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Olfactory disfunction and its relation olfactor bulbus volume in Parkinson's disease

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Abstract. – OBJECTIVE: Olfactory dysfunction is the most frequently seen non-motor symptom of Idiopathic Parkinson's disease (IPD). The aim of this study is to analyze selective olfactory dysfunction, and olfactory bulb volume (OBV) in subtypes of IPD, and compare them with those of the healthy controls.

PATIENTS AND METHODS: Our study included 41 patients with IPD and age and gender matched 19 healthy controls. IPD patients were either tremor dominant (65.9%; TDPD) or non-tremor dominant (34.1%; NTDPD) type. All patients underwent neurological, ear, nose, and throat examinations, and orthonasal olfaction testing. Magnetic resonance imaging (MRI) technique was used to measure the volume of the olfactory bulb.

RESULTS: A significant decrease in olfactory identification scores was found in the patient group. The patients had difficulty in discriminating between odors of mothballs, chocolate, Turkish coffee and soap. OBV did not differ between the patient, and the control groups. In the TDPD group, odor identification ability was decreased when compared to the control group. However, odor test results of NTDPD, control and TDPD groups were similar. OBV estimates of the TDPD group were not different from those of the control group, while in the NTDPD group OBVs were found to be decreased. In all patients with Parkinson's disease OBV values did not vary with age of the patients, duration of the disease, age at onset of the disease, and Unified Parkinson's Disease Rating Scale motor scores (UPDRS-m).

CONCLUSIONS: Olfactory function is a complex process involving olfactory, and cortical structures as well. In Idiopathic Parkinson's disease, changes in OBV do not seem to be directly related to olfactory dysfunction.

Key Words:
Parkinson's Disease, Olfactory disfunction, Olfactor bulbus volume.

Introduction

Idiopathic Parkinson's Disease (IPD), is a movement disorder characterized by bradykinesia, rigidity, rest tremor and postural instability. However, IPD symptoms are accompanied by cardiovascular, gastrointestinal and cognitive symptoms, sleep and mood disorders, sweating, and various non-motor findings related to olfactory, and gustatory functions).

Olfactory dysfunction is the most frequently seen manifestation after rigidity, and bradykinesia[2]. They are seen in nearly 90% of IPD patients in the early stages of their disease. They might even emerge years before the onset of motor symptoms[3]. Neuropathological studies have also suggested that olfactory system is involved in the earliest stages of the disease[2].

Olfactory function is evaluated in three domains; olfactory threshold, identification and discrimination. Which of these domains is impaired in olfactory dysfunction seen in IPD is not known yet. Not only the relevant studies have rather evaluated olfactory performance as a whole[4,5], but scarce information exists about the presentation of dysfunction in different clinical subtypes of the disease.

Olfactory bulb (OB) is an important component of the olfactory system and OB volume can be reliably evaluated with MRI. Studies estimating OBV have been performed during investigation of peripheral olfactory dysfunction, and the impact of olfactory dysfunction on olfactory bulb volume has already been demonstrated[6-8]. Very limited number of studies evaluated OBV in patients with functional impairment originated from central nervous system. The relationship between OBV and olfactory dysfunction seen in IPD has been investigated in a scarce number of MRI investigations. Some of these studies have suggested that OBV is not affected, while others have demonstrated decrease in OBVs. Thus, relationship between structural changes in OB, and olfactory dysfunction in IPD is not known precisely[2]. Similarly, the association between OBV and subtypes of IPD is not known exactly.

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Herein, we aimed to investigate selective olfactory dysfunction and OBV in subtypes of IPD by using MRI techniques, and also compare the results obtained with those of the healthy controls.

Patients and Methods

We investigated 41 patients with IPD (24 men, 17 women, mean age: 61.39 ± 10.54 years, range: 26-77 yrs) diagnosed according to the United Kingdom PD Society Brain Bank diagnostic criteria, and age and gender matched 19 healthy controls (10 men, 9 women, mean age: 60.47 ± 8.49 years, range: 49-77 years).

Mean age of the patients at the onset of the disease was 56.60±10.85 years, and mean duration of the disease was 56.21±42.20 months (4.6 years). Mean UPDRS-m was 21.51 ± 9.55 (range: 5-45) in patients group.

According to the Hoehn and Yahr scale (H&Y), the patients were in Stages 1 (n: 6; 14.6%), 2 (n: 20; 14.6%), 3 (n: 31; 31.7%) and 4 (n: 2; 4.9%). The patients were using L-Dopa (n: 25; 61%), a dopamine agonist (n: 35; 85.4%), a COMT (Catechol-O-methyltransferase) inhibitor (n: 14; 34.1%) and amantadine HCl (n: 8; 19.5%). Four of our patients were recently diagnosed and they were not using any medication.

According to clinical subtypes, the patients were divided into tremor dominant PD (TDPD) (n: 27; 65.9%), and non-tremor dominant-akinetic rigid-PD (NTDPD) (n: 14; 34.1%) groups[9]. Any intergroup difference did not exist for age, gender, age at disease onset, duration of the disease and stage of the disease.

All volunteers were provided with information about the procedures and written informed consent was obtained from all participants. The study was approved by the Local Ethics Committee of Clinical Studies according to the Declaration of Helsinki on Biomedical Studies Involving Human Subjects.

All participants were selected among non-smokers. In the patient group all causes of Parkinsonism except from IPD were excluded. Healthy controls included individuals without a diagnosis of IPD, dementia or other neurodegenerative and rhinologic disorders. Also participants reporting any symptoms of the upper respiratory tract infection on the test day were excluded from the study. Complete neurological, ear, nose and throat examinations, orthonasal olfaction tests and MRI so as to measure olfactory bulb volume were carried out. All participants were examined using a nasoendoscope, and any condition with potential cause for olfactory dysfunction such as rhinosinusitis, nasal polyposis, allergic rhinitis, septum deviation, history of septal operation and head trauma, congenital olfactory dysfunctions were excluded.

Olfactory Test

A well-established orthonasal olfactory test, defined by the Connecticut Chemosensory Clinical Research Center (CCCRC)[10,11] was applied on both IPD patients and healthy controls. CCCRC tests were applied on each subject individually in a quiet well-ventilated room. CCCRC tests include butanol threshold test and odor identification test using common household odorants as described previously.

Butanol threshold and identification tests were evaluated separately for each nostril and arithmetic means of the scores were calculated to find olfactory test score.

Butanol Threshold Test

It estimates threshold of stepwise dilutions of butanol on the basis of the subject's olfactory responses. The strongest olfactory response was elicited at butanol concentration of 4 percent (bottle 1). Each subsequent dilution was a 1:3 dilution (bottles 2-9 respectively) with deionized water. The recognition threshold of butanol was defined as the lowest concentration at which the odor can be identified.

Odor Identification Test

Eight common household odorants [coffee, cinnamon, soap, peanut, mothballs, chocolate, baby powder and Vicks VapoRub (Procter & Gamble, Cincinnati, OH, USA)] with specific odors were placed in opaque jars. The ability to sense the scent of Vicks VapoRub indicates intact trigeminal nerve function and it is easily identified by the participants. Possible scores ranged from 0 to 7 items correctly identified without Vicks VapoRub.

MR Imaging

MR imaging was performed by using a 1.5-T system (Magnetom Avanto; Siemens, Erlangen, Germany) with a standard quadrature head coil. After scout images, to visualize the OB, 3D T2-weighted turbo spin-echo sequences were applied with the following parameters: slices per slab, 56; 1200/263 ms (TR/TE); section thick-

ness, 0.6 mm; matrix, 320; FOV, 200x100 mm; flip angle, 15°. Acquired datasets were transferred to a Workstation (OsiriX MD FDA-cleared). Volume measurements were performed by an experienced radiologist by manual segmentation of coronal sections through the OBs on both sides separately (Figure 1). The change of diameter at the beginning of the olfactory tract was used as the proximal demarcation of the OB. The boundaries of the OB were determined by using the surrounding CSF and the anterior cribriform plate as markers. Volume measurements were performed as previously described (12). The OB volume was expressed in cubic milimetres. All the measurements were done by an individual who was blinded to the diagnosis.

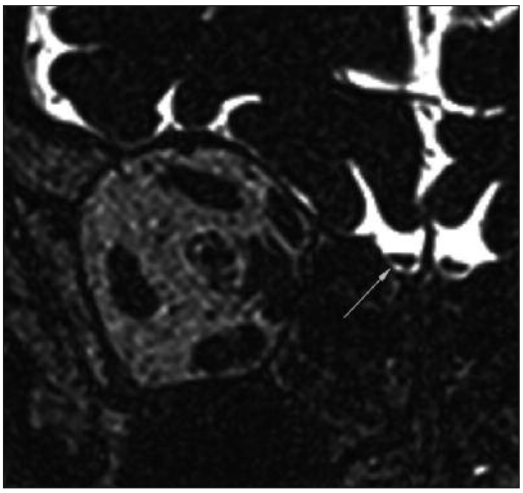

Figure 1. Coronal magnetic resonance image shows olfactor bulb.

Statistical Analysis

Statistical analysis of data was performed using the SPSS v. 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as the mean ± standard deviation (SD) while categorical variables were expressed as ratios. Intergroup differences in demographics (age, sex, education), disease characteristics (duration of the disease, age at the onset of the disease, Hoehn and Yahr stage) UPDRS-m scores and olfactory test scores were determined using independent samples *t*-tests for scale variables or chi-squared tests for proportions. Non-parametric Mann-Whitney-U tests were used for non-normally distributed variables (Hoehn and Yahr stage). OBV and olfactory test scores between groups (all IPD patients, TDPD group, NTDPD group and controls) on the left- and right-sided measures were compared by the analysis of variance (ANOVA) test. For a post-hoc analysis, a LSD (least significant difference) correction was performed when appropriate. $p < 0.05$ was accepted as the level of significance.

Results

There was not significant difference between left- and right-side butanol threshold test results of the patients and controls. However odor identification scores of the right- and left–sided measurements were significantly lower in the patients ($p = 0.004$ and $p = 0.010$ respectively). Correlating with this finding, olfactory test score was significantly lower in the patient group ($p = 0.035$) (Table I).

When odor identification test results were evaluated separately, in IPD patients odor discrimination rates were significantly lower compared to controls both for right- and left-sided tests; mothball ($p = 0.022$ and $p = 0.047$, respectively), chocolate ($p = 0.05$ and $p = 0.032$, respectively), Turkish coffee ($p = 0.043$ and $p = 0.013$, respectively) and soap ($p = 0.012$ and $p = 0.001$, respectively) (Table II).

Mean right- and left-sided OBV values of all IPD patients were not statistically different from those of the control group ($p = 0.751$ and $p = 0.611$, respectively) (Table I).

Table I. Olfactory test results, and OBVs in the patient, and the control groups.

	Patient group (n:41)	Control group (n:19)	*p*
Butanol threshold test	2.53 ± 1.73	2.63 ± 1.57	0.744
	2.34 ± 1.38	2.53 ± 1.67	0.408
Odor identification test	2.17 ± 2.02	3.89 ± 2.02	0.004
	2.48 ± 2.43	4.16 ± 1.98	0.010
OTS	2.53 ± 1.68	3.30 ± 1.25	0.035
OBV (mm^3)	40.06 ± 13.45	44.05 ± 19.23	0.751
	38.89 ± 13.71	41.84 ± 14.76	0.611

OTS: olfactory test score; OBV: olfactory bulb volume; R: Right; L: Left.

Table II. Selective odor identification tests in the patient and the control groups.

		Patient group (incorrect/correct)	Control group (incorrect/correct)	p
Mothball	R	28/13	7/12	0.022
	L	24/17	6/13	0.047
Chocolate	R	26/15	7/12	0.050
	L	25/16	6/13	0.032
Turkish coffee	R	22/19	5/14	0.043
	L	20/21	3/16	0.013
Soap	R	33/8	9/10	0.012
	L	32/9	6/13	0.001

R: Right; L: Left.

When all patients were categorized into their subtypes, right- and left-side odor identification test scores were lower in the TDPD group compared to the control group (post-hoc LSD analysis $p = 0.003$ and $p = 0.013$, respectively), while butanol threshold values did not change. Olfactory test scores did not differ among NTDPD, control and TDPD groups.

There was no difference between OBV values of the TDPD and control groups with post-hoc LSD. However in the NTDPD group, OBV values were lower compared to the control and TDPD groups. The decrease of OBV was statistically significant for the left-side ($p = 0.036$ and $p = 0.043$, respectively) and borderline p values were noticing for the right side tests ($p = 0.058$ and $p = 0.060$, respectively) (Table III).

OBV values did not demonstrate variations with age, age at the onset of the disease and UPDRS-m (Unified Parkinson's Disease Rating Scale-Motor subsection score).

Discussion

In this study we couldn't find a significant difference between the patient and control groups for right and left nostril butanol threshold test values. However right- and left side odor identification scores were significantly lower compared to the controls.

To our knowledge, in most of the studies, olfactory function in IPD has been evaluated totally. In other words, olfactory threshold, odor identification, and discrimination scores have not been evaluated separately, but expressed as an integral unit[4,5,13]. Based on these studies, a decrease in overall olfactory function is already known. However, it is not known precisely whether or not subparameters of olfactory function differ from each other.

Boesveldt et al[14] defined a more impaired olfactory identification performance than olfactory discrimination in IPD. However, not only the olfactory identification test used in their study differs from ours, but olfactory threshold was not tested as well.

Lötsch et al[15] have reported different sensitivities in IPD for olfactory threshold, identification and discrimination tests. They suggested that evaluation of a single olfactory function would not be adequate for the early stages of olfactory dysfunction.

As mentioned previously, selective insensitivity in IPD to some odors have been reported in

Table III. Olfactory test results, and OBVs in TD PD and NTD PD patients with ANOVA test.

		Control group (n: 19)	TDPD (n: 27)	NTDPD (n: 14)	p
Butanol threshold test	R	2.63 ± 1.57	2.14 ± 1.46	3.29 ± 2.02	0.115
	L	2.53 ± 1.67	2.19 ± 1.18	2.64 ± 1.74	0.519
Odor identification test	R	3.89 ± 2.02	1.81 ± 2.02	2.86 ± 1.92	0.004
	L	4.16 ± 1.98	2.15 ± 2.32	3.14 ± 2.60	0.018
OTS		3.30 ± 1.25	2.31 ± 1.74	2.98 ± 1.56	0.096
OBV	R	44.05 ± 19.23	43.33 ± 12.71	33.76 ± 13.01	0.110
	L	41.84 ± 14.76	42.64 ± 12.50	31.66 ± 13.46	0.041

OTS: Olfactory test score; OBV: Olfactory bulb volume; R: Right; L: Left.

limited number of investigations. In various studies performed using many different odorants; selective hyposmia to pizza, wintergreen, licorice, pineapple, aniseed, banana, dill pickle, gasoline, smoke, cinnamon, and mint have been detected in IPD patients[14]. In our study, when compared with the healthy controls, IPD patients were found to discriminate hardly among odors of mothball, chocolate, Turkish coffee and soap.

Bohnen et al[16] compared IPD patients with healthy controls regarding the presence of selective olfactory identification deficits. In their study, The University of Pennsylvania Smell Inventory Test (UPSIT) which analyzed 40 different odorants was used. Only 3 odorants of UPSIT were common with our odor identification test. As is the case in Bohnen et al study, common odorant soap could be hardly identified and cinnamon was discerned by the patient and the control groups similarly, as in our study

Olfactory discrimination involves coordinated functions of the olfactory epithelium, olfactory bulb and piriform cortex of the olfactory system. However, proper olfactory identification requires coordination of more complex structures as hippocampus and entorhinal-perirhinal cortex, orbitofrontal, insular and inferior frontal cortex[16].

Odor is related to the molecular structure of the substance to which chemical and psychophysical characteristics contribute[14]. Therefore, different presentations of the test material can yield diverse results. This phenomenon can explain differences among the results of studies. We think that IPD patients might find it more difficult to identify some odors due to their presentation, so reliable results require more standardized odorants.

It is not clear whether severity of olfactory dysfunction changes with the subtypes of IPD. In our report, IPD patients were grouped based on the subtypes of the disease. In the TDPD group right- and left-side odor identification test scores were lower compared to the control group, while any change could not be detected in the butanol threshold test. Additionally, olfactory test results did not differ among NTDPD, control and TDPD groups.

Stern et al[17] in 1994 reported the changes of severity of olfactory dysfunction in different subtypes of IPD. They mentioned that olfactory function in tremor-dominant patients was relatively preserved compared to the patients with predominant gait and balance disorders, and also olfactory dysfunction was more severe in rapidly progressive malignant IPD when compared with benign IPD.

Ondo and Lai[9] were reporting lack of any difference between groups of TDPD and NTDPD for olfactory test scores. The scores were better in TDPD patients with a family history of tremor, when compared to the NTDPD and negative familial history group. While in another work, any difference between groups of TDPD and mixed (tremor-dominant/akinetic rigid IPD) type could not be defined[18].

Recently, Baba et al[19] evaluated the association between olfactory and cognitive dysfunctions, and could not find any relationship between hyposmia and motor subtypes of IPD.

We demonstrated more deteriorated olfactory identification test scores in TDPD which differs from other reports. This difference probably results from the standardization of the odorants used in our olfactory tests.

Herein this study, we could not find any difference between IPD patients and the control groups for OBV estimates similar to one of the first researches conducted by Mueller et al[4]. However Wang et al[2] in 2010, and Brodoehl et al[5] in 2012, found smaller OBVs in IPD patients. On the other hand, in a study conducted by Kim et al[13], as a different approach, depth of olfactory sulcus was measured and any correlation with olfactory dysfunction was not reported.

An interesting postmortem work performed by Huisman et al[20] could not find any significant difference in OBVs between IPD patients and controls, but the same study revealed 2-fold higher number of dopaminergic cells contained in olfactory bulbs of the patient group. Dopamine essentially blocks olfactory transmission through olfactory glomeruli. This finding might explain the reason why OBV and olfactory dysfunction in IPD does not correlate, as is the case in our study.

Despite contradictory publications, olfactory dysfunction seems to change with time in IPD. While anosmia develops in some patients, some anosmic patients convert to hyposmic state as well. This phenomenon might indicate that irreversible structural changes in the olfactory system may not account for the olfactory deficit seen in IPD, but it might be also explained by functional changes which would be subject to central nervous system modulation[21].

Our results for OBV estimates were comparable with those found by Mueller et al[4] and Huisman et al[20]. Olfactory dysfunction in IPD does not appear to be related to OBV, in other words with structural alterations in the olfactory bulb.

In our study, right- and left-side OBVs in NTDPD patients were markedly smaller compared to the

TDPD patients. However, any correlation between predominant complaints and olfactory performance could not be found. This finding suggests the relationship between OBV and degenerative processes of PD, and alterations in OBVs do not exactly correlate with olfactory dysfunction.

Conclusions

We have detected that olfactory dysfunction is more prominent in the identification, and it is more difficult to discriminate especially odors of mothball, chocolate, Turkish coffee and soap. Additionally, olfactory identification ability was more impaired in TDPD, when compared to NTDPD. Also smaller OBVs were detected in the NTDPD group when compared with the TDPD group. Changes in OBV do not seem to be directly related to olfactory dysfunction. Olfactory function is a complex process including olfactory and cortical structures both. Therefore, we think that olfactory dysfunction should be evaluated in the context of degenerative processes in IPD, rather than changes in OBV.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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