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Cardiac Sympathetic Degeneration Correlates with Olfactory Function in Parkinson's Disease

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Abstract: Autonomic and olfactory dysfunctions are considered markers for preclinical diagnosis in Parkinson's disease (PD), because pathological changes in these systems can start before motor symptoms develop. We investigated whether cardiac sympathetic function and olfactory function are associated in PD. Participants comprised 40 nondemented patients with idiopathic PD, and age-matched controls. Cardiac sympathetic function was evaluated by ^{123} I-metaiodobenzylguanidine (MIBG) uptake, in terms of the heart to mediastinum (H/M) ratio in both early and delayed images, and the washout rate (WR). Olfactory function was evaluated using the Odor Stick Identification Test for Japanese, which evaluates the detection of 12 odorants familiar to Japanese participants. Smell identification scores were significantly lower ($P < 0.001$) in patients with PD than in controls. Smell identification scores correlated positively with early ($P < 0.05$) and delayed H/M ratios ($P < 0.01$), and inversely with the WR ($P < 0.005$) especially in patients with early PD (below 5 years of the start of motor symptoms), whereas smell identification scores did not correlate with any parameters of MIBG in the advanced PD (above 5 years of the start of motor symptoms). There was no correlation between motor symptom scores and smell identification scores, H/M ratios, or WR. The results suggest that the cardiac sympathetic nervous system might degenerate in parallel with the olfactory system in patients with early PD, and that these two systems might degenerate at a different rate of speed in advanced PD. © 2010 Movement Disorder Society

Key words: Parkinson's disease; odor stick identification test; MIBG

INTRODUCTION

Olfactory and autonomic dysfunctions are nowadays recognized as nonmotor symptoms in patients with Parkinson's disease (PD). These features are considered diagnostic markers of preclinical PD[1–3] because pathological changes of the olfactory and autonomic systems begin before motor symptoms develop.[4]

The sensitivity of olfactory disturbance as a marker of PD is 80–90%.[1,2,5] The proportion of patients with olfactory disturbance who develop PD is 7–10%.[6–11]

Metaiodobenzylguanidine (MIBG) is a physiologic analog of norepinephrine, and iodone-123 (^{123}I) MIBG cardiac scintigraphy is a noninvasive tool for assessing myocardial sympathetic nerve terminals.[12] In patients with PD, cardiac uptake of MIBG decreases from the early stage of the disease[12,13] and correlates with the severity of hypokinesia and rigidity.[14,15,16] The sensitivity of MIBG cardiac scintigraphy in PD is 80–90%.[13,14,17–19] In this case-control study, we investigated whether there is an association between cardiac autonomic function and olfactory function in patients with PD.

METHODS

Participants

Participants comprosed 40 patients with idiopathic PD (25 men and 15 women), ranging in age from 41 to 82 (mean ± SD, 66.6 ± 10.6) years, and 40 age-

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and gender-matched healthy controls who reported no olfactory complaints (25 men and 15 women, 43–83 years of age; mean ± SD, 67.8 ± 7.0). Patients with diabetes mellitus, and those taking medication affecting MIBG uptake were excluded. The diagnosis of idiopathic PD was made based on the Criteria of the United Kingdom Brain Bank[20] and a negative family history of PD. The patients' disease duration ranged from 6 to 252 (mean ± SD, 58.0 ± 51.8) months. Motor performance was assessed using the Hoehn and Yahr (H&Y) scale and the motor section (part III) of the Unified Parkinson's Disease Rating Scale (UPDRS): 8 patients were in H&Y stage I, 21 were in stage II, 10 were in stage III, and 1 was in stage IV (mean stage ± SD: 2.1 ± 0.7). The patients were divided into tremor-dominant type (TDT), akinetic rigid type (ART), and mixed type (MT) PD subgroups by means of part III of the UPDRS in a manner similar to Spiegel et al., on the basis of tremor and nontremor scores.[21] The tremor score was derived from the sum of UPDRS items 20 (*tremor at rest*) and 21 (*action or postural tremor of hands*). The nontremor score was obtained from the sum of UPDRS items 18 (*speech*), 19 (*facial expression*), 22 (*rigidity*), 27 (*arising from chair*), 28 (*posture*), 29 (*gait*), 30 (*postural stability*), and 31 (*body bradykinesia and hypokinesia*). PD was classified as TDT if the tremor score was at least twice the nontremor score (n = 9), as ART if the nontremor score was at least twice the tremor score (n = 22), or as MT for the remainder (n = 9). Cognitive function was evaluated using the Mini-Mental State Examination (MMSE), and MMSE scores for the PD patients ranged from 25 to 30 points. At the time of testing, 30 of the PD patients were taking anti-parkinsonian medication as follows: levodopa (100–600 mg/day, n = 20), pramipexole (0.25–2.5 mg/day, n = 13), cabergoline (0.75–4.0 mg/day, n = 9), pergolide (1250 ug/day, n = 1), amantadine (100–200 mg/day, n = 5), trihexyphenidyl (3.0–4.0 mg/day, n = 2), droxidopa (200 mg/day, n = 1), and selegiline hydrochloride (3.0 mg/day, n = 1). Ten patients were newly diagnosed and not on any medication.

Informed consent was obtained from all participants following a full explanation of the study. This study was done in accordance with the guidelines of the Committee of Medical Ethics of Tokyo Women's Medical University.

Odor Stick Identification Test

This test included 12 odorants: perfume, rose, condensed milk, Japanese orange, curry, roasted garlic, fermented beans/sweaty socks, cooking gas, menthol, India ink, wood, and Japanese cypress (*hinoki*).[22,23] These odors were chosen from clusters representing Japanese daily life and are familiar to the Japanese population, and each odorant was selected from the essential oils, pure chemicals, or mixed odorants produced by Takasago International Corporation Ltd. (Tokyo, Japan). Each odorant was enclosed in melamine resin microcapsules, which were mixed into an odorless solid cream and then shaped like a lipstick. The examiner painted each odor stick in a 2-cm circle on thin paraffin paper, folded the paper in half, rubbed it to grind the microcapsules, and then passed it to the participant. The participant opened the paraffin paper and sniffed it. He or she then chose one of six possible answers from four labeled pictures of entities associated with the odors, one of which was correct, and two others ("unknown" and "not detected"). Participants were directed to avoid eating and smoking 30 minutes prior to being examined. The order in which the odorants were presented was randomized.

Healthy controls were examined at the National Institute of Advanced Industrial Science and Technology (Tsukuba, Japan). The OSIT identification rate has been calculated for 10-year age groups.[23]

Subjective symptoms were evaluated in PD patients. It's ranging from normosmia to anosmia were assessed on a 5-point scale: 1, could smell normal-strength odors; 2, some decline in sense of smell; 3, could smell only strong odors; 4, much diminished sense of smell; and 5, no sense of smell.

^{123}I-MIBG Myocardial Scintigraphy

For MIBG myocardial scintigraphy, planar scintigraphic imaging in the anterior view was performed using a single head gamma camera (GCA7200, Toshiba, Japan), 15 minutes (early) and 4 hours (delayed) after intravenous injection of MIBG (111 MBq). To measure MIBG uptake, heart (left ventricle) and mediastinal regions of interest were drawn manually. The heart to mediastinum ratio (H/M) for both early and delayed images and the myocardial washout rate (WR) for delayed images were calculated as previously reported.[24] MIBG scintigraphy was performed within two months after the odor tests for all participants.

Statistical Analysis

Smell identification scores were compared between the control group and the patient group using nonparametric analysis (Mann-Whitney *U* test). Spearman's rank correlation was used to examine correlations

between smell identification scores and H/M ratios and WR. Simple regression was performed to investigate correlations between MIBG parameters (early and delayed H/M ratios and WR) and age, duration of illness, and UPDRS scores. ANOVA was used for group comparisons in age, duration of illness, UPDRS scores, H/M ratios, WR, smell identification scores or subjective symptoms of olfactory disturbance. Chi-square test for independence was used between genders and subtypes. Where indicated by a significant *F*-value, post-hoc comparisons were carried out using Bonferroni's test. Two factorial ANOVA was used to compare smell identification scores between genders and subtypes. Results were given as mean ± SD where applicable. In addition, the patients were divided into the early PD and the advanced PD by the duration of illness. We defined that the early PD was below 5 years of the start of motor symptoms, and the advanced PD was above 5 years of it. A sub-analysis of the association between MIBG and smell identification scores was done in each patient' group.

RESULTS

Olfactory Functions

Subjective Symptoms of Olfactory Disturbance

Twelve patients with PD (30.0%) had a score of 1, 16 (40.0%) had a score of 2, 9 (22.5%) had a score of 3, 3 (7.5%) had a score of 4, and none had a score of 5.

Smell Identification Test

The smell identification score was significantly lower in patients with PD (5.6 ± 3.3) than in controls (8.7 ± 1.9) ($P < 0.001$) (Fig. 1). Twenty patients (50.0%) had low smell identification scores based on a normal value of 4 points (mean − 2SD in controls). There was no correlation between smell identification scores and disease duration or UPDRS scores.

Cardiac ^{123}I-MIBG Scintigraphy

Normal values at our hospital are below 1.6 (mean – 2SD) for both early and delayed H/M ratio, and above 35% for WR. In patients with PD, early H/M ratio was 1.75 ± 0.38 (range: 1.19–2.84), delayed H/M ratio was 1.63 ± 0.54 (range: 1.05–3.04), and WR was 48.0 ± 23.4% (range: –12–90%). Early H/M ratio was reduced in 16 patients (40.0%) and delayed H/M ratio was reduced in 25 patients (62.5%). WR was increased in 32 patients (80.0%). There was no correlation between MIBG parameters and disease duration or UPDRS scores.

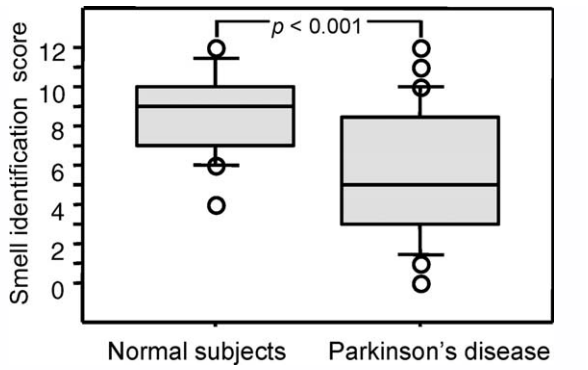

FIG. 1. Comparison of smell identification scores on the odor stick identification test between normal participants and patients with Parkinson's disease. Median and quartile (box plats) as well as 10th and 90th percentiles (whiskers) of individual smell identification scores.

Correlation Between Cardiac ^{123}I-MIBG Scintigraphy and Odor Identification

Smell identification scores on the OSIT correlated positively with the H/M ratio in both the early ($Z = 2.99$, $P < 0.005$) and the delayed images ($Z = 3.28$, $P < 0.005$), and inversely with the WR ($Z = – 3.07$, $P < 0.005$) (Fig. 2).

Olfactory Disturbance and ^{123}I-MIBG Scintigraphy in PD Subtypes

Results of intergroup comparisons for characteristics, subjective olfactory disturbance and MIBG scintigraphy are shown in Table 1. There were no significant differences in age, duration of illness, or H&Y stage among the clinical subtypes. Significant gender difference ($P < 0.05$) among the clinical subtypes was shown by Chi-square test. The score of UPDRS part III in ART was higher than in TDT ($F = 3.50$, $P < 0.05$).

TDT patients demonstrated significantly higher smell identification scores ($F = 3.39$, $P < 0.05$) and less subjective olfactory disturbance ($F = 3.59$, $P < 0.05$) than ART patients. The sex ratio was different among the clinical subtypes, however, there was no gender effect on the smell identification score among subtypes by using two factorial ANOVA.

Neither H/M ratios nor WR differed significantly among the three PD subtypes; however, H/M ratios

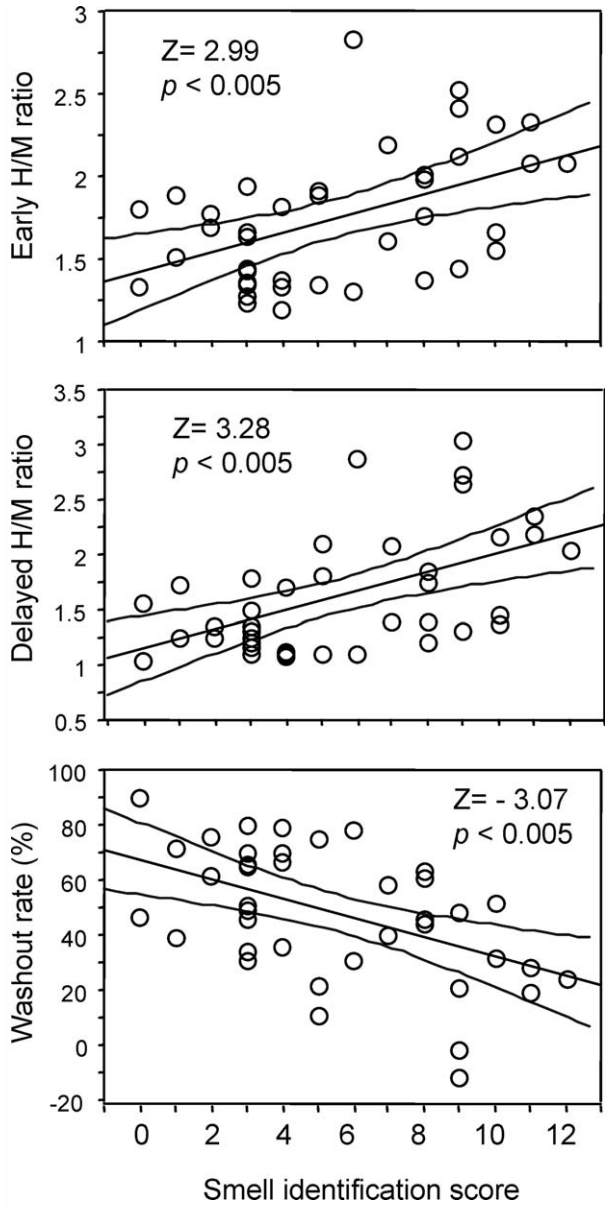

FIG. 2. Correlation between smell identification scores on the odor stick identification test and heart/mediastinum (H/M) ratio, and washout rate for ^{123}I-MIBG uptake.

tended to be higher in TDT patients than in ART patients or MT patients.

Olfactory Disturbance and ^{123}I-MIBG Scintigraphy Patients with in Early and Advanced PD

Twenty-three patients were into the early PD, and 17 patients into the advanced PD. Table 2 showed that the MIBG scintigraphy and odor functions in patients with early and advanced PD. The early and delayed H/M ratio decreased significantly ($P < 0.01$), and WR increased significantly ($P < 0.05$) in the advanced PD than that in the early PD, whereas odor functions were not any different between the early and the advanced PD. As regarding the association between MIBG and smell identification scores, the early PD group had the positive correlations between the early ($Z = 2.41$, $P < 0.05$) and the delayed H/M ratio ($Z - 2.57$, $P < 0.01$) and smell identification scores, and inverse correlation ($Z = -2.82$, $P < 0.005$) between WR and smell identification scores. There was no correlation between MIBG and smell identification scores in the advanced PD.

DISCUSSION

This study showed significant positive correlations between smell identification scores and H/M ratios in both the early and delayed images, and a significant inverse correlation between smell identification scores and WR in patients with the early PD. The sensitivity of early H/M ratio, delayed H/M ratio and WR on MIBG scintigraphy in PD was 40.0, 62.5, and 80.0%, respectively. Smell identification score in patients with PD was significantly lower than that in controls, and its sensitivity in PD was 50.0%.

The previous reports using the OSIT in Japanese patients with PD (mean Hoehn and Yahr stage: 2.2) showed that the mean smell identification score was 4.4–4.8.[25,26] In this study, the mean smell identification score was higher, and the sensitivity of odor identification score in PD was lower than in previous reports.[1,2,5] This might be due to the relatively early stage of PD (mean Hoehn and Yahr stage: 2.08 ± 0.71 in the present participants), or to the strict cut-off ratio for a normal score. In addition, the discrepancy in sensitivity could result from the use of different olfactory tests. A recent study of 295 nondemented patients with PD found impaired olfactory identification in 61% of patients and impaired discrimination in 43%, using the Sniffin' Sticks test.[11] This study showed the relatively low percentage of PD patients with olfactory impairment similar in rate to our results. It was interesting that smell identification scores differed significantly among the PD subtypes in this study. TDT patients had significantly better olfactory function than ART patients. This might imply that patients with severe olfactory disturbance already have marked degeneration of the nigrostriatal dopaminergic neurons. Stern et al.[27] found that University of Pennsylvania Smell Identification Test scores were higher in tremor-dominant type PD than in postural instability-gait disorder predomi-

TABLE 1. *Cardiac ^{123}I MIBG scintigraphy and odor functions in subtypes of Parkinson's disease*

	Tremor-dominant type	Akinetic-rigid type	Mixed type	*P* value
Numbers (males, females)	9 (2, 7)	22 (16, 6)	9 (7, 2)	
Age (year)	64.3 ± 11.0	66.9 ± 10.0	64.2 ± 13.6	0.74
Duration of illness (months)	63.4 ± 75.7	53.1 ± 44.3	63.8 ± 46.9	0.82
Heohn and Yahr stage	1.7 ± 0.5	2.3 ± 0.8	2.0 ± 0.7	0.07
UPDRS part III	9.8 ± 4.0	20.0 ± 10.5	17.7 ± 11.5	<0.05
Cardiac MIBG scintigraphy				
Early H/M ratio	1.89 ± 0.38	1.69 ± 0.42	1.73 ± 0.38	0.46
Delayed H/M ratio	1.73 ± 0.54	1.56 ± 0.56	1.68 ± 0.53	0.69
Wash out ratio	34.3 ± 19.8	53.9 ± 24.9	38.2 ± 2.2	0.32
Odor functions				
Subjective symptom	1.3 ± 0.7	2.4 ± 1.0	1.9 ± 1.2	<0.05
Correct answers of the OSIT	7.8 ± 3.3	4.5 ± 3.0	5.8 ± 3.2	<0.05

H/M ration: heart to mediastinum ratio, OSIT: odor stick identification test (mean ± SD).

nant type PD. In addition, a study using TRODAT-1 SPECT imaging showed that reduced dopamine transporter binding in the striatum correlated with olfactory impairment in patients with early PD.[28]

The H/M ratios in this study were similar to results in the previous studies.[13,14,19] The sensitivity of ^{123}I-MIBG uptake in PD is generally recognized as 80–90%,[1,2] but drops down to 72% in the early stage of the disease.[13] The sensitivity of the H/M ratios was lower in this study than in previous reports; however, that of the WR was 80%. The difference in the sensitivity of H/M ratios might relate to variation in normal values among institutions; the cut-off value for early H/M was 1.6 in our study, but 1.8–2.1 in previous reports.[13,15–17,19] Early uptake of ^{123}I-MIBG may reflect mainly presynaptic sympathetic system integrity and distribution, while delayed uptake may in addition reflect the functional status or washout of norepinephrine from sympathetic nerve terminals.[29] Based on these results and previous reports, reduced ^{123}I-MIBG uptake could start from the delayed image, and raised WR might suggest enhanced spillover of, or reduced ability to preserve norepinephrine in the cardiac sympathetic terminals in PD.

Spiegel et al.[14] reported a significant correlation between myocardial sympathetic degeneration and symptoms of hypokinesia and rigidity, and a significant positive correlation between MIBG uptake and striatal ^{123}I-FP-CIT uptake in the early stage of PD. Furthermore, decreased striatal FP-CIT uptake has been found to correlate significantly with extent of hypokinesia and rigidity.[30] These results suggest that myocardial sympathetic degeneration and severe loss of nigrostriatal neurons are closely coupled. In this study, the H/M ratios were higher in TDT patients than in ART patients and MT patients but these differences were not significant. We excluded 30 patients who were taking medications from subtypes during "on phase" in our study. On the other hand, Spiegel et al.[14] evaluated motor function during the "off" (nonmedicated) phase. Thus, the influence of medication on UPDRS scores might have modified the categorization from subtypes.

This study showed significant correlations between the smell identification function and parameters of MIBG scintigraphy in patients with early PD (below 5 years of the start of motor symptoms), however, there was no correlation the smell identification function and parameters of MIBG scintigraphy in patients with advanced PD. These results suggest that patients with severe olfactory impairments have marked myocardial sympathetic hypofunction, and that the myocardial sympathetic nervous system degenerates in parallel with the olfactory system in the early PD, and that these two systems might degenerate at a different rate of speed in the advanced PD. Olfactory disturbance in

TABLE 2. *Cardiac ^{123}I MIBG scintigraphy and odor functions in the early and the advanced Parkinson's disease*

	Early PD	Advanced PD	*P* value
Numbers (males, females)	23 (15, 8)	17 (10, 7)	
Age (year)	66.0 ± 11.0	67.4 ± 10.1	0.69
Duration of illness (months)	25.7 ± 15.0	101.8 ± 51.9	<0.0001
Heohn and Yahr stage	1.9 ± 0.6	2.4 ± 0.9	0.63
UPDRS part III	16.1 ± 10.3	18.5 ± 10.5	0.48
Non-medication (n)	8	2	
Cardiac MIBG scintigraphy			
Early H/M ratio	1.90 ± 0.42	1.54 ± 0.28	<0.01
Delayed H/M ratio	1.82 ± 0.59	1.37 ± 0.33	<0.01
Wash out ratio	41.1 ± 23.5	57.4 ± 20.4	<0.05
Odor functions			
Subjective symptom	1.9 ± 1.1	2.2 ± 1.0	0.45
Correct answers of the OSIT	6.2 ± 3.8	4.6 ± 2.3	0.22

H/M ration: heart to mediastinum ratio, OSIT: odor stick identification test (mean ± SD).

Early PD: below 5 years of duration of illness, advanced PD: above 5 years of duration of illness.

PD is generally thought to be one of the early nonmotor symptoms and not to correlate with disease durations.[5] On the other hand, the cardiac H/M ratios are correlated with duration of illness, and decrease with the progression of Hoehn and Yahr stage.[13] There have been few studies on the relationship between olfactory function and cardiac MIBG scintigraphy in patients with PD.[31,32] In accordance with the present findings, Lee et al.[31,32] showed a significant positive correlation between odor identification function evaluated by the Cross-Cultural Smell Identification test and cardiac MIBG uptake in patients with PD (mean durations 3.3 years), but they found no such correlation in patients with multiple system atrophy or drug-induced parkinsonism.

Recently, degeneration of cardiac sympathetic nerves has been shown to precede neuronal cell loss in the dorsal vagal nucleus in PD.[33,34] Alpha synuclein, a presynaptic protein and one of the regulators of dopamine synthesis, was demonstrated in epicardial neurites in normal individuals with incidental Lewy bodies (iLB) and in PD.[33,34] Moreover, immunoreactive nerve fibers for tyrosine hydroxylase and the density of positive neurites for alpha synuclein correlated with the Braak PD stage, and with disease duration.[34] On the other hand, Lewy bodies first develop in the olfactory bulb and the anterior olfactory nucleus (Braak stage I). Cortical Lewy bodies are mainly found in the orbitofrontal cortex, the amygdala and the hippocampus.[35,36] Hubbard et al.[36] demonstrated that Lewy pathology showed in the olfactory bulb in 28% patients for Braak stage I, and in 90% for Braak stage II-IV. Interestingly, Huisman et al.[37] showed an increase of thyosine hydroxylase-positive periglomerular neurons in the olfactory bulb in PD when compared with healthy controls. It is possible that the increase in dopaminergic periglomerular cells represents a compensatory response to the primary cause of olfactory dysfunction in PD. In addition, a functional imaging study of the cerebral olfactory system in early PD demonstrated decreased activity in the amygdala and hippocampus, and increased activity in the inferior frontal gurus, anterior cingulate gyrus, and left dorsal and right ventral stratum.[38] Since impairment of odor identification is a cognitive task involving olfactory discrimination, olfactory dysfunction in PD patients could also be caused in part by semantic processing impairment, and might be associated with disruption of olfactory areas in the temporal lobes and prefrontal cortex.[39] Our previous study showed the decrease of smell identification scores even in patients who subjectively detected odors at normal strength.[25] This study suggested that olfactory dysfunction in PD patients was not simply due to an increased threshold for olfactory stimuli but also related to impairment of odor identification. Early pathological changes in the olfactory bulb may cause incorrect odor information, which then might project to compensatory cortical areas in olfactory processing.

In conclusion, our study showed that ^{123}I-MIBG H/M ratios and WR were significantly correlated with the odor identification function in patients with early PD, whereas there was no correlation between the odor identification function and MIBG in patients with the advanced PD. The results suggest that the cardiac sympathetic nervous system might degenerate in parallel with the olfactory system in patients with early PD, and that these two systems might degenerate at a different rate of speed in advanced PD. To confirm this hypothesis, a prospective cohort study is needed.

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Author's Role: 1. Research project: A. Conception; B. Organization; C. Execution; 2. Statistical analysis: A. Desingn; B. Execution; C. Review and Critique; 3. Maniscript: A. Writing of first draft; B. Review and Critique. Iijima: 1A+1B+1C+2A+2B+3A; Osawa: 1B+1C+2A+2C+3B; Momose: 1B+1C+2C+3B; Kobayakawa: 1C+2C+3B; Saito: 1C+2C+3B; Iwata: 2C+3B; Uchiyama: 2C+3B.

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