

Clinical Study

Nonmotor Symptoms in Patients with *PARK2* Mutations

Asako Yoritaka,¹ Yumi Shimo,¹ Yasushi Shimo,¹ Yuichi Inoue,² Hiroyo Yoshino,¹
and Nobutaka Hattori¹

¹ Department of Neurology, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan

² Japan Somnology Center, Neuropsychiatric Research Institute, 1-24-10 Yoyogi, Shibuya-ku, Tokyo 151-0053, Japan

Correspondence should be addressed to Asako Yoritaka, ayori@juntendo.ac.jp

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Decreased ¹²³I-meta-iodobenzylguanidine (MIBG) uptake in MIBG myocardial scintigraphy, olfactory dysfunction, and rapid eye movement (REM) sleep behavior disorder (RBD) are considered useful early indicators of Parkinson disease. We investigated whether patients with *PARK2* mutations exhibited myocardial sympathetic abnormalities using MIBG scintigraphy, olfactory dysfunction using the Sniffin' Sticks olfactory test, and RBD using polysomnography. None of the examined patients had RBD, and all except 1 patient exhibited an increase in the olfactory threshold. Moreover, one of the oldest patients exhibited impairment in identification and discrimination. Of 12 patients with *PARK2* mutations, 4 patients, who were older than patients without abnormal uptake, exhibited decreased MIBG uptake. The results obtained in this study suggest that some patients with *PARK2* mutations have increased thresholds of olfactory function and myocardial sympathetic dysfunction as nonmotor symptoms.

1. Introduction

Mutations in the *parkin* gene (*PARK2*) are considered to be the predominant cause of early-onset Parkinson disease particularly when the family history is compatible with autosomal recessive inheritance [1]. This condition is characterized by early onset of disease, usually before the age of 40 years, dystonia, sleep benefit, early complications from levodopa treatment, and slow progression. *Parkin*-associated tremor-dominant parkinsonism includes a spectrum of late-onset disorders without manifestations of foot dystonia, hyperreflexia, diurnal fluctuations, sleep benefit, or early susceptibility to levodopa-induced dyskinesia [2]. Therefore, patients with *PARK2* mutations are often clinically indistinguishable from those with sporadic Parkinson's disease (PD).

PD patients exhibit decreased myocardial uptake of meta-iodobenzylguanidine (MIBG) during ¹²³I-MIBG myocardial scintigraphy—a finding indicative of cardiac sympathetic denervation [3]. Olfactory impairment, an early symptom of PD, occurs in more than 70% of patients with PD [4]. Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by a loss of normal skeletal muscle atonia and complex motor activity, specifically during REM sleep associated with dream mentation. Thirty-eight percent

of RBD patients aged ≥ 50 years were eventually diagnosed with PD [5]; therefore, RBD may serve as an early indicator of PD.

Here, we examined nonmotor symptoms in patients with *PARK2* mutations.

2. Methods

Mutation of the *parkin* gene was confirmed by gene analysis [1]. Eight women and 7 men possessed mutations in the *PARK2* gene: cases 1, 2, 3, 8, and 13 carried homozygous deletions, and the remaining carried heterozygous mutations or deletions (Table 1). Clinical findings and medications are shown in Table 1.

The MIBG study involved 6 women and 7 men (mean (SD) age, 58.5 (11.4) years) with *PARK2* mutations: 5 subjects had homozygous deletions, and 8 had heterozygous mutations or deletions. Patients had parkinsonism for a mean (SD) period of 22.0 (11.59) years (range, 10–44 years). When MIBG scintigraphy was performed, the patients were not medicated with monoamine oxidase B (MAOB) inhibitors, selective serotonin reuptake inhibitors, or antidepressant drugs. Data was collected by E CAM at 30 minutes and 3 hours after injection of ¹²³I-MIBG

TABLE 1: Clinical findings and medication of patients with PARK2 mutation.

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age sex	71 F	55 M	46 M	41 F	38 M	36 F	76 M	70 M	63 M	61 F	61 F	60 F	57 M	44 F
Parkin	exon 2-4 homo deletion	exon 5 homo deletion	exon 6,7 homo deletion	exon 6 hetero deletion	exon 4, intron 4 acceptor site, A → G	exon 10 hetero mutation	exon 10 hetero mutation	exon 2 homo-deletion	exon 2,3,4 hetero deletion	exon 2,3,4 hetero deletion	exin 4 hetero deletion	exon 3,4 hetero deletion	exon 2,3,4 homo-deletion	exon 5 hetero deletion
On set	61	28	28	27	18	20	65	45	33	29	47	16	45	34
Disease duration	10	27	18	14	20	16	11	28	36	34	14	44	12	10
Family history	-	+	+	-	-	+	+	-	-	+	-	+	+	+
Hoehn & Yahr stage on	2	2	2	1	1.5	2	2	3	3	3	3	3	1	1
Rigidity*	1	1	0	1	2	0	1	0	0	1	0	0	0	0
Tremor*	1	0	0	1	0	0	1	1	0	0	0	0	0	0
Hesitation*	0	1	1	0	0	2	0	1	1	2	2	1	0	0
Wearing-off	+	+	+	-	+	+	-	+	+	+	+	-	+	-
Dementia	-	-	-	-	-	+	-	-	-	-	-	-	-	-
Hallucination	-	-	-	-	-	+	-	-	-	-	+	-	-	-
Sleep violent behavior	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Constipation	+	+	-	-	-	-	-	-	-	-	+	-	-	-
Levodopa	700 mg	600 mg	600 mg	300 mg	400 mg	300 mg	-	300 mg	500 mg	995 mg	800 mg	200 mg	450 mg	-
Agonist non-ergot	prami-pexole 1.5 mg	prami-pexole 4.5 mg	prami-pexole 3 mg	ropinirole 9 mg	prami-pexole 1.5 mg	ropinirole 12 mg	prami-pexole 4.5 mg	-	prami-pexole 0.75 mg	prami-pexole 1.5 mg	prami-pexole 2.25 mg	ropinirole 16 mg	-	prami-ipexole 1.5 mg
Agonist ergot	-	pergolide 2.25 mg	-	-	caber-goline 4 mg	-	-	-	-	-	-	-	caber-goline 2 mg	-
Selegiline	-	5 mg	-	-	10 mg	5 mg	-	-	-	-	5 mg	-	2.5 mg	-
Entacapone	-	400 mg	600 mg	-	300 mg	600 mg	-	-	400 mg	-	-	-	-	-
Trihexyphenidyl	-	-	-	-	3 mg	-	-	5 mg	-	-	-	-	-	-
Amantadine	300 mg	150 mg	300 mg	-	300 mg	-	-	-	150 mg	200 mg	100 mg	300 mg	-	-

DID: dopa induced dyskinesia.

*UPDRS mean score **Thalamotomy *** no medication.

(MyoMIBG-I 123 injection, 111 MBq; FUJIFILM RI Pharma Co. Ltd.). The cut-off ratio of the heart to mediastinum (H/M) uptake ratio of ^{123}I -MIBG in our hospital was set at 1.45.

The olfactory function and polysomnography (PSG) study involved 3 women and 3 men (mean (SD) age, 47.8 (13.2) years) with *PARK2* mutations (Table 1).

The mean olfactory function scores of the PD patients and 10 age-matched Japanese controls, who were evaluated for comparison with patients with *PARK2* mutations, were determined by the Sniffin' Sticks test. Mean age of the controls without neurological disease or dementia was 46.0 (15.3) years (range, 39–79 years). The PD patients (mean age, 69.6 (6.6) years; range, 60–89 years; not age matched to patients with *PARK2* mutations) fulfilled the UK Brain Bank criteria for possible or probable clinical PD, with Hoehn-Yahr stages II and III without dementia.

Olfactory testing was examined by following 3 components. Olfactory threshold and odor discrimination and identification were investigated in 3 separate substrates using standardized Sniffin' Sticks [6]. Sniffin' Sticks are commercially available felt-tip pens.

Odor Thresholds. The olfactory threshold subset consisted of 16 Sniffin' Stick triplets with different concentrations of *n*-butanol. Three sticks were presented to the subject in randomized order. Two contained only the solvent and the third the odorant at a particular dilution. The subjects were tasked to identify the stick with the odorant.

Odor Discrimination. In the odor discrimination subset, 16 Sniffin' Stick triplets were presented in randomized order. Two pens contained the same odorant and the third a different odorant. The task was to identify the stick that had the different smell.

Odor Identification. The third subtest consisted of 16 single sticks and assessed the ability to identify an odor. Using a multiple-choice task, identification of individual odorants was performed from a list of 4 descriptors.

RBD was confirmed by studying the patients' clinical history and video-PSG findings (International Classification of Sleep Disorders, 2nd edition) [7].

Informed consent was obtained from patients with *PARK2* mutations, and patients with PD, and normal volunteers.

The data was statistically analyzed using SPSS ver.11 for Windows.

3. Results

The mean H/M uptake ratio of ^{123}I -MIBG scintigraphy in *PARK2* patients was 1.79 (0.31) in the early phase and 1.75 (0.51) in the delayed phase (Table 2). However, a 58-year-old woman, with a 10-year disease duration and orthostatic hypotension and constipation without myocardial damage, exhibited accelerated MIBG elimination (H/M ratio: early,

1.23; delayed, 1.15). Three patients (cases 2, 7, and 12) had exhibited slightly decreased uptake in the delayed phase.

The Sniffin' Sticks test revealed a slight olfactory dysfunction with the following mean scores in examined *PARK2* patients (Table 3): threshold score, 6.1 (1.6) ($P < .05$ when compared with controls); odor discrimination score, 10.0 (2.4); odor identification score, 10.1 (4.8) (no significant differences when compared to controls). Odor discrimination and identification functions were not impaired in any of the patients with *PARK2* mutations, except in patient 1. In the Japanese examined normative controls, the mean olfactory function scores were as follows: threshold score, 8.0 (1.3); discrimination score, 11.9 (2.4); identification score, 10.9 (2.0); in PD patients, these mean scores were 2.2 (6.6), 6.1 (2.5), and 5.1 (1.8), respectively.

PSG did not reveal tonic responses in the mentalis and tibialis muscles during REM (Table 3). Twitching of the tibialis muscle was observed in 2 patients. None of the patients with *PARK2* mutations met the ICSD-II criteria for RBD.

4. Discussion

Decreased ^{123}I -MIBG uptake was observed clearly in 1 patient with *PARK2* mutations who had autonomic dysfunction. Early phase myocardial uptake of MIBG in all of the other patients showed no decrease, and patients had no autonomic dysfunction. Similar to our study, in a previous study [8], 1 of 4 patients with *PARK2* mutations with a 12-year disease duration and unclear autonomic dysfunction exhibited decreased uptake of ^{123}I -MIBG. Additionally, 3 patients in our study who showed decreased ^{123}I -MIBG uptake were slightly older than the other patients, although a significance in mean age (63.0 (9.1) versus 55.9 (10.8); $P > .05$) did not exist. Estorch et al. and Tsuchimochi et al. reported that the uptake of ^{123}I -MIBG decreased with age, suggesting that aging could affect patients with *PARK2* mutations [9, 10]. Decreased myocardial uptake of MIBG is considered to indicate the presence of alpha-synuclein aggregates in the axons in PD [11]. In MIBG-myocardial scintigraphy, the H/M ratio of patients with *PARK2* mutations was reported to be within the range of the normal controls [12]. Moreover, postmortem examination of patients with *PARK2* mutations revealed that tyrosine hydroxylase immunoreactive nerve fibers in the epicardium were well preserved [13]. These findings might reflect normal functioning myocardial sympathetic nerve terminals in patients with *PARK2* mutations. MIBG scintigraphy might be a marker for alpha-synuclein in patients with *PARK2* mutations; however, there are no pathological reports on the presence of Lewy bodies in patients with *PARK2* mutations exhibiting decreased MIBG uptake.

Olfactory impairment is a nonmotor symptom of PD. We found that the olfactory threshold was slightly higher in patients with *PARK2* mutations than in controls. The oldest woman in our study, who did not have dementia, exhibited the highest degree of olfactory impairment. Although in self-completed questionnaire study, 3 of 16 patients with *PARK2* mutation had loss of taste/smell [14]. However, in previous

TABLE 2: The findings of ^{123}I MBG myocardial scintigraphy in PARK2 patients.

Case	1	2	3	5	7	8	9	10	11	12	13	14	Average \pm SD
Examined age	65	55	46	41	76	70	63	61	61	60	57	44	58.3 \pm 10.5
Early H/M	2.27	1.64	1.91	1.75	1.52	2.05	1.75	1.66	1.23	1.75	1.62	2.35	1.79 \pm 0.31
Delay H/M	2.14	1.33	1.67	1.93	1.34	2.93	1.65	1.54	1.15	1.40	1.60	2.35	1.75 \pm 0.51

H/M: the heart to mediastinum uptake ratio of ^{123}I MBG.

TABLE 3: Olfactory function by Sniffin' sticks and PSG study in patients with PARK2 mutation, controls, and Parkinson's disease.

Case	1	2	3	4	5	6	PARK2 total (n = 6)	Control (n = 10)	Parkinson's disease (n = 15)
Age	71	55	46	41	38	36	47.8 \pm 13.2	46.0 \pm 15.3	69.6 \pm 6.6
Sniffin' sticks Test									
Threshold test	4.5	6.3	6.3	5.8	5.0	9.0	6.1 \pm 1.6	8.0 \pm 1.3*	2.2 \pm 2.3**
Discrimination test	8.0	9.0	12.0	14.0	9.0	8.0	10.0 \pm 2.4	11.9 \pm 2.4	6.1 \pm 2.5
Identification test	1.0	13.0	10.0	14.0	13.0	10.0	10.1 \pm 4.8	10.9 \pm 2.0	5.1 \pm 1.8
PSG findings									
Apnea index (times/H)	10.1	22.5	1.2	0.4	1.0	2.1			
Hypopnea index (times/H)	2.2	14.0	4.7	0.3	1.9	9.4			
Apnea Hypopnea index (times/H)	12.3	36.5	5.9	0.8	3.0	11.4			
Arousal index (times/H)	16.0	39.8	37.7	13.4	14.3	11.1			
Respiratory arousal index (times/H)	5.5	27.3	4.6	0.2	1.6	3.3			
PLM index(times/H)	7.8	0.0	7.7	0.0	29.5	0.0			
PLM arousal index(times/H)	0.0	0.0	5.3	0.0	2.8	0.0			
REM sleep twitching on TA muscle	-	+	-	+	-	-			

H/M: the heart to mediastinum uptake ratio, NE: not examined.

PLM: periodic limb movements, TA: tibialis anterior.

* *t*-test: compared with PARK2 patients $P < .05$.

** *t*-test: compared with PARK2 patients and control $P < .01$.

studies, individuals with PARK2 mutations were found to have normal olfactory function [15, 16]. The discrepancy between our results and previous ones may be because previous studies used the Pennsylvania Smell Identification Test, which does not include the threshold test. In Kahn's study [15], the odor identification score did not significantly differ between patients with PARK2 mutations and controls, although this did not necessarily imply that the threshold score was normal in the patients.

PSG did not reveal RBD in any of our patients. However, in a study by Kumru et al., 6 of 10 patients had RBD [17]. We cannot explain this discrepancy, but we hypothesize that it may be due to the differences in patient mean age between the 2 studies. Some of our patients with PARK2 mutations have twitching in the tibialis muscle; therefore, the possibility that they will eventually develop RBD cannot be ruled out. Neuropathological studies on patients with PARK2 mutations have revealed neuronal loss and gliosis in the pars compacta of the substantia nigra and in the locus coeruleus [18]. However, these studies have not described the state of the subcoeruleus nucleus, which is considered the primary site affected in RBD.

The results obtained in this study suggest that some patients with PARK2 mutations have increased thresholds of olfactory function and myocardial sympathetic dysfunction as nonmotor symptoms. We might show that the nonmotor symptoms of PARK2 were impaired heterogeneously.

Author Contributions'

A. Yoritaka was responsible for conception, execution of research projects, statistical analysis, writing of first draft and review and critique; Yasushi Shimo was responsible for execution of research project; Yumi Shimo and Y. Inoue were responsible for execution of research project (PSG study); H. Yoshino was responsible for gene analysis; N. Hattori was responsible for conception and organization of research project.

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