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# Retrospective analysis of parkinsonian patients exhibiting normal $^{123}$I-MIBG cardiac uptake

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ABSTRACT

*Background:* Although most patients with Parkinson's disease (PD) show decreased cardiac $^{123}$I-metaiodobenzylguanidine (MIBG) uptake, some exhibit normal uptake. We evaluated the clinical characteristics of such patients.
*Methods:* We enrolled 154 non-demented patients showing parkinsonism with normal cardiac MIBG uptake and had been clinically followed up during 29.9 ± 27.6 months. We defined the patients who did not fit the exclusion criteria for PD and demonstrated ≥30% reduction in the Unified Parkinson's Disease Rating Scale (UPDRS) motor score after anti-Parkinson agent administration as probable PD. We compared clinical characteristics and the cardiac MIBG heart-to-mediastinum (H/M) ratio between the probable PD group (N = 37) and other groups (N = 117).
*Results:* The probable PD group showed significantly higher UPDRS motor scores and greater incidence of tremor/rigidity than those of other groups. In addition, they showed a significantly lower cardiac MIBG H/M ratio in the delayed phase (delayed, $p < 0.0001$). Washout-rate (WR) was significantly higher in probable PD cases ($p < 0.0001$). Among 16 probable PD patients undergoing serial cardiac MIBG scintigraphy, the delayed phase cardiac MIBG H/M ratio showed a significant decrease and WR significantly increased during follow-up periods.
*Conclusions:* An increase in WR and lower delayed phase cardiac MIBG uptake were found to be characteristics of such patients.



## 1. Introduction

Autonomic dysfunction is known to precede motor symptoms in Parkinson's disease (PD) [1]. With regard to the cardiovascular system, several reports have demonstrated that degeneration of the autonomic nervous system is evident in the premotor phase of PD [1–4]. In particular, decreased myocardial uptake in $^{123}$I-metaiodobenzylguanidine (MIBG) scintigraphy is observed in approximately 90% of PD cases. Therefore, it has been regarded as a useful biomarker for early differential diagnosis, as a decrease in MIBG uptake often exists even in the early stages of PD [5–7].

However, approximately 10% of PD cases show normal myocardial MIBG uptake; therefore, a diagnosis differentiating between PD and other disorders displaying parkinsonisms is sometimes difficult. It remains to be elucidated whether probable PD patients who show normal MIBG uptake have any common clinical characteristics. Here, we retrospectively assessed the clinical characteristics and cardiac MIBG uptake findings of patients in the probable PD group and compared these to the characteristics of other groups.

## 2. Methods

### 2.1. Subjects

Three hundred twenty-nine patients who exhibited parkinsonisms underwent myocardial MIBG scintigraphy examination for differential diagnosis at Fujita Health University Hospital between June 2008 and January 2015. Individuals who had diabetes mellitus, any known heart disease, dementia (Mini Mental State Examination score ≤ 24), a family history of PD, or any other disease showing dysautonomia were excluded. With regard to a cut-off value for the myocardial MIBG heart-to-mediastinum (H/M) ratio for the diagnosis as PD, we adopted a cut-off value of 2.0, which was the converted value in accordance with our camera-collimator conditions based on a cut-off value of 1.77 in previous meta-analyses [8,9]. After excluding patients whose myocardial MIBG H/M ratio was <2.0 in the early phase and/or the delayed phase and those who did not exhibit parkinsonian symptoms and signs defined by the UK Parkinson's Disease Society (UKPDS) Brain Bank clinical diagnostic criteria [10], 154 patients with parkinsonism showing normal MIBG uptake were enrolled in this study. We retrospectively investigated their clinical characteristics, neurological findings, responses to medications, brain magnetic resonance imaging (MRI) results and brain perfusion scintigraphy during a follow-up period of 29.9 ± 27.6 months.

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We then defined the patients who did not fit the exclusion criteria for PD using the UKPDS diagnostic criteria and demonstrated a ≥30% reduction in the Unified Parkinson's Disease Rating Scale (UPDRS) motor score with anti-Parkinson agent administration as the probable PD group (N = 37) based on a previous report [11]. The 117 patients that were not included in the probable PD group were diagnosed as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), vascular parkinsonism (VaP), drug-induced parkinsonism, essential tremor (ET), or idiopathic normal pressure hydrocephalus (iNPH) according to the diagnostic criteria of each disease at first visits and/or follow-up periods [12–17] and we defined the rest of them (N = 33) whose diagnoses were unclear even during follow-up periods as the unclassified parkinsonism group (Fig. 1). Therefore, the other groups consisted of 33 unclassified parkinsonism cases, 24 MSA cases, 24 PSP/CBD cases, 14 VaP cases, 9 drug-induced parkinsonism cases, 7 ET cases, and 6 iNPH cases. The dopamine transporter (DAT) imaging with $^{123}$I-ioflupane ($^{123}$I-FP-CIT) could be performed in four probable PD patients and three PSP/CBD patients, and all results were compatible with their respective diagnoses. We compared the detailed clinical findings (age at onset, sex, previous history of cardiac diseases, interval from onset to cardiac MIBG scintigraphy, UPDRS motor score, incidence of tremor, rigidity, and postural instability) and myocardial MIBG H/M ratio between the probable PD group and the other groups. We regarded the following clinical findings as the cardinal signs for PD as follows: (i) resting tremor, a UPDRS motor score of ≥1 for a lower limb or any limb; (ii) bradykinesia, a UPDRS motor score of ≥1 in 2 motor tests on the same side of the body (arm/leg) or a score of ≥2 in one motor test of a limb; (iii) rigidity, a UPDRS motor score of ≥1 of any limb; and (iv) postural instability, a UPDRS motor score of ≥2 [18]. Furthermore, a change in the myocardial MIBG H/M ratio and washout-rate (WR, %) was evaluated in 16 probable PD cases and 12 patients in the other groups who underwent follow-up myocardial MIBG scintigraphy (interval period; 31.0 ± 20.8 months, 9–85 months), and their daily levodopa dosage and levodopa equivalent dose at the serial MIBG scintigraphy were calculated and compared in both groups [19].

This study was approved by the ethical committee of Fujita Health University, and all subjects provided informed consents before participation.

### 2.2. Cardiac-MIBG scintigraphy

MIBG (111 mBq) was injected intravenously. Early images were obtained 15 min following injection, and delayed images were obtained after 3 h. Myocardial MIBG uptake was measured using the H/M uptake ratio according to methods described previously [20]. Camera-collimator type in our institution was low-medium-energy general-purpose type (Toshiba, Japan). The MIBG WR was calculated using the following formula: [(early heart counts − early background counts) − (late heart counts − late background counts)] × 100 / (early heart counts − early background counts). None of the patients had taken drugs known to affect the MIBG uptake (e.g., tricyclic antidepressants, $Ca^{++}$ blockers, or selegiline). None of the patients showed signs of cardiac decompensation over the course of the study. In patients who underwent the ultrasonic cardiography, the ventricular function was within normal range.

### 2.3. Statistical analyses

JMP software, version 10 (SAS Institute, Cary, NC, USA) was used for statistical analyses. Significant differences were defined at $p < 0.05$. Pearson's chi-square test was used for comparisons between 2 groups for sex as well as the incidence of tremor, rigidity, and postural instability. Student's t-test was used for comparisons between 2 groups for continuous variables. Wilcoxon signed-rank test was used for a statistical analysis of a change in the myocardial MIBG H/M ratio and WR. To calculate the WR cut-off value to differentiate the patients in the probable PD group from the patients in the other groups, a receiver operator characteristic (ROC) curve was configured. Values are expressed as mean ± standard deviation.

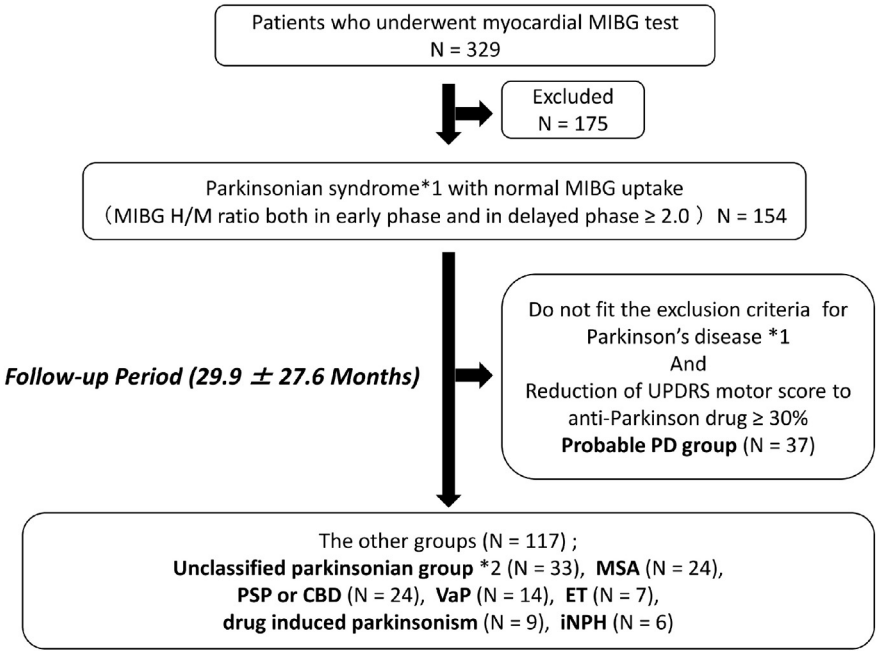


**Fig. 1.** Diagnosis and definition of normal MIBG uptake cases. MIBG = $^{123}$I-metaiodobenzylguanidine; H/M ratio = heart-to-mediastinal ratio; MSA = multiple system atrophy; PSP = progressive supranuclear palsy; CBD = corticobasal degeneration; VaP = vascular parkinsonism; ET = essential tremor; iNPH = idiopathic normal pressure hydrocephalus; UPDRS = Unified Parkinson's Disease Rating Scale.