

## HALLUCINATION AND RISK FACTORS IN PATIENTS WITH PARKINSON'S DISEASE

### *Parkinson Hastalarında Halusinasyon ve Risk Faktörleri*

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#### ABSTRACT

**Objective:** Hallucination is one of the non-motor symptoms in Parkinson disease (PD). Several factors may affect the presence of hallucination. In the present study, we aimed to compare PD patients presenting with and without hallucinations, to determine risk factors, and to find out common hallucination types.

**Material and Methods:** Idiopathic Parkinson patients regarding to UK Parkinson Disease Society Brain Bank with and without hallucinations were compared. The patients with psychotic symptoms due to metabolic, infectious, and structural causes were excluded. Disease severity was evaluated by Unified Parkinson Disease Rating Scale and Hoehn and Yahr staging. Cognitive status was assessed by Minimental State Examination test. Depression was diagnosed on the basis of DSM-V Tr. Description of hallucination, treatment, co-morbidity, sleep disturbances, REM sleep behavioral disorder, age, gender, scores of test and scale, stage of disease were recorded.

**Results:** A total of 91 (59 female, 32 male) patients with idiopathic PD were enrolled. The group with hallucinations (Group 1) had 40 (43.9%) patients and the one without hallucinations (Group 2) had 51 (54.9%) patients. Total score of Unified Parkinson Disease Rating Scale was significantly higher in Group 1 than Group 2 (37.83±16.65; 30.18±14.83; p=0.028). Sleep disturbances were high in Group 1 (n=24, 60%) when compared to Group 2 (n=14, 27.4%) (p=0.007). The mean duration of hallucinations was 24.87±56.47 months in Group 1. Twenty-one patients (23.9%) had visual hallucinations; 15 (16.5%) patients had illusions (minor hallucinations); and four (4.4%) patients had auditory hallucinations.

**Conclusion:** Disease severity in Parkinson's disease may be a factor in the presence of hallucinations. Hallucinations may also occur with sleep disorders. Minor hallucinations are frequently observed in early stages, with visual hallucinations being the most common hallucinations that may occur in every disease stage.

**Keywords:** Minor hallucination, visual hallucination, disease severity, sleep

#### ÖZ

**Amaç:** Halusinasyon Parkinson hastalığındaki non-motor semptomlardan biridir. Halusinasyon varlığında birçok risk faktörü rol oynayabilir. Bu çalışmada halusinasyonu olan ve olmayan Parkinson hastalarının karşılaştırılması, risk faktörlerinin belirlenmesi, sık görülen halusinasyon tiplerinin bulunması amaçlandı.

**Gereç ve Yöntemler:** İngiltere Beyin Bankası kriterlerine göre idiopatik Parkinson hastalığı tanısı olan hastalarda halusinasyonu olan ve olmayanlar karşılaştırıldı. Metabolik, enfeksiyöz ve yapısal nedenlere bağlı psikotik semptomu olan hastalar çalışmaya dahil edilmedi. Hastalık şiddeti Birleşik Parkinson Hastalığı Değerlendirme Ölçeği ve Hoehn ve Yahr evrelemesine göre belirlendi. Kognitif durum Minimental Durum Değerlendirme testi ile değerlendirildi. Depressif duyu durum tanısı DSM-5 ile konuldu. Mevcut ise halusinasyon tanımlaması, tedavi, komorbidite, uyku bozuklukları, REM uyku davranış bozukluğu, yaş, cinsiyet, ölçek ve test skorları ile hastalık evresi kayıt edildi.

**Bulgular:** Çalışmaya toplam 91 (59 kadın, 32 erkek) idiopatik Parkinson hastası alındı. Halusinasyonu olan grup (Grup 1) da 40 (%43.9), halusinasyonu olmayan grupta (Grup 2) 52 (%54.9) hasta vardı. Birleşik Parkinson Hastalığı Değerlendirme Ölçeği toplam skoru Grup 1 de Grup 2 ye göre anlamlı oranda yüksekti (37.83±16.65; 30.18±14.83; p=0.028). Uyku bozuklukları Grup 2 (n=14, %27.4) ile karşılaştırıldığında Grup 1'de (n=24, %60) anlamlı oranda yüksekti (p=0.007). Halusinasyon süresi Grup 1'de ortalama 24.87±56.47 aydı. 21 (%23.9) hasta görsel halusinasyon, 15 (%16.5) hasta illüzyon (minör halusinasyon) ve dört (%4.4) hasta işitsel halusinasyona sahipti.

**Sonuç:** Parkinson hastalığında hastalık şiddeti halusinasyon varlığında etken olabilir. Halusinasyonlar uyku bozuklukları ile birlikte görülebilir. Minör halusinasyonlar sıklıkla erken evrede izlenirken, en sık görülen görsel halusinasyon her evrede izlenebilir.

**Anahtar Kelimeler:** Minör halusinasyon, görsel halusinasyon, hastalık şiddeti, uyku



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## INTRODUCTION

Parkinson disease (PD) is the second most common movement disorder after tremor. Its prevalence increases with aging and it affects more than 1% of people older than 60 years. Its cardinal motor signs include bradykinesia/akinesia, tremor, rigidity, and postural instability. The diagnosis of the disease is made if one of the other signs is present in addition to bradykinesia (1,2). The non-motor symptoms including neuropsychiatric, gastrointestinal, cardiovascular, urological, sleep and sexual function disorders may also accompany the motor symptoms. Psychosis is one of the common non-motor symptoms.

Hallucination is an unreal perception without outside stimulus. It is simple at early PD but becomes complex at advanced stage (3). Visual hallucinations are the most common type (4). Defining hallucinations is an important task for determining and correcting risk factors and improving patients' and their relatives' quality of life. In the present study it was aimed to compare PD patients with and without hallucinations, to determine risk factors, and to find out common hallucination types.

## MATERIALS AND METHODS

Patients with idiopathic PD were allocated from two tertiary centers. All patients were evaluated clinically by two neurologists. Parkinson's patients with hallucination (Group 1) were compared with Parkinson's patients without hallucination (Group 2). This study was approved by the university's ethics committee (Date: 24.07.2019; decision number:2019/11-2019.06.21). All patients or their relatives were provided written informed consent.

### *Selection of Patients*

This study included patients with resting tremor, rigidity, or postural instability in addition to bradykinesia on the basis of UK Parkinson Disease Society Brain Bank (UKPDSBB) criteria and known

levodopa response. Patients with conditions potentially causing secondary parkinsonism, such as hydrocephalus, brain tumor, recurrent head trauma, and long-term neuroleptic use prior to PD onset were excluded, as were those with sudden-onset disease symptoms or with a gradual progression, those without levodopa response, and those having Parkinson plus (2). Patients with psychotic symptoms due to metabolic, infectious, and structural causes were also excluded.

### *Clinical Assessment of Patients*

Patients were assessed on the basis of UPDRS and Hoehn and Yahr (H&Y) staging for disease severity. Cognitive status was evaluated by Minimental Status Examination (MMSE). Depression was diagnosed on the basis of DSM-V Tr scales. Diagnosis was made by the presence of at least five of the disturbances including weight and sleep problems, psychomotor agitation or retardation, fatigue or energy loss, feeling of worthlessness, reduced concentration, and thought of death in addition to at least one of depressed mood for at least two weeks, loss of interest in favorite activities or things, or inability to enjoy (5). Sleep disorders were questioned as daytime sleepiness, night sleep disturbances.

Presence of hallucinations, and if present, their detailed description, treatment, patients' co-morbidities, REM sleep behavioral disorder (RBD), sleep disturbances, scores of test and, if present, depressive mood were recorded. Information about patients who were unable to respond was obtained from a relative or caregiver. All examinations and data recording were done by neurologists.

### *Unified Parkinson Disease Rating Scale (UPDRS)*

This scale assesses many aspects of PD and provides a clinical ratio for disease severity. It consists of four sections, namely mental section, motor examination, daily life activities (DLA), and treatment complications. The sections are scored between 0 (no

symptom or sign) and 4 (severe symptom or sign possible) (6).

#### *Hoehn and Yahr (H&Y) Staging*

Staging of Parkinson disease is done with the H&Y scale. Accordingly, the disease is defined in 5 stages (7).

#### *Minimental Status Examination (MMSE)*

Used for evaluation of cognitive status, this test assesses 5 cognitive domains, namely orientation (10 points), registration (3 points), attention and calculation (5 points), recall (3 points), and language (9 points). Over a total of 30 points, 27-20 points indicate normal cognition; 24-26 points indicate mild cognitive impairment; and below 24 points indicate dementia (8,9).

#### *Statistical Analysis*

The study data were analyzed using SPSS 21 (SPSS Inc, Chicago, III, USA) software package. The results were expressed as mean±standard deviation for normally distributed variables and median (minimum-maximum) for non-normally distributed ones.  $P<0.05$  was considered statistically significant. Inter-group comparisons were performed with Chi-Square test or Fisher's exact test for categorical variables, independent samples t test for normally distributed quantitative variables, and Mann Whitney-U test for non-normally distributed quantitative variables. More than two groups were compared with Kruskal-Wallis test. Correlations between study variables were tested with Pearson correlation test.

## RESULTS

A total of 91 (59 female, 32 male) patients with PD were enrolled in this study. There were 40 (43.9%) patients (27 male, 13 female) in Group 1 and 51 (54.9%) patients (32 male and 19 female) in Group 2. The two groups did not differ significantly with respect to age and sex ( $p=0.139$ ;  $0.637$  respectively).

Demographic and clinical characteristics of the study group are presented in Table 1. The total UPDRS score was significantly higher in Group 1 than Group 2 ( $37.83\pm 16.65$ ;  $30.18\pm 14.83$ ;  $p=0.028$ ). Sleep disturbances were high in Group 1 ( $n=24$ , 60%) compared to Group 2 ( $n=14$ , 27.4%) ( $p=0.007$ ). In Group 1, 17 (41.4%) patients had sleep problems at night and 7 (17%) patients had daytime sleepiness.

The groups did not differ significantly with respect to other characteristics. According to H&Y staging, 8 (20%) patients in Group 1 had stage 1 disease; 23 (57.5%) patients had stage 2 disease; 7 (17.5%) patients had stage 3 disease; and 2 patients had stage 4 disease. Nineteen (37.3%) patients in Group 2 had stage 1 disease; 27 (52.9%) patients had stage 2 disease; and 5 (9.8%) patients had stage 3 disease. The groups had no significant differences with respect to the H&Y stage ( $p=0.110$ ).

The comparison with regard to the UPDRS subgroup scores revealed that mental subscore and DLA scores were significantly higher in group 1 compared to Group 2 ( $4.38\pm 1.82$ ;  $2.55\pm 1.99$   $p<0.001$ ;  $13.05\pm 6.86$ ,  $9.78\pm 6.20$ ;  $p=0.001$ ) (Table 2).

A treatment-based analysis showed a significant difference between the two groups with regard to COMT inhibitor (with levodopa) and antipsychotic use ( $p=0.038$ ;  $0.040$  respectively) (Table 3). The mean duration of hallucinations was  $24.87\pm 56.47$  months. Twenty-one (23.9%) patients had visual hallucinations; 15 (16.5%) patients had illusions (minor hallucinations); four (4.4%) patients had auditory hallucinations. The distribution of hallucinations was assessed by H&Y staging (Table 4). Among patients with visual hallucinations, three patients saw hallucinations in the form of a close relative; one patient saw a distant relative; five patients saw an unknown person; five patients saw animals; four patients saw animals and humans; and three patients saw unidentified objects. Four patients with auditory hallucinations heard human voice.

**Table 1:** Demographic and disease characteristics of Group 1 and Group 2

Data	Total (n:91)	Group 1 (n:40)	Group 2 (n:51)	p
Age, mean±SD	71.08±8.74	69.55±8.74	72.27±8.64	0.139
Gender, n (%)				0.637
Female	59 (64.8)	27 (67.5)	32 (62.7)	
Male	32 (35.2)	13 (32.5)	19 (37.3)	
UPDRS total score	33.54±16.03	37.83±16.65	30.18±14.83	0.028*
MMSE score, mean±SD	26.10±3.39	26.45±3.07	25.82±3.62	0.413
Depression, n (%)	23 (25.3)	11 (27.5)	12 (23.5)	0.665
RBD, n (%)	16 (17.6)	7 (17.5)	9 (17.6)	0.985
Sleep disturbances, n (%)	38 (41.7)	24 (60)	14 (27.4)	0.007*
Comorbidity, n (%)				
HT	34 (37.4)	17(42.5)	17 (33.3)	0.370
DM	11 (12.1)	7 (17.5)	4 (7.8)	0.161
CVD	13 (13.9)	5 (12.1)	8 (15.3)	0.279
COPD	6 (6.6)	1 (2.5)	5 (9.8)	0.666
Malignancy	3 (3.3)	1 (2.5)	2 (3.9)	0.224
Prostate	3 (3.3)	1 (2.5)	2 (3.9)	1.000
Thyroid	2 (2.2)	-	2 (3.9)	0.502

\*p<0.05 MMSE; Minimental Status Examination, UPDRS; Unified Parkinson's Disease Rating Scale, RBD; Rem Sleep Behaviour Disease, HT; Hypertension, DM; Diabetes Mellitus, CVD; Cardiovascular Disease, COPD; Chronic Obstructive Pulmonary Disease Group 1; Patients with hallucination, Group 2; Patients without hallucination

**Table 2:** Scores of UPDRS in Group 1 and Group 2

UPDRS parts	Total (n:91)	Group 1 (n:40)	Group 2 (n:51)	p value
UPDRS mental status	3.35±2.11	4.38±1.82	2.55±1.99	<0.001*
UPDRS motor	17.84±9.25	18.5±9.24	17.31±9.31	0.547
UPDRS DLA	11.22±6.67	13.05±6.86	9.78±6.20	0.001*
UPDRS complication	0.41±0.94	0.63±1.25	0.24±0.55	0.052

\*p<0.05 UPDRS; Unified Parkinson's Disease Rating Scale, DLA; Daily Life Activities  
Group 1; Patients with hallucination, Group 2; Patients without hallucination

**Table 3:** Treatment modalities in Group 1 and Group 2

Treatment, n (%)	Total (n:91)	Group 1 (n:40)	Group 2 (n:51)	p value
Levodopa	35 (38.4)	11 (27.5)	24 (47.1)	0.058
DA	55 (60.4)	25 (62.5)	30 (58.8)	0.722
COMT inhibitor (with levodopa)	53 (58.2)	36 (90)	17 (33.3)	<0.001*
Rasagiline	29 (31.9)	15 (37.5)	14 (27.5)	0.307
Amantadine	4 (4.4)	4 (10)	-	0.034
Antidepressant	12 (13.2)	4 (10)	8 (15.7)	0.426
Antipsychotic	11 (12.1)	8 (20)	3 (5.9)	0.040*

\*p<0.005 DA; Dopamine Agonist, COMT; Catechol O-Methyltransferase,  
Group 1; Patients with hallucination, Group 2; Patients without hallucination

**Table 4:** Hallucinations according to disease stage in Group 1

Hoehn and Yahr stage	Hallucination, n (%)			Total
	Visual	Audituar	Minor	
1	3 (37.5)	-	5 (62.5)	8
2	13 (56.5)	2 (8.7)	8 (34.8)	23
3	3 (42.9)	2 (28.6)	2 (28.6)	7
4	2 (100)	-	-	2

## DISCUSSION

In the present study, hallucinations and their risk factors in idiopathic PD were examined, and visual hallucinations were found to be most common form of hallucination. Total UPDRS score showed significant difference between the groups with and without hallucination.

The UPDRS is a widely accepted scale for rating PD's severity and progression (10). A higher total UPDRS score in the hallucinating group indicates that disease involvement and disease severity are more advanced. In PD, the incidence of hallucinations and psychosis may increase with disease severity (11). Furthermore, an analysis of UPDRS subgroups showed that the hallucinating group had significantly higher mental subscale and daily life activity scores. Questioning hallucination in the mental subscore caused a high score. Both groups had mild cognitive impairment. Worsening of cognitive status is one of the well-known risk factors for hallucination in Parkinson's disease. However, dementia is expected in advanced stage patients (12). According to disease H&Y stage, there was a very small number of advanced patients, and the study may be limited in this manner; however, unintelligible speech, hypophonia, or aphonia may have prevented clinicians from noticing hallucinations or the rate of physician visits may have been reduced.

In Parkinson disease the agents used for therapy, especially dopamine agonists, amantadine and monoaminoxidase B inhibitors induce hallucinations by causing progressive dysfunction in amygdala, limbic system, and cortical centers where visual inputs are processed (13-15). High-dose levodopa may cause

visual hallucinations in PD (16). In this study, the rate of the use of COMT inhibitor (with levodopa) was higher in patients with hallucination. Use of this combination was thought to be higher in patients with hallucination because of the severity of the disease. Additionally, antipsychotic agent use due to a need for symptomatic treatment was also higher among patients with hallucinations than those without. Treatment modalities of hallucination and psychosis in PD include non-pharmacologic strategies, dose reduction of offending agents, and the addition of non-dopaminergic antipsychotics (17).

Visual hallucinations are the most common hallucination form in PD and occur with a prevalence of 22-38% (18). Patients commonly see a family member or an unknown person. Seeing animals is the second most common type. They do not commonly create problems in patients' daily lives. The present study also revealed that hallucinations were mostly in the form of a human (unknown person) or animal. In PD, visual hallucination occurs in elderly with sleep disturbance. Sleep disorders in patients are thought to cause bad dreams and subsequent hallucinations (16). In a study conducted in Asian society, visual hallucinations were observed in 22.5% of HY I and II in Parkinson's patients and were associated with vivid dreams and sleep disorders (19). In this study, where visual hallucinations were frequently observed, sleep disorders were higher in patients with hallucinations. Visual hallucinations were observed at each stage regarding to H&Y staging. Second most commonly, patients suffered minor hallucinations in present study. The latter are also described as a sense of as if there

was something, seeing a silhouette, or illusions. They may be seen from the early stages of the disease (20). Presence of sense is the most common minor hallucination (15,21,22). They have been previously reported that it is present even in the premotor stage. They are not related to depression, anxiety, apathy, and treatment and closely related to RBD (23). In the present study, minor hallucinations were also observed at an earlier stage (stage 1) regarding to H&Y. The groups did not differ with regard to depression and RBD. Minor hallucinations have been reported to occur in a lower proportion of normal populations than PD (24). In the present study auditory hallucinations were observed in a small number of cases (4 cases). The patients heard human voices. Two patients had isolated auditory hallucinations while two others had combined visual and auditory hallucinations. In patients with isolated auditory hallucinations, the latter disappeared upon gradual cessation of DA.

In PD auditory hallucinations are rarer than visual hallucinations. They do not show paranoid properties. They show an association with visual hallucinations in 8-13% of cases, but isolated occurrence is rare (23,24). In a study of 216 Parkinson's patients, the hallucination rate was 39%. Minor hallucination was observed in 25% of these cases, visual hallucination was observed in 22 % and auditory hallucination was observed in 9.7% (isolated in 2.3%) (25).

Tactile, olfactory hallucinations seen in PD were not observed in this study. Gustatory hallucinations, on the other hand, are reported in case reports in the literature (21,26).

In summary, hallucinations may be seen in every stage of PD. Disease severity is an important determinant for the occurrence of hallucinations. Minor hallucinations are frequently observed in early stages, with visual hallucinations being the most common hallucinations that may occur in every disease stage.

*Conflict of Interest:* None

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