Epidemiology of psychosis in Parkinson's disease

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A B S T R A C T

Psychotic symptoms are frequent and disabling in patients with Parkinson's disease (PD). Methodological issues in the epidemiology of PD associated psychosis (PDP) include differences in the symptoms assessed, the methods of assessment, and the selection of patients. Most studies are prospective clinic-based cross-sectional studies providing point prevalence rates in samples on dopaminergic treatment. Visual hallucinations are present in about one quarter to one third of the patients, auditory in up to 20%. Tactile/somatic, and olfactory hallucinations are usually not systematically sought. Minor phenomena such as sense of presence and visual illusions affect 17 to 72% of the patients, and delusions about 5%. Lifetime prevalence of visual hallucinations reaches approximately 50%. Prospective longitudinal cohort studies suggest that hallucinations persist and worsen in individual patients, and that their prevalence increases with time.

A facilitating role of treatment on PDP is demonstrated at least for dopaminergic agonists, but there is no simple dose–effect relationship between dopaminergic treatment and the presence or severity of hallucinations. The main endogenous non-modifiable risk factor is cognitive impairment. Other associated factors include older age/longer duration of PD, disease severity, altered dream phenomena, daytime somnolence, and possibly depression and dysautonomia. PDP reduces quality of life in patients and increases caregiver distress, and is an independent risk factor for nursing home placement and development of dementia.

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1. Introduction

Besides the cardinal motor symptoms, Parkinson's disease (PD) may be associated with a large spectrum of non-motor symptoms, including cognitive impairment and neuropsychiatric disturbances [1]. Psychotic symptoms are common in patients with PD. Long regarded as mere side effects of the dopaminergic treatments, psychotic symptoms are now viewed as resulting from complex interactions between disease and treatment-related effects [2]. PD associated psychosis (PDP) leads to increased disability and poor quality of life in patients [3], and to greater stress in caregivers [4]. Its treatment is often a challenge for the clinician. We here review the epidemiologic aspects of PDP.

2. Methodological issues

2.1. Definitions, criteria, and assessment

Taking into account methodological issues is critical in interpreting published data and designing new studies on PDP. The first questions to be addressed are what data should be collected, and how to collect them. Psychosis is commonly defined as hallucinations, delusions, or both, in patients with a clear sensorium [5–7]. However, no definition is universally accepted. In early works, subjects with delirium were not necessarily excluded from studies of psychosis, as were not patients with other potentially confounding features such as severe depression or mania [5]. Moreover, the definition of psychosis outlined above does not encompass other “minor” psychotic symptoms commonly reported in PD, such as visual illusions and sense of presence. Therefore, new criteria for PDP have been recently provided by a NINDS/NIMH Work Group [8]. These criteria include hallucinations, illusions, false sense of presence, and visual illusions as characteristic symptoms, which have to occur with a clear sensorium and a chronic course, thus excluding delirium (Fig. 1). Although these criteria will be helpful in the future, available studies have included a variable array of psychotic symptoms, often limited to the sole visual hallucinations.

To identify and rate psychosis, the examiner relies on the patient's and/or the caregiver's accounts. As few patients (10–20%) spontaneously report their hallucinations [9,10], the information has to be sought by using specific questions or scales. However, there is no gold standard for the rating of psychosis [11,12]. Many studies have applied single items from the section I of the Unified Parkinson's disease Rating Scale (UPDRS) (item 3: “thought disorder”) or from the...
Neuropsychiatric Inventory (NPI) to assess psychosis, or more detailed self-constructed questionnaires or inventories. While the latter are useful to record the variety of psychotic symptoms, they do not allow rating. Scales for rating PDP include scales which have been specifically designed for PD but are generally insufficiently validated, or scales from the psychiatry field (e.g., the Positive and Negative Syndrome Scale or the Scale for Assessment of Positive Symptoms) or the dementia field, such as the Neuropsychiatric Inventory (NPI)[12]. Although some of these scales have interesting characteristics, a Movement Disorders Task Force concluded that a new scale should be developed [12].

2.2. Study population and study period
Most published studies on PDP comprised patients from movement disorders clinics, potentially leading to a selection bias. The consequences of this bias are unclear, as both mild uncomplicated PD (with a lower probability of PDP) and advanced stages in institutionalized patients (with a higher probability of PDP) may be underrepresented in movement disorders clinics. Patients were consecutive or selected patients, and inpatients or outpatients. Only few studies have been performed on community-based samples. The assessed time frame of PDP varied from the preceding week to the entire life. Finally, it should be emphasized that most studies were performed in a limited number of geographic areas. There is for instance a lack of data from African countries or many Asian subregions. Genetic and cultural influences could be important in the susceptibility to PDP and its phenomenologic expression [13].

3. Prevalence

3.1. Point prevalence in cross-sectional studies
Cross-sectional prevalence studies of PD patients [9,10,14–24] are summarized in Table 1. The prevalence rates for complex visual hallucinations (VH) are relatively homogenous, ranging from 22 to 38%. Values are scattered for auditory hallucinations (0 to 22%) and even more for minor psychotic symptoms (17 to 72%). The total prevalence of hallucinations or psychotic symptoms in general is hardly comparable between these studies because of a number of methodological differences, particularly a large variation in the range of psychotic symptoms investigated. Generally, tactile, olfactory and gustatory hallucinations were not assessed, although these types of hallucinations may be more prevalent than generally thought [25].

3.2. Longitudinal studies

3.2.1. Repeated point prevalences
Point prevalences of hallucinations have been repeatedly assessed during a few longitudinal studies of PD patients. The point prevalence rates increased from 33% (n = 89) to 55% (n = 49) after 6 years in a selected clinic-based sample [26], from 23% (n = 82) to 56% (n = 68) after 4 years in a community-based sample [27] and from 21% (n = 52) to 77% (n = 30) after respectively 15 and 20 years in patients originally included in a drug trial [28].

3.2.2. Period prevalence
Two long-term studies included de novo patients participating to drug trials. In a 4-year trial, the period prevalence of hallucinations was 17% [29]. In a 20-year follow-up of patients initially recruited in a bromocriptine trial, the period prevalence was 74% [28]. Another study was devoted to the follow-up of a community-based sample. The 12-year period prevalence was 42% [30].

3.2.3. Lifetime prevalence
In a retrospective study of 445 patients who had died with a pathologically confirmed diagnosis of PD, 50% had a history of visual hallucinations and/or minor psychotic symptoms [31].

3.2.4. Incidence
No published data on the annual incidence of PDP are currently available.

4. Associated factors
Historically, an emphasis has been put on the potential role of dopaminergic treatment, hence terms such as “dopaminergic” or “dopamimetic” psychosis [7]. However, other antiparkinsonian drugs or other treatments, such as analgesics, psychopharmaceuticals, or non-antiparkinsonian drugs with anticholinergic properties may
induce psychotic symptoms. Although pharmacological agents probably have a facilitating role, there is now a consensus on the prominent role of disease-related factors [2]. Genetic factors may also play a part.

4.1. Pharmacological factors

4.1.1. What is the prevalence of psychosis in untreated PD patients?

As early as in the end of the nineteenth century, PD patients could receive anticholinergic alkaloids, and, from the 1950s, synthetic anticholinergic. Moreover, after the pandemics of lethargic encephalitis, series often mixed up PD and post-encephalitic patients. Early data on PDP are thus scarce and difficult to interpret. However, although cases of hallucinations or delusions in patients with severe depression, confusion, or dementia were reported, there is no description in the early literature of the typical hallucinatory syndrome with a chronic course and a clear sensorium, as encountered nowadays [32]. Modern studies of early, untreated PD patients are rare. In a prospective study of such patients, visual hallucinations were present in 8 of 30 patients [9,10,14,15,17,19,21,23,40]. In only few studies the presence of hallucinations was associated with higher doses of dopaminergic drugs [41,42] or a different drug profile, including the use of DA [31,42] or of selegiline [43]. The explanation of this “dopaminergic paradox” is not trivial. There may be a bias due to the fact that physicians often decrease the doses of dopamine replacement therapy in patients with PDP. In addition, the specific influence of DA dose and of DA type (ergot versus non-ergot derivative) has not been assessed but might be critical.

4.2. Disease-related factors

4.2.1. Cognitive impairment

In clinical studies, the main disease-related factor associated with hallucinations and more severe psychotic symptoms is the existence of severe cognitive impairment or dementia. Prevalence studies consistently found hallucinations [9,21,40,44,45] (Table 2) as well as delusions [44] to be significantly more frequent in demented than non-demented PD patients. In line with this, both cross-sectional and longitudinal studies identified cognitive impairment and dementia to be independent risk factors for hallucinations [9,21,31,40,43,44,46]. In patients with early PD, a lower MMSE at baseline was associated with a higher risk of developing hallucinations on treatment [29].

4.2.2. Age and duration of PD

Older age [14,23], and a longer PD duration [9,15,47] are associated with the presence of hallucinations. These variables are intercorrelated. Multivariate analyses show that the duration of PD rather than the age at onset or at inclusion, is an independent predictor of VH [9,40,46], a result not replicated in the autopsy study of Williams et al. [31] where patients with Lewy body pathology (PD and dementia with Lewy bodies) were pooled for analysis. In most patients, hallucinations occur late in the disease course. Conversely, early hallucinations occurring in the first

### Table 1

Prevalence of psychotic symptoms in Parkinson’s disease in cross-sectional studies.

<table>
<thead>
<tr>
<th>Patients from movement disorders clinics [prospective studies]</th>
<th>n</th>
<th>Total prevalence</th>
<th>Visual hallucinations</th>
<th>Minor psychotic symptoms</th>
<th>Auditory hallucinations</th>
<th>Delusions</th>
<th>Study period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanchez-Ramos et al. [14]</td>
<td>214</td>
<td>26</td>
<td>26</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Graham et al. [15]</td>
<td>129</td>
<td>25</td>
<td>23</td>
<td>NA</td>
<td>12</td>
<td>7</td>
<td>Past and present</td>
</tr>
<tr>
<td>Inzelberg et al. [16]</td>
<td>121</td>
<td>37</td>
<td>37</td>
<td>NA</td>
<td>8</td>
<td>NA</td>
<td>Past and present</td>
</tr>
<tr>
<td>Fénelon et al. [9]</td>
<td>216</td>
<td>40</td>
<td>22</td>
<td>25</td>
<td>10</td>
<td>NA</td>
<td>Past 3 months</td>
</tr>
<tr>
<td>Holroyd et al. [10]</td>
<td>98</td>
<td>NA</td>
<td>27</td>
<td>1</td>
<td>3</td>
<td>NA</td>
<td>Past and present</td>
</tr>
<tr>
<td>Paleacu et al. [17]</td>
<td>276</td>
<td>32</td>
<td>NA</td>
<td>17</td>
<td>8</td>
<td>7</td>
<td>Past 6 months</td>
</tr>
<tr>
<td>Pacchetti et al. [18]</td>
<td>289</td>
<td>30</td>
<td>30</td>
<td>3</td>
<td>22</td>
<td>–</td>
<td>Past 3 months</td>
</tr>
<tr>
<td>Williams et al. [19]</td>
<td>115</td>
<td>75</td>
<td>38</td>
<td>72</td>
<td>22</td>
<td>–</td>
<td>Past month</td>
</tr>
<tr>
<td>Papapetropoulos et al. [20]</td>
<td>70</td>
<td>44</td>
<td>34</td>
<td>17</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients from movement disorders clinics [retrospective studies]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merims et al. [21]</td>
</tr>
<tr>
<td>Marsh et al. [22]</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients from the community [prospective studies]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aarsland et al. [23]</td>
</tr>
<tr>
<td>Schrag et al. [24]</td>
</tr>
</tbody>
</table>

Values are expressed as percentages. All the authors used a questionnaire on hallucinations, with the exception of Aarsland et al. who used the section I of the UPDRS. NA: not available.
months of dopaminergic treatment are suggestive of other psychiatric or degenerative conditions [48].

4.2.3. Severity of PD

Hallucinations are associated with a greater severity of PD as assessed with the UPDRS activities of daily living subscale [10,23] or the Hoehn and Yahr stage [14,47].

4.2.4. Sleep disorders

The possible association of sleep disorders with hallucinations has been the subject of extensive research. A strong association between hallucinations or psychosis and sleep disruption was found, and the authors suggested that the latter was an early feature of “levodopa psychosis” [49]. Others have found a close association between hallucinations and altered sleep phenomena (vivid dreams, nightmares, RBD) but not sleep fragmentation [50]. In a prospective longitudinal study, Goetz et al. [26] confirmed an association between hallucinations and the presence and severity of vivid dreams/nighmares but not other sleep aberrations, including sleep fragmentation. However, vivid dreams/nighmares did not independently predict future onset of hallucinations. Finally, daytime somnolence has been found to be a significant and independent predictor of VH [9].

4.2.5. Visual disorders

A lower visual acuity secondary to incident ocular disease is associated with a higher probability of experiencing VH in PD [10,51]. PD patients have reduced contrast sensitivity and color discrimination, which are more marked in PD patients with hallucinations than in non-hallucinating patients [52].

4.2.6. Depression

Studies of the relationships between depression and psychosis or hallucinations yielded inconsistent results. Most investigators found a positive association [10,14,16,47,53] while others found that this association was not maintained in multivariate analysis [9] or was negative (with more depression in non-hallucinators) [15]. Using a comprehensive assessment of the psychiatric status of PD patients with psychosis (hallucinations and/or delusions), Marsh et al. [22] found a high rate of co-morbid psychiatric disorders, especially depressive disorders, while Weintraub et al. [42] found that co-morbid psychosis and depression did not occur more frequently than expected by chance.

4.2.7. Dysautonomia

In the retrospective autopsy study of Williams et al. [31], autonomic dysfunction was an independent predictor of onset of VH in patients with Lewy body pathology.

4.3. Genetic studies

In one study, hallucinations were associated with a positive family history of dementia [17], suggesting a role for genetic factors. A few studies investigated the association of hallucinations or psychosis with genetic polymorphisms. Studies examining the allele frequencies or distribution of genotypes between PD subjects with and without hallucinations for the dopamine receptor genes and the dopamine transporter yielded inconsistent results [54–56]. An association of VH with a cholecystokinin [CT/TT] and a combination of cholecystokinin [CT/TT] and cholecystokinin-A receptor [TC/CC] genotypes have been found in two studies [57,58], suggesting that the cholecystokinin system may influence the development of hallucinations in PD subjects. Finally, no association of VH in PD with polymorphisms of serotonin 5-HT2A receptor and transporter genes [59] nor with HLA typing [60] was found.

5. Course and prognosis

5.1. Clinical course

In two independent studies, it was found that 14% of 29 hallucinators (hallucinations, illusions) at baseline were non-hallucinators at four years [61] and that 17% of 53 hallucinators (visual, auditory, minor phenomena) were non-hallucinators at one year [62]. In the first study, having hallucinations at baseline and at any given assessment was a strong predictor at all subsequent assessments of continued hallucinations. Hallucinations not only persist, they worsen: during a three-year follow-up, 39 (81%) of 48 PD patients with hallucinations and retained insight had progressed to more severe forms of psychosis characterized by loss of insight and (or) delusions [63]. Recently, it has been suggested that early antipsychotic drug treatment in patients with “mild” hallucinations may reduce the risk of later deterioration towards more severe psychosis [64].

5.2. Prognosis

5.2.1. Nursing home placement

In a small case-control study of 11 patients admitted to nursing homes, hallucinations were more frequent than in 22 matched controls in the community [65]. During a 26-month prospective study of 59 patients enrolled in a trial of clozapine, the proportion of patients admitted to nursing homes increased from 12% to 42% [66]. However, predictors of nursing home placement were older age and paranoia, but not hallucinations. Finally, in a 4-year prospective study of community-based sample of 178 patients, Aarsland et al. [67] found that 26% were admitted to a nursing home, and that hallucinations were an independent predictor of this endpoint, together with old age, functional impairment, and dementia.

5.2.2. Dementia

In two longitudinal studies, hallucinations at baseline were an independent risk factor for later developing dementia [68,69].

5.2.3. Mortality

A higher mortality was found in PD patients with hallucinations who had entered nursing homes than in controls living in the community [70]. Psychosis is associated with dementia which
predicts increased mortality risk in PD [71]. However, evidence that hallucinations or psychosis constitute an independent risk factor for mortality is presently lacking.

6. Conclusion

Several methodological issues contribute to the variability of the estimates of the prevalence of psychosis. The lifetime prevalence of psychotic symptoms is over 50%, and the more prevalent symptoms are hallucinations or psychosis. The lifetime prevalence of hallucinations or psychosis constitutes an independent risk factor for dementia in Parkinson’s disease. A prospective study. Mov Disord 2007;22:938–43.

References


