MIBG Cardiac Scintigraphy as a Potential Biomarker That Reflects Severity in Idiopathic REM Sleep Behavior Disorder

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Research Article

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Abstract

Study Objectives: 123I-metaiodobenzylguanidine (MIBG) cardiac scintigraphy was performed to demonstrate the correlation with clinical characteristics of patients with idiopathic REM sleep behavior disorder (iRBD) and we found the factors that are associated with neurodegenerative diseases.

Methods: All subjects including 39 patients with iRBD and 17 healthy controls underwent MIBG cardiac scintigraphy to assess cardiac autonomic dysfunction. The iRBDs were confirmed by in-lab overnight polysomnography. Receiver operating curve was performed to determine cut-off value of early and delayed heart to mediastinum ratio (HMR) in patients with iRBD. Based on each cut-off value, comparison analysis about RWA was performed by dividing into two groups within iRBD patients.

Results: MIBG uptake below the cut-off value is associated with higher REM sleep without atonia (RWA). The lower HMR had significantly higher RWA (%) both with the cut-off value of early (11.0±5.6 VS 29.3±23.2, p=0.018) and delayed HMR (9.1±4.3 VS 30.0±22.9, p=0.011).

Conclusion: This study suggests that MIBG uptake is a potential biomarker of the severity of RWA in iRBD.

Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by dream-enactment behavior with vivid dreams and REM sleep without atonia (RWA).[1] The disease was first reported in 1986 by Schenck et al.[2] The disease can include ‘secondary RBD’ due to neurodegenerative disease, brainstem lesions, adverse drug reactions by antidepressants. If the cause is not known, it is considered idiopathic RBD (iRBD).[3] There is a well-established concept to associate RBD with neurodegenerative diseases caused by alpha-synucleinopathy, such as Parkinson's disease (PD), multiple system atrophy (MSA) and dementia with Lewy bodies (DLB). In previous studies, more than 50% of RBD patients became patients with parkinsonian disorders within a decade; Between 81 and 90 percent of patients had one or more neurodegenerative diseases.[4–6] Accordingly, recent studies have suggested that iRBD is a potential marker for later development of neurodegenerative changes, as the concept of ‘isolated’ RBD has been suggested to represent an early expression of α-synucleinopathy,[7] As interest in ‘disease-modifying therapy’ for neurodegenerative disease has increased, the identification of prodromal stage or pre-motor stage of PD has been also a field of interest.[8] Therefore, there is a growing need for early biomarkers to identify and predict the disease course in RBD patients who could progress to neurodegenerative diseases such as PD.[9]

123I-MIBG myocardial scintigraphy is a non-invasive nuclear medicine test used to measure myocardial sympathetic nervous system function. It is also utilized for differential diagnosis of neurodegenerative diseases such as PD and MSA.[10–12] It has been mentioned as a supportive tool in the Movement Disorders Society (MDS) diagnostic criteria of PD published in 2015.[13] In PD, the heart-to-mediastinum

ratio (HMR) of MIBG cardiac scintigraphy is reduced, suggesting a degenerative change in the postganglionic sympathetic nerve endings in the heart.[14] This is in contrast to the normal MIBG uptake, which is the characteristic of MSA.[15,16]

In previous studies related to MIBG cardiac scintigraphy, MIBG uptake was reduced in patients with iRBD.[17–21] MIBG uptake was abnormal in the patients with some prodromal symptoms of PD, such as autonomic dysfunctions and hyposmia.[22] In the light of these findings, the use of MIBG as an early diagnostic method for PD may be considered. MIBG myocardial scintigraphy is useful because it can produce consistent and quantitative results in patients without underlying cardiac disease.

In this study, the results of 123I-MIBG cardiac scintigraphy were compared between the patients with iRBD and healthy controls. We also want to find out whether there are differences in MIBG scintigraphy results within the iRBD group, and how they relate to clinical data. Moreover, we analyzed the MIBG uptake and clinical data to find the clinical usefulness of MIBG cardiac scintigraphy as an early marker neurodegenerative disease.

Methods

This is a prospective study, performed between May 2018 and October 2019.

This study was approved by the Institutional Review Board (IRB) of Keimyung University Dongsan Medical Center (IRB No. 2018-05-018). All subjects provided written informed consent before enrolling in this study, in accordance with the Declaration of Helsinki.

Subjects

In this study, all the 157 patients with RBD were confirmed by an overnight polysomnography and clinical interview according to the 3rd edition of the International Classification of Sleep Disorders (ICSD-3).[23] Patients with any medical history of neurodegenerative disease or MMSE score less than 21 were excluded. Epilepsy and sleep disorders that can mimic iRBD (e.g., obstructive sleep apnea with AHI > 5, restless legs syndrome, other parasomnias) were also excluded. In addition, all patients with major medical disease that can affect the result of MIBG cardiac scintigraphy was excluded: heart failure, arrhythmia, coronary artery disease, hypertrophic and dilated cardiomyopathy, and drug-induced cardiomyopathy), diabetes mellitus, or history of medication or substance use that could affect MIBG uptake results (e.g. reserpine, labetalol, or sympathomimetics such as tyramine, tricyclic antidepressants, and cocaine). Consequently, 39 patients with iRBD. These exclusion criteria were also applied to the recruitment of age-matched normal controls to gather 17 age-matched healthy controls, recruited after detailed clinical interviews as well as neurologic examinations to conform “there is no clinical abnormalities related to sleep and autonomic dysfunction suspected” (Fig. 1).

Clinical assessments

The Unified Parkinson's Disease Rating Scale Part III (UPDRS-III), and the Hoehn and Yahr (H&Y) stage were used to assess motor symptoms of parkinsonism. After an offline face-to-face interview and physical examination, all subjects were asked to complete a series questionnaires, including the Korean-validated versions of the Beck Depression Index (BDI),[24] Beck Anxiety Index (BAI),[25] Insomnia Severity Index (ISI),[26] Epworth Sleepiness Scale (ESS),[27] Pittsburgh Sleep Quality Index (PSQI),[28] RBD questionnaire (RBDQ-KR; cut-off value for total scoring is 18.5),[29] Scales for Outcomes in Parkinson's Disease for Autonomic Symptoms (SCOPA-AUT),[30] Korean version of the Sniffin' stick (KVSS) test for olfactory function,[31] and Korean version of the mini-mental status examination (K-MMSE). Neurological examination was conducted by a movement specialist.

Polysomnographic recording

All patients with iRBD underwent an overnight video-polysomnography (PSG) recorded in a sleep laboratory. The electromyography (EMG) activity to detect RWA was measured in the mentalis muscle. The PSG data was analyzed according to the criteria described in the American Academy of Sleep Medicine (AASM) manual.[32] Quantification of REM sleep without atonia (RWA) was performed manually through a review of PSG records. The tonic activity was defined as a period in which an amplitude increased more than 4 times compared to the existing EMG findings in 50% or more continuously in one epoch designated as 30 seconds. We obtained the ratio of time with tonic activities out of the total REM sleep time; and the ratio of the number of epochs showing tonic activity among the total number of REM sleep, respectively. The phasic activity was defined as the time when a single epoch divided by 10 is divided into a mini epoch in 3-sec increments, and when there are 5 or more non-contiguous mini epochs in which the EMG findings with an amplitude increase of more than 4 times exist for 0.1 to 5 seconds. We calculated the ratio of the period in which the phasic activity appeared during the total REM sleep time and the ratio of the number of mini epochs showing the phasic activity among the total number of mini epochs in REM sleep.

123I-metaiodobenzylguanidine cardiac scintigraphy

All subjects in this study underwent MIBG cardiac scintigraphy with intravenous ^{123}I-MIBG 111 MBq (3 mCi). Early and delayed images were obtained after 15 minutes and 3 hours, respectively. MIBG cardiac scintigraphy All images were acquired using a Signature E.CAM Dual camera (Siemens Healthcare) with a medium energy collimator. At the same time, gated myocardial perfusion single-photon emission computed tomography (SPECT) with Tc-99m MIBI (methoxy isobutyl isonitrile) at rest was also performed with D-SPECT camera (Spectrum Dynamics). Image processing and calculation of early and delayed HMR were conducted by a nuclear medicine specialist. Whole MIBG uptake was assessed using the early and delayed images by manual drawing the region of interest (ROI) over the whole heart and mediastinum.[33] Gated myocardial perfusion SPECT with Tc-99m MIBI at rest was used to distinguish asymptomatic myocardial infarction or cardiomyopathy.

Statistical analysis

Statistical analysis was performed with SPSS Statistics (version 25.0, IBM Corp., Armonk, NY, USA). Statistical significance was set at $p < 0.05$. Demographic, clinical, and MIBG data were compared between patients with iRBD and healthy controls. Independent t-tests were used to compare the characteristics of patients with iRBD and healthy controls. The Mann-Whitney U-test and fisher's exact test were applied for statistical comparisons of demographics and MIBG results between the iRBD and healthy control groups. Receiver operating curve (ROC) was performed to determine cut-off value of early and delayed HMR in patients with iRBD. Based on each cut-off value, data comparison analysis was performed by dividing into two groups within patients with iRBD. Spearman correlation analyses were performed between the results of MIBG cardiac scintigraphy, and the clinical and PSG data of patients with iRBD.

Results

In total, 39 patients with iRBD (25 males, 64.1%) and 17 healthy controls (6 males, 35.3%) were enrolled in this study (Table 1). The mean age of the patients with iRBD and healthy controls were 65.4 ± 6.5 and 66.0 ± 7.4, respectively. The ratio of males in the patients with iRBD was significantly higher than healthy controls ($p = 0.044$), and the patients with iRBD showed higher scores of RBDQ-HR and gastrointestinal subscore of SCOPA-AUT. However, there was no statistically significant difference in the total score of SCOPA-AUT and KVSS between the two groups.

Table 1
Demographic features and clinical data of patients with iRBD and control subjects

	iRBD (n = 39)	Healthy control (n = 17)	p-value

Data are mean ± SD or n (%) values. #Fisher's exact test. *$p < 0.05$.

RBD: REM sleep behavior disorders, UPDRS: Unified Parkinson's Disease Rating Scale, H & Y: Hoehn and Yahr, ISI: Insomnia Severity Index, ESS: Epworth Sleepiness Scale PSQI: Pittsburgh Sleep Quality Index, RBDQ-KR: RBD Questionnaire-Korean version, BDI: Beck Depression Index, BAI: Beck Anxiety Index, MMSE: Mini-Mental Status Examination, SCOPA-AUT: Scales for Outcomes in Parkinson's Disease for Autonomic Symptoms, KVSS: Korean Version of Sniffin' Sticks Test

	iRBD (n = 39)	Healthy control (n = 17)	p-value
Age	65.4 ± 6.5	66.0 ± 7.4	0.954
Sex (male, %)	25 (64.1)	6 (35.3)	0.044#*
RBD disease duration (range, years)	6.5 ± 4.8 (0.25-13.0)	-	-
H & Y stage	0	0	1.000
UPDRS part III	0.3 ± 1.0	0.6 ± 1.5	0.258
Sleep questionnaire			
ISI	6.1 ± 5.8	7.1 ± 7.2	0.961
ESS	4.8 ± 4.2	2.8 ± 2.8	0.065
PSQI	6.5 ± 3.6	6.2 ± 7.3	0.349
RBDQ-KR	42.8 ± 18.2	14.7 ± 19.4	< 0.001*
BDI	12.0 ± 10.8	11.5 ± 9.2	0.842
BAI	7.2 ± 7.9	6.3 ± 7.3	0.828
MMSE	27.1 ± 2.4	26.1 ± 2.8	0.184
SCOPA-AUT, total	8.9 ± 4.7	6.7 ± 5.3	0.054
Gastrointestinal	2.6 ± 2.1	1.2 ± 1.4	0.014*
Urinary	4.7 ± 2.9	4.1 ± 3.0	0.415
Cardiovascular	0.5 ± 0.8	0.7 ± 1.3	0.911
Pupilomotor	0.4 ± 0.7	0.2 ± 0.7	0.293
Thermoregulatory	0.4 ± 0.9	0.2 ± 0.4	1.000
Sexual	0.4 ± 0.9	0.2 ± 0.8	0.279
KVSS test	4.2 ± 2.8	5.5 ± 2.2	0.185
Early HMR	1.8 ± 0.3	2.7 ± 0.4	< 0.001
Delayed HMR	1.6 ± 0.5	2.8 ± 0.6	< 0.001

Data are mean ± SD or n (%) values. #Fisher's exact test. *$p < 0.05$.

RBD: REM sleep behavior disorders, UPDRS: Unified Parkinson's Disease Rating Scale, H & Y: Hoehn and Yahr, ISI: Insomnia Severity Index, ESS: Epworth Sleepiness Scale PSQI: Pittsburgh Sleep Quality Index, RBDQ-KR: RBD Questionnaire-Korean version, BDI: Beck Depression Index, BAI: Beck Anxiety Index, MMSE: Mini-Mental Status Examination, SCOPA-AUT: Scales for Outcomes in Parkinson's Disease for Autonomic Symptoms, KVSS: Korean Version of Sniffin' Sticks Test

Gated myocardial perfusion scans revealed normal perfusion and function of left ventricle in all the subjects. This confirmed that there was no underlying heart disease that could cause MIBG uptake abnormalities in all subjects. Comparison of MIBG cardiac scintigraphy results between patients with iRBD and healthy controls showed statistically differences in early HMR and delayed HMR. Both HMR results were obtained at an early (1.8 ± 0.3 vs. 2.7 ± 0.4, $p < 0.001$) and delayed time point (1.6 ± 0.5 vs. 2.8 ± 0.6, $p < 0.001$) and were lower in patients with iRBD than healthy controls (Table 1 and Fig. 2). PSG data for the 39 patients with iRBD who underwent MIBG myocardial scintigraphy is summarized in supplement 1.

ROC analysis of the early and delayed HMR showed an area under the curve of 0.95 (95%, CI = 0.90-1.00) and 0.94 (95%, CI = 0.88-1.00) for iRBD (Fig. 3). Early HMR with a cut-off value of 2.15 showed a sensitivity and specificity of 100% and 87.2% to differentiation between the patients with iRBD and healthy controls; and delayed HMR with a cut-off value of 2.05 showed 88.2% and 89.7%.

According to the cut-off value, the patients with iRBD can be divided into two groups. The comparison within the patients with iRBD is shown in Tables 2 and 3. The lower HMR had significantly higher RWA (%) both with the cut-off value of early (Table 2) and delayed HMR (Table 3). However, RWA showed no significant correlation with early ($p = 0.604$) or delayed HMR ($p = 0.806$) (Supplement 2).

Table 2
Comparative analysis within iRBD group based on the cut-off value of early HMR.

	≥2.15 (n = 5)	< 2.15 (n = 34)	p-value
Age	63.6 ± 7.9	65.6 ± 6.3	0.752
Sex (male, %)	3 (60.0)	22 (64.7)	1.000#
UPDRS part	0.8 ± 1.8	0.2 ± 0.9	0.243
Onset age, year	54.6 ± 2.6	60.2 ± 7.0	0.269
Duration, year	11.6 ± 10.7	5.7 ± 2.8	0.304
Interval of symptoms to PSG, year	9.8 ± 4.4	3.0 ± 0.5	0.186
ISI	6.4 ± 6.9	6.0 ± 5.7	0.909
ESS	2.2 ± 2.2	5.2 ± 4.4	0.120
BDI	9.2 ± 10.6	12.4 ± 11.0	0.646
BAI	5.2 ± 7.1	7.4 ± 8.1	0.532
PSQI	6.4 ± 3.0	6.6 ± 3.3	0.925
MMSE	26.2 ± 3.1	27.2 ± 2.3	0.527
RBDQ-KR	35.4 ± 18.5	43.9 ± 18.2	0.467
Factor 1	10.6 ± 7.4	13.3 ± 5.7	0.360
Factor 2	25.2 ± 17.1	31.0 ± 14.6	0.424
SCOPA-AUT total	6.8 ± 4.3	9.2 ± 4.7	0.289
Gastrointestinal	2.4 ± 1.7	2.6 ± 2.1	0.963
Urinary	3.4 ± 3.1	4.9 ± 2.9	0.248
Cardiovascular	0.2 ± 0.5	0.6 ± 0.8	0.483
Pupilomotor	0.4 ± 0.6	0.4 ± 0.7	0.609
Thermoreulatory	0.2 ± 0.5	0.3 ± 0.5	1.000
Sexual	0.2 ± 0.5	0.5 ± 0.9	0.794

#Fisher's exact test. *$p < 0.05$.

RBD: REM sleep behavior disorders, UPDRS: Unified Parkinson's Disease Rating Scale, ISI: Insomnia Severity Index, ESS: Epworth Sleepiness Scale PSQI: Pittsburgh Sleep Quality Index, RBDQ-KR: RBD Questionnaire-Korean version, BDI: Beck Depression Index, BAI: Beck Anxiety Index, MMSE: Mini-Mental Status Examination, SCOPA-AUT: Scales for Outcomes in Parkinson's Disease for Autonomic Symptoms, KVSS: Korean Version of Sniffin' Sticks Test, HMR: Heart to mediastinal ratio, RWA: REM sleep Without Atonia, A/H: Apnea/Hypopnea

	≥2.15 (n = 5)	< 2.15 (n = 34)	p-value
KVSS test	4.6 ± 3.1	4.1 ± 2.7	0.745
MIBG			
Early HMR	2.5 ± 0.4	1.7 ± 0.2	< 0.001*
Delayed HMR	2.6 ± 0.7	1.5 ± 0.2	< 0.001*
Total sleep time (min)	355.3 ± 80.8	384.8 ± 55.4	0.522
N1 (%)	13.9 ± 4.9	13.8 ± 6.1	0.669
N2 (%)	47.6 ± 10.1	50.0 ± 8.4	0.419
N3 (%)	20.1 ± 3.4	15.0 ± 9.1	0.205
REM (%)	18.4 ± 6.3	21.4 ± 7.4	0.358
Latency to sleep onset	48.4 ± 84.1	12.6 ± 13.2	0.592
Latency to sleep stage 2 (min)	55.7 ± 82.8	18.1 ± 15.5	0.481
Latency to REM sleep stage (min)	110.1 ± 87.5	118.5 ± 70.0	0.967
RWA (%)	11.0 ± 5.6	29.3 ± 23.2	0.018*
Sleep efficiency (%)	73.8 ± 16.5	79.17 ± 10.7	0.557
A/H index, Total	3.7 ± 5.2	4.3 ± 6.5	0.859
Arousal index, Total	11.4 ± 4.7	12.3 ± 8.0	0.974
#Fisher's exact test. *$p < 0.05$.			
RBD: REM sleep behavior disorders, UPDRS: Unified Parkinson's Disease Rating Scale, ISI: Insomnia Severity Index, ESS: Epworth Sleepiness Scale PSQI: Pittsburgh Sleep Quality Index, RBDQ-KR: RBD Questionnaire-Korean version, BDI: Beck Depression Index, BAI: Beck Anxiety Index, MMSE: Mini-Mental Status Examination, SCOPA-AUT: Scales for Outcomes in Parkinson's Disease for Autonomic Symptoms, KVSS: Korean Version of Sniffin' Sticks Test, HMR: Heart to mediastinal ratio, RWA: REM sleep Without Atonia, A/H: Apnea/Hypopnea			

Table 3
Comparative analysis within iRBD group based on the cut-off value of delayed HMR.

	≥2.05 (n = 4)	< 2.05 (n = 35)	p-value
Age	63.5 ± 9.1	65.6 ± 6.2	0.831
Sex (male, %)	3 (75.0)	22 (62.9)	0.545#
UPDRS part	1.00 ± 2.0	0.2 ± 0.9	0.197
Onset age, year	53.0 ± 13.9	60.2 ± 6.9	0.166
Duration, year	13.8 ± 11.0	5.6 ± 2.8	0.078
Interval of symptoms to PSG, year	12.5 ± 10.3	3.6 ± 3.0	0.179
ISI	6.3 ± 7.9	6.0 ± 5.6	0.902
ESS	2.0 ± 2.5	2.1 ± 4.3	0.122
BDI	7.8 ± 11.6	12.5 ± 10.8	0.426
BAI	4.3 ± 7.9	7.5 ± 8.0	0.293
PSQI	5.5 ± 2.5	6.7 ± 3.8	0.644
MMSE	25.5 ± 3.1	27.3 ± 2.3	0.242
RBDQ-KR	38.3 ± 20.1	43.3 ± 18.2	0.815
Factor 1	9.8 ± 8.3	13.3 ± 5.6	0.268
Factor 2	29.0 ± 17.2	30.4 ± 14.8	0.865
SCOPA-AUT total	7.0 ± 5.0	9.1 ± 4.7	0.455
Gastrointestinal	2.0 ± 1.6	2.6 ± 2.1	0.659
Urinary	4.3 ± 2.9	4.8 ± 3.0	0.664
Cardiovascular	0.0 ± 0.0	0.6 ± 0.8	0.251
Pupilomotor	0.3 ± 0.5	0.4 ± 0.7	0.920
Thermoreulatory	0.3 ± 0.5	0.3 ± 0.4	1.000
Sexual	0.3 ± 0.5	0.5 ± 0.9	0.822

#Fisher's exact test. *p < 0.05.

RBD: REM sleep behavior disorders, UPDRS: Unified Parkinson’s Disease Rating Scale, ISI: Insomnia Severity Index, ESS: Epworth Sleepiness Scale PSQI: Pittsburgh Sleep Quality Index, RBDQ-KR: RBD Questionnaire-Korean version, BDI: Beck Depression Index, BAI: Beck Anxiety Index, MMSE: Mini-Mental Status Examination, SCOPA-AUT: Scales for Outcomes in Parkinson’s Disease for Autonomic Symptoms, KVSS: Korean Version of Sniffin' Sticks Test, HMR: Heart to mediastinal ratio, RWA: REM sleep Without Atonia, A/H: Apnea/Hypopnea

	≥2.05 (n = 4)	< 2.05 (n = 35)	p-value
KVSS test	4.0 ± 3.3	4.2 ± 2.7	0.827
MIBG			
Early HMR	2.6 ± 0.4	1.7 ± 0.2	< 0.001
Delayed HMR	2.8 ± 0.7	1.5 ± 0.2	< 0.001
Total sleep time (min)	354.8 ± 93.3	384.0 ± 54.8	0.656
N1 (%)	14.2 ± 5.5	13.6 ± 6.0	0.725
N2 (%)	49.1 ± 11.0	49.8 ± 8.4	0.795
N3 (%)	20.05 ± 3.90	15.1 ± 9.1	0.272
REM (%)	16.6 ± 5.7	21.6 ± 7.3	0.141
Latency to sleep onset	54.5 ± 95.8	12.9 ± 13.1	1.000
Latency to sleep stage 2 (min)	57.4 ± 95.6	19.0 ± 16.1	0.991
Latency to REM sleep stage (min)	114.4 ± 89.9	117.7 ± 69.1	0.945
RWA (%)	9.1 ± 4.3	30.0 ± 22.9	0.011*
Sleep efficiency (%)	72.9 ± 18.9	79.1 ± 10.5	0.697
A/H index, Total	4.7 ± 5.5	4.2 ± 6.4	0.733
Arousal index total	12.7 ± 4.4	12.2 ± 7.9	0.528
#Fisher's exact test. *p < 0.05.			
RBD: REM sleep behavior disorders, UPDRS: Unified Parkinson's Disease Rating Scale, ISI: Insomnia Severity Index, ESS: Epworth Sleepiness Scale PSQI: Pittsburgh Sleep Quality Index, RBDQ-KR: RBD Questionnaire-Korean version, BDI: Beck Depression Index, BAI: Beck Anxiety Index, MMSE: Mini-Mental Status Examination, SCOPA-AUT: Scales for Outcomes in Parkinson's Disease for Autonomic Symptoms, KVSS: Korean Version of Sniffin' Sticks Test, HMR: Heart to mediastinal ratio, RWA: REM sleep Without Atonia, A/H: Apnea/Hypopnea			

Discussion

Since RBD is known as a prodromal stage of alpha-synucleinopathy related neurodegenerative disease, an objective marker of iRBD may suggest or predict the presence of alpha-synucleinopathy. In this study, we identified the decrease in MIBG uptake in patients with iRBD compared to healthy controls, and, also found that RWA is correlated with the degree of decreased MIBG uptake. Previous studies have reported a decrease in MIBG uptake in patients with iRBD.[17,18,22,34] The pattern of MIBG uptake in RBD patients is analogous to that of PD/DLB.[35] Therefore, a decrease of MIBG uptake before the occurrence of presynaptic dopaminergic neuronal loss indicates that MIBG cardiac scintigraphy may be a biomarker.

However, there is insufficient evidence to determine whether reduced MIBG absorption in RBD patients predicts a conversion to PD or suggests a worse outcome.

A previous study has reported that cognitive functions of patients with RBD may deteriorate after the diagnosis of PD, not before conversion to PD.[36] However, decreased MIBG uptake in cardiac scintigraphy, which stands for sympathetic denervation of heart is profound in PD with RBD, PD with orthostatic hypotension, and PD with wearing off.[37,38] In addition, low MIBG uptake predict Lewy body pathology before the motor symptoms of parkinsonism.[19,39] This suggests that the decreased uptake in MIBG cardiac scintigraphy may be an indicator of disease progression in alpha synucleinopathy.[40]

There have been several studies that suggested cut-off value of MIBG uptake value for differentiation between iRBD and normal controls, PD, or OSA.[18,41,42] RWA is associated with increased rigidity, progression of Lewy body dementia, and PD development.[43–45] Consequently, recent studies indicated that RWA may serve as a biomarker for neurodegenerative disease emerged from iRBD.[46,47] To the best of our knowledge, this is the first study that demonstrated the lower HMR may predict higher RWA. In this study, we set the cut-off value within the iRBD group and showed the association between decreased MIBG uptake and RWA. This suggests clinical applicability of MIBG cardiac scintigraphy to predict the diagnosis or disease progression of alpha-synucleinopathy. It is unclear why there was a relationship between MIBG uptake and RWA severity. It has been suggested that the medullary magnocellular reticular formation is related to the mechanism of RWA in RBD.[48] In addition, ventromedial medulla, tegmental periacqueductal grey matter, and mesopontine cholinergic nuclei also suggested to be related to RBD.[49,50] Since these brain stem structures are close to the sympathetic nerve activation center, there is abundant probability of a connection between them.

Although this study failed to show statistical quantitative associations, we believe that there will be a significant correlation between the severity of RWA and HMR. We surmise that the widely distributed RWA (%) might resulted in non-significance. In other words, the significance of this study is that we found clinical significance of MIBG cardiac scintigraphy based on the cut-off value, although we could not show statistical correlation between RWA and MIBG uptake due to the sharp changes in RWA.

In subgroup analysis in the patients with iRBD, when comparing the total, factor 1 (dream-related), and factor 2 (behavioral manifestation) scores of RBDQ-KR, there was no difference between the two groups. This means that changes in HMR precede differences in RBD symptoms, such as dream related or behavioral manifestations. Although statistical significance was not observed, in the group where HMR was higher than the cut-off value, the RBD onset age was younger, and the disease duration and interval of symptoms to PSG were longer. Even if the age of MIBG cardiac scintigraphy was similar, it can be considered that postganglionic heart sympathetic nerve endings is more preserved in patients whose RBD symptoms begin at a younger age. Although advanced age is known as a risk factor for PD incidence in patients with iRBD,[51] no research has been reported on RBD onset age.

There are several limitations in this study. First, the small number of subjects from a single hospital. Second, we cannot exclude secondary RBD caused by structural brain lesion. Third, no quantified autonomic function test performed in all subjects, and PSG was not performed in the healthy control group. Fourth, when sub-analysis was performed within the iRBD group, there was a large numerical difference between the two subgroups. Lastly, if this study had a comparative group of neurological degenerative diseases, it would have been a better study.

This study showed decreased uptake of MIBG cardiac scintigraphy in patients with iRBD were associated with severity of RWA. Combination of MIBG cardiac scintigraphy and RWA is a potential biomarker that may predict the emergence of neurodegenerative disease. Further long-term follow-up study of the iRBD with the high and low levels of HMR is needed.

Declarations

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Author contributions

S.Y. and K.S.W., these two authors equally contributed to paper writing and data analysis as first author.

K.T.K. participated in recruiting patients and controls and organizing data.

Y.W.C. and H.W.L. supervised the paper writing.

All the authors participated in analysis and interpretation of data. All the authors revised the manuscript critically and approved the manuscript in its final form.

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Competing interest

The authors declare that they do not have any competing interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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Figures

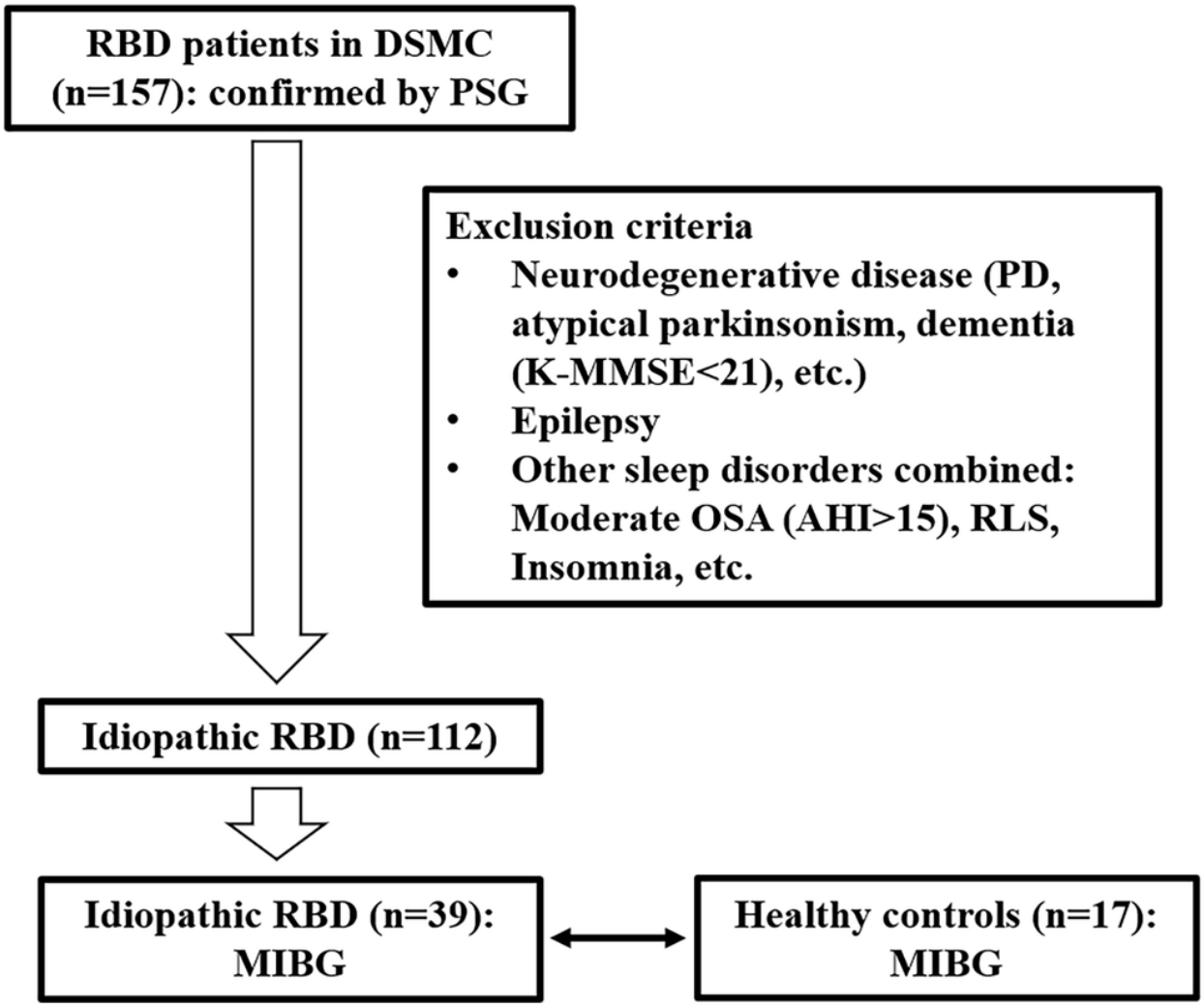

Figure 1

Recruitment process of idiopathic REM sleep behavior disorder patients for MIBG myocardial scintigraphy study.

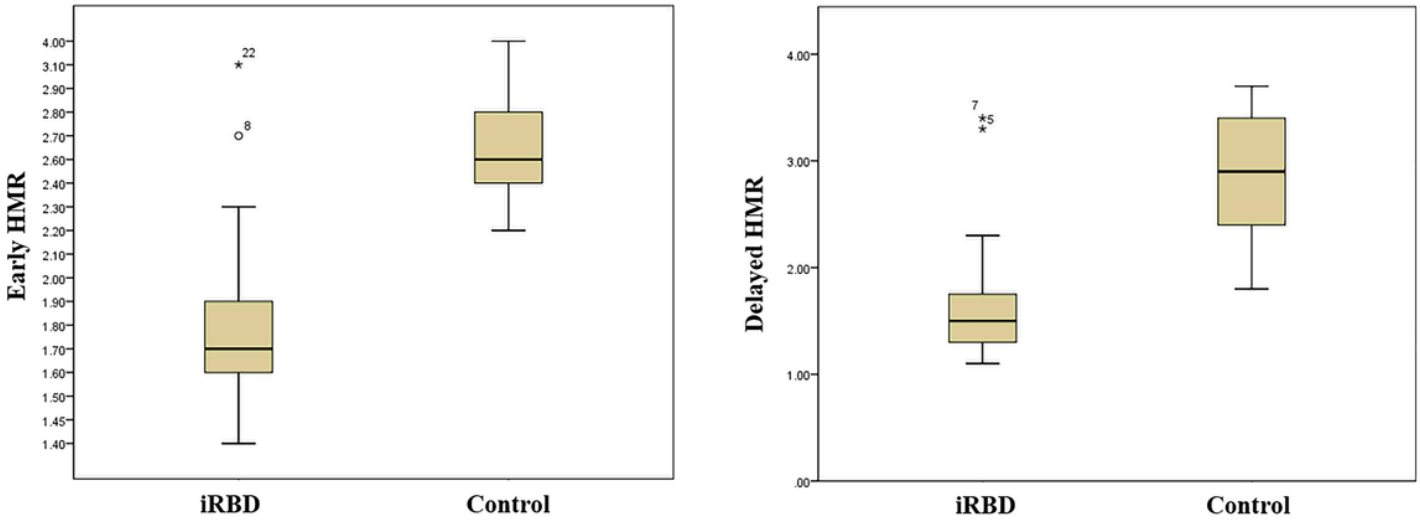

Figure 2

Distribution of the early and delayed HMR in control subjects and patients with iRBD. The horizontal lines indicate the median values. The early (15min) (A) and delayed (3hrs) (B) HMR are decreased in patients with iRBD.

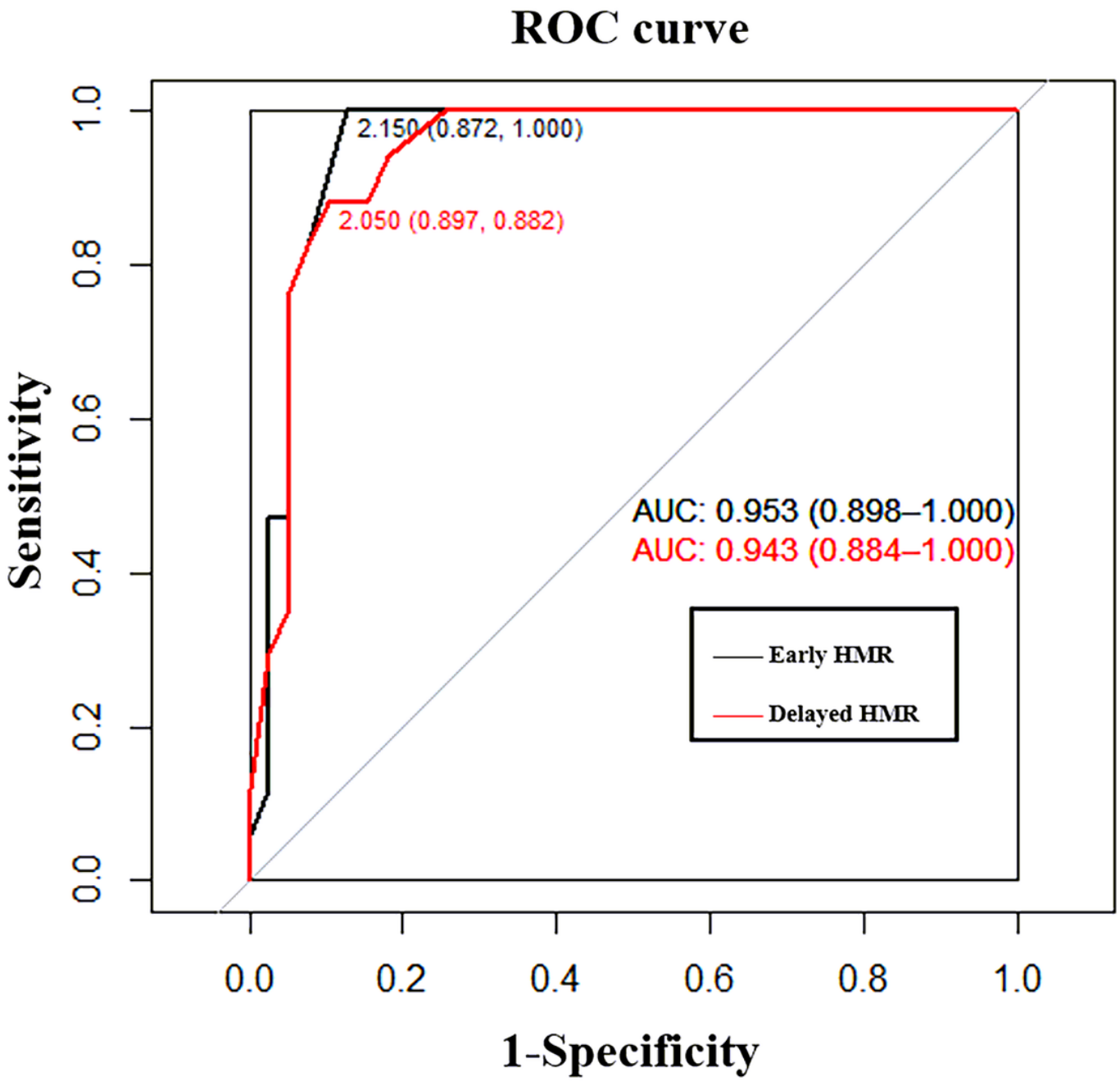

Figure 3

ROC analysis of the early or delayed HMR for patients with iRBD.

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