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Olfactory function deteriorates in patients with Parkinson's disease complicated with REM sleep behavior disorder

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ABSTRACT

Introduction: It is not concluded whether the association between olfactory dysfunction and REM sleep behavior disorder (RBD) were worsen cognitive function in patients with Parkinson's disease (PD). We sought to evaluate the impact of these symptoms in PD.

Methods: We examined 62 patients with PD using an olfactory test (Odor Stick Identification Test for Japanese: OSIT-J) and polysomnography (PSG). We divided the patients into 3 groups: PD with clinical RBD (n = 32), PD with subclinical RBD (n = 11), and PD with normal REM sleep (n = 19). We compared their clinical backgrounds, results of OSIT-J, autonomic functions, and cognitive functions such as Montreal cognitive assessment Japanese version (MoCA-J). Some factors associated with RBD were analyzed by multiple regression.

Results: There were significant differences in the results of OSIT-J, and autonomic and cognitive functions between the 3 groups. There were significant differences in the total OSIT-J score between the 3 groups (PD with clinical RBD: 3.3 ± 2.2, PD with subclinical RBD: 4.0 ± 2.6, PD with normal REM sleep: 6.7 ± 3.0, $p < 0.001$). Patients in the group with PD with clinical RBD had a significantly lower score than those with normal REM sleep ($p < 0.001$). Logistic regression analysis showed that OSIT-J score was significantly associated with RBD. The PD group with clinical RBD had more patients with mild cognitive impairment than the group with normal REM sleep. Multiple regression analysis revealed that olfactory dysfunction was correlated with MoCA-J.

Conclusions: Olfactory dysfunction is associated with RBD. Especially, it is important to screen olfactory function in RBD complicated patients with PD in view of cognitive impairment.

1. Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by vigorous, injurious behaviors related to vivid, action-filled, violent dreams during nocturnal REM sleep [1]. Reportedly, more than one third of patients with PD have RBD comorbidity [2]. The presence of RBD is known to be associated with more advanced autonomic dysfunction such as orthostatic hypotension and reduced ^{123}I-labeled meta-iodobenzylguanidine (MIBG) uptake in patients with PD [3]. Moreover, the presence of RBD and this autonomic dysfunction have been regarded as predictive markers of developing dementia in this population of patients [4].

Olfactory identification and discrimination as well as olfactory threshold are impaired in more than 80% of patients with PD [5]. Moreover, olfactory dysfunction has been proposed as a candidate predictive marker for developing dementia in PD [6]. Idiopathic RBD is associated with orthostatic hypotension, reduced MIBG scintigrams, and motor symptoms [4]. Anang et al. indicated that RBD, cardiovascular autonomic dysfunction, color discrimination ability, and gait dysfunction are associated with the development of dementia in patients with PD excluded olfactory dysfunction [4]. However, some papers support that the association between olfactory dysfunction and RBD were worsen cognitive function in patients with PD [7]. Thus, it is not clear whether these signs are risk factors for the development of dementia in PD patients. To clarify these associations, we compared olfactory functions between PD patients divided by RBD characteristics. Moreover, we examined whether RBD categories and olfactory dysfunction are predictive of the development of dementia in PD patients.

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2. Methods

The ethics committee of Tottori University approved the current study (No. 1979). Consecutive outpatients with PD (n = 62; age 69.8 ± 8.3 years, 27 male, 35 female) gave their informed consent to participate in the present study. All the patients were diagnosed according to standard UK Brain Bank criteria for the diagnosis of PD. Exclusion criteria were evidence of relevant central nervous system comorbidities revealed by history or clinical neurological examination, comorbidity with diabetes mellitus, clinically relevant cardiovascular, lung or kidney disease. They had no history of otorhinolaryngological diseases responsible for olfactory dysfunction. To identify the presence or absence of RBD, physicians with expertise in sleep disorders systematically interviewed all the patient participants and their bed partners regarding sleep problems, with an emphasis on dream enactment behavior or vocalization while dreaming. Overnight polysomnography (PSG) with measured variables as follows was also performed for each patient: electroencephalography (EEG) with 4-channel scalp EEG montages (C3, C4, O1, and O2 referred to the contralateral ear), electrooculography, electromyography (EMG) (submental, left lower limb, and right lower limb), oronasal airflow using thermistors, thoracic and abdominal respiratory movements with inductive plethysmography, transcutaneous oxygen saturation, electrocardiography, and nocturnal behaviors with simultaneous video monitoring. Sleep stages were scored according to the criteria established by the American Academy of Sleep Medicine [7]. During REM sleep, the presence of submental phasic EMG activity (3-s miniepochs containing phasic twitches exceeding 4× background EMG activity) or submental tonic EMG activity (more than half of a 30-s epoch in duration) was used to determine stage REM sleep without atonia (RWA) [8]. A diagnosis of clinical RBD was made according to the criteria described in the third edition of the American Academy of Sleep Medicine International Classification of Sleep Disorders [1]. Patients with RWA, but without having RBD symptoms were defined as having subclinical RBD [2]. Patients with PD were categorized into 3 groups: with clinical RBD, subclinical RBD, or normal REM sleep.

For autonomic examination, orthostatic hypotension (OH) and MIBG scintigraphy were evaluated. OH was examined to evaluate drops of systolic and diastolic blood pressure during 60° tilt for 10 min and was defined as a systolic blood pressure (sBP) drop of ≥20 mmHg or a diastolic blood pressure (dBP) drop of ≥10 mmHg during the tilt according to the consensus criteria of the American Academy of Neurology. Cardiac uptake of ^{123}I-MIBG (Daiichi Radioisotope Laboratories, Tokyo, Japan) was examined at 30 min after injection of ^{123}I-MIBG as the early image and the 3.5 h after the injection as the delayed image, and these variables were calculated as heart-to-mediastinum (H/M) ratio [3].

To identify olfactory function in the PD patient participants, we used the Odor Stick Identification Test for Japanese (OSIT-J, Daichi Yakuhin Sangyo Co., Tokyo, Japan) developed specifically for Japanese with confirmed efficacy for olfactory examination [9]. The OSIT-J was composed of 12 different odorants familiar to the Japanese population. Test odorants were microencapsulated in a melamine resin and incorporated within an odorless solid cream dispensed in a lipstick container. The cream was applied in a circle 2 cm in diameter to a 5.3 cm × 10.5 cm strip of paraffin paper. The paper strip was folded in two and rubbed together to release the odorant. Subjects opened the folded paper in front of their nostrils and sniffed. For each odorant, subjects were presented with a card showing the names of 4 odors and were asked to select the odor presented.

To evaluate cognitive function, we used a Mini-Mental Status Examination (MMSE) and Montreal cognitive assessment Japanese version (MoCA-J) including the evaluation of a trail making test, copy of a cube and a clock, name of an animal, attention, language, abstract thought, remote recall, orientation, and education. The PD patients were diagnosed with dementia if they scored < 26 on the MMSE according to the specific criteria proposed by a Movement Disorder Society Task Force [10]. Also, we diagnosed our subjects as mild cognitive impairment (MCI) according to the criteria that is more than 1.5 standard deviation below the normative data mean on tests in at least 1 cognitive domain, self-reported or cognitive decline, and preserved IADLs [11].

At first, descriptive variables including age, sex, educational years, the presence or absence of psychiatric symptoms, dose of dopaminergic agents as levodopa dose equivalents [12], length of PD morbidity, Hoehn and Yahr grade, OSIT-J score, the presence or absence of orthostatic hypotension, the values for drops of systolic and diastolic blood pressure at the tilt, H/M ratio on delayed image of MIBG uptake, scores from the MMSE and MoCA-J, and the presence or absence of dementia and MCI were compared between the 3 groups. On MoCA-J, subcategories including the trail making test, copy of a cube and a clock, name of an animal, attention, language, abstract thought, remote recall, orientation, and education were evaluated. For the statistical comparison, we used chi-square tests followed by residual error tests for categorical variables and one way analysis of variance (ANOVA) followed by post hoc Bonferroni correlation for continuous variables. Next, logistic regression analyses were conducted to investigate the factors associated with the presence of clinical RBD with the variables indicated above including OSIT-J score, drop of systolic blood pressure, H/M ratio on the delayed images of MIBG, and MOCA-J score as independent variables. All variables having a significance level of $p \leq 0.2$ in univariate logistic regression analyses were analyzed further in multiple regression analysis conducted to estimate the association of MOCA-J score with descriptive variables with the purpose of ascertaining factors predictive for developing dementia in PD.

A $p < 0.05$ was considered to be significant. The statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS, ver. 23.0 J, 2015; Tokyo, Japan).

3. Results

According to the definition indicated above, 32 patients were categorized as having PD with clinical RBD (age71.2 ± 7.2 years), 11 patients as having PD with subclinical RBD (age70.5 ± 9.3 years), and 19 patients as having PD with normal REM sleep (age66.9 ± 9.0 years). There three groups were matched for age, gender and length of PD morbidity. There was no significant difference in education years, the number of patients with psychiatric symptoms, Hoehn and Yahr grade, LDEs, MMSE score, and the number of patients positive for dementia between the 3 groups. However, there were significant differences in the number of patients with orthostatic hypotension (p = 0.034), total score of OSIT-J ($F_{2,61}$ = 11.978, $p < 0.001$), drop of systolic blood pressure ($F_{2,59}$ = 5.343, p = 0.008), H/M ratio of early ($F_{2,59}$ = 6.82, p = 0.002) and delayed image ($F_{2,59}$ = 10.661, $p < 0.001$) of MIBG, score of MoCA-J ($F_{2,61}$ = 4.058, p = 0.023) and OSIT-J ($F_{2,61}$ = 11.978, $p < 0.001$), and the number of patients with MCI (p = 0.012) between the 3 groups. Post hoc analyses revealed that patients in the group with clinical RBD had significantly lower scores for OSIT-J ($p < 0.001$) and MoCA-J (p = 0.026), larger drops of systolic blood pressure (p = 0.012), and lower H/M ratio of both early (p = 0.001) and delayed ($p < 0.001$) MIBG images than those in the group with normal REM sleep. Patients in the PD group with subclinical RBD had lower scores of OSIT-J than those with normal REM sleep (p = 0.015) (Table 1).

As for each odorant, the correct answer rate of perfume, cooking gas, rose, and socks smelling of sweat showed significant differences among three groups (p = 0.017, p = 0.004, p = 0.023, respectively) (Table 2). Rest error tests showed clinical RBD group included significantly larger numbers of patients giving correct answers to cooking gas and rose. PD patients with normal REM sleep had significantly larger numbers of patients giving correct answer to perfume and rose (Table 2).

Table 1
Comparison of descriptive variables among three groups.

	PD with Clinical RBD (n = 32)	PD with subclinical RBD (n = 11)	PD with normal REM sleep (n = 19)	p
Age	71.4 ± 7.2	70.5 ± 9.3	66.9 ± 9.0	n.s.
Gender (male/female)	17/15	4/7	6/13	n.s.
Length of PD morbidity	7.0 ± 5.6	7.6 ± 8.1	4.6 ± 4.5	n.s.
Educational years	12.1 ± 1.3	11.8 ± 1.8	12.1 ± 1.2	n.s.
Psychiatry symptoms (yes/no)	8/24	3/8	1/5	n.s.
Hoehn &Yahr	2.6 ± 0.9	2.9 ± 0.5	2.7 ± 0.9	n.s.
Levodopa dose equivalents (mg/day)	371 ± 223	317 ± 219	282 ± 280	n.s.
Orthostatic hypotension (yes/no)	25/7*	7/4	8/11	0.034
Drop of systolic blood pressure (mmHg)	32.8 ± 18.2*	19.3 ± 21.2	17.3 ± 14.1	0.008
Drop of diastolic blood pressure (mmHg)	16.9 ± 15.7	13.8 ± 15.2	8.3 ± 14.4	n.s.
H/M ratio of early image of MIBG	1.48 ± 0.16^{+}	1.63 ± 0.34	1.88 ± 0.57	0.002
H/M ratio of delay image of MIBG	1.26 ± 0.13^{+}	1.46 ± 0.38	1.76 ± 0.58	< 0.001
MMSE	26.0 ± 4.0	27.7 ± 3.5	27.9 ± 2.0	n.s.
MoCA	22.1 ± 4.2^{+}	24.4 ± 5.3	24.9 ± 4.1	0.023
OSIT-J	3.3 ± 2.2^{+}	4.0 ± 2.6^{+}	6.7 ± 3.0	0.001

MMSE: Mini Mental State Examination. MIBG: ^{123}I-labeled meta-iodobenzylguanidine, MoCA: Montreal cognitive assessment, OSIT-J: Odor Stick Identification test for Japanese, Values are mean ± SD or numbers. n.s. = not significant.
$^{+}$ was significant different from PD with normal REM sleep. * was lower than other groups by rest error test.

Table 2
Subjective olfactory and odor item identification rates of OSIT-J among three groups.

Odor item	PD with Clinical RBD	PD with subclinical RBD	PD with normal REM sleep	P
Subjective olfaction	59.4*	18.2	15.8☆	0.003
Indian ink	18.9	18.2	52.6☆	0.025
Wood	31.3	9.1	52.6☆	0.047
Perfume	12.5*	18.2	42.1☆	0.047
Menthol	25.0	36.4	52.6	0.137
Japanese orange	18.9	9.1	36.8	0.163
Curry	21.9*	63.6	52.6	0.016
Cooking gas	12.5*	18.2	68.4☆	< 0.001
Rose	34.4	54.5	63.2	0.117
Hinoki	43.8	45.5	73.7	0.099
Sweaty smelling Socks	31.3*	27.3	73.7☆	0.006
Condensed milk	25.0	27.3	47.4	0.237
Roasted garlic	46.9	72.7	57.9	0.315

Values are percentages. * and ☆ were lower and higher than other groups by rest error test, respectively.

There was no significant difference in other parameters between the groups. In the subcategories of MoCA-J, there were significant differences in the scores for the copy of a clock ($F_{2,49}$ = 3.575, p = 0.036) and remote recall ($F_{2,49}$ = 4.535, p = 0.016) between the 3 groups. Patients in the group with clinical RBD also had significantly lower scores for the copy of a clock (p = 0.036) and remote recall (p = 0.030). Logistic regression analysis revealed that OSIT-J score, drop of systolic blood pressure, and delayed image of MIBG, but not MoCA-J score were significantly associated with RBD.

Multiple regression analysis was conducted with the variables that showed significant partial correlations to the MoCA-J score. There were no significant correlations to the MoCA-J with motor symptoms, RBD, and autonomic functions. The result of the regression analysis yielded the following multiple regression equation: MoCA-J score = 35.695–0.221 × age + 0.563 × OSIT-J score. For the equation, the R was 0.549, R^2 was 0.301, and the regression coefficients were − 0.363 for age and 0.332 for OSIT-J (F = 10.137, p < 0.001) (Table 3).

Table 3
Multiple regression analysis correlated to the MoCA-J score.

	β	Standard Errors	Significance	Coefficients
Constant	35.695	5.034	0.001	
Age	−0.221	0.068	0.001	−0.363
OSIT-J	0.563	0.203	0.017	0.332

MoCA-J: Montreal cognitive assessment Japanese version, OSIT-J: Odor Stick Identification test for Japanese.

4. Discussion

The PD patient participants in the present study had similar OSIT-J scores to those in others reported previously [13]. However, of note, the present study revealed that olfactory function was more deteriorated in PD patients with clinical RBD than in others. This finding is consistent with the hypothesis that individuals with idiopathic RBD have disturbed olfactory function [6], suggesting that the presence of RBD symptoms is associated with aggravated olfactory dysfunction.

Consistent with previous reports, the presence of RBD symptoms was associated with autonomic dysfunction such as orthostatic hypotension and reduced MIBG uptake. The existence of RBD has been reported as a risk factor for developing dementia in patients with PD. Similarly, olfactory impairment is known to be a strongly aggravating factor of the development of dementia in patients with PD [6,7,14,15]. Olfactory dysfunction, clinical symptoms of RBD, and autonomic failure might be useful to detect PD patients who could develop dementia [4,6,7]. In the present study, patients in the PD group with clinical RBD had cognitive dysfunction. In particular, patients in the PD group with clinical RBD had impaired spatial function and memory in the MoCA-J. A comprehensive assessment revealed that cardiovascular autonomic dysfunction, RBD, color discrimination ability, and gait dysfunction, but not olfactory dysfunction strongly predicted development of dementia in PD [4]. However, the present study indicated that olfactory function, but not RBD was correlated with cognitive function. These symptoms might develop simultaneously. As a result, they were associated with cognitive dysfunction. In clinical setting, we should check not only motor symptoms but also non motor symptoms such as RBD findings, olfactory functions, and autonomic functions in patients with PD. Also, it is important to detect specific smells in patients with PD.

Pathological expansion of PD is divided into two processes: one advances anterogradely from the olfactory pathway and the other advances retrogradely along fiber tracts in the brain stem [16]. The former process brings about olfactory dysfunction and the later process is causative of both autonomic dysfunction and RBD. The present study showed patients with clinical RBD had greater olfactory dysfunction and autonomic failure, simultaneously, possibly indicating that the expansion of these two processes occurs at the same time in a certain

number of patients with PD. The difference in the expansion of the two pathological processes might reflect the heterogeneity seen in PD. However, it might also reflect the different speed of progression between the two pathological pathways. These findings reflect that olfactory functions but not RBD finding could affect cognitive function in our results.

The present study suffers from the following two limitations. The first was that we diagnosed dementia in the PD patient participants using only screening tools without detailed evaluations. The second was that there were no patients who were detected by pathological findings in the present study.

In conclusion, RBD and olfactory dysfunction are associated factors in PD. These symptoms might be related and show pathological expansion of PD from the olfactory bulb in parallel with that from the brainstem. These pathological processes might be heterogeneities in patients with PD. Olfactory dysfunction might be more associated with cognitive impairment than RBD symptoms. A more detailed examination of a greater number of patients with PD is warranted for future studies.

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