Prevalence, associated factors and phenomenology of psychosis in patients with Parkinson’s disease (PD)

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Abstract

Introduction: Psychosis associated with Parkinson’s disease is a major neuropsychiatric complication; it has been reported that 60% of patients will develop psychosis during the disease evolution. Its pathophysiology is multifactorial and clinically psychotic phenomena include minor hallucinations and confusional states. Material and Methods: We performed a cross-sectional study in patients with Parkinson’s disease from a tertiary hospital using a thoughtful neurological and neuropsychiatric evaluation along with specific scales for non-motor symptoms, depression, cognition, and presence and severity of psychotic symptoms and hallucinations. Results: We included a total of 236 patients with Parkinson’s disease, of which 33 (13.9%) patients met the criteria for psychosis at the time of the evaluation. Visual hallucinations were the most common symptom. Age (p = 0.004), age at onset of the disease (p = 0.007) and its duration (p = 0.004), use of levodopa (p = 0.02), and use of amantadine (p = 0.004) were the main factors associated with the presence of psychosis. Conclusion: Psychosis in Parkinson’s disease is a relatively common manifestation and is mainly associated with clinical and demographic factors. Early recognition will optimize management and improve the quality of life of patients and their caregivers. (Gac Med Mex. 2015;151:157-63)

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Introduction

Psychotic symptoms are common in Parkinson’s Disease (PD). Prevalence of psychosis in PD has been reported to range between 16 and 75%, depending on the employed methodology, the study population and definition1-4. Psychosis in PD has a high impact on disease evolution and is associated with physical, cognitive and affective disability, as well as excessive burden for the caregiver5,6.

The risk of visual hallucinations is 50-60% over the course of the disease7,8, with an increase as it progresses9,10. Traditional conceptualization of the pathophysiology of psychosis in PD has focused on dopaminergic overstimulation at the mesocorticolimbic circuit; the presence of hallucinations in PD has also been associated with the presence of Lewy bodies in...
the amygdala. Finally, visual hallucinations in PD have been proposed to originate in the visual pathway dysfunction at off-periods (state with no beneficial effect of medication on motor symptoms) and in pontine cholinergic and noradrenergic structures at on-periods (clinical state with beneficial effect of medication on motor symptoms).

As for anti-parkinsonian medication, especially dopaminergic drugs, there is a non dose-dependant relationship of the treatment and the presence or severity of psychotic symptoms. The main endogenous, non-modifiable risk factors are cognitive impairment, age of the patient, age at disease onset, duration and severity of the disease, sleep disturbance phenomena, daytime sleepiness, depression, dysautonomia, onset of motor symptoms in right hemibody and female sex.

Clinical profile of psychosis in PD is different from that in other psychotic disorders and, therefore, definitions and measuring instruments used in other psychiatric conditions have by themselves little usefulness to describe and quantify the psychotic phenomenon in PD. Clinical spectrum includes mainly visual hallucinations and confusional or delirious states, but there are symptoms referred to as minor psychotic phenomena, including sense of presence or passage hallucinations, delusions and illusions, which generally have been excluded from studies on psychosis in PD because they are not considered in the definition of psychosis of the DSM-IV-TR. Another characteristic aspect of PD-associated psychosis is the preservation of introspection at initial phases: i.e., the subject knows that hallucinations are false and, as a consequence, personality changes or disorganized thinking are infrequent.

Currently, the use of the National Institute of Health (NIH), the National Institute of Neurological Diseases and Stroke (NINDS) and the National Institute of Mental Health (NIMH) criteria is recommended to define and standardize psychosis characteristics in PD.

The purpose of the present work is to determine the prevalence of psychosis among Mexican patients with PD treated in the National Institute of Neurology and Neurosurgery, as well as to describe clinical and demographic characteristics and factors associated with the presence of psychosis.

Material and methods

Consecutive patients treated in the National Institute of Neurology and Neurosurgery of Mexico City, diagnosed with PD using the United Kingdom Brain Bank criteria, from either sex, with an age ≥ 40 years at motor symptoms onset and on antiparkinsonian treatment for at least 6 weeks were included. The recorded demographic variables included: gender, laterality, age in completed years, family history of Parkinson, family history of dementia and psychiatric disorders. Data collected on PD included time of evolution since the onset of motor symptoms, hemibody where motor symptoms started, current antiparkinsonian treatment and use of psychotropic medications, with levodopa equivalent daily dose calculation; this last concept is used to directly compare doses of different antiparkinsonian drugs.

A neurologist with experience in movement disorders performed the neurological evaluation. PD severity was determined using the Hoehn and Yahr (HY) stages, while motor assessment was performed using part 3 of the modified Unified PD Rating Scale III (UPDRS III). Additionally, Beck’s Depression Inventory (BDI) and the Mini Mental State Examination (MMSE) were applied.

The Spanish language version of the Non-motor Symptoms Questionnaire (NMSQuest) was applied to all participants. In case of positive answers to items related to hallucinations or illusions, the psychosis diagnosis based on NINDS/NIMH criteria was intentionally assessed by means of a structured interview (Table 1). Once the diagnosis was verified, the Positive and Negative Syndrome Scale (PANSS) was applied to these patients, as recommended by the Movement Disorder Society (MDS), in order to determine the presence of psychosis and its severity. The PANSS was applied on the same day by a neuro-psychiatrist blinded to other clinical aspects of the patient.

Additionally, two instruments were applied in order to assess, in a standardized form, characteristics of these patients’ hallucinations. The Tottori University Hallucination Rating Scale (TUHARS) comprises 5 items evaluating the type, frequency and severity of hallucinations, the burden to the caregiver and nighttime psychiatric status. The instrument is applied both to the patient and the caregiver. The score is rated according to severity and it is calculated as the total sum of all questions. The University of Miami Parkinson’s Disease Hallucinations Questionnaire (UM-PDHQ) is comprised by 20 items divided into 2 domains: one of the quantitative type with 6 questions investigating the modality, frequency, duration, introspection or insight
Table 1. NINDS/NIMH diagnostic criteria for PD-associated psychosis

**Characteristic symptoms**
Presence of at least one of the following symptoms:
- Illusions
- False sense of presence
- Hallucinations
- Delusions

**PD primary diagnosis**
- United Kingdom Brain Bank criteria for PD

**Chronology of the onset of symptoms of psychosis**
- Psychosis symptoms occur after the onset of PD

**Duration**
- Psychosis symptom(s) is (are) recurrent or continuous for 1 month

**Exclusion of other causes**
Psychosis symptoms are not better accounted for by other cause of parkinsonism, including:
- Dementia with Lewy bodies. Psychiatric disorders such as schizophrenia, schizoaffective disorder, primary delusional disorder, mood disorders with psychotic symptoms or a general medical condition, including delirium

**Associated alterations**
- With/without introspection
- With/without dementia
- With/without treatment for PD

and emotional charge; and one of the qualitative type with 14 questions. This instrument allows for the frequency of hallucinations, their daytime/nighttime variation and its contents (persons, animals, objects, non-formed hallucinations) to be known31.

None of these instruments has been properly validated in PD, but they provide complete information on hallucinations’ phenomenology.

The descriptive statistical analysis was performed in terms of percentages for nominal variables, median and range for ordinal variables and mean and standard deviation for numeric variables. The bivariate analysis was performed using the chi-square test or Student’s t-test or its non-parametric equivalent (Mann-Whitney U-test). Significance was established at p < 0.05.

**Results**

A total of 236 PD-diagnosed patients were included, out of which 33 (13.9%) met the criteria for psychosis in PD. Clinical and demographic characteristics of the PD patients with and without psychosis are shown in table 2. Patients with psychosis were characterized for being older and for having PD with longer evolution time. With regard to the HY stage, statistical significance was obtained for the presence of psychosis when the mild stage was compared with moderate states of the disease (HY 1 and 2 versus 3, 4 and 5; p = 0.02).

With regard to antiparkinsonian treatment, 75.9% of the patients without psychosis and 93.9% of those with psychosis received treatment with levodopa (p = 0.02); additionally, patients with psychosis were receiving amantadine more frequently (15.3% vs. 36.4%; p = 0.004). There were no differences in

<table>
<thead>
<tr>
<th></th>
<th>PD patients without psychosis</th>
<th>PD patients with psychosis</th>
<th>p</th>
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<tbody>
<tr>
<td>n</td>
<td>203</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>96 (47.3%)</td>
<td>18 (54.5%)</td>
<td>0.44</td>
</tr>
<tr>
<td>No family history</td>
<td>175 (86.2%)</td>
<td>28 (84.8%)</td>
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<tr>
<td>Current age</td>
<td>61.1 ± 13.6)</td>
<td>68.2 ± 11.4</td>
<td>0.004*</td>
</tr>
<tr>
<td>Age at onset</td>
<td>52.6 ± 13.8</td>
<td>57.5 ± 12.5</td>
<td>0.007*</td>
</tr>
<tr>
<td>Duration of PD</td>
<td>8.4 ± 5.2</td>
<td>10.7 ± 4.8</td>
<td>0.004*</td>
</tr>
<tr>
<td>Predominance of tremor</td>
<td>142 (70%)</td>
<td>21 (63.6%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Right predominance</td>
<td>123 (60.6%)</td>
<td>24 (72.7%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Use of levodopa</td>
<td>(75.9%)</td>
<td>(93.9%)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Use of amantadine</td>
<td>(15.3%)</td>
<td>(36.4%)</td>
<td>0.004*</td>
</tr>
<tr>
<td>HY stage</td>
<td>2.4 ± 0.9</td>
<td>2.8 ± 0.7</td>
<td>0.06</td>
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*Statistically significant
the use of dopaminergic antagonists (p = 0.07), catechol-O-methyltransferase inhibitors (p = 0.36), monoamine oxidase inhibitors (p = 0.31) or anticholinergics (p = 0.45). Regarding the levodopa equivalent daily dose, there were also no differences between groups (618.3 ± 297.6 vs. 683.9 ± 355.7 mg; p = 0.28). In the case of dopaminergic agonists, the most widely used was pramipexole, with no difference in the daily dose between groups (1.7 vs. 2.3 mg/day; p = 0.13). The 2 x 2 table and the odds-ratio (OR) for the use of pramipexole and the presence of psychosis are shown in table 3.

Mean BDI score of patients with PD and psychosis was 18.6 ± 10.5, and for those without psychosis, 21.3 ± 5, with the difference failing to reach statistical significance (p = 0.081). Using a cutoff point of 16/17 in the BDI, patients with PD and psychosis had depression.

### Phenotypic characteristics of patients with PD and psychosis

The PANSS score for positive symptoms (PANSS-P) was 16.4 ± 6.4 (range: 0-25) and for negative symptoms (PANSS-N), 17.8 ± 8.5 (range: 0-39). The score for general psychopathology (PANSS-G) was 35.9 ± 13.3 (range: 0-111). Items 1 to 4 of the PANSS-P are of particular interest given the criterion used to define psychosis; delusions (item P1) were present in 45% of the sample; conceptual disorganization (item P2), in 10%; hallucinations (item P3), in 100% and excitement (item P4), in 15%.

When the TUHARS was applied, 90% (n = 18) of the patients had visual hallucinations; 60% (n = 12), auditory hallucinations; 20% (n = 4), tactile hallucinations, and only 10% (n = 2) had kinesthetic hallucinations. A total of 6 patients referred experiencing only one type of hallucinations (30%); 9 subjects (45%) experienced two different types of hallucinations and the remaining 35% had three or more types. With regard to

<table>
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<th>Table 3. Comparison between the use of pramipexole and the presence of psychosis in subjects with PD</th>
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<td>PD patients without psychosis</td>
</tr>
<tr>
<td>--------------------------------</td>
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<tr>
<td>No treatment with pramipexole</td>
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<tr>
<td>Treatment with pramipexole</td>
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CI: confidence interval.
The contents of visual hallucinations were reported as non-formed in 30% (n = 6) of the cases, as fragmented faces in 5%, as complete familiar persons in 35% (n = 7) and as unfamiliar in 30% (n = 6). Seventy-five percent of the patients referred not being able to “make them disappear”. Other referred characteristics included: in 30% of the cases, visual hallucinations produced sounds, in 80%, they had movement, in 65%, they had normal dimensions, in 85%, they were solid (opaque), in 70%, they had color and in 80%, their appearance was sudden.

Mean score of the TUHARS was 12.1 ± 5.2 (range: 3-21); on the other hand, mean score of the UM-PDHQ was 10.8 ± 3.5 (range: 4-14). The correlation between the scores in both instruments was high (rs = 0.70; p < 0.001).

Discussion

Psychosis in PD generally appears at late stages of the disease. Its prevalence ranges from 8 to 30%, depending on the instrument, the definition and the used criteria. The criteria employed in the present study include the presence of hallucinations, illusions, false senses of presence and delusion. Hallucinations are defined as a perception, generally sensorial, not corresponding to any real physical external stimulus, whereas illusion refers to the erroneous perception of a real external stimulus. False presence refers to the vivid sensation that somebody is near, when actually there is nobody present. Delusion (or delirious idea) refers to false beliefs based on erroneous or illogical inferences of reality; it is important not to confuse delusion with delirium, which is characterized for acute and fluctuating changes in the states of conscience, alertness and mood secondary to medical or toxic causes.

In the present study, the prevalence of psychosis using a screening instrument (presence of hallucinations or delusions) in a sample of 236 patients was 13.9%, and was confirmed in all cases with the use of specific criteria. This number is consistent with most of international publications. Hallucinations occurred in all subjects with PD-associated psychosis, and delusions, in 45%. Conceptual disorganization and excitement were much less frequent.

Currently, evidence suggests the existence of a multifactorial process in the genesis of psychosis in PD, since, in addition to dopaminergic disregulation, cholinergic and serotonergic systems are involved; dysfunction of the ventral-temporal portion of the base nuclei is associated with an accumulation of Lewy bodies in these structures, and there is evidence of dysfunction of the visual pathway and the pontogeniculocipital structures, which are responsible for REM sleep regulation; this dysfunction has been proven to be an independent risk factor for psychosis in Parkinson

Risk factors for the development of psychosis in patients with PD include antiparkinsonian treatment (particularly dopaminergic antagonists), duration of the disease, older age, severity of the disease, sleep disorders, cognitive impairment or dementia and depression. In the case of psychosis in early PD, factors such as cognitive symptoms and depression have been suggested to play a key role.

In the series of patients here presented, there are differences in current age and age at PD onset; both were higher in patients with psychosis, which is consistent with what was expected. Similarly, the time of evolution or duration of PD in years was longer in subjects with PD and psychosis. With regard to disease severity, subjects with PD and psychosis had also more advanced HY stages. Importantly, although this variable showed a tendency towards statistical significance, it is not possible to assure that the 0.4 difference, i.e., one stage, is clinically significant.

No differences were found in the type of motor onset (tremor, rigidity-bradykinesia or gait instability) between both groups. There were also no differences with regard to the side of motor onset, since patients with right onset (left cerebral hemisphere) have been reported to possible be at increased risk for suffering hallucinations and sleep disturbances.

Finally, with respect to the use of antiparkinsonian medications, there were no differences between groups on the proportion of patients using dopaminergic agonists. There were also no differences in dopaminergic agonists’ total daily doses between groups. As previously mentioned, dopaminergic agonists have been associated with psychosis in patients with PD, particularly in older subjects; the lack of association in the present study may be due to the used dose. The maximum dose of pramipexole, the most widely used agonist, is 4.5 mg/day, and in this study, patients without psychosis received 1.7 mg, whereas those with psychosis received 2.3 mg per day.

On the other hand, the proportion of subjects who used levodopa was higher in the group with PD and psychosis; in fact, practically all of them received some preparation with levodopa. Levodopa daily dose did not show statistically significant differences between both groups, as well as in levodopa daily equivalents.
This suggests that it is the use of levodopa, rather than the dose, what increases the risk of psychosis. However, it should be kept in mind that, in general terms, younger patients are initially treated with agonists, whereas in older subjects or in those with longer time of evolution, levodopa is the most widely used medication. Other variable probably involved and that was not reported in this study, is the daily dose adjusted to body weight or body mass index.

Other drugs of interest due to their potential risk for the induction of hallucinations are anticholinergics (biperiden and trihexyphenidyl)\textsuperscript{36}, in this topic, no differences were found.

In the final sample of patients with psychosis, three clinical instruments were applied to assess this disorder. To date, there is no instrument with sufficient metric properties to be recommended as the gold standard, and that’s the reason questionnaires and scales were chosen to complement each other and standardize information collection. In general terms, it can be established that most patients with PD and psychosis had visual hallucinations, that 70% of them had two or more different types of hallucinations, that more than half experienced these episodes every day and at least once, and that 20-30% of the patients considered them to be real, and the rest, to be mild and not to cause anxiety or discomfort.

As previously mentioned, the pathophysiology of psychosis in PD appears to involve disturbances in visual processing, disturbances in visual acuity and ophthalmologic conditions\textsuperscript{16}; 55% of the patients with PD and psychosis referred having been previously diagnosed with some ocular disorder in the corresponding item of the UM-PDHQ.

The main limitation of the study was the absence of a specific clinical instrument for psychosis in PD. However, it should be mentioned that the combined use of scales in this study satisfies the desired requirements for the detection of psychotic symptoms in PD. The PANSS scale allows for the quantification of symptom severity, in particular positive symptoms (illusions and hallucinations). To date, this scale has been used only in PD patients with psychosis secondary to drug therapy; however, in the positive symptoms section, a mean score ranging from 16.3 to 16.8 has been reported for those cases\textsuperscript{37-39}, similar to figures obtained in our patient sample.

The fact that the importance of ophthalmologic disturbances in the pathophysiogenesis of visual hallucinations in patients with PD has recently been established, together with the fact that more than half of the patients with psychosis in the present study referred these problems, makes the inclusion of a complete and structured assessment by the Neuro-Ophthalmology Service desirable.

In conclusion, psychosis in PD is a relatively common neuropsychiatric manifestation and, although it can be generated as an effect of antiparkinsonian medications, clinical factors such as older age and longer time of evolution appear to be the main associated factors. The fact of identifying these patients at higher risk for the development psychosis, will allow for treatment strategies to be optimized, in order to improve their quality of life and lighten the burden for the caregiver.

References