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# Cardiac sympathetic denervation and dementia in de novo Parkinson's disease: A 7-year follow-up study

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ABSTRACT

*Background:* Postganglionic cardiac sympathetic denervation is evident in patients with early-stage Parkinson's disease (PD). Cardiac iodine-123-meta-iodobenzylguanidine (MIBG) uptake is correlated with the non-motor symptoms of PD, suggesting that low cardiac MIBG uptake may reflect wider alpha-synuclein pathology. In addition, low cardiac MIBG could be related to orthostatic hypotension in PD, which may affect cognition. However, the prognostic validity of baseline MIBG scintigraphy in terms of the risk of subsequent dementia remains unclear. We investigated whether cardiac MIBG uptake was associated with a later risk of dementia.

*Methods:* We retrospectively enrolled 93 drug-naive patients with de novo PD who underwent MIBG scanning on initial evaluation. The patients visited our outpatient clinic every 3–6 months and were followed-up for a minimum of 4 years from the time they were begun on dopaminergic medication. The predictive powers of baseline MIBG cardiac scintigraphic data in terms of dementia development were evaluated using Cox's proportional hazard models.

*Results:* During a mean follow-up period of 6.7 years, 27 patients with PD (29.0%) developed dementia. These patients had less baseline MIBG uptake than did others (delayed H/M ratios: 1.19 vs. 1.31). Multivariate Cox's proportional hazard modeling revealed that both MIBG uptake (hazard ratio [HR] 3.40; $p = 0.004$) and age (HR 1.08, $p = 0.01$) significantly predicted dementia development.

*Conclusion:* A reduction in cardiac MIBG uptake by PD patients may be associated with a subsequent risk of dementia; reduced uptake may reflect wider extension of alpha-synuclein pathology in PD.

## 1. Introduction

Cognitive impairment is one of the most disabling non-motor symptoms associated with Parkinson's disease (PD) [1]. Cardiac iodine-123-meta-iodobenzylguanidine (MIBG) uptake can reveal sympathetic cardiac denervation caused by Lewy bodies (LB) [2] and, reduced uptake is correlated with various non-motor symptoms of PD including cognition, orthostatic hypotension, hyposmia, and rapid eye movement behavior disorder (RBD) [3–7]. Of interest, patients affected with dementia with Lewy bodies (DLB) and presenting with mild cognitive impairment can exhibit reduced cardiac MIBG uptake [8–10], suggesting that the reduction in uptake reflects wider extension of alpha-synuclein pathology [11]. In addition, impaired cardiac sympathetic innervation could be related to orthostatic hypotension in PD, which may affect cognition in PD [12–14].

Although several cross-sectional and the few existing prospective studies have revealed correlations between MIBG uptake and the neuropsychiatric symptoms of PD [6,7,15,16], no work has yet explored the utility of cardiac MIBG uptake in terms of predicting the risk of subsequent dementia in patients with de novo PD.

In our present cohort study, we hypothesized that low MIBG uptake reflected a wider involvement of alpha-synuclein pathology in PD, increasing the rate of cognitive decline. Thus, we explored the possible associations between baseline MIBG uptake and dementia development over time in patients with PD.

## 2. Methods

Study participants (n = 123) were selected from the database of the "Ajou Movement" registry and fulfilled the following criteria: de novo drug-naive PD with onset after 55 years of age and diagnosis within 2 years from the onset; MIBG scanning on initial evaluation [17]; a lack of dementia at enrolment; and a minimal follow-up period of 4 years.

The exclusion criteria were as follows: (1) any clinical sign suggestive of atypical parkinsonism developing during follow-up; (2) a delayed heart-to-mediastinum (H/M) ratio ≥ 1.7 (2 SDs above the

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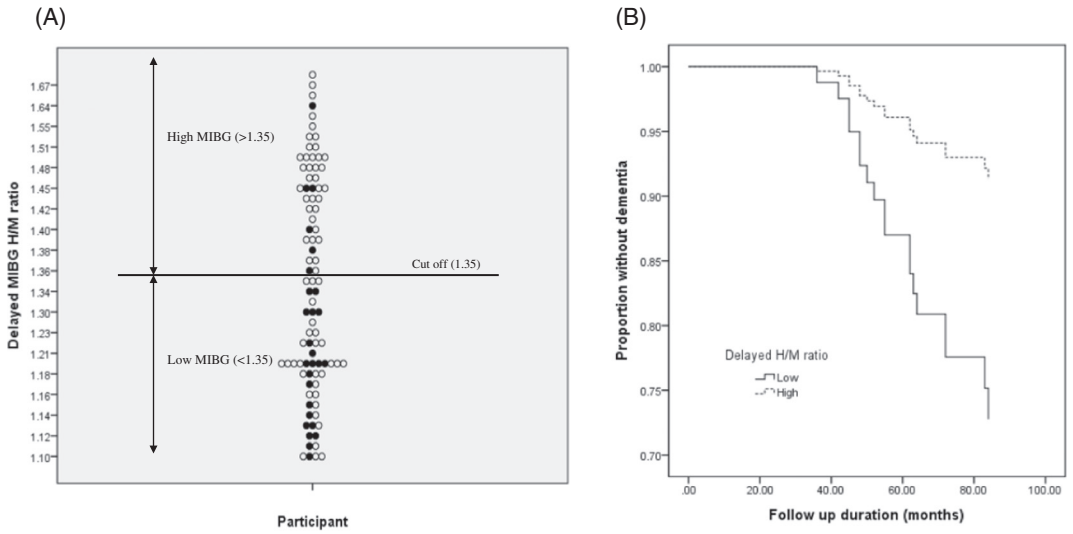


**Fig. 1.** (A) Distribution of delayed heart-to-mediastinum ratio in patients with Parkinson's disease. (B) Cumulative dementia-free survival based on delayed heart-to-mediastinum ratio. Bars in (A) indicate cut-off values of delayed H/M ratio (1.35) based on the distribution of delayed heart-to-mediastinum ratios. Dark circles in (A) indicate those who progressed to dementia during follow-up.

mean of PD in our hospital) to exclude atypical parkinsonism [18,19]; (3) significant cerebral lesions evident on magnetic resonance imaging and/or computed tomography; (4) any severe concomitant disease that might explain the presence of cognitive disturbance or focal changes in brain metabolism; (5) medical comorbidities including diabetes mellitus or a previous cardiac disease, or any abnormalities on routine chest radiography and electrocardiography because cardial hypoperfusion might influence MIBG uptake.

Ultimately, 93 PD patients were enrolled and were divided into low MIBG (H/M ratio $<$ 1.35) and high MIBG group (H/M ratio $\geq$ 1.35) based on the distribution of delayed H/M ratios at baseline (cutoff, 1.35, median value). (Fig. 1A).

Changes in cognition and motor symptom were evaluated annually using the Mini-Mental State Examination (MMSE), the Clinical Dementia Rating (CDR) scale, and the Unified Parkinson's disease Rating Scale (UPDRS). When a patient showed evidence of dementia (a score $<$ 26 on the MMSE or a score $>$ 0.5 on the CDR scale) during follow-up, we evaluated several cognitive functions and diagnosed PD with dementia, defined as impairment of more than two cognitive domains using a standardized battery called the Seoul Neuropsychological Screening Battery (SNSB) [20,21]. The SNSB includes cognitive subsets of attention (forward and backward digit span and letter-cancellation tests), language and related functions (reading, writing, comprehension, repetition, confrontational naming using the Korean version of the Boston Naming Test, visuospatial function (drawing an interlocking pentagon and the Rey Complex Figure Test), verbal memory (the Seoul Verbal Learning Test), visual memory (immediate recall, 20 min delayed recall and recognition of a Rey Complex Figure), and frontal executive function (contrasting program, go-no-go test, phonemic and semantic Controlled Oral Word Association Test, and Stroop test).

Based on UPDRS motor score, patients were divided into one of three subtype: akinetic-rigid (ART), mixed (MT), and tremor dominant (TDT) subtypes [22].

## 3. MIBG measurement

$^{123}$I-MIBG (111 mBq) was injected intravenously and cardiac uptake was imaged for 30 min (early) and 3 h (late) using a dual-head C-camera system (MultiSPECT III, Siemens Medical Systems, Inc., Iselin, NJ, USA). The regions of interest on the frontal image were the entire heart and the mediastinum; the H/M uptake ratio was calculated.

## 4. Statistics

The Mann-Whitney *U* and Fisher's exact tests were used for pairwise comparisons of continuous and categorical variables, respectively. A p-value of 0.05 was considered statistically significant. All analyses were performed using SPSS version 12.0 software.

The predictive powers of MIBG cardiac scintigraphy data and other clinical factors, in terms of dementia development, were evaluated using Cox's proportional hazard modeling. The time of dementia onset was estimated as the midpoint between the latest assessment without dementia and the assessment when dementia was diagnosed. Models with delayed H/M ratio as continuous variable (model 1) and delayed H/M ratio dichotomized into low MIBG (H/M ratio $<$ 1.35) and high MIBG (H/M ratio $\geq$ 1.35) (model 2) were performed controlled for age, gender and UPDRS III, MMSE at baseline.

Ethical approval was given by the local ethics committee, and written informed consent was obtained from each patient.

## 5. Results

Patient demographic and clinical characteristics at baseline and on follow-up are summarized in Table 1. At baseline, we found no significant difference in sex distribution, motor UPDRS, MMSE score, or CDR score between patients with low MIBG (L-MIBG) and high MIBG (H-MIBG) uptake. However, mean patient age was lower in the H-MIBG than in the L-MIBG group. TDT patients exhibited a slightly higher MIBG uptake (1.37 $\pm$ 0.14) than ART (1.30 $\pm$ 0.15) or MT patients (1.31 $\pm$ 0.16), although there was no significant difference between groups ($p = 0.236$).

On follow-up, the L-MIBG group exhibited greater impairment of motor UPDRS, a lower Korean-MMSE, CDR score, and a higher levodopa equivalent dose requirement than the H-MIBG group (Table 1). Dementia (45.6% vs 12.7%, $p = 0.02$) and visual hallucinations (21.7% vs 12.7%, $p = 0.21$) were more common in the L-MIBG than in the H-MIBG group. (Fig. 1A) (Table 1).

During a mean follow-up time of 6.7 years, 27 of 93 patients with PD (29.0%) converted into PD dementia. Such patients were older (69.7 vs. 65.3 years) and had lower MIBG uptakes (1.19 vs 1.31) than those without dementia (Table 2).

Estimated cumulative progression rate to dementia based on the Kaplan-Meier analysis were 1.1% at year 3, 7.5% at year 4, 19.3% at year 5, and 26.8% at year 6 (Table 3). The estimated progression rates