A clinical profile of patients with Parkinson's disease and psychosis

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Abstract

Aims: The aim of the study was to study the clinical profile of the patients with Parkinson's disease (PD) and psychosis. **Settings and Design:** This was a prospective, cross sectional, hospital-based study done at the Department of Neurology, National Institute of Mental Health and Neurosciences, Bangalore, India from September 2009 to January 2011. All patients with PD, diagnosed by United Kingdom PD Society Brain Bank criteria, having with features of psychosis as diagnosed by the neuropsychiatric inventory (NPI) were included. Patients without a caregiver who could validate the patient's symptoms were excluded. **Results:** A total of 40 patients (5 women, 35 men) with PD with psychosis (mean age: 54.2 ± 11.5 years, mean duration of illness: 6.5 ± 4.5 years, and mean duration of psychosis: 4.3 ± 4.3 years) were included in the study. The Global NPI score was 19.1 ± 11.5. Majority of the patients had pure hallucinations (85%), while the rest had either pure delusions (7.5%) or a combination of delusions and hallucinations (7.5%). In those with hallucinations, visual hallucinations were the commonest (60%) (pure only in 22.5%), followed by auditory (45%), minor hallucinations (45%), and tactile (20%). Only one person reported having olfactory hallucinations (2.5%). Loss of insight was most often observed during the visual hallucinations (52%), followed by tactile (44.4%), auditory (38.9 %), and minor hallucinations (33.3%). **Conclusions:** In patients with PD and psychosis, pure hallucinations are common and visual hallucinations are the commonest among the hallucinations. A large proportion of patients have minor hallucinations, which need to be recognized early for effective and early management. The limitations of the study were small sample size, use of a single scale to assess psychosis and subjective assessment of insight.

Key Words

Delusions, hallucinations, NPI, PD, psychosis

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Introduction

Parkinson's disease (PD) is one of the commonest movement disorders in the world.[1] In spite of PD being a predominantly motor disorder, majority of patients develop a variety of non-motor manifestations. The most challenging nonmotor symptom is psychosis. The clinical spectrum of psychosis in PD includes visual hallucinations with or without retained insight, other hallucinations (auditory, tactile, olfactory, and minor hallucinatory phenomena) and delusions.[2] These psychotic symptoms have a major impact on the natural course and prognosis of the disease and are important risk factors for nursing home placement and mortality of PD.[3,4]

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The prevalence of the psychotic symptoms have varied largely in most studies, mostly owing to a lack of uniform definition of psychosis, lack of disease-specific scales to measure psychosis, and also use of scales that are not validated to measure psychotic symptoms.[5-7] In addition, there are only limited data on the pattern of psychosis in PD, especially from India.[8] Therefore, the present study was undertaken to study the clinical profile of the patients with Parkinson's disease and psychosis using the neuropsychiatric inventory (NPI) for rating of psychotic symptoms. Although various scales have been used to assess psychosis in PD,[9-11] the NPI is a well-validated scale to screen for various psychotic symptoms in PD.[12]

Materials and Methods

This prospective, cross-sectional, hospital-based study was conducted at the Department of Neurology, National Institute of Mental Health and Neurosciences, Bangalore, Karnataka,

India from September 2009 to January 2011. The study was approved by the institute's ethics committee and all the patients and their caregivers who were interviewed gave written informed consent. A diagnosis of PD was made according to the United Kingdom PD Society (UKPDS) Brain Bank criteria for PD[13] and all patients were evaluated by the UPDRS-part III (motor part) scale,[13] Hoehn and Yahr staging, the NPI,[12] the mini mental status examination (MMSE) score for cognitive screening.

The NPI evaluates 12 neuropsychiatric domains: delusions, hallucinations, agitation, depression, anxiety, apathy, irritability, euphoria, disinhibition, aberrant night time behavior, night time behavior, and appetite change. The frequency, severity, and distress of each domain is rated on the basis of scripted questions administered to the patient's caregiver. The product of frequency and severity of each domain and the total NPI score was calculated in all patients. The test-retest variability, interrater variability has been already established.[12] The patients were diagnosed to have psychosis based on diagnostic criteria for psychosis in PD.[14] The diagnosis of PD associated psychosis was made in a case of PD with symptoms starting after the onset of PD with the presence of at least one of the following symptoms (1) illusions, (2) false sense of presence, (3) hallucinations, and (4) delusions. The symptoms should last for at least 1 month and the other mimickers should be excluded.[14] The patients who were excluded were those as per UKPDS brain bank criteria, those who were unwilling to participate in the study or did not cooperate for the interview and those without a caregiver who could validate the history of patient's symptoms. The patients with cognitive deficits were not excluded.

A predesigned proforma was used to record comprehensively all the information pertaining to PD and the psychotic symptoms. Hallucinations, when present, were classified into visual, auditory, tactile, olfactory, minor, or mixed. Further characterization of hallucinations included frequency, threatening or nonthreatening, presence or absence of insight, time of occurrence, and so on. All effort was made to collect accurate information of the past and current medications for Parkinsonian symptoms as well for other disorders, if any. Details of anti-Parkinsonian drugs, especially dosage, duration of treatment, and temporal association between medications and onset of psychosis were ascertained. The total levodopa equivalent dosage (TLED) was calculated after converting all drug dosages patients were currently taking into their levodopa equivalent dosages.[15] These were then added up and the mean TLED calculated.

Statistical analysis

Statistical analysis was done using SPSS 16.0 package. Data were expressed using descriptive statistics, that is, mean, standard deviation (SD) for continuous variables and frequency, percentages for categorical variables. Comparisons between groups were done using independent Student's t-test for continuous variables and chi-square test for categorical variables. Correlation between continuous variables was done using Pearson's correlation coefficient. A $P < 0.05$ was considered statistically significant.

Results

A total of 40 patients were recruited for this study. The mean TLED was 683.36 ± 404.33 mg/day [Table 1]. Majority of the patients had prior use of anticholinergics (62.5%), followed by use of dopamine agonists (47.5%), levodopa (35%), and amantadine (35%). Approximately, 15% of patients had prior exposure to antipsychotics [Table 2]. Six patients had an MMSE <24.

Characteristics of psychosis

The mean duration of psychotic symptoms (hallucinations/delusions) was 4.34 ± 4.26 years. The psychotic symptoms included pure hallucinations in 34 patients (85%), pure delusions in 3 patients (7.5%), and a combination of delusions and hallucinations in 3 patients (7.5%) [Tables 3-6]. Visual hallucinations were the commonest type of hallucinations, followed by other hallucinations, such as auditory, minor, tactile, and olfactory [Table 5]. Majority of the patients had a mixed type of hallucinations (45%). Nine (22.5%) had pure visual hallucinations, five (12.5%) had pure auditory, and only two patients (5%) had minor hallucinations. A combination

Table 1: Demographic variables of patients with Parkinson's disease and Psychosis (*n* = 40)

Clinical variables	Mean ± SD
Mean age (years)*	54.21±11.55
Gender-Men	35 (87.5%)
Women	5 (12.5%)
Mean age of onset of PD (years)	52.07±11.83
< 40 years	7 (17.5%)
Mean UPDRS-III score	28.7±14.1
Mean H &Y score	1.9±0.78
Mean duration of PD (years)	6.5±4.5
Mean duration of treatment of PD (months)	58.9±55.8
Mean duration of onset of PD to onset of treatment (months)	21.3±33.4
Positive family history of PD	2.5%
Positive family history of tremors	15%
TLED (mg/day)	683.36±404.33
MMSE score	27.4±4.5

UPDRS = Unified Parkinson's disease rating scale, H & Y scale = Hoen and Yahr scale, TLED = Total levodopa equivalent dose (mg/day), MMSE = Mini mental status examination

Table 2: Pharmacotherapy in patients with Parkinson's disease and psychosis

Drugs	(*n* = 40) (%)
Levodopa	14 (35)
Anti cholinergics	25 (62.5)
Dopa agonist	19 (47.5)
Catechol-o-methyl transferase inhibiters	7 (17.5)
Amantadine	14 (35)
Antipsychotics	6 (15)
Antioxidants	4 (10)
MAO B inhibitors	7 (17.5)
Miscellaneous	6 (15)

MAO = Monoamine oxidase

Table 3: Neuropsychiatric inventory (NPI) domains of delusions and hallucinations in patients with Parkinson's disease and psychosis

Psychosis rating scale domains	Measure	(*n* = 40)
Delusions	Incidence%	6 (15.0%)
	Frequency	1.17±0.41
	Severity	1.00±0.00
	Product	1.17±0.41
Hallucinations	Incidence%	37 (92.5%)
	Frequency	2.35±1.16
	Severity	1.78±0.75
	Product	4.79±3.85

Table 4: Details of NPI domains of agitation, depression, anxiety, elation, apathy, irritability, aberrant motor behaviour, sleep disturbance, appetite and eating disorder

Psychotic Rating scale Domains	Measurement	PD-PSY (*n* = 40)
Agitation/Aggression	Incidence%	1 (2.5%)
	Frequency	1.00
	Severity	1.00
	Product	1.00
Depression/Dysphoria	Incidence%	28 (70.0%)
	Frequency	2.19±0.96
	Severity	1.68±0.55
	Product	4.18±2.72
Anxiety	Incidence%	25 (62.5%)
	Frequency	2.15±0.97
	Severity	1.62±0.49
	Product	3.92±2.42
Elation/Euphoria	Incidence%	1 (2.5%)
	Frequency	1.0
	Severity	1.0
	Product	1.0
Apathy/indifference	Incidence%	23 (57.5%)
	Frequency	2.61±0.94
	Severity	1.83±0.49
	Product	5.13±2.65
Irritability	Incidence	20 (50%)
	Frequency	2.65±0.99
	Severity	1.85±0.49
	Product	5.47±2.34
Aberrant motor behaviour	Incidence	4 (10%)
	Frequency	2.75±1.26
	Severity	2±0.82
	Product	6.25±4.5
Sleep disturbance	Incidence	18 (45%)
	Frequency	2.33±1.14
	Severity	1.72±0.67
	Product	4.53±3.59
Appetite and Eating disorders	Incidence	9 (22.5%)
	Frequency	1.56±1.01
	Severity	1.33±0.5
	Product	2.44±2.46

*Disinhibition was not detected in any patient

Table 5: The types of hallucinations observed in patients of Parkinson's disease with psychosis

Type of hallucinations	Number of patients	
	(*n* = 40)	%
Visual	25	62.5
Auditory	18	45.0
Tactile	9	22.5
Olfactory	1	2.5
Minor	18	45.0
Visual+auditory+tactile+olfactory	1	2.5

Table 6: Pattern of visual and auditory hallucinations in patients with Parkinson's disease and psychosis

Description	Visual Hallucinations (*n* = 25) (%)	Auditory hallucinations (*n* = 18) (%)
Type of Hallucinations		
Simple	2 (8)	4 (22.2)
Complex	23 (92)	14 (77.8)
Content of Hallucinations		
Familiar persons	18 (72)	11 (61.1)
Strangers	4 (16)	2 (11.1)
Animals	3 (12)	5 (27.8)
Frequency of Hallucinations		
Several times per day	19 (76)	12 (66.7)
Several times per week	6 (24)	6 (33.3)
Response to Hallucinations		
Ignores	12 (48)	11 (61.1)
Acts out	7 (28)	5 (27.7)
Talks	3 (12)	2 (11.1)
Scared	1 (4)	–
Absent Insight	13 (52)	7 (38.9)

of visual and auditory hallucinations was seen in six patients (15%).

NPI

NPI consisted of 12 domains. The global NPI score was calculated by calculating the sum of products of all domains and then the mean NPI score was calculated [Tables 3 and 4]. The mean NPI score was 15.70 ± 11.25 in the study group (range: 1-55).

Visual hallucinations

A total of 11 patients (44%) had hallucinations only during the ON-period after taking various Parkinsonian drugs and 3 patients (12%) had them only during the OFF-period [Tables 5 and 6]. A total of 11 patients (44%) reported no specific relation of hallucinations to drug intake.

Auditory hallucinations

Most (11; 61.1%) patients heard human voices either talking among themselves or talking to the patient, two patients heard inanimate or animal sounds like bullet sounds, dogs, barking, or tigers and lions roaring, tinkling of bells [Tables 5 and 6]. Four patients had hallucinations during the ON-period of various Parkinsonian drugs (22.2%) and two patients had

them during the OFF-period (11.1%). A total of 12 patients reported no specific relation of hallucinations to drug intake (66.7%).

Minor hallucinations

There were 18 patients (45%) with minor hallucinations, which included passage hallucinations in 7 (38.6%), sense of presence in 6 (33.3%), and a combination of both in 5 (27.8%) [Table 5]. Majority of patients reported a perception of seeing people (94.4%), one person reported a feeling of seeing a white cloth passing by him in the peripheral field of vision. Most of these hallucinations were stereotyped (83.3%) and nonthreatening in nature (77.8%). Insight into the hallucinations was absent in 6 patients (33.3%) and present in 12 patients (66.7%). Four patients had hallucinations during the ON-period of various Parkinsonian drugs (22.2%) and three patients had them during the OFF-period (16.7%). In 11 patients, there was no specific temporal relationship of the occurrence of hallucinations to drug intake (61.1%).

Tactile hallucinations

There were nine patients with tactile hallucinations. Five patients reportedly felt contact with insects and small animals (ants, mosquitoes crawling on hands and legs, one person reportedly felt snakes crawling on his legs), four patients reported contact with small insects [Table 5]. Most of the hallucinations were stereotyped (88.9%) and nonthreatening in nature (88.9%).

Olfactory hallucinations

A 66-year-old man was the only patient who reported presence of olfactory hallucinations [Table 5]. He used to perceive smell of oils and spices used during cooking.

The global NPI score correlated significantly with UPDRS ($r = 0.43$, $P = 0.006$) and H&Y Stage ($r = 0.32$, $P = 0.05$).

Discussion

The clinical features of psychosis in PD have been studied and there are various clinicoradiological and clinicopathological correlations showing the involvement of parahippocampus and amygdala and multiple neurotransmitter pathways.[16] Our study, which focussed on the clinical characterisation of psychosis in patients with PD, had several significant observations.

We found a higher mean age of onset of PD at presentation, younger age of onset of PD, and longer duration of illness in patients with PD and psychosis compared with previous studies. [17,18] This was due to a higher number of younger-onset patients with PD (17.5%) in our study.

Papapetropoulos *et al*.,[17] compared 31 patients of PD with psychosis with 39 patients without psychosis. They reported a similar age of onset of 54.4 ± 12.5 years in hallucinators and 55.8 ± 11.8 years in nonhallucinators. They also reported a duration of 9.5 ± 5.6 years in hallucinators and 8.5 ± 5.3 years in nonhallucinators.[17] Our study also revealed a significantly longer duration of illness (6.5 ± 4.5 years) in psychotic patients, though the mean age of onset of psychosis (54.21 ± 11.55 years) was slightly less as compared with the above study.[17]

Even though PD is viewed as a homogeneous group, some studies have tried to divide PD into subgroups: younger onset, tremor-dominant, nontremor dominant, and rapid disease progression.[19,20] It has also been found that younger-onset patients and tremor-dominant patients have a slower rate of progression and a lesser cognitive impairment than the nontremor dominant subgroup.[21] But whether these subgroups of PD patients have any relation to the future development of psychosis has not been studied till now. The higher incidence of cognitive impairment in patients of PD with psychosis suggests that the presence of psychosis may itself be a risk factor for future development of dementia. Even though PD has been traditionally thought to spare the intellectual functions, dementia has been reported to range from 40% to 78%.[22-24]

Determinants of psychosis

The severity of PD as measured by modified H&Y stage was high in the study group (1.9 ± 0.78). A study by Aarsland *et al*.,[18] reported higher UPDRS "ON" scores in patients with hallucinations (44.7 ± 15.4) compared with patients without hallucinations (24.0 ± 13.4). The authors also reported higher H&Y stage in patients with hallucinations (stages 3-5) as compared with patients without hallucinations (stages 2-3).[18] Duration of illness and Hand Y stage were also found significant determinants of psychosis by Gupta *et al*.,[8] from India. Our patients with psychosis also had a higher stage of severity of PD as measured by H&Y staging.

Treatment history

All the available dopaminergic drugs may produce adverse psychotic reactions, there being a higher incidence with dopamine receptor agonists than with levodopa.[25] In PD, the psychotic symptoms may reduce after a decrease in dopaminergic medication. However, there is no simple dose-response relationship between dopaminergic treatment and development of hallucinations.[25] Moreover, two prospective studies by Sanchez-Ramos *et al*., and Graham *et al*.,[26,27] have reported that hallucinations were not associated with the dosage of dopaminergic medication (levodopa or dopaminergic agonists). However in the present study, PD patients with psychosis had high TLED which indicates that our group had advanced PD as shown by H & Y stage, therefore required higher doses. A large proportion of our patients had prior exposure to anticholinergics (62.5%) and dopaminergic agonists (47.5%), reflecting the prescription patterns to treat PD in the community. Anticholinergic drug usage has been found to be a predictor of severe psychosis by Sawada *et al*.,[28] although it was not considered significant in another study.[29]

The mean TLED in our study was 683.4 ± 404.3 mg. Sanchez-Ramos *et al*., reported mean levodopa dosage of 426 ± 216 mg in psychosis patients and 443 ± 310 mg in nonpsychosis group while Graham *et al*., reported a dosage of 614 ± 433 mg in late hallucinators group and 667 ± 286 mg in the non-hallucinators group.[26,27] In addition, Fenelon *et al*., reported a levodopa dose of 367 ± 154 mg in patients with visual hallucinations (disease duration of <5 years) and 431 ± 204 mg in patients without

hallucinations (disease duration of >5 years).[29] Therefore, the dose-response relationship of levodopa with psychosis in PD is still not clear.

Clinical profile of psychosis in PD

Visual hallucination was the most frequent type of hallucination observed in our patients. Molho *et al*.,[30] reported visual hallucinations in about 30% of patients. They described the presence of animals and inanimate objects as a part of visual hallucinations. These authors also reported that 28% of the hallucinations were threatening to the patients. Another study by Fenelon *et al*.,[25] also reported visual hallucinations which consisted of complex hallucinations, involving familiar persons, single or few in number, seen usually in dim light, superimposed on a normal background. The findings of our study are comparable to these previous studies. The threatening visual hallucinations were reported by three (8%) patients in our study.

Auditory hallucinations were seen in 45% of patients in our study. Most of the previous studies have reported auditory hallucinations occurring as a part of visual hallucinations[25,27,30,31] which was also seen in our study. Pure auditory hallucinations are rare in PD and there has been no systematic report of auditory hallucinations in PD. Other studies have reported an incidence varying from 25% to 40%.[18,25,31] Molho *et al*.,[30] reported auditory hallucinations which consisted of musical tunes of a particular type which the patient could not identify. Fenelon *et al*.,[25] also reported auditory hallucinations occurring as a "sound-track" of visual hallucinations.

In our study, minor hallucinations were seen in a large number of patients (45%). These hallucinations have been largely ignored in most studies. Fenelon *et al*.,[7,25] reported that if these types of hallucinations were taken into account, the prevalence of hallucinations would increase to about 40%-75%. The authors reported minor hallucinations which consisted of seeing an inanimate object as a living being and passage hallucinations consisting of a brief vision of a person or an animal passing sideways.[7]

The importance of minor hallucinations like presence and passage is significant in view of the new diagnostic criteria given by Ravina *et al*.,[14] where it is incorporated as one of the four characteristic features for diagnosis of PD psychosis.

Tactile hallucinations were seen in 22.5% of patients in our study. Fenelon *et al*.,[25] reported tactile hallucinations consisting of contact with small animals or a feeling of being touched by someone. They also reported that tactile hallucinations are usually combined with visual hallucinations which increase their realistic experience, which was not seen in our study. One patient in our study reported having olfactory hallucinations. He reported having a sense of smell of oily and spicy foods, occurring in the afternoons, during the off periods with a retained insight. Olfactory hallucinations are extremely rare and reported in 2.1%-10% of study populations in different studies.[32,33] [Table 6]

There were several limitations in our study namely, small sample size, chance of investigator bias, lack of follow-up data that could have given information of treatment response in the patients with psychosis and the limitation of NPI as an instrument to assess psychosis in PD. Insight was assessed only subjectively; hence, this was also a limitation of the study.

To conclude, among our patients with PD and psychosis, visual hallucinations were most common, followed by auditory and tactile hallucinations. Keeping in mind the implications of psychosis in PD, this study highlights the common patterns of hallucinations and delusions observed in a cohort of Indian patients with PD. Minor hallucinations in patients with PD have been largely ignored in most previous studies. These are harbinger of psychosis in the future. By giving importance to these minor hallucinations, our study has attempted to characterize these hallucinations, the recognition of which is as important as other common types of hallucinations.

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