OBJECTIVE: RBD is considered to be a manifestation of an evolving synucleinopathy, such as Parkinson disease (PD), dementia of Lewy bodies (DLB), and multiple system atrophy (MSA). We tested whether the degree of accumulation of cardiac $^{123}$I-MIBG scintigraphy can distinguish the clinical syndromes associated with Lewy body-related disease from the syndrome of PSP (a tauopathy) and MSA.

Design: Cross-sectional.

Setting: University-based sleep disorders laboratory.

Patients: Subjects comprised 95 patients (31, idiopathic RBD; 26, PD; 10, MSA; 6, DLB; 13, progressive supranuclear palsy [PSP]) and 9 control subjects.

Intervention: To compare tracer uptake of cardiac $^{123}$I-MIBG between idiopathic RBD, PD, MSA, DLB, and PSP and control subjects.

Measurements and Results: Cardiac $^{123}$I-MIBG accumulation was evaluated by the heart/mediastinum (H/M) ratio. Mean value of the H/M ratio (early, delayed) was significantly reduced in patients with idiopathic RBD compared to MSA patients, PSP patients, control subjects (P < 0.001 in each group) and PD patients in early images (P < 0.05). There was a correlation between the H/M ratio and disease duration in the idiopathic RBD group. ROC analysis revealed that an H/M cut-off value of 1.9 was useful for differentiating RBD from MSA and PSP as well as distinguishing control subjects from those with RBD in both early and delayed images.

Conclusion: Cardiac $^{123}$I-MIBG findings are similar among idiopathic RBD and the syndromes of PD and DLB, but differ from those of PSP and MSA.

Keywords: REM sleep behavior disorder (RBD), Parkinson disease (PD), synucleinopathies, Lewy body disease (LBD), cardiac $^{123}$I-MIBG scintigraphy

Citation: Miyamoto T; Miyamoto M; Suzuki K; Nishibayashi M; Iwanami M; Hirata K. $^{123}$I-MIBG cardiac scintigraphy provides clues to the underlying neurodegenerative disorder in idiopathic REM sleep behavior disorder. SLEEP 2008;31(5):717-723.

PATIENTS WITH REM SLEEP BEHAVIOR DISORDER (RBD) DISPLAY ENHANCED MUSCLE ACTIVITY IN THE FORM OF TONIC AND PHASIC DISCHARGES IN CHIN AND LIMB MUSCLES AS CONFIRMED BY EMG. FURTHERMORE, THESE MOVEMENTS APPEAR TO CORRESPOND TO THE ACTIONS OCCURRING DURING THE DREAM. ALTHOUGH THE MECHANISM BY WHICH THIS OCCURS IS STILL UNCLEAR, IT HAS BEEN SPELLED OUT THAT DISTURBANCES IN REGIONS OF THE BRAINSTEM THAT COORDINATE REM SLEEP ARE INVOLVED.1,4 ONLY A FEW LONGITUDINAL PUBLISHED STUDIES HAVE ADDRESSED THE NATURAL COURSE OF RBD. IN SEPARATE REPORTS, 11 OF 29 OLDER MEN (38%) DIAGNOSED WITH IDIOPATHIC RBD DEVELOPED PARKINSON DISEASE (PD) WITHIN 3.7 YEARS,5 AND 17 OF 26 PATIENTS (65.4%) DEVELOPED THE DISEASE WITHIN 13 YEARS OF BEING DIAGNOSED WITH RBD.6 THE ONSET OF PD USUALLY BEGINS A FEW YEARS TO A LITTLE OVER A DECADE AFTER THE DEVELOPMENT OF RBD. ACCORDING TO THE RETROSPECTIVE STUDY, AMONG 44 PATIENTS WHO HAD INITIALLY RECEIVED A DIAGNOSIS OF IDIOPATHIC RBD, PD (9 PATIENTS), DEMENTIA OF LEWY BODIES (DLB) (6 PATIENTS), MULTIPLE SYSTEM ATROPHY (MSA) (ONE PATIENT), AND MILD COGNITIVE DYSFUNCTION (4 PATIENTS) DEVELOPED IN ~45% OF THE PATIENTS OVER AN AVERAGE OF 11.5 YEARS.7 THESE DATA SUGGEST THAT RBD REPRESENTS A PRODROMAL PHASE OF NEURODEGENERATIVE DISEASES SUCH AS PD, DLB, AND MSA.

RECENT STUDIES HAVE DEMONSTRATED CHANGES IN RESULTS OF ELECTROENCEPHALOGRAPHY, SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY, NEUROPSYCHOLOGICAL TESTING, SMELL TESTING, COLOR DISCRIMINATION, CARDIAC AUTONOMIC ACTIVITY, AND MORE SUBTLE ABNORMALITIES ON MEASURES OF AUTONOMIC, MOTOR, AND GAIT FUNCTIONING.1,3 THESE RESULTS INDICATE THAT A MORE WIDESPREAD MULTISYSTEM NEUROLOGICAL DISORDER IS PRESENT. CARDIAC MIBG SCINTIGRAPHY ALLOWS FOR THE VISUAL AND QUANTITATIVE ASSESSMENT OF THE FUNCTION OF ADRENERGIC NEURONS AND IS CONSIDERED TO BE A USEFUL TOOL FOR THE DIFFERENTIAL DIAGNOSIS OF NEURODEGENERATIVE DISEASES, SUCH AS PD,8 DLB, AND MSA, AS WELL AS BETWEEN 2 KINDS OF DEMENTIA, I.E., DLB AND ALZHEIMER DISEASE (AD).9,10 RECENT REPORTS SHOWED THAT ABNORMAL CARDIAC $^{123}$I-MIBG UPTAKE WAS RECOGNIZED PARTICULARLY IN LEWY BODY-RELATED $\alpha$-SYNUCLEINOPIATHIES SUCH AS PD, DLB, AND PAF AMONG NEURODEGENERATIVE DISEASES; AND DEGREES OF $^{123}$I-MIBG UPTAKE DIFFERED IN NEURODEGENERATIVE DISEASE, INCLUDING TAUNOPIATHIES WITHOUT THE APPEARANCE OF LEWY BODIES, SUCH AS FAMILIAL PD, MSA, PSP, CBD, AND AD.11 THE DELAYED H/M RATIO COULD PROVIDE SENSITIVITY AND SPECIFICITY AS HIGH AS 100% FOR DIFFERENTIATION BETWEEN DLB AND AD.12 THEREFORE, $^{123}$I-MIBG SCINTIGRAPHY HAS BEEN ESTABLISHED AS A USEFUL MODALITY FOR THE DIFFERENTIATION OF THESE DISORDERS.9,12,16 ACCORDING TO RECENT STUDIES, REDUCED MIBG UPTAKE HAS REVEALED A POSSIBLE CORRELATION BETWEEN PD AND IDIOPATHIC RBD.17,19 HOWEVER, IDIOPATHIC RBD MAY BE A MANIFESTATION OF SEVERAL NEUROLOGICAL DISORDERS WITH DIFFERENT PATHOLOGICAL BACKGROUNDS, CALLED SYNUCLEINOPIATHIES, SUCH AS PD, MSA, DLB, AND CALLED TAUNOPIATHIES, SUCH AS PSP, CBD, AND AD. HERE, WE TESTED WHETHER THE DEGREE OF ACCUMULATION OF CARDIAC $^{123}$I-MIBG SCINTIGRAPHY CAN DISTINGUISH THE DISORDER FROM RBD.
clinical syndromes associated with Lewy body-related disease from the syndrome of PSP (a tauopathy) and MSA.

METHODS

Patients and Control Subjects

Studied were 95 subjects. These included 31 patients with polysomnography (PSG)-confirmed idiopathic RBD, 26 age-matched patients with PD, 6 age-matched patients with DLB, 10 age-matched patients with MSA, 13 age-matched patients with PSP, and 9 age-matched control subjects.

Data were analyzed on 31 of the 48 consecutive patients with idiopathic RBD who underwent MIBG from July 2004 to June 2007 and who were not excluded for any of the following reasons (Figure 1A). Exclusion criteria were an abnormal neurological examination, alcohol or psychotropic drug use, psychiatric disorders, cardiac or diabetic diseases, and moderate or severe obstructive sleep apnea hypopnea syndrome (OSAHS) (apnea-hypopnea index ≥15/h).20 Interval between PSG and MIBG examinations was a median of 3 days. Idiopathic RBD was defined according to the following standard criteria published in the International Classification of Sleep Disorders, second edition:21 excessive phasic or tonic EMG activity during recorded REM sleep, a history of injuries or disruptive sleep behavior or documentation of abnormal behavior during REM sleep in the PSG laboratory, and no EEG epileptiform activity during REM sleep. Patient interviews focused on whether the patients experienced motor events during sleep that were associated with dreaming, which may have included screaming, self-injury, or injury to their bed partner; information on the latter was confirmed by interviews with the patients’ bed partner. PSG and videotape recordings were made simultaneously as the patients slept. Patients with idiopathic RBD underwent one night (8 h) of polysomnographic recording in our sleep laboratory. PSG consisted of the use of a standard montage for scoring sleep stages: left and right oculograms, chin EMG, central (C3-A2, C4-A1) and occipital (O1-A2, O2-A1) EEG, and ECG. Sleep staging followed the recommendations of Rechtschaffen and Kales.22 REM sleep was scored without the chin EMG criterion, thereby allowing for the maintenance of muscle tone during REM sleep. Recordings of oral and nasal airflow, thoracic and abdominal movements, and oximetry were carried out in order to detect apnea and hypopnea. Surface EMG recordings of the right and left anterior tibialis muscles were made to quantify leg movements. The scoring of arousal and periodic limb movements followed published guidelines.23,24

The following polysomnographic variables were measured: sleep latency (SL), total sleep time, sleep efficacy (SE), and percentage of stages 1, 2, 3, 4, and REM sleep. Stages 3 and 4 were pooled together as slow wave sleep (SWS). SE represents the percentage of time spent asleep over the total recording time from sleep onset to the last awakening.

Study subjects included 55 patients with a neurodegenerative disease of a duration less than 5 years, which excluded those with young-onset PD,25 among 70 patients registered with the MIBG database for Neurodegenerative Disease in Dokkyo Medical University from August 2002 to July 2007 (Figure 1B). Clinical diagnosis of PD,26 DLB,27 PSP,28 and MSA29 was made by neurological specialists according to established consensus criteria.

The 9 age-matched control subjects had no clinical symptoms of RBD10 or autonomic nervous system disorders, were taking no medications, and had no history of cardiac or diabetic diseases. Five of the 9 control subjects had an essential tremor, with 2 subjects exhibiting cervical or lumbar spondylosis; 2 others had no history of morbidity. Even though the presence of an essential tremor is indicative of a nervous system disease, subjects with an essential tremor were included in the control group based on reports that showed that their cardiac MIBG uptake was not reduced.31,32

Figure 2—Cardiac 123I-metaiodobenzylguanidine scintigraphy. Anterior view at 4 h after injection in a patient with idiopathic RBD (A) and a patient with PD (B). Regions of interest regarding MIBG uptake in the heart (irregularly-shaped region labeled H) and MIBG uptake in the mediastinum (rectangular region indicated by M) are shown in the figure. The figures show a similar marked reduction in cardiac uptake for both patients. RBD = REM sleep behavior disorder; PD = Parkinson disease.

123I-MIBG Myocardial Scintigraphy

After subjects were in the supine position for 15 min, they were injected intravenously with 111 MBq 123I-MIBG (Daichi Radioisotope Laboratories Co, Tokyo, Japan). 123I-MIBG photon emission computed tomography (SPECT) and planar images of the chest were obtained using a triple-headed gamma camera (GCA-9300A-HG, Toshiba Co, Tokyo, Japan) or double-headed gamma camera equipped with a low-energy, high-resolution parallel-hole collimator (PRISM 2000VP, Picker, Cleveland, OH) 15~20 min (early phase) and 4 h (delayed phase) after
injection. Planar imaging for 5 min in the anterior projection was automatically performed during SPECT. Photopake energy was centered at 159 keV ($^{123}$I-MIBG) with a window of 10%. Relative organ uptake of $^{123}$I-MIBG was determined by setting the region of interest (ROI) on the anterior view. The heart-to-mediastinum (H/M) ratio was calculated by dividing the count density of the left ventricular ROI by that of the mediastinal ROI, as previously described. After rapid distribution of the $^{123}$I-MIBG from the vascular compartment within the first hour, cardiac uptake within the following hours results from both neuronal and nonneuronal biodistribution. Neuronal uptake is visualized in isolation after the early clearance phase is completed within 4 h. None of the subjects were taking medications that could potentially influence the MIBG examination (e.g., tricyclic and tetracyclic antidepressants, sympathomimetics, and sympatholytics).

All procedures described in this study were approved by the Ethics Review Committee of Dokkyo Medical University, and informed consent was obtained from each subject.

### Statistical Analysis

The difference in H/M ratio between idiopathic RBD, PD, DLB, MSA, PSP, and control subjects was age-matched within disease groups. As shown, there were 23 men and 8 women with confirmed idiopathic RBD of a duration of 5.7 ± 4.9 years (range, 0.25-17) (age 66.3 ± 6.7 years, range, 52-82); 12 men and 14 women with PD (age 67.5 ± 6.3 years, range, 57-82; disease duration 1.9 ± 1.3 years), 4 men and 2 women with DLB (age 71.0 ± 5.9 years, range, 62-79; disease duration 0.9 ± 0.2 years), 6 men and 4 women with MSA patients (age, 64.7 ± 9.0 years, range 54-76; disease duration 2.5 ± 1.5 years), 10 men and 3 women with PSP (age 70.7 ± 7.6 years, range, 61-79; disease duration 2.3 ± 1.4 years) and 5 men and 4 women who were the control subjects (age 72.2 ± 7.7 years, range 62-82). There were more men than women among the idiopathic RBD and PSP patients. No significant difference was found between the H/M ratio of men and women for MIBG uptake among the control subjects (P > 0.05). Thus, gender ratio bias should not affect comparisons of MIBG uptake. Age did not differ significantly among those with idiopathic RBD, PD, DLB, MSA, and PSP, as well as control subjects. There was no significant difference in disease duration among patients with PD, DLB, MSA, and PSP.

Demographic and PSG findings on the 31 patients with PSG-proven idiopathic RBD are shown in Table 2. The majority were men (23 men [74%], 8 women [26%]). The average age at onset was 60.4 years (range 41-78), with 77.4% being older than 50 years at onset. Four patients (12.9%) had ESS >10 and 4 had PLMD (PLMS ≥15/h) (12.9%). Among this group, the apnea hypopnea index was 3.3/h, sleep efficiency was 68.9 ± 14.5%, and the presence of REM sleep without atonia (RWSA) was 100%.

Markedly reduced cardiac radioactivity was detected in both the early and delayed images in 29 of 31 (93.5%) patients with idiopathic RBD (Fig. 2A), 21 of 26 (75.0%) patients with PD (Fig. 2B), and 6 of 6 (100%) patients with DLB. The cardiac radioactivity of $^{123}$I-MIBG was normal in the MSA, PSP and control groups.

The mean ratio of $^{123}$I-MIBG uptake in the ROI of the heart was 100%.

### RESULTS

Table 1 shows demographic and clinical data on the patients with idiopathic RBD, PD, MSA, PSP, and DLB as well as the control subjects. All values are shown as means ± S.D. and all subjects were age-matched within disease groups. As shown, there were 23 men and 8 women with confirmed idiopathic RBD of a duration of 5.7 ± 4.9 years (range, 0.25-17) (age 66.3 ± 6.7 years, range, 52-82); 12 men and 14 women with PD (age 67.5 ± 6.3 years, range, 57-82; disease duration 1.9 ± 1.3 years), 4 men and 2 women with DLB (age 71.0 ± 5.9 years, range, 62-79; disease duration 0.9 ± 0.2 years), 6 men and 4 women with MSA patients (age, 64.7 ± 9.0 years, range 54-76; disease duration 2.5 ± 1.5 years), 10 men and 3 women with PSP (age 70.7 ± 7.6 years, range, 61-79; disease duration 2.3 ± 1.4 years) and 5 men and 4 women who were the control subjects (age 72.2 ± 7.7 years, range 62-82). There were more men than women among the idiopathic RBD and PSP patients. No significant difference was found between the H/M ratio of men and women for MIBG uptake among the control subjects (P > 0.05). Thus, gender ratio bias should not affect comparisons of MIBG uptake. Age did not differ significantly among those with idiopathic RBD, PD, DLB, MSA, and PSP, as well as control subjects. There was no significant difference in disease duration among patients with PD, DLB, MSA, and PSP.

Demographic and PSG findings on the 31 patients with PSG-proven idiopathic RBD are shown in Table 2. The majority were men (23 men [74%], 8 women [26%]). The average age at onset was 60.4 years (range 41-78), with 77.4% being older than 50 years at onset. Four patients (12.9%) had ESS >10 and 4 had PLMD (PLMS ≥15/h) (12.9%). Among this group, the apnea hypopnea index was 3.3/h, sleep efficiency was 68.9 ± 14.5%, and the presence of REM sleep without atonia (RWSA) was 100%.

Markedly reduced cardiac radioactivity was detected in both the early and delayed images in 29 of 31 (93.5%) patients with idiopathic RBD (Fig. 2A), 21 of 26 (75.0%) patients with PD (Fig. 2B), and 6 of 6 (100%) patients with DLB. The cardiac radioactivity of $^{123}$I-MIBG was normal in the MSA, PSP and control groups.

The mean ratio of $^{123}$I-MIBG uptake in the ROI of the heart was 100%.
There was a correlation between the H/M ratio and the duration of disease in both of the idiopathic RBD groups (early: \( r = -0.477, P = 0.0066 \); delayed: \( r = -0.3578, P = 0.0481 \)). There was no correlation between the H/M ratio and the duration of disease in the largest area under the curve with the best accuracy to differentiate between patients with idiopathic RBD and control subjects or patients with PD, MSA, or PSP (Table 3).

### DISCUSSION

In this study, we found a marked reduction in cardiac MIBG uptake in patients with idiopathic RBD. A reduction in cardiac MIBG uptake has been reported to be characteristic of patients with Lewy body-related \( \alpha \)-synucleinopathies such as PD, DLB, and pure autonomic failure (PAF).\(^9,12,14,31,34,35\) Degrees of reduction in accumulation were not significantly different between RBD and DLB patients. The finding that the degrees of reduction in cardiac \(^{125}\text{I-MIBG}\) uptake were similar in patients with idiopathic RBD compared with PD and DLB patients supports the notion that Lewy body-related \( \alpha \)-synucleinopathies, including PD, DLB, and PAF, represent a clinical and pathologic spectrum.\(^9,35,37,39\)

In idiopathic RBD, a cut-off value of 1.9 for both early and delayed H/M ratios was useful for differentiating between control subjects and those with tauopathies and MSA. \(^{125}\text{I-MIBG}\) accumulation in idiopathic RBD based on the H/M ratio was also compared with the duration of disease. In most cases, a marked reduction in \(^{125}\text{I-MIBG}\) accumulation occurred soon after the onset of the disease. In PD, the H/M ratio is related to disease duration, with the ratio decreasing with length of disease. However, long-term PD patients with a normal H/M ratio were found among patients with juvenile Parkinsonism and specific disease.

### Table 2—Demographic and PSG Findings of All Patients with Idiopathic RBD (n=31)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Gender</th>
<th>Mean age of onset (years)</th>
<th>Onset age over than 50 years</th>
<th>Mean age at diagnosis (years)</th>
<th>Disease duration (years)</th>
<th>BMI (kg/m(^2))</th>
<th>ESS</th>
<th>ESS&gt;10</th>
<th>Apnea hypopnea index</th>
<th>Increased phasic and tonic EMG in REM sleep</th>
<th>Periodic leg movement</th>
<th>Sleep efficiency (%)</th>
<th>Mean % REM sleep</th>
<th>Mean % stage 1</th>
<th>Mean % stage 2</th>
<th>Mean % slow wave sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>23 (74%) man; 8 (26%) woman</td>
<td>60.4 (range 41-78)</td>
<td>77.4%</td>
<td>66.3 (range 52-82)</td>
<td>5.7 (range 0.25-18)</td>
<td>23.3 (range 16.9-30.0)</td>
<td>5.7 (range 0-16)</td>
<td>4 (12.9%)</td>
<td>3.3 (range 0-14.9)</td>
<td>31 (100%)</td>
<td>68.9 ± 14.5</td>
<td>67.5 ± 8.3</td>
<td>17.1%</td>
<td>31%</td>
<td>50%</td>
</tr>
<tr>
<td>Subjects with controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with PD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with MSA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with PSP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 3—Diagnostic Discrimination Between Groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cutoff value of each measure</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
<th>Likelihood ratio</th>
<th>ROC AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>eH/M</td>
<td>dH/M</td>
<td>eH/M</td>
<td>dH/M</td>
<td>eH/M</td>
<td>dH/M</td>
<td>eH/M</td>
</tr>
<tr>
<td>Compared with IRBD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with controls</td>
<td>2.05</td>
<td>2.39</td>
<td>100</td>
<td>100</td>
<td>93.5</td>
<td>96.8</td>
<td>100</td>
</tr>
<tr>
<td>Patients with PD</td>
<td>1.82</td>
<td>–</td>
<td>65.4</td>
<td>–</td>
<td>77.4</td>
<td>–</td>
<td>71.9</td>
</tr>
<tr>
<td>Patients with MSA</td>
<td>2.02</td>
<td>1.97</td>
<td>90.0</td>
<td>100</td>
<td>93.5</td>
<td>93.5</td>
<td>96.7</td>
</tr>
<tr>
<td>Patients with PSP</td>
<td>2.08</td>
<td>2.08</td>
<td>100</td>
<td>100</td>
<td>93.5</td>
<td>93.5</td>
<td>100</td>
</tr>
</tbody>
</table>

ROC analysis was used to determine the optimal cutoff values to evaluate the usefulness of \(^{125}\text{I-MIBG}\) cardiac scintigraphy in differentiating IRBD from controls, PD, MSA, and PSP. ROC AUC = receiver operating characteristic area under curve; eH/M= early H/M ratio; delayed H/M ratio; IRBD = idiopathic REM sleep behavior disorder; PD = Parkinson Disease; MSA = multiple system atrophy; PSP = progressive supranuclear palsy.
and PD with a family history, which suggested the necessity for careful interpretation.

A correlation with RBD is most frequently observed in α-synucleinopathies among neurodegenerative diseases, and, in particular, MSA is frequently associated with or preceded by RBD. However, most studies have found only a mildly reduced $^{123}$I-MIBG uptake. Meanwhile, tauopathies such as AD, PSP, and CBD are rarely associated with RBD. Therefore, it could be speculated that those patients with normal or very mildly reduced $^{123}$I-MIBG uptake are more likely either to continue having the diagnosis of a tauopathy or to develop MSA, rather than developing PD or DLB. Two of 31 patients with idiopathic RBD did not show reduced cardiac $^{123}$I-MIBG uptake. Their disease duration was less than 1 year. They could be classified as being in the very early stage of RBD or RBD without Lewy body-related disease.

Several reports show pathological evidence for the involvement of cardiac postganglionic sympathetic and intrinsic neurons in PD or incidental Lewy body disease (ILBD). Examination of cardiac tissue, Lewy bodies and α-synuclein-positive neurites were found in 9 of the 11 patients with PD and all 7 ILBD patients. Autopsies of patients who underwent cardiac $^{123}$I-MIBG scintigraphy and had abnormal accumulation of cardiac $^{123}$I-MIBG revealed a marked decrease in tyrosine hydroxylase (TH)-immunoreactive nerve fibers in the epicardial nerve bundle in patients with PD compared with control subjects and patients with MSA. This was reported to be the cause of reduced cardiac $^{123}$I-MIBG accumulation. Furthermore, autopsy of a 71-year-old PD patient who had a marked reduction in cardiac $^{123}$I-MIBG accumulation one year before revealed that the cardiac plexus was damaged more severely than the sympathetic ganglia. In particular, sympathetic nerve ganglia were the main focus of injury rather than cardiac muscle in MSA, and it was speculated that $^{123}$I-MIBG accumulation was mildly reduced by this mechanism.

Furthermore, injury of cardiac sympathetic nerves was compared between PD and DLB patients. In patients with the same disease duration, a more profound reduction in cardiac $^{123}$I-MIBG uptake was shown in those with DLB. In addition, the reduction in cardiac $^{123}$I-MIBG accumulation in RBD patients was particularly evident at the early stage after onset, which was similar to findings for DLB patients. These results suggest that degeneration of cardiac peripheral nerves occurs more readily during the early stage of DLB and RBD than in patients with PD. Thus, as a result of injury to peripheral sympathetic nerves, $^{123}$I-MIBG uptake is more strongly affected at an early stage after onset of DLB and RBD than with PD.

In addition, patients in whom Parkinsonism was not recognized but in whom Lewy bodies happened to be found in the substantia nigra or ceruleus nucleus were designated as having ILBD, which was considered to be a prodrome to the onset of PD. In ILBD patients, the cardiac sympathetic nerves were examined, and denervation was found in some of these patients. Therefore, it was speculated that the denervation of cardiac sympathetic nerves started at an early stage of PD, which pathologically supported the reduced cardiac $^{123}$I-MIBG accumulation. There is pathological evidence on RBD to support this proposal. Specifically, an autopsy of ILBD patients developing only RBD symptoms for more than 20 years revealed the presence of Lewy bodies in the locus ceruleus, which was similar to pathological findings for PD. A more recent report showed that an autopsy of a patient 72 years of age, who had been diagnosed as having idiopathic RBD at 57 years of age and died 15 years later, revealed the presence of Lewy bodies, but the absence of neuronal loss and/or gliosis despite the presence of Lewy bodies in the substantia nigra, locus ceruleus, and medullary reticular formation that are usually observed in RSWA.

Although assessing cardiac sympathetic denervation is not yet possible as a routine laboratory test, these studies have been unable to confirm postganglionic nerve injury.

As to limitations of this study, using the diagnostic criteria by ISCD-2, we performed PSG only when we diagnosed idiopathic RBD. It is unclear as to the presence of secondary RBD because we used only MIBG data for neurodegenerative diseases. Therefore, we were unable to compare the difference in degrees of accumulation by MIBG that were derived from the presence or absence of complications with RBD in neurodegenerative diseases in this study.

In conclusion, a marked reduction in cardiac MIBG uptake was found in patients with idiopathic RBD compared to control subjects and patients with clinically diagnosed PSP and MSA, but similar to those with clinically diagnosed PD and DLB. Thus, we believe that this technique may be a useful early diagnostic marker of RBD with Lewy body-related pathology; neuropathologic studies will be required to support or refute this contention.

ACKNOWLEDGMENTS

We are indebted to our colleagues with whom we work on the RBD, namely Y. Inoue (Japan Somnology Center, Neuropsychiatry Research Institute) and T. Usui (Second Department of Internal Medicine, Tokyo Medical University). The authors thank T. Hashimoto (Department of Radiology, Dokkyo Medical University School of Medicine) for helpful comments.

REFERENCES

6. Schenck CH, Bundlie SR, Mahowald MW. REM behavior disorder (RBD): delayed emergence of parkinsonism and/or dementia in 65% of older men initially diagnosed with idiopathic RBD, and an analysis of the minimum & maximum tonic and/or phasic electromyographic abnormalities found during REM sleep. Sleep 2003;26:A316.


