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ORIGINAL COMMUNICATION

Olfactory dysfunction and cardiovascular dysautonomia in Parkinson's disease

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Abstract Several studies have reported that olfactory dysfunction is an early neuropathological manifestation of Parkinson's disease (PD). Reduced cardiac meta-iodobenzylguanidine (^{123}I-MIBG) uptake may be one of the earliest signs of PD. We studied the relation of olfactory dysfunction to cardiovascular dysautonomia in patients with PD. The study group comprised 66 patients with PD (70.5 years) and 26 controls (70.3 years) for olfactory assessment, 21 controls (72.1 years) for cardiac ^{123}I-MIBG scintigraphy and heart rate variability (HRV), assessed using the coefficient of variation for RR intervals (HRV), and 23 controls (69.2 years) for orthostatic blood pressure response. Olfactory function was assessed by the odor stick identification test Japan (OSIT-J), and cardiovascular autonomic function was evaluated by ^{123}I-MIBG scintigraphy of the heart, the fall in orthostatic blood pressure, and HRV. Patients with PD had a significantly lower OSIT-J score than did the controls (4.1 ± 3.0 vs. 9.9 ± 1.7, $p = 0.001$). The OSIT-J score was unrelated to variables other than gender, including age, disease duration, motor score on the unified Parkinson's disease rating scale, score on the mini-mental state examination, motor phenotype, visual hallucinations, and dopaminergic medication on multiple regression and logistic regression analyses. The OSIT-J score was related to the heart/mediastinum ratio of cardiac ^{123}I-MIBG uptake, the fall in orthostatic blood pressure, and HRV, after adjustment for other clinical variables. Olfactory dysfunction in PD was, thus, significantly related to both cardiac sympathetic and parasympathetic dysfunction, as well as vascular sympathetic dysfunction. As non-motor symptoms of PD, olfactory dysfunction and autonomic network failure appear to be closely related in PD.

Keywords Olfactory dysfunction · Meta-iodobenzylguanidine (^{123}I-MIBG) scintigraphy · Orthostatic hypotension · Heart rate variability · Cardiovascular dysautonomia

Introduction

Parkinson's disease (PD) presents not only with motor disturbances, such as resting tremor, rigidity, bradykinesia, or gait disturbance, but also with cognitive impairment, autonomic dysfunction, depression, nighttime sleep problems, daytime sleepiness, and psychiatric complications [4]. Olfactory dysfunction is also an important non-motor feature of PD. Olfactory dysfunction may occur at an early stage of the disease [56] and may even precede motor symptoms [21]. Previous studies reported that olfactory function was unrelated to cognitive function, motor ability, general motor tremor, and oral motor function [10]. Olfactory test scores were considered to be independent of all other measures in PD.

Clinically significant autonomic dysfunction, including constipation, orthostatic hypotension, postprandial hypotension, impaired baroreceptor reflex, and sweating disturbance, can also occur in PD [39, 40, 46]. Cardiac autonomic dysfunction may develop in early PD, because ^{123}I-meta-iodobenzylguanidine (^{123}I-MIBG) uptake by the heart is reduced even in patients with very early PD according to the Hoehn–Yahr staging system, without clinically significant signs or symptoms of autonomic

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dysfunction [42, 44]. Spiegel et al. [52] demonstrated degeneration of cardiac sympathetic neurons even in very early PD. These findings suggest that reduced cardiac MIBG uptake may be one of the earliest signs of PD.

Pathologic neurodegenerative changes in PD may start in the lower brainstem, including the dorsal vagal nucleolus, locus coeruleus, raphe nucleus, and olfactory bulb, and extend gradually to the rostral brainstem and cerebral cortex [3]. In the autonomic system, peripheral lesions associated with reduced cardiac ^{123}I-MIBG uptake may also develop in association with impairment of the central autonomic nerve network.

We studied the relation of olfactory function to cardiovascular function as evaluated by cardiac ^{123}I-MIBG uptake of the heart, orthostatic hypotension, heart rate variability (HRV) assessed by coefficient of variation of RR intervals, and other clinical variables.

Methods

Subjects

A total of 91 patients who met the diagnostic criteria of the UK Parkinson's Disease Society Brain Bank [27] were entered into a research database at The Jikei University School of Medicine. Sixty-six of these patients were recruited into this study, after excluding patients in whom olfactory function, orthostatic tolerance, and HRV could not be evaluated because of motor impairment, cardiac disorders, or other reasons (Table 1). No patient had abnormal findings on magnetic resonance imaging (MRI), such as brainstem or cerebellar atrophy. All patients received levodopa or a dopamine agonist and had good responses. No patient had signs or symptoms of cardiac disease or any abnormalities on chest radiography, electrocardiography, or cardiac echography. Patients who smoked were excluded.

Table 1 Clinical characteristics of patients with PD

Number of patients	66
Age (range) (years)	70.5 ± 9.3 (48–87)
Female/male	34/32
Disease duration (range) (years)	5.5 ± 4.5 (1–25)
Hoehn–Yahr scale	2.3 ± 0.8
UPDRS motor score	22.4 ± 12.3
Motor subtype (PIGD/TDT or INT)	40/26
Patients with VH	20
MMSE (range)	27.9 ± 2.1 (24–30)
Mean dose of levodopa	313 ± 154
Mean LED	204 ± 140
Mean dose of selegiline	3.7 ± 1.6

UPDRS unified Parkinson's disease rating scale, *PIGD* posture and gait instability phenotype, *TDT* tremor phenotype, *INT* indeterminate phenotype, *VH* visual hallucinations, *MMSE* mini-mental state examination, *LED* daily levodopa-equivalent-unit dose

Levodopa was given to 49 patients, ergot dopamine agonists to 11, non-ergot dopamine agonists to 19, and selegiline hydrochloride to 15. Treatment was continued during the study. Daily levodopa-equivalent-unit doses (LED) were calculated on the basis of the theoretical equivalence to levodopa, i.e., the doses of ergot dopamine agonists in milligrams were multiplied by the following factors: bromocriptine ×10, cabergoline ×67, pergolide ×100, pramipexole ×100, and ropinirole ×67 [7, 20, 25]. The severity of PD was assessed using the motor subsection of the unified Parkinson's disease rating scale (UPDRS motor score). Subjects were determined to have tremor phenotype (TDT), posture and gait instability phenotype (PIGD), or indeterminate phenotype (INT) by calculating the ratio of the global tremor score to the global posture and gait score, derived from the motor subsection of the UPDRS score [13]. Subjects with a ratio of less than 1.0 were considered to have a PIGD phenotype, and those with a ratio of 1.0 or more were considered to have a TDT/INT phenotype.

A mini-mental state examination (MMSE) [14] was performed in all patients. Descriptions of visual hallucinations (VH) were derived from clinical interviews with the patients and their caregivers [26]. Patients with VH had to have experienced VH at least several times previously, irrespective of the relation of VH to medication.

We excluded patients who had an MMSE score of less than 24, because it was unlikely that they could adequately comprehend and respond to the odor or VH questions [38].

As controls for olfactory assessment, 26 healthy subjects (15 women, 11 men, age 70.3 ± 9.8 years, range 46–84 years) who were not smokers were studied. As controls for cardiac ^{123}I-MIBG scintigraphy and HRV, 21 subjects (11 women, 10 men, age 72.1 ± 6.3 years, range 57–79 years) with no autonomic disorders were studied. As controls for orthostatic blood pressure response on standing, 23 subjects (17 women, 6 men, age 69.2 ± 7.9 years, range 50–80 years) with no autonomic disorders were studied. We excluded smokers from our study since smoking has a mild, but significant detrimental effect on olfactory function [15].

The study was approved by the Ethics Committee of Jikei University School of Medicine, and all subjects gave informed consent.

Olfactory assessment

Olfactory function was assessed by the odor stick identification test Japan (OSIT-J) (Daiichi Yakuhin Sangyo Co. Ltd., Tokyo, Japan), which includes the following 12

different odorants familiar to the Japanese population: India ink, wood, perfume, menthol, Japanese orange, curry, gas for cooking, rose, Japanese cypress (*hinoki*), condensed milk, socks smelling of sweat, and roasted garlic [28, 37]. These odorants were packed in microcapsules and were mixed with paste. The examiners painted the paste in a 2 cm circle on a 5.25 cm × 10.50 cm strip of thin paraffin paper. They folded this paper in half and rubbed it to grind the microcapsules and then passed it to a patient. The patient next opened and sniffed the paper. The patient was then given six alternatives: four odor names (including one correct name in principle), 'not detected' and 'unknown'. First, we asked patients to choose the correct response among the four odor names. We suggested that patients select 'unknown' or 'no odor detected', if it was difficult to decide on one of the four odor names. 'Unknown' indicates that the presented odorant was detected, but not recognized [23]. This procedure was repeated for each odorant. The total number of correct answers for the 12 odorants was defined as the OSIT-J score.

Cardiac ^{123}I-MIBG scintigraphy

The subjects were given an intravenous injection of 111 MBq ^{123}I-MIBG (FUJIFILM RI Pharma Co., Ltd. Tokyo, Japan). Relative organ uptake of ^{123}I-MIBG was determined by region-of-interest (ROI) analysis in the anterior view. The ratio of the average pixel count in the heart (H) to that in the mediastinum (M) was calculated (H/M ratio) after 3 h, because delayed images more accurately reflect cardiac sympathetic nerve activity [55].

Orthostatic blood pressure response

All patients underwent active standing testing to evaluate orthostatic blood pressure response in a room maintained at an ambient temperature of 22–24°C. Systolic blood pressure (SBP, mmHg) was measured after 5 min of rest in the supine position. The change in SBP was evaluated immediately after standing and at 1-min intervals, while the subject remained in an active standing position for 3 min. The difference between the SBP at rest and the maximum decrease in SBP after standing was measured as the change in orthostatic blood pressure. Orthostatic hypotension (OH) defined as a fall in SBP by 20 mmHg or greater [31].

Heart rate variability (HRV)

After 5 min of rest, RR intervals were measured on electrocardiograms (ECG), recorded with the use of an ECG recorder with an automated analyzer (FCP-4731, FX-7192, Fukuda-Denshi Co., Ltd., Tokyo, Japan). A total of RR intervals during 1 min or 100 RR intervals were measured in supine position at rest with normal breathing, and HRV was analyzed. HRV was automatically calculated as a percentage of the standard deviation of the RR intervals divided by their mean. HRV at rest while the subject breathed normally was considered an index of parasympathetic activity [50, 54, 59]. For the autonomic tests, most subjects were studied in the morning in a fasting state or at least 3 h after a light meal to exclude the possibility of postprandial hypotension.

Statistical analysis

Statistical analyses were performed using a statistical data analysis system (Esumi Co., Ltd., Tokyo, Japan). Differences between groups were compared with the use of Wilcoxon rank-sum test for continuous variables. Pairwise comparisons, such as the presence or absence of OH, were made using χ^2 tests for binary variables. Correlations between the OSIT-J score and clinical characteristics were evaluated by multiple regression analysis. Relations between the OSIT-J score and motor phenotypes, or VH were evaluated by multiple logistic-regression analysis, adjusted by risk factors such as age, gender, disease duration, MMSE, UPDRS motor score, and dopaminergic medication. Correlations of the OSIT-J score with the results of cardiac ^{123}I-MIBG scintigraphy, the change in orthostatic blood pressure, and HRV were also evaluated by multiple regression analysis, adjusted by risk factors such as age, gender, disease duration, MMSE, UPDRS motor score, and dopaminergic medication. Correlations of the OSIT-J score with the results of cardiac ^{123}I-MIBG scintigraphy, the change in orthostatic blood pressure, and HRV were assessed with the use of Spearman's rank correlation test.

Results

OSIT-J score in PD and controls

The OSIT-J score was significantly lower in patients with PD than in the control subjects (4.1 ± 3.0 vs. 9.9 ± 1.7, $p = 0.001$). In PD, the number of incorrect responses on the OSIT-J was 3.4 ± 2.4, the number of 'unknown' responses was 2.7 ± 3.0, and that of 'not detected' responses was 1.9 ± 3.3.

Cardiac ^{123}I-MIBG scintigraphy, HRV, and the change in orthostatic blood pressure in PD and controls

Cardiac ^{123}I-MIBG uptake and HRV were significantly lower in patients with PD than in the control subjects (1.37 ± 0.28 vs. 2.35 ± 0.35, $p = 0.001$, 1.68 ± 0.95 vs. 2.47 ± 1.65, $p = 0.008$). The change in orthostatic blood pressure was significantly greater in patients with PD than

in the control subjects (−11.6 ± 19.5, range, 26 to −64 mmHg, vs. −4.3 ± 10.2, range, 7 to −37 mmHg, $p = 0.0002$). OH, defined as a fall in SBP of 20 mmHg or greater, was present in 24 patients with PD, but absent in 42. In controls, OH was absent in 21 subjects, but was present in 2 subjects (OH: PD vs. controls, $p = 0.025$).

Multiple regression analyses of the OSIT-J score and clinical characteristics

On multiple regression analyses, the OSIT-J score was significantly associated with only gender and was not associated with age, disease duration, UPDRS motor score, MMSE, or dopaminergic medication (levodopa, LED, or selegiline) (Table 2).

Multiple logistic-regression analyses of OSIT-J score and motor phenotype or VH

The OSIT-J score did not differ significantly between patients with PIGD phenotype and those with TDT/INT phenotype, although patients with PIGD phenotype had a higher UPDRS motor score than did patients with TDT/INT phenotype (odds ratio: 1.073, 95% confidence interval: 1.006–1.145, $p = 0.033$) on multiple logistic-regression analyses. There was also no significant difference in the OSIT-J score between patients with and those without VH, after adjustment for age, gender, disease duration, motor subsection of the UPDRS, MMSE, and dopaminergic medication (levodopa, LED, or selegiline) on multiple logistic-regression analyses.

Multiple regression analyses of OSIT score and cardiac ^{123}I-MIBG scintigraphy, the change in orthostatic blood pressure, or HRV

The OSIT-J score was associated with a reduced H/M ratio of cardiac ^{123}I-MIBG uptake, the change in orthostatic blood pressure, and HRV (Tables 3, 4) after adjustment for age, gender, disease duration, MMSE, motor subsection of the UPDRS, and dopaminergic medication on multiple regression analyses.

The OSIT-J score was associated with HRV after adjustment for age, gender, disease duration, MMSE, motor subsection of the UPDRS, and dopaminergic medication on multiple regression analyses; the OSIT-J score was also associated with MMSE (Table 5).

Table 2 Multiple regression analysis of the correlation between OSIT-J score and clinical characteristics

OSIT-J score	Parameter estimate	Standard error	*p* Value
Age	−0.066	−0.205	0.142
Gender	−1.738	−0.290	0.029
Disease duration	−0.026	−0.039	0.801
MMSE	0.338	0.231	0.074
UPDRS motor score	0.003	0.012	0.932
Levodopa	−0.001	−0.072	0.617
LED	0.002	0.074	0.578
Selegiline	−0.192	−0.109	0.407

OSIT-J odor stick identification test Japan, *MMSE* mini-mental state examination, *UPDRS* unified Parkinson's disease rating scale, *LED* daily levodopa-equivalent-unit dose

Table 3 Multiple regression analysis of the correlation between OSIT-J score and H/M ratio of cardiac ^{123}I-MIBG scintigraphy

OSIT-J score	Parameter estimate	Standard error	*p* Value
H/M ratio of ^{123}I-MIBG	3.835	0.355	0.005
Age	−0.065	−0.202	0.124
Gender	−1.023	−0.170	0.190
Disease duration	0.004	0.006	0.966
MMSE	0.230	0.157	0.203
UPDRS motor score	0.001	0.004	0.977
Levodopa	−0.001	−0.031	0.820
LED	0.002	0.092	0.464
Selegiline	−0.178	−0.101	0.412

OSIT-J odor stick identification test Japan, *MMSE* mini-mental state examination, *UPDRS* unified Parkinson's disease rating scale, *LED* daily levodopa-equivalent-unit dose

Table 4 Multiple regression analyses of the OSIT-J score and the change in orthostatic blood pressure

OSIT-J score	Parameter estimate	Standard error	*p* Value
Change in orthostatic blood pressure	0.062	0.399	0.002
Age	−0.043	−0.133	0.311
Gender	−0.641	−0.107	0.426
Disease duration	−0.032	−0.047	0.746
MMSE	0.264	0.180	0.134
UPDRS motor score	0.011	0.044	0.742
Levodopa	−0.002	−0.117	0.381
LED	0.001	0.064	0.604
Selegiline	−0.013	−0.008	0.952

OSIT-J odor stick identification test Japan, *MMSE* mini-mental state examination, *UPDRS* unified Parkinson's disease rating scale, *LED* daily levodopa-equivalent-unit dose

Correlation between OSIT score and cardiac ^{123}I-MIBG scintigraphy, the change in orthostatic blood pressure, or HRV

The OSIT-J score correlated significantly with the cardiac ^{123}I-MIBG uptake, the change in orthostatic blood pressure, and HRV as assessed with the use of Spearman's rank

Table 5 Multiple regression analyses of the OSIT-J score and HRV

OSIT-J score	Parameter estimate	Standard error	*p* Value
HRV	1.208	0.381	0.002
Age	−0.051	−0.159	0.220
Gender	−1.195	−0.199	0.110
Disease duration	−0.038	−0.056	0.698
MMSE	0.379	0.258	0.031
UPDRS motor score	0.014	0.058	0.663
Levodopa	−0.003	−0.020	0.881
LED	0.000	0.002	0.987
Selegiline	−0.180	−0.102	0.398

OSIT-J odor stick identification test Japan, *HRV* heart rate variability using the coefficient variation of RR intervals, *MMSE* mini-mental state examination, *UPDRS* unified Parkinson's disease rating scale, *LED* daily levodopa-equivalent-unit dose

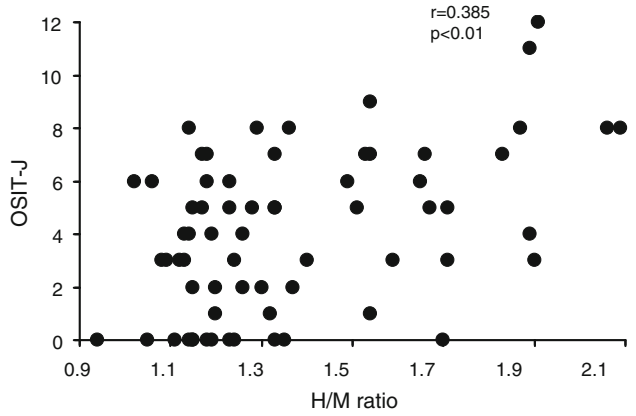

Fig. 1 Correlations between the OSIT-J score and cardiac ^{123}I-MIBG scintigraphy. The OSIT-J score began to decrease in association with the reduction in H/M ratio of cardiac ^{123}I-MIBG uptake. *OSIT-J* odor stick identification test Japan. *H/M ratio* the ratio of the average pixel count in the heart (H) to that in the mediastinum (M)

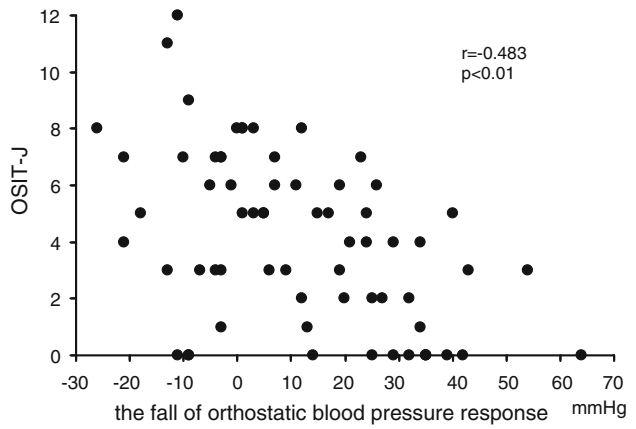

Fig. 2 Correlations between the OSIT-J score and the change in orthostatic blood pressure. The OSIT-J score significantly correlated with the change in orthostatic blood pressure. *OSIT-J* odor stick identification test Japan

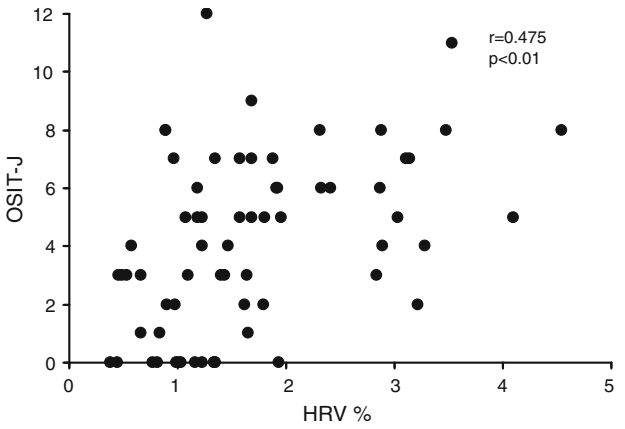

Fig. 3 Correlations between the OSIT-J score and HRV. Significant correlation between the OSIT-J score and HRV was found. *OSIT-J* odor stick identification test Japan. *HRV* heart rate variability as assessed by the coefficient of variation for RR intervals

correlation test (cardiac ^{123}I-MIBG uptake, $r = 0.385$, $p < 0.01$; change in orthostatic blood pressure, $r = -0.483$, $p < 0.01$; and HRV $r = 0.475$, $p < 0.01$) (Figs. 1–3).

Discussion

In this study, olfactory dysfunction was significantly associated with cardiac ^{123}I-MIBG uptake, the change in orthostatic blood pressure, and HRV, adjusted by age, gender, disease duration, UPDRS motor section, MMSE, dopaminergic medication, motor phenotype, and VH.

Doty et al. used the University of Pennsylvania smell identification test (UPSIT) and cross-cultural, smell identification test (CC-SIT) to evaluate olfactory function in PD. The 12-odorant Sniffin' sticks test, the standard tool used by the German Otological Society, is used for smell identification testing in Europe [33]. Since some odors included in these tests are unfamiliar to Japanese and consequently the olfactory ability of Japanese subjects may not be measured correctly by these tests, OSIT-J was developed as a new type of smell identification test designed for Japanese subjects [48]. The rate of correct odor identification on OSIT-J has been shown to significantly correlate with that on CC-SIT [23]. OSIT-J is considered a valid procedure for evaluating olfactory function in Japanese patients with PD.

Relations between olfactory function and clinical characteristics have been studied in PD. Females possess higher olfactory sensitivity than males [57]. Impairments of the olfactory bulb and nuclei of cranial nerves IX and X in PD may represent accelerated normal aging or a disease-specific process [24]. Olfaction declines with age, particularly after 60 years in healthy subjects [9]. The

OSIT-J score was associated with gender, although there was no significant correlation between olfactory dysfunction and age in this study on multiple regression analysis.

Some studies have reported that the olfactory disorder is independent of cognitive deficits [11] and disease stage and duration in parkinsonism [10], whereas others have proposed that olfactory impairment is a predictor of cognitive decline in patients with either mild or no cognitive impairment [60]. In our study, OSIT-J was found to be slightly but significantly related to cognitive dysfunction when the correlation between OSIT-J and HRV was analyzed. Olfactory function has been reported to be impaired in tremor-dominant PD as compared with akinetic PD [53]. In our study, the OSIT-J score did not differ significantly between patients with PIGD phenotype and those with TDT/INT phenotype.

In our study, selegiline hydrochloride was given to 15 patients. Metabolites of selegiline hydrochloride are methamphetamine and amphetamine [16]. These metabolites can reduce cardiac MIBG uptake in heart [51] and cause orthostatic hypotension [6]. Therefore, we evaluated the correlations between the OSIT-J score and the results of cardiac ^{123}I-MIBG scintigraphy, HRV, or orthostatic blood pressure response after adjustment for selegiline hydrochloride as well as other risk factors.

The effects of levodopa on blood pressure and MIBG uptake remain unclear. Goldstein et al. [17] have suggested that levodopa treatment is unrelated to orthostatic hypotension in PD. However, others have reported that orthostatic hypotension in patients with PD is related to the use of higher doses of levodopa [49]. Regulation of blood pressure may be related to dopamine, because dopaminergic receptors are widely distributed not only in the central nervous system, but also in the peripheral autonomic nervous system [12]. Dopamine medication may induce vasodilatation by stimulating peripheral dopamine receptors or by directly affecting the control center of the central autonomic nervous system. However, interactions between MIBG and levodopa are poorly understood. Experimental studies have shown that uptake of MIBG is inhibited by epinephrine, dopamine, and dopa [35]. Dopa may competitively inhibit norepinephrine-transporter-mediated MIBG uptake. These reports suggested that orthostatic blood pressure response or cardiac scintigraphy with MIBG might be affected by treatment with levodopa or dopamine agonists. We therefore evaluated the influence of dopamine medication on the significant correlation between OSIT-J and orthostatic blood pressure response or MIBG uptake. OSIT-J was found to significantly correlate with the fall in orthostatic blood pressure, reduced MIBG uptake, as well as HRV, after adjustment for dopaminergic medication.

Lee et al. [34] reported a significant positive correlation between cardiac MIBG uptake and smell identification in patients with PD, independent of disease duration and clinical rating of motor status. Goldstein et al. [19] also reported that olfactory function positively correlated with cardiac 6-[^{18}F]fluorodopamine-derived radioactivity. They, therefore, proposed that olfactory dysfunction is related to Lewy body pathology and cardiac sympathetic denervation, independently of parkinsonism or striatal dopamine deficiency in synucleinopathies. These reports suggested that functional losses of the olfactory and cardiac sympathetic systems are closely coupled in PD. However, our study demonstrated that olfactory dysfunction in PD was associated with cardiac parasympathetic dysfunction and vascular sympathetic dysfunction such as the fall in orthostatic blood pressure, in addition to reduced cardiac ^{123}I-MIBG uptake.

Braak et al. found that Lewy body pathology is initially confined to the medulla oblongata and olfactory nucleus. Lesions develop within the lower raphe nuclei and in magnocellular portions of the reticular formation. Lewy neurites or Lewy bodies also occur in the coeruleus/subcoeruleus complex. With disease progression, the focus of pathological changes shifts to the temporal mesocortex, which sends bidirectional projections to the hippocampal formation and the amygdala. In the end stage of disease, the mature neocortex is affected [3]. Orimo et al. demonstrated that degeneration of the cardiac sympathetic nerve is profound in the presence of Lewy bodies in diseases such as PD and dementia with Lewy bodies [42, 43]. Moreover, degeneration begins in early PD, accounting for the reduced cardiac MIBG uptake even in the early stages of Lewy body disease [44, 45]. Not only olfactory, but also autonomic systems including peripheral postganglionic lesions may be initially affected in early PD.

We also found that olfactory dysfunction correlated with HRV. HRV during normal breathing is considered a reliable index of cardiac parasympathetic activity [54, 59]. It is unclear whether cardiac parasympathetic dysfunction occurs in the early stage of PD, with no apparent motor symptoms, although no HRV dysfunction was detected in patients with very mild, untreated PD [8]. Benarroch et al. [1, 2] reported that PD did not involve the ventrolateral portion of the nucleus ambiguus, a main location of cardiac preganglionic vagal neurons [5], although multiple system atrophy is associated with a clinically significant reduction in neurons in the ventrolateral region of the nucleus ambiguus. Therefore, HRV is unlikely to be impaired in the early stage of PD. However, Lewy bodies and Lewy neuritis were present in the cardiac plexus in a series of patients with incidental Lewy body disease, which is a presymptomatic phase of PD [29]. Okada et al. [41] reported that Lewy bodies were frequently found in

extracranial organs, especially in the sinoatrial nodal ganglion, in patients with Lewy body disease and proposed that neuronal changes involving Lewy bodies in the sinoatrial nodal ganglion may cause arrhythmias and ischemic heart disease as a result of vasoconstriction.

These findings suggest that PD affects parasympathetic fibers as well as sympathetic nerves in the heart in association with olfactory dysfunction. Our results suggest that olfactory dysfunction is impaired parallel to cardiac sympathetic and parasympathetic dysfunction in PD.

Olfactory dysfunction was also associated with the fall in orthostatic blood pressure response in addition to reduced MIBG uptake and HRV in our study. Cardiac sympathetic denervation in itself is not thought to cause OH [47]. Goldstein et al. reported that cardiac sympathetic denervation probably does not contribute to OH in patients with PD, because OH resolves in patients with cardiac transplants [18, 22]. The cardiovascular system is also thought to be regulated by centers responsible for autonomic nervous control, such as the locus coeruleus, amygdala, hippocampal or paraventricular region, and frontobasal cortex [36]. The locus coeruleus is believed to have an important role in the central regulation of cardiovascular function [58]. A previous study indicated that the noradrenergic neurons in the locus coeruleus project into the cardiovascular regulatory area of the ventrolateral medulla, dorsal vagal complex, nucleus ambiguous, and nucleus tractus solitarius [30, 32].

The fall in orthostatic blood pressure response is, therefore, apparently caused by the central autonomic network, including the coeruleus/subcoeruleus complex or limbic system, as well as by cardiovascular sympathetic dysfunction, as indicated by reduced cardiac MIBG uptake and peripheral vascular resistance. Olfactory dysfunction may be impaired parallel to central and peripheral sympathetic autonomic dysfunction in some patients.

Our findings suggest that olfactory dysfunction in PD is associated with both cardiac sympathetic and parasympathetic dysfunction as well as with vascular sympathetic dysfunction, as reflected in OH, after adjustment for age, disease duration, motor impairment, and dopaminergic medication. As non-motor symptoms, olfactory dysfunction and autonomic network failure appear to be closely related in PD.

References

1. Benarroch EE, Schmeichel AM, Parisi JE (2003) Preservation of brachiomotor neurons of the nucleus ambiguus in multiple system atrophy. Neurology 60:115–117
2. Benarroch EE, Schmeichel AM, Sandroni P, Low PA, Parisi JE (2006) Involvement of vagal autonomic nuclei in multiple system atrophy and Lewy body diseases. Neurology 66:378–383
3. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E (2003) Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 24:197–211
4. Chaudhuri KR, Healy DG, Schapira AH (2006) Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol 5:235–245
5. Cheng Z, Powley TL (2000) Nucleus ambiguus projections to cardiac ganglia of rat atria: an antegrade tracing study. J Comp Neurol 424:588–606
6. Churchyard A, Mathias CJ, Phil D, Lees AJ (1999) Selegiline-induced postural hypotension in Parkinson's disease: a longitudinal study on the effects of drug withdrawal. Mov Disord 14:246–251
7. Deep Brain Stimulation for Parkinson's Disease Study Group (2001) Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med 345:956–963
8. Devos D, Kroumova M, Bordet H, Vodougnon JD, Guieu JD, Libersa C et al (2003) Heart rate variability and Parkinson's disease severity. J Neural Transm 110:997–1011
9. Doty RL, Shaman P, Applebaum SL, Giberson R, Siksorski L, Rosenberg L (1984) Smell identification ability: changes with age. Science 226:1441–1443
10. Doty RL, Deems DA, Stellar S (1988) Olfactory dysfunction in parkinsonism: a general deficit unrelated to neurologic signs, disease stage, or disease duration. Neurology 38:1237–1244
11. Doty RL, Riklan M, Deems DA, Reynolds C, Stellar S (1989) The olfactory and cognitive deficits of Parkinson's disease: evidence for independence. Ann Neurol 25:166–171
12. Emilien G, Maloteaux JM, Geurts M, Hoogenberg K, Cragg S (1999) Dopamine receptors—physiological understanding to therapeutic intervention potential. Pharmacol Ther 84:133–156
13. Fahn S, Elton RL, Members of the UPDRS committee (1987) Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M (eds) Recent developments in Parkinson's disease. Macmillan Healthcare information, Florham Park, pp 153–163
14. Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state" A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198
15. Frye RE, Schwartz BS, Doty RL (1990) Dose-related effects of cigarette smoking on olfactory function. JAMA 263:1233–1236
16. Goldberg LI (1964) Monoamine oxidase inhibitors: adverse reactions and possible mechanisms. JAMA 190:456–462
17. Goldstein DS, Eldadah BA, Holmes C, Pechnik S, Moak J, Saleem A et al (2005) Neurocirculatory abnormalities in Parkinson disease with orthostatic hypotension: independence from levodopa treatment. Hypertension 46:1333–1339
18. Goldstein DS (2003) Dysautonomia in Parkinson's disease: neurocardiological abnormalities. Lancet Neurol 2:669–676
19. Goldstein DS, Sewell L (2009) Olfactory dysfunction in pure autonomic failure: implications for the pathogenesis of Lewy body diseases. Parkinsonism Relat Disord 15:516–520
20. Grosset K, Needleman F, Macphee G, Grosset D (2004) Switching from ergot to nonergot dopamine agonists in Parkinson's disease: a clinical series and five-drug dose conversion table. Mov Disord 19:1370–1374
21. Haehner A, Hummel T, Hummel C, Sommer U, Junghanns S, Reichmann H (2007) Olfactory loss may be a first sign of idiopathic Parkinson's disease. Mov Disord 22:839–842
22. Haensch CA, Lerch H, Jörg J, Isenmann S (2009) Cardiac denervation occurs independent of orthostatic hypotension and impaired heart rate variability in Parkinson's disease. Parkinsonism Relat Disord 15:134–137
23. Hashimoto Y, Fukazawa K, Fujii M, Takayasu S, Muto T, Saito S et al (2004) Usefulness of the odor stick identification test for

Japanese patients with olfactory dysfunction. Chem Senses 29:565–571
24. Hawkes CH (2008) Parkinson's disease and aging: same or different process? Mov Disord 23:47–52
25. Hobson DE, Pourcher E, Martin WR (1999) Ropinirole and pramipexole, the new agonists. Can J Neurol Sci 26(Suppl 2):S27–S33
26. Holroyd S, Keller AS (1995) A study of visual hallucinations in Alzheimer's disease. Am J Geriatr Psychiatry 3:198–205
27. Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatr 55:181–184
28. Iijima M, Kobayakawa T, Saito S, Osawa M, Tsutsumi Y, Hashimoto S, Iwata M (2008) Smell identification in Japanese Parkinson's disease patients: using the odor stick identification test for Japanese subjects. Intern Med 47:1887–1892
29. Iwanaga K, Wakabayashi K, Yoshimoto M, Tomita I, Satoh H, Takashima H et al (1999) Lewy body-type degeneration in cardiac plexus in Parkinson's and incidental Lewy body diseases. Neurology 52:1269–1271
30. Jones BE, Yang TZ (1985) The efferent projections from the reticular formation and the locus coeruleus studied by anterograde and retrograde axonal transport in the rat. J Comp Neurol 242:56–92
31. Kaufmann H (1996) Consensus statement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. Clin Auton Res 6:125–126
32. Kawamura H, Gunn CG, Frohlich ED (1978) Cardiovascular alterations by nucleus locus coeruleus in the spontaneously hypertensive rat. Brain Res 140:137–147
33. Kobal G, Hummel T, Sekinger B, Barz S, Roscher S, Wolf S (1996) "Sniffin Sticks": screening of olfactory performance. Rhinology 34:222–226
34. Lee PH, Yeo SH, Kim HJ, Youm HY (2006) Correlation between cardiac ^{123}I-MIBG and odor identification in patients with Parkinson's disease and multiple system atrophy. Mov Disord 21:1975–1977
35. Lode HN, Bruchelt G, Seitz G, Gebhardt S, Gekeler V, Niethammer D et al (1995) Reverse transcriptase-polymerase chain reaction (RT-PCR) analysis of monoamine transporters in neuroblastoma cell lines: correlations to meta-iodobenzylguanidine (MIBG) uptake and tyrosine hydroxylase gene expression. Eur J Cancer 31A:586–590
36. Mathias CJ, Bannister RS (1999) Autonomic failure: a textbook of clinical disorders of the autonomic nervous system, 4th edn. Oxford University Press, New York
37. Miyamoto T, Miyamoto M, Iwanami M, Suzuki K, Inoue Y, Hirata K (2009) Odor identification test as an indicator of idiopathic REM sleep behavior disorder. Mov Disord 24:268–273
38. Oishi N, Udaka F, Kameyama M, Sawamoto N, Hashikawa K, Fukuyama H (2005) Regional cerebral blood flow in Parkinson disease with nonpsychotic visual hallucinations. Neurology 65:1708–1715
39. Oka H, Mochio S, Sato H, Katayama K (1997) Prolongation of QTc interval in patients with Parkinson's disease. Eur Neurol 37:186–189
40. Oka H, Mochio S, Yoshioka M, Morita M, Inoue K (2003) Evaluation of baroreflex sensitivity by the sequence method using blood pressure oscillations and R–R interval changes during deep respiration. Eur Neurol 50:230–243
41. Okada Y, Ito Y, Aida J, Yasuhara M, Ohkawa S, Hirokawa K (2004) Lewy bodies in the sinoatrial nodal ganglion: clinicopathological studies. Pathol Int 54:682–687
42. Orimo S, Ozawa E, Nakade S, Sugimoto T, Mizusawa H (1999) [123] I-metaiodobenzylguanidine myocardial scintigraphy in Parkinson's disease. J Neurol Neurosurg Psychiatry 67:189–194
43. Orimo S, Amino T, Itoh Y, Takahashi A, Kojo T, Uchihara T et al (2005) Cardiac sympathetic denervation precedes neuronal loss in the sympathetic ganglia in Lewy body disease. Acta Neuropathol 109:583–588
44. Orimo S, Takahashi A, Uchihara T, Mori F, Kakita A, Wakabayashi K et al (2007) Degeneration of cardiac sympathetic nerve begins in the early disease process of Parkinson's disease. Brain Pathol 17:24–30
45. Orimo S, Uchihara T, Nakamura A, Mori F, Kakita A, Wakabayashi K et al (2008) Axonal alpha-synuclein aggregates herald centripetal degeneration of cardiac sympathetic nerve in Parkinson's disease. Brain 131:642–650
46. Rajput AH, Rozdilsky B (1976) Dysautonomia in Parkinsonism: a clinicopathological study. J Neurol Neurosurg Psychiatry 39:1092–1100
47. Robertson D, Hollister AS, Biaggioni I, Netterville JL, Mosqueda-Garcia R, Robertson RM (1993) The diagnosis and treatment of baroreflex failure. N Engl J Med 329:1449–1455
48. Saito S, Ayabe-Kanamura S, Takashima Y, Gotow N, Naito N, Nozawa T et al (2006) Development of a smell identification test using a novel stick-type odor presentation kit. Chem Sense 31:379–391
49. Senard JM, Raï S, Lapeyre-Mestre M, Brefel C, Rascol O, Rascol A et al (1997) Prevalence of orthostatic hypotension in Parkinson's disease. J Neurol Neurosurg Psychiatry 63:584–589
50. Shibata M, Morita Y, Shimizu T, Takahashi K, Suzuki N (2009) Cardiac parasympathetic dysfunction concurrent with cardiac sympathetic denervation in Parkinson's disease. J Neurol Sci 276:79–83
51. Solanki KK, Bomanji J, Moyes J, Mather SJ, Trainer PJ, Britton KE (1992) A pharmacological guide to medicines which interfere with the biodistribution of radiolabelled meta-iodobenzylguanidine (MIBG). Nucl Med Commun 13:513–521
52. Spiegel J, Mollers MO, Jost WH, Fuss G, Samnick S, Dillmann U et al (2005) FP-CIT and MIBG scintigraphy in early Parkinson's disease. Mov Disord 20:552–561
53. Stern MB, Doty RL, Dotti M, Corcoran P, Crawford D, McKeown DA et al (1994) Olfactory function in Parkinson's disease subtypes. Neurology 44:266–268
54. Task Force of the European Society of Cardiology, the North American Society of Pacing, Electrophysiology (1996) Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Eur Heart J 17:354–381
55. Tateno F, Sakakibara R, Saiki A, Miyashita Y, Shirai K (2008) Levodopa might affect metaiodobenzylguanidine myocardial accumulation. Mov Disord 23:2097–2098
56. Tissingh G, Berendse HW, Bergmans P, DeWaard R, Drukarch B, Stoof JC et al (2001) Loss of olfaction in de novo and treated Parkinson's disease: possible implications for early diagnosis. Mov Disord 16:41–46
57. Thuerauf N, Reulbach U, Lunkenheimer J, Lunkenheimer B, Spannenberger R, Gossler A et al (2009) Emotional reactivity to odors: olfactory sensitivity and the span of emotional evaluation separate the genders. Neurosci Lett 456:74–79
58. Ward DG, Gunn CG (1976) Locus coeruleus complex: different modulation of depressor mechanism. Brain Res 107:407–411
59. Wheeler T, Watkins PJ (1973) Cardiac denervation in diabetes. Br Med J 4:584–586
60. Williams SS, J Williams J, Combrinck M, Christie S, Smith AD, McShane R (2009) Olfactory impairment is more marked in patients with mild dementia with Lewy bodies than those with mild Alzheimer disease. J Neurol Neurosurg Psychiatry 80:667–670