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Associations Between Olfactory Impairment and Cognitive Functions in Patients with Parkinson Disease

Parkinson Hastalarında Koku Bozukluğunun Kognitif Fonksiyonlarla İlişkisi

Nilüfer BÜYÜKKOYUNCU PEKEL[1], Demet YILDIZ[1], İbrahim TAYMUR[2], Ersin BUDAK[2], Suay ÖZMEN[3], Çağla ÇAPKUR[3], Meral SEFEROĞLU[1], Aygül GÜNEŞ[1], Deniz SIĞIRLI[4]

[1]Department of Neurology, University of Health Science, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey
[2]Department of Psychiatry, University of Health Science, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey
[3]Department of Otorhinolaryngology, University of Health Science, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey
[4]Department of Biostatistics, University of Uludağ, School of Medicine, Bursa, Turkey

ABSTRACT

Introduction: Olfactory impairment and cognitive impairment are common non-motor symptoms in Parkinson's disease (PD). Olfactory impairment may be present even many years before the main symptoms of the disease develop. The associations between olfactory loss and cognition in PD are evaluated in this study.

Methods: 31 patients with PD and 31 healthy subjects were included in this study. The Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr Scale (H&Y Scale) were administered to all subjects. Butanol threshold test and Sniffin'Sticks test were used to assess olfaction. The Mini Mental State Examination (MMSE) and Clock Drawing Test (CDT) and Stroop Color Word Test (SCWT) were used to assess cognition.

Results: The Sniffin'Sticks test scores were significantly lower in the Parkinson group in comparison to the control group (p<0.001). The rate of anosmia was 90% in the PD group while this rate was found to be 54.8% in control group (p=0.005). A significant correlation was found between butanol test scores and stoop 5 and 5 errors. Significant correlations were found between the Sniffin'Sticks scores and MMSE scores (p=0.047) and orientation (p=0.041) and language (p=0.003) functions of the MMSE test. Worse olfaction was associated with worse memory.

Conclusions: In PD, olfactory impairment correlates with cognitive impairment and olfactory tests may be used to predict the likelihood of developing dementia in this patient population.

Keywords: Parkinson's disease, hyposmia, cognitive dysfunction, dementia

ÖZ

Amaç: Koku kaybı ve kognitif bozukluk Parkinson hastalığında (PH) sıklıkla görülen non-motor semptomlardır. Hastalığa ait ana semptomlar ortaya çıkmadan yıllar öncesinde bile koku kaybı görülebilir. Bu çalışmada PH'da koku kaybı ile kognisyon arasındaki ilişki incelenmiştir.

Yöntem: Çalışmaya 31 Parkinson hastası, 31 sağlıklı birey dahil edildi. Tüm hastalara nöroloji uzmanı tarafından Birleşik Parkinson Hastalığı Değerlendirme Ölçeği (BPHDÖ) ve Hoehn Yahr evrelemesi (HYE) yapıldı. Koku duyusunu değerlendirmek amacıyla butanol threshold test ve sniffin sticks test kullanıldı. Kongnisyonu değerlendirmek amacıyla standardize minimental test (SMMT), saat çizme testi (SÇT) ve stroop testi yapıldı.

Bulgular: Parkinson grubunda Sniffin'Sticks testi puanları kontrol grubuna göre anlamlı derecede düşüktü (p<0,001). PH grubunda anosmi görülme oranı %90 iken, kontrol grubunda bu oran %54,8'di (p=0,005). Butanol test puanı ile stoop 5 ve 5 hata arasında anlamlı ilişki bulundu. Sniffin'Sticks test puanı ile SMMT puanı (p=0,047) ve SMMT'nin yönelim (p=0,041) ve lisan (p=0,003) fonskiyonları arasında anlamlı ilişki bulundu. Koku kaybı hafızanın zayıflaması ile ilişki bulundu.

Sonuç: PH'da koku kaybı, kognitif bozukluk ile ilişkilidir ve koku testleri bu hasta grubunda demans gelişimini saptamada yol gösterici olarak kullanılabilir.

Anahtar Kelimeler: Parkinson hastalığı, hyposmia, cognitive dysfunction, demans

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INTRODUCTION

Parkinson's Disease is the second most common neurodegenerative disease after Alzheimer's dementia. The prevalence of this condition is 1% in population over 55 years of age and affects millions of people around the World. Cardinal symptoms of PD include tremor, rigidity, bradykinesia and postural instability. REM behavior disorders, loss of olfaction (anosmia) and constipation are common premotor symptoms. These symptoms may appear many years before the appearance of motor symptoms. Although patients usually seek medical aid due to

Correspondence Address/Yazışma Adresi: Nilüfer Büyükkoyuncu Pekel, Department of Neurology, University of Health Science, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey • **E-mail:** niluferbuyuk@hotmail.com
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motor symptoms, the importance of non-motor symptoms is increasing day by day (1). The estimated rate of olfactory impairment among patients with Parkinson's Disease is as high as 90% and occurs many years before the motor signs appear (2–5). Olfactory testing has been reported as a potential predictor for early stage PD (6). Parkinson's dementia may develop as the disease progresses and the rate of dementia may be as high as 50 to 80%, between 15th and 20th years of the disease (1). There are studies evaluating the associations between olfactory dysfunction and cognitive impairment in PD (7, 8). The association between cognitive dysfunction and progression to dementia has been demonstrated (9, 10).

This study aimed at evaluating the association between the impairment of olfaction and cognitive functions in patients with PD and the feasibility of the use of olfactory tests to predict the risk for developing dementia in the population of Parkinson's patients.

METHODS

Subjects

31 patients with idiopathic Parkinson's disease and 31 healthy subjects were included in this study. Control patients were healthy people attending neurology outpatient clinics for a routine check-up and had no history of Parkinson's disease or any other neurodegenerative disease. The diagnosis of PD was made according to UK Parkinson's Disease Society (UK PDS) brain bank clinical diagnostic criteria (11). Both newly diagnosed patients with Parkinson's disease and patients who had been on long term follow up were included in the study. UPDRS and H&Y Scale were administered to all subjects by a neurologist. The UPDRS includes 4 main sections assessing mental state, daily living activities, motor functioning and treatment complications. The test has 42 items rated on a 0 to 4 scale. Higher scores were associated poor prognosis (12). Validity and reliability of the Turkish version of the UPDRS have been demonstrated (13).

H&Y staging scale was used to assess the severity and progression of the disease (14). All subjects underwent computed tomography and MRI scanning of the brain. Patients with secondary Parkinsonism due to any causes, including drugs, poisoning, vascular causes, hypoxia, trauma, infections, normal pressure hydrocephalus or brain tumors and patients with Parkinson-plus syndrome were excluded from the study. A complete medical history was obtained from each subject, demographic characteristics were recorded and all subjects underwent comprehensive physical examination and neurological examination. The present study was approved by University of Health Science Bursa Yüksek İhtisas Training and Research Hospital Regional Ethics Committee and it was conducted in accordance with the World Medical Association Declaration of Helsinki. Written informed consent of each participant was obtained.

Olfactory Tests

Exclusion criteria consisted of uncontrolled diabetes, pregnancy, breastfeeding, history of malignancy, any pathological conditions that may affect olfactory functions such as history of nose surgery, deviated nasal septum, allergic rhinitis, chronic rhinosinusitis, smokers or ex-smokers who had a history of smoking in the preceding 3 months, history of head trauma, cerebrovascular accident, multiple sclerosis, intracranial mass lesions. Subjects without a sinonasal disorder that might affect olfactory function according to their physical examination, who were in a good medical condition, oriented and cooperative on the test and able to communicate without problems, were included in the study.

Butanol Threshold Test

This test is an odor perception test. Each nostril is tested separately. Diluted solutions prepared using pure butanol and distilled water are used in this test. 10 bottles of solution are prepared with the highest concentrated one containing 4% butanol and each of the remaining bottles containing a solution 1/3 lesser concentrated than the preceding bottle. First participants are presented with highest concentrated solution at a distance of 5 centimeters for 3 seconds to let them know the odor that they will be asked to identify. Then the bottle caps are opened one by one at a distance of 2 to 3 centimeters from nose with in an ascending order (from the lowest dilution mixture) and any contact with the skin should be strictly avoided. Each bottle of solution mixture is paired by bottle of pure distilled water and subjects are asked to smell the solution mixture and distilled water, for 2 to 3 seconds for each, and to identify which of the bottles contains the odorant, the procedure is repeated for each bottle pair with 30-second intervals. The lowest concertation of the dilution mixture identified by the subject is recorded as the butanol threshold of the subject. Then the other nostril is tested separately, and the scores for both nostrils were averaged to reach the final score. Possible scores ranged from 0 to 9, but all scores 7 and higher were scored as 7 (15).

In Turkish population normative data for butanol threshold test are; normosmic: 6.00–7.00, mildly hyposmic: 5.00–5.75, moderately hyposmic: 4.00–4.75, severely hyposmic: 2.00–3.75, anosmic: 0–1.75 (16).

Odor Identification Test

the Sniffin'Stick Screening Test is an identification test. Subjects smell 12 different odor pens and are asked to pick the most likely definition for the odor, from four options offered for each. This test is performed in a quiet, well aired room. Subjects are asked to identify the odor of orange, leather, cinnamon, peppermint, banana, lemon, licorice, coffee, garlic, pineapple, rose and fish among four options for each and the answers are recorded. The results are compared to population means. This test is validated on patients in Turkey (17). Hyposmic subjects are defined as subjects identifying <10 but >6 out of 12 odors, correctly and anosmic subjects are defined as the subjects identifying 6 or less odors out of 12, correctly (18).

Cognitive Tests

The Mini Mental State Examination test (MMSE) and Clock Drawing test (CDT) were administered to the subjects by a specialist psychologist and Stroop Color Word test (SCWT) was administered to cooperative subjects.

The Mini-Mental State Examination

The mini-mental test is a short, easy to administer and standardized test extensively used all around the world to assess cognitive level. The mini-mental test is a 30-point, 11-item questionnaire comprising five sections including orientation, registration, attention, calculation, recall and language. This test was first introduced by Folstein et al. in 1975 (19). Güngen et al. demonstrated the validity and reliability of the Turkish version of the Mini-Mental State Examination for literate individuals, in 2002 and the study demonstrating its validity and reliability for illiterate individuals was performed by Yildiz et al., in 2015. The ideal cut-off score of MMSE in Turkish population was found to be 23/24 in both studies (20, 21).

Clock Drawing Test

This test was first introduced by Goodglass and Kaplan in 1983 and is a screening test that measures executive functions such as planning, organizing, reconstructing (22). During this test, subjects are not given a pre-drawn clock circle and are asked to draw a circle, to draw the numbers in the circle and draw the hands of the clock to read ten after eleven (11:10). Although various versions are available, the 4-point scoring (0 to 4) method was used in our study. In the 4-point method: A closed circle/square/rectangle (outer frame of the clock)=1 Point, Times are represented in accurate places and positions=1 Point, All twelve numbers are written (completely)=1 Point, Hands are in an accurate position (11:10)=1 Point. Therefore the maximum score to be obtained

from this version of CDT is 4. The validity and reliability of the Turkish version of the 4-point version was demonstrated in population aged 50 years and over (23).

Stroop Color Word

Stroop Test is a neuropsychological test that reflects the functioning of the frontal region of the brain. Although various versions of SCW test are available, Turkish version consists of 4 white cards; each card includes 4 items in six lines. These cards are the stimuli of the test and the reactions of the respondent against these stimuli are the sections of the test. In the first card, the color names are written in black on a white page. In the second card color names are written in different colors. However, the name of a color is printed in a color that is not denoted by the name; e.g. the Word "red" is printed in "yellow". The colors of blue, green, red and yellow and their name are used in this card. This card is the main stimulus and the critical section of the test; other cards and sections are included in the test for control purposes. The third card includes circles printed in different colors. The fourth card includes neutral words printed in different colors. This test consists of 5 sections. The second card is used in two steps. Three basic scores are calculated for each of the cards. These scores are the time spent after the start command until the last word is read, the number of errors and the number of the reactions corrected by the subject. Basic scores are obtained from separate calculations for each section. The number of the corrections was first used in the Turkish version of the test. The critical section that interference appears is the 5. section (second card) of the Stroop test where the color the printed name and the name of the color are different. The Stroop Effect occurs when the name of the color is printed in a color that is not denoted by the name. If the color of the printed name differs from the color denoted, naming the color of the word takes longer than when the color of the word is the same with the name of the color. The Stroop interference effect is about this delay. The validity and reliability of the Turkish version of the Stroop test have been demonstrated (24).

Statistical Methods

The Shapiro Wilk test was used to control whether the continuous variables were normally distributed. Normally distributed variables were summarized as mean ± standard deviation and t-test was used for comparisons between the two independent groups. Non-normally distributed variables were summarized as median (minimum-maximum) and Mann-Whitney U test was used for comparisons between the two independent groups. Categorical variables were summarized as frequency and percent (%) and the Pearson's chi-square test, Fisher's exact chi-square test, and Fisher-Freeman-Halton test were used in the comparisons for categorical variables. The Spearman's correlation test was used to analyze the correlations between the variables. The analyses were performed using and IBM SPSS Statistics 21.0 software. The significance level was set at α=0.05. The statistic program was produced by International Business Machines (IBM) in United States of America in California.

RESULTS

The patient group consisted of 31 patients, including 16 female and 15 male patients; the control group consisted of 31 participants including 14 female and 17 male subjects. No differences were found in age, sex, body mass index (BMI), diabetes mellitus (DM), hypertension (HT), educational attainment and marital status between the two groups. The disease duration varied from 6 months to 20 years in the Parkinson group. Median UPDRS score was 26 (2.0–56.0) and H&Y score was 1.0 (1.0–4.0). Most of the subjects were elementary school graduates with 5 years of schooling; the rate of elementary school graduates in the Parkinson group was 77.4% while this rate in the control group was 64.5%. Demographic characteristics of the patient and control groups are summarized in Table-1. The butanol threshold test scores were similar in the two groups (p=0.994). The Sniffin'Sticks test scores were significantly lower in the PD group (p<0.001). Based on the Sniffin'Sticks test results indicated that the rate of anosmia in the PD group was 90% while the rate of anosmia in the control group was found to be 54.8% ; the rate of the subjects with hyposmia was 10% in the Parkinson group and 45.2% in the control group (p=0.005). The results of olfactory tests in the PD and control groups are summarized in Table-2. The median MMSE score was 25.00 both in the patient and control groups (p=0.904). The median clock drawing test score was 4.00 in both groups (p=0.026).

Table 1. Comparison of the demographic features between the patient and control group

	Parkinson Group (n=31)	Control Group (n=3)	p
Gender* Female Male	 16(51.6) 15(48.4)	 14(45.2) 17(54.8)	0.779
Age#	68.03±6.09	65.48±6.26	0.110
BMI#	28.83±5.40	28.53±4.17	0.081
Marital Status* Married Widow	 23(74.2) 8(25.8)	 24(77.4) 7(22.6)	1.000
HT*	14(45.2)	11(35.5)	0.605
DM*	10(32.3)	7(22.6)	0.569

#Data are given as frequency (percentage), *median (minimum-maximum).
HT: Hypertension
DM: Diabetes mellitus

Table 2. Comparison of the olfactory test scores between two groups

	Parkinson Group (n=31)	Control Group (n=3)	p
Butanol Threshold Test Score*	4(1-7)	4(1-7)	0.994
Sniffin' Sticks Test Score*	5(1-8)	6(2-10)	**<0.001**
Hyposmic Anosmic Normosmic	3(10%) 27(90%) 0	14(45.2%) 17(54.8%) 0	**0.005**

#Data are given as frequency (percentage), *median (minimum-maximum).

Table 3. MMSE, SCWT and CDT results in the patient and control groups

	Parkinson Group (n=31)	Control Group (n=3)	p
MMSE Stroop 1	25.00(16.0-30.00) 13.20(10.1-22.3)	25.00(20.0-29.00) 12.20(8.2-22.9)	0.904 0.124
Stroop 2	16.20(10.2-28.2)	12.60(8.2-22.9)	**0.010**
Stroop 3	18.20(14.3-47.4)	16.30(11.5-29.0)	0.117
Stroop 4	28.10(20.3-53.7)	26.4(15.8-46.8)	0.250
Stroop 5	36.30(25.6-54.8)	36.20(23.8-61.0)	0.754
CDT	4.00(1.00-4.0)	4.00(3.00-4.0)	**0.026**

MMSE: Mini mental state examination
SCWT: Stroop color word test
CDT: Clock drawing test

Table 4. Correlation between butanol threshold test score and other variables in parkinson group

Butanol Theshold test score	r	p
Parkinson time UPDRS	- -	0.646 0.071
HYS	-	0.840
MMSE	-	0.339
Orientation	-	0.388
Recording Memory*	-	-
Attention	-	0.489
Recollection	-	0.205
Language Stroop 1	- -	0.656 0.268
1 error*	-	-
1 correction*	-	-
Stroop 2	-	0.985
2 error*	-	-
2 correction	-	0.132
Stroop 3	-	0.743
2 error*	-	-
2 correction	-	0.132
Stroop 3	-	0.743
3 error	-	0.421
3 correction	-	0.421
Stroop 4	-	0.939
4 error 4 correction Stroop 5	- - -0.587	0.845 0.774 **0.027**
5 error	-0.695	**0.006**
5 correction	-	0.343
CDT	-	0.888

*Data not applicable for analysis.
UPDRS: Unified Parkinson's Disease Rating Scale, HYS: Hoehn and Yahr Scale, MMSE: Mini Mental State Examination, CDT: Clock Drawing Test.

Table 5. Correlation between the Sniffin' Sticks test scores and other variables in parkinson group

Stick test score	r	p
Parkinson time UPDRS	0.451 -	**0.012** 0.872
HYS	-	0.983
MMSE	0.365	**0.047**
Orientation	0.388	**0.041**
Recording Memory*	-	-
Attention Recollection	- -	0.719 0.788
Language	0.542	**0.003**
Stroop 1	-	0.157
1 error*	-	-
1 correction*	-	-
Stroop 2	-	0.566
2 error* 2 correction	- -	- 0.924
Stroop 3	-	0.310
Stroop 2	-	0.566
2 error*	-	-
2 correction	-	0.924
Stroop 3 3 error	- -	0.310 0.312
3 correction	-	0.312
Stroop 4	-	0.575
4 error	-	0.715
4 correction	-	0.715
Stroop 5 5 error 5 correction	-0.587 -0.695 -	0.410 0.082 0.216
CDT	-	0.647

*Data not applicable for analysis.
UPDRS: Unified Parkinson's Disease Rating Scale, HYS: Hoehn and Yahr Scale, MMSE: Mini Mental State Examination, CDT: Clock Drawing Test.

Cognitive test scores of the patient and control groups are summarized in Table-3. Significant correlations were found between butanol test scores and stroop 5 (p=0.027) and 5 errors (p=0.006) in the PD group**,** while no significant correlations were found among the other variables. Significant correlations were found between the Sniffin'Sticks test scores and MMSE scores and orientation and language functions of the MMSE test (p=0.047, p=0.041, p=0.003, respectively). The correlations that were found among the olfactory test scores and other variables are shown in Table-4 and Table-5.

DISCUSSION

Associations between olfactory dysfunction and cognitive impairment in PD have been extensively studied and significant associations were found between these two variables and olfactory loss has been reported to be a potential predictor of the development of dementia (7, 8, 10). In our study, we found significant correlations between the Sniffin'Stick Test results and MMSE scores and have demonstrated the associations between olfactory loss and cognitive impairment in a Turkish population. These results are in line with the results of previous studies. The incidence of olfactory impairment among patients with PD is about 90%. Non-motor symptoms such as olfactory impairment may be present even many years before the onset of the disease symptoms (2–5). Patients who present with motor symptoms do not mention non-motor symptoms such anosmia, unless particularly asked for. However, recent improvements in the understanding of Parkinson's disease and the interrogation of these symptoms by clinicians more commonly, took non-motor symptoms forefront.

No significant correlations were found between the severity of olfactory dysfunction and disease duration (25). But a significant correlation was found between disease duration and Sniffin'Stick Test scores in our study. Considering that olfactory impairment may be present even many years before the onset of the disease, it seems unlikely to demonstrate any correlation between disease duration and olfactory dysfunction.

A study in newly diagnosed Parkinson patients analyzed the association between non-motor symptoms and the risk of developing dementia during two years of follow up. Depression, abnormal stereopsis, vivid dreaming, REM behavior disorders and hyposmia were found to be independent predictors of developing dementia in 2-year follow (9). In another study with 3 years of follow up, the association between olfactory dysfunction and the risk of developing dementia was investigated and in this study all subjects with severe olfactory dysfunction at the baseline developed dementia at the end of follow-up period (10). Severe hyposmia and visuospatial disorders have been reported to be independent risk factors for the development of future dementia. Every 1 SD (2.8) reduction in the odor stick identification test score was reported to be associated with an 18.7 fold increase in the risk for dementia, in Japanese population. In this study, the rate of severe hyposmia among patients with Parkinson's disease was found to be 55% and this rate was slightly lower than the rate found in our study (10).

No effect was observed on the global cognitive functions measured by the MMSE in Parkinson patients with olfactory dysfunction, while abnormalities were observed in verbal memory and executive functions. Odor identification scores have been considered as a predictor for poor performance in cognitive tests (26). In our study, significant correlations were found between Sniffin'Sticks test scores and MMSE and MMSE orientation and language scores in the patient group. In our study, the severity of olfactory impairment correlated with the severity of cognitive impairment. Significant differences were not observed between the Parkinson group and control group in MMSE scores; significant differences in CDT between Parkinson group and control group were considered to be associated with tremor that prevent the patients from performing well in CDT.

The associations between olfactory dysfunction and motor disability in Parkinson patients have remained uncertain. Although significant associations were not found between olfactory dysfunction and UPDRS, H&Y and disease duration (25); inverse correlations have been found between olfactory tests and clinical variables in certain studies (27–29). Disease progression was not associated with a linear reduction in the olfactory test results while certain studies reported a linear decline in olfactory function (30–32). In our study, any significant association was not found between the Stiffin'Sticks test scores and UPDRS and H&Y while a significant association was found between the Stiffin'Sticks test scores and disease duration. No significant association was found between the butanol test score and UPDRS, HYS and disease duration. In conclusion, no significant association was found between olfactory test results and motor disability in this study, in concordance with the studies in literature.

Limitations of the study include small sample size, lower levels of educational attainment both in the patient and control groups, inadequate cooperation of the subjects in the olfactory tests due to a poor socio-cultural background.

In conclusion, the rates of anosmia were high and olfactory dysfunction was found to be associated with cognitive dysfunction. Considering the risk of dementia in Parkinson's disease may increase up to 80% over the years during the course of the disease, the use of olfactory loss as a precursor in patients at high risk of dementia may provide guidance for clinicians. Further studies may ensure future use of olfactory tests as markers of the risk for dementia, in routine practice. Comprehensive studies with larger population are required in this area.

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Ethics Committee Approval: The present study was approved by University of Health Science Bursa Yüksek İhtisas Training and Research Hospital Regional Ethics Committee and it was conducted in accordance with the World Medical Association Declaration of Helsinki.

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