sense of presence, or visual illusions). Values are percentages.

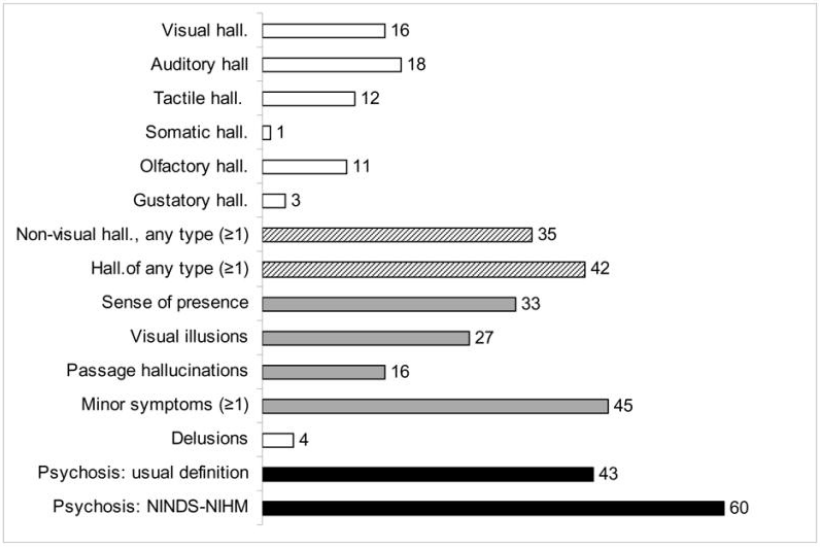

TABLE 1

NINDS-NIMH Diagnostic Criteria for PD-Associated Psychosis (adapted from reference [2])

Characteristic Symptoms
Presence of at least one of the following symptoms:
Illusions
False sense of presence
Hallucinations
Delusions
Primary Diagnosis
UK Brain Bank criteria for PD
Chronology of the onset of symptoms of psychosis
The symptoms in Criterion A occur after the onset of PD
Duration
The symptom(s) in Criterion A are recurrent or continuous for 1 month
Exclusion of other causes
The symptoms in Criterion A are not better accounted for by another cause of parkinsonism such as dementia with Lewy bodies, psychiatric disorders (…), or a general medical condition including delirium

TABLE 2

Characteristics of the 116 patients

Age (years)	67.0 (9.9)*
Gender (M/F)	75/41
Manual laterality (n)	
Right/Left/Ambidextrous	107/7/2
Age at onset (years)	57.9 (10.7)*
Predominant side of PD (n)	
Right/Left/Bilateral	53/54/9
Duration of PD (years)	9.1 (5.8)*
Hoehn and Yahr stage (in “on” state)	2.1 (0.8)*
Daily levodopa-equivalent dose (mg)	758 (429)*
Use of psychoactive drugs (n)**	46 (40%)
Use of clozapine (n)***	4 (3.4%)

* mean (SD);

** psychoactive drugs include antidepressants, anxiolytics, and hypnotics;

*** Clozapine was the only antipsychotic drug used in this population.