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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 definition[1-4]. 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 caregiver[5,6].

The risk of visual hallucinations is 50-60% over the course of the disease[7,8], with an increase as it progresses[9,10]. 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

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the amygdala[11-15]. 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)[16,17].

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[18,19].

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 psychtic 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 recommeded to define and standardize psychosis characteristics in PD[20].

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 clincal 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[21], 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[22].

A neurologist with experience in movement disorders performed the neurological evaluation. PD severity was determined using the Hoehn and Yahr (HY) stages[26,24], while motor assessment was performed using part 3 of the modified Unified PD Rating Scale III (UPDRS III)[25]. Additionally, Beck's Depression Inventory (BDI)[26] and the Mini Mental State Examination (MMSE)[27] were applied.

The Spanish language version of the Non-motor Symptoms Questionnarie (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[28.29]. The PANSS was applied on the same day by a neuropsychiatrist 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 cargiver 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[30]. The Universoty 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[20]

Characteristic symptoms
Presence of al 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 simptoms 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 known[31].

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-parametrc 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 psycosis 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 2. Main characteristics of the PD patients according to the presence or absence of psychosis

	PD patients without psychosis	PD patients with psychosis	p
n	203	33	
Female gender	96 (47.3%)	18 (54.5%)	0.44
No family history	175 (86.2%)	28 (84.8%)	0.83
Current age	61.1 ± 13.6)	68.2 ± 11.4	0.004*
Age at onset	52.6 ± 13.8	57.5 ± 12.5	0.007*
Duration of PD	8.4 ± 5.2	10.7 ± 4.8	0.004*
Predominance of tremor	142 (70%)	21 (63.6%)	0.34
Right predominance	123 (60.6%)	24 (72.7%)	0.18
Use of levodopa	(75.9%)	(93.9%)	0.02*
Use of amantadine	(15.3%)	(36.4%)	0.004*
HY stage	2.4 ± 0.9	2.8 ± 0.7	0.06

*Statistically significant

Table 3. Comparison between the use of pramipexole and the presence of psychosis in subjects with PD

	PD patients without psychosis	PD patients with psychosis	p	OR
No treatment with pramipexole	83 (40.9%)	19 (57.6%)	0.07	0.51 (95% CI: 0.24-1.1)
Treatment with pramipexole	120 (59.1%)	14 (42.4%)		

CI: confidence interval.

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 simptoms (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 diffent types of hallucinations and the remaining 35% had three or more types. With regard to the frequency of hallucinations, 50% of the patients had them more than once a day; 20%, several times per week; 10%, two or three times per week; 5%, once a week, and the remaining 15%, up to 3 times per month. As to severity and insight, 30% (n = 6) were certain that hallucinations weren't real; 20% (n = 4) required for them to be explained that hallucinations were not real and they understood it; an additional 20% believed that hallucinations were real even after explaining them that they weren't. In 30% of the cases, hallucinations were also accompanied by illusions. Sixty percent of the patients' primary caregivers reported a higher burden as a consequence of the presence of hallucinations; of these, 50% mentioned dedicating most part of the time to provide care and attention associated with hallucinations. Eighty percent (n = 16) of the patients also experienced hallucinations at night; of note, of these subjects, only 19% referred symptoms suggestive of a sleep behavioral disorder.

On the other hand, in the UM-PDHQ, 55% (n = 11) referred hallucinations as being very frequent (one or more times per day), 15% (n = 3) characterized them as frequent (several times per week, but less than once daily), 20% referred having them once weekly and 10% (n = 2), less than once monthly. Hallucinations duration was shorter than 1 s in 15% (n = 3) of the cases, longer than 1 s and shorter than 10 s in 30% (n = 6), and longer than 10 s in 55% (n = 11). About the severity of hallucinations, interpreted as the level of anxiety or discomfort, 50% (n = 10) described them as with no effect; 20%, as moderate, and 15%, as severe. With regard to general questions, 55% (n = 11) answered positively to having been previously diagnosed with an ocular disorder. Only 25% (n = 5) had received recently an adjustment of the antiparkinsonian treatment that they associated with the onset of hallucinations. Seventy-five percent (n = 15) of the cases did not associate the presence of hallucinations with the on/off state; 15% associated it with on-periods and 10%, to off-periods.

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 dissappear". 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 stimulis. False presence refers to the vivid sensation that somebody is near, when actually there is nobody present[32]. Delusion (or delirious idea) refers to false beliefs based on erroneous or ilogic 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 part 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 serotoninergic 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 pontogeniculooccipital structures, which are responsible for REM sleep regulation; this dysfunction has been proven to be an independent risk factor for psychosis in Parkinson[33].

Risk factors for the development of psychosis in patients with PD include antipakinsonian treatment (particularly dopaminergic antagonists), duration of the disease, older age, severity of the disease, sleep disorders, cognitive impairment or dementia and depression[2,10,19,34]. 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[35].

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)[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[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[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.

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