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Examination and clinical correlation of olfactory system disorders by an objective method Sniffin' Sticks odor test in Parkinson's disease

Nur Türkmen, Yeşim Sücüllü Karadağ, Zeynep Neşe Öztekin

Department of Neurology, University of Health Sciences, Ankara Numune Training and Research Hospital, Ankara, Turkey

ABSTRACT

Objectives: This study is aimed to investigate the frequency of olfactory dysfunction in Parkinson's Disease (PD) and its relationship with motor/non-motor symptoms and treatment in comparison to isolated olfactory dysfunction patients and healthy controls.

Methods: This study includes 40 PD patients, 37 anosmia patients and 42 healthy controls. PD patients are evaluated with PD evaluation form including; sociodemographic features, disease history, Unified Parkinson's Disease Rating Scale (UPDRS) score, and Hoehn and Yahr (H-Y) score. All patients were evaluated with cranial CT and MRI. Olfactory function was evaluated with Sniffin' Sticks Test (SST). A p value < 0.05 was considered to be statistically significant.

Results: The mean age and median disease duration of PD patients were 62.2 ± 11.9 and 4.5 years, respectively. Fifteen of them had comorbid diseases. Median UPDRS score was 19.5 (4-60) and 67.5% of subjects were H-Y Stage-1. Most frequent non-motor symptom was constipation (67.5%). Olfactory dysfunction was found in 75% of PD patients by SST. No difference was observed between PD patients with or without olfactory dysfunction regarding non-motor symptoms and dementia (p > 0.05). Patients with isolated olfactory dysfunction were significantly younger than both patients with PD and the healthy controls (p <0.001). Non-motor symptoms were not significantly different between isolated olfactory dysfunction group and healthy subjects (p > 0.05).

Conclusions: Most of the patients with PD had olfactory dysfunction, which was found not to be correlated with disease duration and stage based on the results of an objective test, namely Sniffin-Sticks odor test.This result might support the role of non-dopaminergic pathways in the etiopathogenesis of olfactory dysfunctions in PD. In clinical practice, data from further studies is required to comment on an ideal screening or diagnostic test in the olfactory system evaluation of early stage PD patients that would be repeatable and objective.

Keywords: Parkinson's disease, olfactory dysfunction, Sniffin' Sticks test, anosmia

Parkinson's disease (PD) is a progressive neurological disorder characterized by tremor, rigidity, and slowness of movements. With a lifetime risk of developing the disease of 1.5%, PD is the second most prevalent neurodegenerative disorder [1, 2]. PD is associated with progressive neuronal loss of the substantia nigra and other brain structures [1, 3]. Very few of the cases are related to mutations in; a-synuclein, leucine-rich repeat kinase-2 and glucocerebrosidase, but the most common form is still idiopathic [3].

Although the motor symptoms of PD are well defined, the non-motor features as altered smell, taste,

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***Address for correspondence:** Nur Türkmen, MD., Ankara Numune Training and Research Hospital, Department of Neurology, Ankara, Turkey. E-mail: drturkmen06@gmail.com*

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vision, cardiovascular function, sleep, gastric and bowel function, salivation, sebaceous gland activity, mood, and cognition are under-recognized and ultimately undertreated [3. 4]. Non-motor symptoms can be present at all stages of disease but the frequency generally increases with progression of disease and some studies have shown that these symptoms have a major impact on the quality of life in advance of motor symptoms [5, 6].

The most remarkable non-motor feature of PD is impairment in smelling with estimates of prevalence ranging from 50% to 90% [7-9]. Olfactory dysfunction is one of the earliest manifestations of PD and although definitive neural mechanisms are still unclear, they appear a few years prior to characteristic motor symptoms. While cardinal motor symptoms are primarily caused by dopamine depletion within the nigrostriatal pathway, olfactory symptoms appear to be unaffected by dopaminergic therapy, suggesting the involvement of other neurotransmitter systems and / or extranuclear pathology. A few recent studies show brain atrophy in regions related to primary olfactory and orbitofrontal cortex in early-stage PD [10, 11].

Based on literature knowledge mentioned above, this study is aimed to investigate the frequency of olfactory dysfunction in PD and its relationship with motor/non-motor symptoms and treatment in comparison with isolated olfactory dysfunction patients and healthy controls.

METHODS

In this study, it was aimed to quantitatively evaluate the olfactory disturbance of the patients who were followed up with diagnosis of Idiopathic Parkinson's Disease (IPD) at Ankara Numune Training and Research Hospital Neurology Clinic by quantifying Sniffin' Sticks odor test and to investigate the relationship between olfactory dysfunction and motor / non-motor symptoms.

The study population is consisted of 40 IPD patients who admitted to Ankara Numune Training and Research Hospital Neurology Clinic, 37 anosmia patients from Ear, Nose and Throat (ENT) Clinic and 42 healthy controls.

Inclusion criteria were (1) having a diagnosis of PD, (2) admission to the hospital with the complaint of selective olfactory sensation loss, (3) absence of any neurological diagnosis other than PD, or excluded the cases with secondary parkinsonism.

Exclusion criteria were, (1) symptoms of non-PD parkinsonism, (2) use of any drugs that cause parkinsonism, (3) to be younger than 18 years of age and (4) to avoid participation in the study.

For the control group 42 healthy volunteer, who had no age-related illness, no parkinsonism, no drug use, no sense of smell loss, no cognitive impairment to prevent cognitive co-operation were selected.

Each patient was assigned to a standard Parkinson's disease assessment form which included; sociodemographic characteristics (age, sex, occupation, education level, socioeconomic level etc.), PD and a family history of olfactory disorder, hand dominance information, disease duration and age at onset, first symptom and localization of the disease, chronological order of symptoms, Unified Parkinson's Disease Rating Scale (UPDRS) score, Hoehn and Yahr (HY) staging and information of drugs used by patients. Other systemic diseases, smoking status and head trauma history of the patients were also recorded.

In addition, presence of non-motor symptoms other than olfactory disturbance were recorded. These symptoms were assessed according to the patient's history. Patients' ear nose and throat examinations were performed at the ENT clinic and the presence of pathological findings were recorded. All patients were evaluated with cranial CT or cranial MRI.

All the patients were evaluated and tested by the same neurologist. Mini Mental State Assessment Scale was used for objective evaluation of the cognitive status of the patients. A Mini-mental status assessment score of 24 and below were considered significant in terms of dementia [12].

The Sniffin' Sticks odor test was given to the patient and control groups to quantitatively assess the sense of smell. This test consists of 12 felt-tipped pencils with different odors and the smell is released when the cover is opened. Multiple choice testing is based on the identification of daily smells. The patient chooses the one that best describes the smell from among the 4 types shown to him. Patients can choose an option to say they do not smell any odor or that they cannot identify the smell. The cut-off value for the test was set at < 7 to be indicative of odor loss [13].

Statistical Analysis

Statistical analyses were performed using the SPSS for Windows software version 11.5. The variables were investigated using Kolmogorov Smirnov test to assess whether or not they are normally distributed and homogeneity of variances were asessed with Levene test. Descriptive analyses were presented as mean ± standard deviation or median (minimum-maximum) for numerical variables, and categorical variables were reported as number of cases (n) and percentages (%). Categorical variables were assessed by Pearson's Chi-Square, Fisher's exact or Likelihood Ratio test. Whether or not there was statistically significant correlation between disease duration, UPDRS and Hoehn-Yahr stage and smell-end result in Parkinson's disease was investigated using Spearman's Correlation test. Comparison between two groups was done with Student's t test/Mann Whitney U test and multiple groups with One-Way ANOVA/ Kruskal Wallis test. One-way ANOVA/ Kruskal Wallis tests were followed by Post Hoc Test (Tukey HSD or Conover's nonparametric multiple comparison test). A *p* - value less than 0.05 was considered to show a statistically significant result.

RESULTS

PD Features

The mean age of 40 PD patients were 62.2 ± 11.9 years, median disease duration were 4.5 years (range between 1-20 years) and 57.5% were male. Almost all

Table 1. Basic demographic and clinical characteristics of PD patients according to olfactory function

	Normal (n = 10)	Olfactory dysfunction (n = 30)	*p*-value
Age (years)	58.6 ± 13.1	63.4 ± 11.4	0.270†
Sex			0.717‡
Male	5 (50.0%)	18 (60.0%)	
Female	5 (50.0%)	12 (40.0%)	
Smoking	4 (40.0%)	12 (40.0%)	1.000‡
Family history	2 (20.0%)	4 (13.3%)	0.629‡
Disease Duration (years)	10.5 (1-20)	3 (1-15)	0.024¶
Leading symptom			0.716‡
Bradykinesia	6 (60.0%)	14 (48.3%)	
Tremor	4 (40.0%)	15 (51.7%)	
Nausea/vomiting	3 (30.0%)	7 (23.3%)	0.689‡
Postural hypotension	5 (50.0%)	15 (50.0%)	1.000$
Visual hallucinations	0 (0.0%)	8 (26.7%)	0.165‡
Wearing off	1 (10.0)	4 (13.3%)	1.000‡
On/off	1 (10.0%)	4 (13.3%)	1.000‡
Dyskinesia	3 (30.0%)	2 (6.7%)	0.089‡
UPDRS	23 (8-60)	18 (4-59)	0.315¶
Hoehn-yahr			0.962¶
Stage 1	7 (70.0%)	20 (69.0%)	
Stage 2	1 (10.0%)	4 (13.8%)	
Stage 3	1 (10.0%)	4 (13.8%)	
Stage 4	1 (10.0%)	1 (3.4%)	

†Student's t test, ‡Fisher's exact test, ¶Mann Whitney U test, $Pearson's Chi-Square test

the patients were right handed, 37.5% had at least one comorbid diseases (32.5% hypotension, 20.0% diabetes mellitus, 10.0% goiter) and 15,0% had a family history of PD. Median UPDRS score of PD patients were 19.5 (range between 4-60) and 67.5% were HY stage 1, 12.5% were HY stage 2, 12.5% were HY stage 3 and 5.0% were HY stage 4.

First symptom of PD were as follows; 27.5% left hand tremor, 12.5% gait disturbance, 10.0% bradykinesia, 7.5% right hand tremor. Distribution of symptoms added to PD were; 45.0% bradykinesia, 12.5% tremor, 10.0% left sided tremor and 5.0% falls and bradykinesia. Most common examination findings were; 12.5% bradykinesia, 12.5% tremor, 10.0% bradykinesia and bilateral tremor, 10.0% bradykinesia and hypomimia. Motor and non-motor symptoms were; 50.0% bradykinesia, 47.5% tremor, 25.0% nausea and vomiting, 50.0% postural hypotension, 20.0% visual hallucinations, 12.5% wearing off, 12.5% on/off and 12.5% dyskinesia. Treatment given to patients were; 45.0 L-dopa/Benserazide, 40.0 pramipexole, 37.5 rasajilin and 35.0 L-dopa/Carbidopa/Entacapone combination.

Sniffin' Sticks Odor Test

With the olfactory system examination, 10 (47.5%) patients had positive results but 30 (75.0%) patients had positive test results according to Sniffin' Sticks odor test.

Sniffin' Sticks odor test scores of PD and isolated anosmia patients were significantly higher than those of the healthy controls ($p < 0.001$) but similar results were obtained for PD and isolated anosmia patients ($p = 0.21$).

There was no positive correlation between disease duration (r=0.28, $p = 0.07$), UPDRS score (r=0.08, $p = 0.61$), HY stage (r=0.02, $p = 0.89$) and level of odor test within the PD group. (Table 1).

Comparison Between PD Patients with and without Olfactory Dysfunction

There was no statistically significant difference between the groups with or without olfactory dysfunction in terms of age, gender, smoking and family history of Parkinson disease, motor symptoms, nausea and vomiting, postural hypotension, visual hallucinations, wearing off, on/off and dyskinesia, but median

Table 2. Comparison between non-motor symptoms of PD patients according to smoking

	No smoking (n = 24)	Smoking (n = 16)	*p*-value
Nausea	5 (20.8%)	6 (37.5%)	0.295†
Constipation	17 (70.8%)	10 (62.5%)	0.581‡
Sialorrhea	8 (33.3%)	6 (37.5%)	0.787‡
Orthostatic	12 (50.0%)	8 (0.0%)	1.000‡
Urogenital	8 (33.3%)	8 (50.0%)	0.292‡
Incontinence	6 (25.0%)	7 (43.8%)	0.215‡
Sexual	7 (29.2%)	8 (50.0%)	0.182‡
Depression	7 (29.2%)	5 (31.3%)	1.000†
Confusion	3 (12.5%)	1 (6.3%)	0.638†
Dementia	4 (16.7%)	2 (12.5%)	1.000†
Psychosis	1 (4.2%)	0 (0.0%)	1.000†
Sleep arrest	7 (29.2%)	7 (43.8%)	0.343‡
REM	1 (4.2%)	1 (6.3%)	1.000†
Restless Leg	2 (8.3%)	0 (0.0%)	0.508†
Periodic leg	1 (4.2%)	0 (0.0%)	1.000†
Olfactory abnormality	13 (54.2%)	6 (37.5%)	0.301‡
Abnormal Sensation	3 (12.5%)	7 (43.8%)	0.059†

†Fisher's exact test, ‡Pearson's Chi-square test

disease duration was significantly lower in PD patients with olfactory dysfunction ($p = 0.024$). PD patients were also evaluated by their smoking status and no statistically significant difference was found between motor and non-motor symptoms and smoking status (Table 2). There was also no difference between olfactory dysfunction in PD patients, according to taking dopaminergic treatment or not ($p = 0.604$).

Comparisons Between Isolated Anosmia and Control Group

Anosmia patients' mean age was lower than PD and control groups ($p < 0.001$). Groups were similar with regard to sex and hand dominance ($p > 0.05$) (Table 3).

Mean Body Mass Index (BMI) values were similar within groups. Median MMT score was significantly lower in the PD group ($p = 0.03$). There were no statistically significant differences with regard to smoking, head trauma history and PD family history between groups ($p > 0.05$). A family history of anosmia was more frequent within the anosmia group than healthy controls ($p < 0.001$). Abnormal brain MRI's were significantly less frequent within anosmia group than PD ($p = 0.03$). There was statistically significant difference between groups regarding abnormal findings at ear ($p = 0.03$), head/neck ($p < 0.001$) examinations (Table 4).

With regard to non-motor features; constipation, sialorrhea, orthostatic hypotension, urogenital and sexual symptoms were more frequent in PD patients group than isolated anosmia patients and healthy control group ($p < 0.05$) (Table 5). Groups were similar

Table 3. Demographic characteristics of groups

	Control (n = 42)	Anosmia (n = 37)	PD (n = 40)	*p*-value
Age (years)	61.8 ± 10.3	50.3 ± 16.4	62.2 ± 11.9	**< 0.001**
Sex				**0.068**
Male	22 (52.4%)	12 (32.4%)	23 (57.5%)	
Female	20 (47.6%)	25 (67.6%)	17 (42.5%)	
Hand dominance				0.526
Right	40 (95.2%)	34 (91.9%)	39 (97.5%)	
Left	2 (4.8%)	3 (8.1%)	1 (2.5%)	

Table 4. Basic clinical characteristics of cases according to groups

	Control (n = 42)	Anosmia (n = 37)	PD (n = 40)	*p*-value
BMI (kg/m^2)	27.6 ± 4.4	27.8 ± 4.5	28.0 ± 4.7	0.933
Mini mental test	27 (10-30)	27 (18-30)	26 (15-29)	39
Smoking	20 (47.6%)	13 (35.1%)	16 (40.0%)	0.522
Head trauma	5 (11.9%)	6 (16.2%)	4 (10.0%)	0.704
PD family history	1 (2.4%)	2 (5.4%)	6 (15.0%)	0.084
Abnormal neurological finding	2 (4.8%)	-	39 (97.5%)	< 0.001
Family history of anosmia	-	7 (18.9%)	4 (10.0%)	3
Abnormality in brain MRI	18 (54.5%)	9 (40.9%)	26 (74.3%)	36
Head and neck problem	14 (33.3%)	27 (73.0%)	26 (65.0%)	< 0.001
Ear problem	1 (2.4%)	4 (10.8%)	-	35
Throat problem	-	-	1 (2.5%)	0.414

Table 5. Distribution of non-motor symptoms within groups

	Control (n = 42)	Anosmia (n=37)	PD (n=40)	*p*- value
Non-motor findings				
Nausea	1 (2.4%)	4 (10.8%)	11 (27.5%)	**0.003**
Constipation	8 (19.0%)	8 (21.6%)	27 (67.5%)	**< 0.001**
Sialorrhea	-	1 (2.7%)	14 (35.0%)	**< 0.001**
Autonomic dysfunction				
Orthostatic	4 (9.5%)	4 (10.8%)	20 (50.0%)	**< 0.001**
Urogenital	3 (7.1%)	5 (13.5%)	16 (40.0%)	**< 0.001**
Urinary incontinence	9 (21.4%)	4 (10.8%)	13 (32.5%)	0.071
Sexual	-	1 (2.7%)	15 (37.5%)	**< 0.001**
Psychiatric				
Depression	5 (11.9%)	10 (27.0%)	12 (30.0%)	0.111
Confusion	2 (4.8%)	1 (2.7%)	4 (10.0%)	0.375
Dementia	1 (2.4%)	-	6 (15.0%)	**0.007**
Psychosis	-	-	1 (2.5%)	0.333
Sleep problems				
Sleep disruption	4 (9.5%)	2 (5.4%)	14 (35.0%)	**< 0.001**
REM Behaviour Disorder	-	1 (2.7%)	2 (5.0%)	0.231
Restless legs	-	-	2 (5.0%)	0.109
Periodic Leg Movement	-	-	1 (2.5%)	0.333
Sensory findings				
Olfactory deficit	-	37 (100.0%)	19 (47.5%)	**< 0.001**
Other abnormal sensory findings	-	-	10 (25.0%)	**< 0.001**

with regard to urinary incontinence, depression, confusion, psychosis ($p < 0.05$) (Table-5).

Sniffin' Sticks odor test scores were statistically significantly higher in anosmia and PD patients than controls (both $p < 0.001$) but results were similar at PD and anosmia patients ($p = 0.21$) (Fig. 1)

DISCUSSION

Olfactory dysfunction is an important nonmotor symptom of IPD that begins before the prodromal phase and before the appearance of characteristic motor symptoms and its pathogenesis is still not clear [14]. In this study, the odor disorder - which is known to be one of the early stage non-motor findings of the Parkinson's Disease - was investigated in relation to other features of the disease. An important objective in the handling of cases is to describe the fact that olfactory dysfunction is an unidentified etiopathogenesis in the early stage of the disease and that it is related to the other components of the disease to elaborate findings present in the approach to PD. In this study Sniffin' Sticks odor test is used to evaluate quantitative differences between groups and 30 (75.0%) patients had positive test results, but test results were similar at PD and anosmia patients ($p = 0.21$).

An objective assessment of olfactory disturbance is a valuable method of allowing patients to obtain scientific and descriptive records without being limited to complaints about olfactory impairment. Therefore, it has been found that qualitative investigation of olfactory deficit has no place in patients' diagnosis of Parkinson and non-Parkinsonian odor disorders [15].

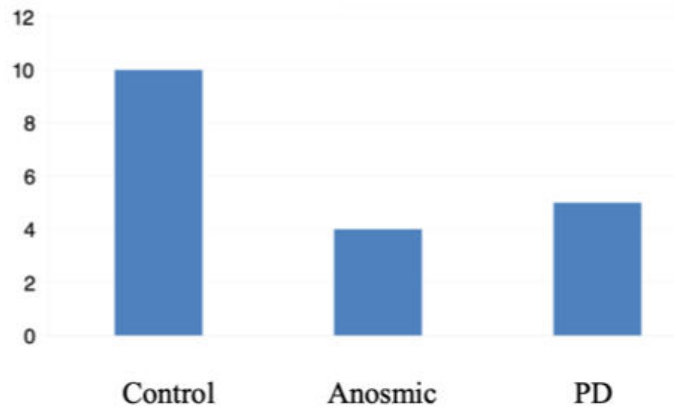

Fig. 1. Sniffin Stick odor test scores.

PD patients with impaired olfactory function had a shorter disease duration but there was no difference between the groups in terms of UPDRS scores and HY staging. On the other hand, it was determined that the olfactory disturbance was not related to motor and non-motor symptoms [8]. Similar to our results, studies showed no correlation between odor impairment and progression of motor symptoms. This result suggests that the olfactory disturbance seen early in the course of Parkinson's disease is a key finding of the disease, and the etiopathogenic mechanism might be different from the known classical mechanisms. There is a need for further screening and pathological studies of this uninformed system.

Smoking and non-smoking PD patients were similar in terms of motor and non-motor symptoms. Contradictory to our work, in one study, the odor test performances of the non-smoker group were higher than both the smoker healthy controls and the smoker and non-smoker Parkinson group [16]. In this study, according to ear and neck examinations, pathological findings were higher in the isolated anosmia group than in PD patients. This difference is thought to be significant in the etiopathology of smell loss belonging to the selective odor loss group independent of the Parkinson's disease pathogenesis.

The presence of studies demonstrating that olfactory dysfunction in Parkinson's patients results from changes in the central nervous system primarily and independently of olfactory epithelium damage [17]. Dementia was more frequent in the PD group than in anosmia patients ($p = 0.007$), but there was no difference between olfactory disorder group in PD patients ($p = 0.026$).

In a study of morphometric Magnetic Resonance detection of gray matter atrophy in the right parietal cortex, also known as primer olfactory area in Parkinson's patients, it has been shown that olfactory disturbance in Parkinson's patients is associated with gray matter atrophy [18]. In our study, percentage of patients with dementia did not differ between PD patients with and without olfactory dysfunction. However, assessment of cognitive functions with test batteries more detailed and sensitive than MMSE might have allowed for a difference between groups.

CONCLUSION

In our study, the quantitative analysis of the olfactory deficits using the Sniffin-Sticks odor test further detected odor deficit in one fourth of the patients, in addition to the subjective questioning. In clinical practice, there is a need for additional data to be obtained from studies conducted based on advanced imaging methods that include more patient groups to comment on an ideal screening or diagnostic test that can be performed which is repeatable and objective in the early stages of Parkinson's disease.

Ethical approval

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

The study was approved by the Local Ethics Committee (Ankara Numune Training and Research Hospital, Ankara, Turkey with Ref: 2014-834). Informed consent statement was provided by patients.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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