Diagnosis of dementia with Lewy bodies: diagnostic performance of combined $^{123}$I-IMP brain perfusion SPECT and $^{123}$I-MIBG myocardial scintigraphy

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Abstract

Objective We assessed the value of combining $^{123}$I-IMP brain perfusion SPECT and $^{123}$I-MIBG myocardial scintigraphy for the discrimination of dementia with Lewy bodies (DLB) from other types of dementia.

Methods We subjected 252 consecutive patients with clinically suspected DLB to both $^{123}$I-IMP brain perfusion SPECT and $^{123}$I-MIBG myocardial scintigraphy. Patients with Parkinson's disease were included. The 252 patients were randomly assigned to an estimation ($n = 152$) or a validation group ($n = 100$). Using univariate analysis, we first analyzed the relationship between various variables and the presence or absence of DLB in estimation group and then proceeded to multivariate analysis to obtain a combined index that predicted the likelihood of DLB. The diagnostic value of the index was assessed by calculating the area under the receiver operating characteristic (ROC) curve (AUC) with the cutoff value selected from the ROC curve. We then tested the predictive accuracy of the index in validation group.

Results The combined index was an arithmetic expression that combined the age, early $^{123}$I-MIBG heart-to-mediastinum uptake (E-H/M) ratio, and the parietal lobe hypoperfusion score. Values for the AUC of the combined index, the E-H/M ratio, the parietal lobe hypoperfusion score, and the patient age in validation group were 0.95, 0.90, 0.72, and 0.73, respectively. There was a significant difference in the AUC of the combined index among other indices ($p < 0.05$). The sensitivity, specificity, and accuracy of the combined index for a diagnosis of probable DLB in validation group were 88, 87, and 87 %, respectively.

Conclusions The combinational diagnosis based on $^{123}$I-IMP brain perfusion SPECT, $^{123}$I-MIBG myocardial scintigraphy, and the patient age is a simple and reliable means for predicting probable DLB.

Keywords Dementia with Lewy bodies · $^{123}$I-IMP brain perfusion SPECT · $^{123}$I-MIBG myocardial scintigraphy · Combined index

Introduction

Dementia with Lewy bodies (DLB), Alzheimer’s disease (AD), and vascular dementia (VaD) are the most common types of dementia. Approximately, 20–30 % of elderly Japanese manifest DLB. Its symptoms are progressive deterioration of cognitive function, fluctuating cognitive impairment, Parkinsonism, recurring specific hallucinations, falls, and syncope [1]. Patients with DLB tend to present with serious behavioral and psychological symptoms of dementia (BPSD) which reduce their quality of life.
and present problems for caregivers [2]. DLB progresses more rapidly than other dementing disorders and these patients have a poor prognosis with worsening cognitive impairment and Parkinsonism.

Patients with DLB are hypersensitive to drugs, some manifest a hypersensitive reaction to antipsychotic or antidepressant drugs resulting in symptom exacerbation. Cholinesterase inhibitors (ChEIs) are effective and regarded as the first-line therapy for BPSD; however, in patients with AD, they may elicit adverse reactions such as the promotion of excitement [3]. While an accurate differential diagnosis is necessary, there are few specific symptoms in the early stages of DLB and symptoms overlap with other dementing disorders. Consequently, it is often difficult to arrive at a correct diagnosis based only on the clinical presentation whose reported sensitivity and specificity are 22–83 and 79–100 %, respectively [4–7].

Diagnostic imaging is thought to improve the diagnostic performance. Current imaging modalities for DLB are 123I-metaiodobenzylguanidine (MIBG) cardiac scintigraphy, computed tomography (CT), magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), and positron emission tomography (PET) [8]. To our knowledge, only Hanyu et al. [9] and Tateno et al. [10] compared the usefulness of 123I-IMP brain perfusion SPECT- and 123I-MIBG myocardial scintigraphy studies to differentiate between DLB and AD.

Many patients suspected of having DLB based on imaging findings and/or their clinical presentation also suffer from comorbidities such as Parkinson’s disease (PD), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD), and AD. Therefore, we conducted a retrospective study of patients with various types of dementia (including PD) who underwent both 123I-IMP brain perfusion SPECT- and 123I-MIBG myocardial scintigraphy studies to evaluate the usefulness of these imaging studies for the diagnosis of DLB.

### Patients and methods

#### Subjects

Our study was approved by our institutional ethics board. Patient informed consent was waived due to its retrospective, purely observational nature.

Between January 2007 and December 2012, 270 patients with clinically suspected DLB underwent both 123I-IMP brain perfusion SPECT and 123I-MIBG myocardial scintigraphy studies at Kumamoto University Hospital. Based on criteria promulgated by the Consortium on DLB International Workshop [11], 72 patients (31 men, 41 women; mean age ± SD. 77.1 ± 6.0 years; range 56–89 years) had probable DLB, 18 (5 men, 13 women; mean age 77.9 ± 4.8 years; range 70–87 years) had possible DLB, and 180 (68 men, 112 women; mean age 71.8 ± 9.3 years; range 34–92 years) had without DLB. There were 25 patients with PD. Patients with congestive heart failure or taking antipsychotic drugs (tricyclic antidepressants, reserpine) that would affect the results of 123I-MIBG myocardial scintigraphy were excluded, while patients with well-controlled diabetes or hypertension treated with small doses of ACE inhibitors or β blockers were included although their 123I-MIBG myocardial scintigraphy findings may have been affected [12]. The diagnoses of the 180 patients with without DLB are shown in Table 1. We excluded patients with possible DLB because both DLB and other types of dementia were included in this category.

#### 123I-IMP brain perfusion SPECT

We used a two-head gamma camera (Millennium VG, GE) equipped with a low-energy general-purpose collimator. 123I-IMP brain perfusion SPECT was performed for approximately 20 min (continuous mode, 2.5 min/rotation, 12 rotations, 64 × 64 matrix) immediately after the intravenous (i.v.) injection of 123I-IMP (167 MBq in 1.5 ml). The energy peak was set at 157 keV with a 20 % energy window. Transaxial images were reconstructed with filtered back projection using a Butterworth filter. An order-10 Butterworth filter (cut-off 0.45) was used for post-reconstruction. The reconstructed slice thickness was 2.95 mm. SPECT image was reconstructed with a uniform attenuation correction using Chang’s methods; we did not correct for scatter. The reconstructed 123I-IMP SPECT images were

#### Table 1 Diagnoses of 252 patients included in this study

|                      | Estimation group (n = 152) | Validation group (n = 100) |
|----------------------|---------------------------|---------------------------|
| Probable DLB (n = 72) | 46                        | 26                        |
| Without DLB (n = 180)| 23                        | 8                         |
| AD                   | 14                        | 11                        |
| PD                   | 13                        | 5                         |
| PSP                  | 7                         | 3                         |
| MSA                  | 6                         | 5                         |
| CBD                  | 6                         | 2                         |
| VaD                  | 5                         | 1                         |
| iNPH                 | 4                         | 4                         |
| Others               | 28                        | 35                        |

AD Alzheimer’s disease, PD Parkinson’s disease, PSP progressive supranuclear palsy, MSA multiple system atrophy, CBD corticobasal degeneration, VaD vascular dementia, iNPH idiopathic normal pressure hydrocephalus, RBD REM sleep behavior disorder
analyzed with Neurostat/(3D-SSP) using image-analysis software (iSSP version 3.5) [13, 14]; data were normalized to the mean global activity. Further analysis was with stereotactic extraction estimation (SEE) software [15]. Using the SEE method, we divided the whole brain into segments (level 2, lobe level-; level 3, gyrus level classification) and assessed the severity of hypoperfusion in the frontal-, parietal-, temporal-, and occipital lobe, the precentral and postcentral gyrus, the precuneus, parahippocampus, anterior and posterior cingulate, and the uncus.

123I-MIBG cardiac scintigraphy

Planar scans were acquired using a two-head gamma camera (Millennium VG, GE) equipped with a medium-energy general-purpose collimator. The patients underwent 123I-MIBG scintigraphy during quiet respiration without breathholding within 1–4 weeks before or after 123I-IMP SPECT. 123I-MIBG anterior planar images were obtained 15 min and 3 h (early and delayed images, respectively) after the i.v. injection of 123I-MIBG. (111 MBq, 3 mCi). The planar-image acquisition time was 5 min, the matrix size was 256 × 256, and the energy window was set at 157 keV (±10 %). The pixel size of the planar images was 1.64 mm. Using the region of interest (ROI) method, we calculated the early and delayed 123I-MIBG heart-to-mediastinum uptake (H/M) ratios on anterior views of the planar images. An irregular circular ROI was manually drawn on the left ventricle and a square ROI was placed in the upper mediastinum area.

Statistical analysis

Our objective was to differentiate patients with probable DLB from patients without DLB using a combination of variables. Diabetes, treatment with ACE inhibitors or β blockers, the results of autonomic dysfunction tests, and typical autonomic neuropathy symptoms (e.g. orthostatic hypotension, urinary incontinence, constipation) [16] were among our variables. We used Microsoft Excel (Microsoft Japan, Tokyo, Japan) to arbitrarily assign a number from 1 to 252 to the patients and then enrolled the first 152 in the estimation group and the other 100 in the validation group.

The diagnoses of the 252 patients are shown in Table 1, and our variables in Table 2.

In estimation group, we identified the variables for predicting a diagnosis of DLB by univariate analysis. Then, we subjected all variables with a significant predictive value to

### Table 2 Characteristics of the 252 patients and the study variables

| Variables                        | Estimation group (n = 152) | Validation group (n = 100) | p value |
|----------------------------------|---------------------------|---------------------------|---------|
| Age                              | 73.9 ± 8.5                | 72.5 ± 10.4               | 0.24    |
| Gender (male:female)             | 56:96                     | 43:57                     | 0.36    |
| Diabetes mellitus                | 29                        | 19                        | 0.988   |
| ACE inhibitor or β blocker       | 6                         | 8                         | 0.169   |
| Autonomic neuropathy symptoms    | 71                        | 42                        | 0.462   |
| Autonomic dysfunction test       | 48                        | 36                        | 0.466   |
| Diagnosis (probable DLB:without DLB) | 48:104                   | 24:76                     | 0.20    |
| MIBG scintigraphy                |                           |                           |         |
| Early H/M ratio                  | 2.53 ± 0.81               | 2.64 ± 0.88               | 0.28    |
| Delayed H/M ratio                | 2.48 ± 1.07               | 2.66 ± 1.09               | 0.20    |
| Washout rate                     | 39.8 ± 17.2               | 38.3 ± 17.7               | 0.51    |
| Brain perfusion scintigraphy     |                           |                           |         |
| Frontal lobe                     | 1.73 ± 0.83               | 1.76 ± 0.76               | 0.80    |
| Parietal lobe                    | 1.87 ± 0.82               | 1.78 ± 0.93               | 0.42    |
| Temporal lobe                    | 1.85 ± 0.97               | 1.72 ± 0.69               | 0.23    |
| Occipital lobe                   | 0.95 ± 0.80               | 0.82 ± 0.70               | 0.18    |
| Precentral gyrus                 | 1.37 ± 0.59               | 1.46 ± 0.86               | 0.33    |
| Postcentral gyrus                | 1.58 ± 0.74               | 1.56 ± 0.109              | 0.86    |
| Precuneus                        | 1.15 ± 0.88               | 1.02 ± 0.75               | 0.22    |
| Parahippocampus                  | 1.62 ± 1.42               | 1.43 ± 0.96               | 0.24    |
| Anterior cingulate               | 1.53 ± 0.78               | 1.62 ± 0.77               | 0.36    |
| Posterior cingulate              | 0.95 ± 0.73               | 0.82 ± 0.57               | 0.14    |
| Uncus                            | 1.59 ± 1.16               | 1.54 ± 0.90               | 0.69    |
multivariate forward stepwise regression analysis to identify independent predictors of probable DLB. Next, we constructed a predictive index, designated the combined index, by modeling the values of the independent variables and their coefficients of regression. The diagnostic value of the combined index was assessed by calculating the area under the receiver operating characteristic (ROC) curve for both patient groups. Diagnostic accuracy was evaluated by calculating sensitivity, specificity, positive and negative predictive value (PPV, NPV), and accuracy. The cut-off value of each index was based on the ROC curve to show the highest accuracy for the differentiation between probable and without DLB. The diagnostic accuracy of this index was then tested in validation group. Statistical analysis was with Stat View version 15.0 (SAS Institute Inc., Cary, NC, USA).

Using the cut-off values of the independent predictors obtained from estimation group analysis, we categorized validation group and created a decision tree to evaluate the diagnostic probability of probable and without DLB.

Results

Combined index

As shown in Table 3, the results of univariate analysis identified 10 variables as statistically significant ($p < 0.05$). Subsequent multivariate forward stepwise regression analysis indicated that 3, the patient age, early H/M ratio, and parietal lobe hypo-perfusion, were independent predictors of probable DLB. Our formula for calculating the combined index for estimation group was:

$$-4.72 - 2.48 \times \text{early H/M} + 1.07 \times \text{parietal lobe hypo-perfusion} + 0.10 \times \text{age}$$

Diagnostic performance of the combined index

Estimation group

Significant variables of the combined index with respect to the diagnosis of probable DLB were the area under the ROC curve (AUC, 0.91), the early H/M ratio (0.87, $p < 0.05$), the parietal lobe hypoperfusion score (0.75, $p < 0.01$), and the patient age (0.63, $p < 0.001$). Table 4 presents the sensitivity (80 %), specificity (92 %), the PPV (82 %), NPV (91 %), and accuracy (88 %) at the selected cut-off values of these 4 indices and shows that the combined index yielded high diagnostic performance for probable DLB.

Validation group

The AUC of the combined index, the early H/M ratio, the parietal lobe hypoperfusion score, and the age were

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|}
\hline
Variables & Univariate analysis & Multivariate analysis & \\
\hline
 & Probable DLB & Without DLB & $p$ value & \\
 & $(n = 46)$ & $(n = 106)$ & & \\
\hline
Age & 76.8 ± 6.3 & 72.5 ± 9.0 & $<0.001$ & $<0.01$ \\
Gender (male:female) & 22:32 & 42:72 & 0.37 & \\
Diabetes mellitus & 7 & 22 & 0.425 & \\
ACE inhibitor or β blocker & 2 & 4 & 0.867 & \\
Autonomic neuropathy symptoms & & & & \\
Autonomic dysfunction test & 8 ($n = 14$) & 15 ($n = 34$) & 0.412 & \\
Early H/M ratio & 1.82 ± 0.63 & 2.85 ± 0.67 & $<0.001$ & $<0.01$ \\
Delay H/M ratio & 1.62 ± 0.80 & 2.87 ± 0.94 & $<0.001$ & 0.58 \\
Washout rate (%) & 49.6 ± 15.4 & 35.2 ± 16.0 & $<0.001$ & 0.56 \\
Frontal lobe & 1.95 ± 0.98 & 1.63 ± 0.73 & $<0.05$ & 0.41 \\
Parietal lobe & 2.29 ± 0.70 & 1.66 ± 0.79 & $<0.001$ & $<0.01$ \\
Temporal lobe & 2.08 ± 0.67 & 1.74 ± 1.06 & $<0.05$ & 0.68 \\
Occipital lobe & 1.16 ± 0.84 & 0.92 ± 0.86 & 0.11 & \\
Parietal central gyrus & 1.47 ± 0.56 & 1.32 ± 0.60 & 0.14 & \\
Postcentral gyrus & 1.78 ± 0.79 & 1.49 ± 0.70 & $<0.05$ & 0.33 \\
Precuneus & 1.51 ± 0.99 & 0.98 ± 0.78 & $<0.001$ & 0.16 \\
Parahippocampus & 1.56 ± 1.50 & 1.65 ± 1.39 & 0.74 & \\
Anterior cingulate & 1.65 ± 0.77 & 1.47 ± 0.78 & 0.19 & \\
Posterior cingulate & 1.14 ± 0.94 & 0.86 ± 0.59 & $<0.05$ & 0.89 \\
Uncus & 1.55 ± 1.05 & 1.60 ± 1.21 & 0.79 & \\
\hline
\end{tabular}
\end{table}
Diagnostic accuracy of each index in validation group

Box plots of the combined index, the early H/M ratio, the parietal lobe hypoperfusion score, and the age in patients with probable and without DLB are shown in Fig. 1. Patients with probable DLB tended to be older and their parietal lobe hypoperfusion score was higher. We observed considerable overlap in patients with probable and without
DLB. The early H/M ratio was significantly lower and the combined index was higher in patients with probable- than without DLB. Compared with the other indices, in the combined index, there was a relatively small overlap between estimation group and 2, indicating that it was the most useful index for the diagnosis of DLB.

Decision tree using independent predictors in validation group

Using the cut-off value of the 3 independent predictors of probable DLB (early H/M ratio, parietal lobe hypoperfusion score, age) calculated from estimation group, we categorized patients in validation group. The total number of patients with probable and without DLB and PPV is shown in Fig. 2 as is the number of patients with PD in each category.

Discussion

A differential diagnosis of dementia can be difficult in the early stage as there is considerable overlap in the clinical features of different types of the disease. However, objective and accurate information regarding vital functions can be obtained with $^{123}$I-IMP brain perfusion SPECT and $^{123}$I-MIBG myocardial scintigraphy studies.

A decrease in the H/M ratio on $^{123}$I-MIBG myocardial scintigraphy images was reported as an independent predictor of DLB [10, 17–19] and is included in the current guidelines to diagnose DLB. Yoshita et al. [19] found that at a cut-off value of 1.68, the H/M ratio was 100 % sensitive and specific for the differentiation between DLB and AD. Estorch et al. [20] reported that at a cut-off value of 1.36, this ratio could distinguish between DLB and other dementias; the sensitivity and specificity were 94 and 96 %, respectively. However, similar finding was obtained in PD patients. We found that the diagnostic performance of the early H/M ratio was relatively low (sensitivity 83 %, specificity of 85 %), probably because our patients with without DLB included 11 PD patients. The PD patients were individuals who presented with symptoms of dementia in the course of this study; based on the 1-year rule [21], they were diagnosed as having dementia with PD (PDD).

The differentiation between DLB and PDD is difficult and both dementias are thought to belong in the spectrum of Lewy body disease (LBD). From a pathological perspective, the deposition of phosphorylated $\alpha$-synuclein aggregates in the substantia nigra and the corresponding selective damage to the dopamine system are severe in PDD. On the other hand, as cerebral lesions are thought to be characteristic in DLB, the pathogenic mechanisms...
involved in DLB and PDD are slightly different [22]. According to Lippa et al. [23], it is appropriate to distinguish between DLB and PDD based on their different clinical symptoms and rate of progression. Therefore, we assigned PD patients to the without-DLB group. This may explain why the performance of the H/M ratio on our $^{123}$I-MIBG myocardial scintigraphy images was not much better than in earlier reports. With respect to LBD that includes DLB and PDD, clinical techniques that closely study and directly detect the distribution and degree of the cerebral pathology are needed.

On brain perfusion SPECT, patients with DLB manifest occipital hypoperfusion, a diagnostic factor cited in the consensus guidelines [8]. However, SPECT findings do not differentiate between DLB and AD as their reported sensitivity ranges from only 65–74 % [9, 10, 17, 18]. Although occipital hypoperfusion has been reported to help in the differentiation between DLB and AD, its specific diagnostic value with respect to DLB and dementias other than AD has not been documented. We found that the average perfusion of the occipital lobe was decreased not only in patients with probable DLB (severity score 1.16 ± 0.84) but also in patients with without DLB who presented with VaD and other dementia types (severity score 0.92 ± 0.86). Thus, occipital hypoperfusion may not be a useful factor for the differentiation between probable and without DLB including not only AD but also other dementias. Among the $^{123}$I-IMP brain perfusion SPECT predictors in this study, multivariate forward stepwise regression analysis identified parietal lobe hypoperfusion as an independent predictor. Limiting the targeted diseases to DLB and AD as was done in earlier studies would not have identified parietal lobe hypoperfusion as an independent predictor. Although we cannot rule out the possibility that patients with dementing disorders other than AD were included in our study population, there are few diseases other than AD with a specific decrease in the flow of blood to the parietal lobe. Therefore, we propose that parietal lobe hypoperfusion is a useful indicator for diseases other than AD. We consider parietal lobe hypoperfusion to be of greater diagnostic value than occipital lobe hypoperfusion because of its higher incidence in patients with probable DLB.

We used both $^{123}$I-IMP brain perfusion SPECT and $^{123}$I-MIBG myocardial scintigraphy to obtain a differential diagnosis of DLB among various dementing disorders. Although the usefulness and diagnostic performance of these imaging modalities have been evaluated individually, there are only two published studies that combined both modalities. Han Yu et al. [9] who compared the clinical value of brain perfusion SPECT and MIBG myocardial scintigraphy in DLB and AD patients reported that the H/M ratio was decreased in all 19 of their DLB patients; only 14 manifested occipital hypoperfusion. They concluded that MIBG myocardial scintigraphy may be a powerful diagnostic tool when a differential diagnosis of DLB or AD based on brain perfusion SPECT findings is difficult. Tateno et al. [10] found that 24 of 25 patients with dementia manifested a decreased cardiac MIBG uptake on delayed images (obtained 3 h post-injection); they observed occipital hypoperfusion in only 17 patients (68 %).

To surmount the limitations of $^{123}$I-MIBG cardiac scintigraphy and $^{123}$I-IMP brain perfusion SPECT, we developed a formula to calculate the combined index for the differentiation of probable DLB from without DLB. We used the combined index, calculated by combining the values obtained in estimation group for the early H/M ratio, the parietal lobe hypoperfusion score, and the age to predict DLB. We then assessed its diagnostic value in validation group. We document that the combined index was more accurate for diagnosing probable DLB at an AUC of 0.94 than the early H/M ratio (0.90), the parietal lobe hypoperfusion score (0.69), or the patient age (0.72).

As shown in Fig. 2, when evaluated with $^{123}$I-MIBG cardiac scintigraphy alone, the PPV for a diagnosis of probable DLB was 70 % in patients with an early H/M ratio ≤2.2. On the other hand, when we included the parietal lobe hypoperfusion score obtained on $^{123}$I-IMP brain perfusion SPECT images, the PPV rose to 90 %. The PPV for probable DLB increased from 5 to 15 % when we included the parietal lobe hypoperfusion score in patients with an early H/M ratio ≥2.2. Although the differentiation between PD and DLB is difficult based on MIBG scintigraphy findings alone, a correct diagnosis can be obtained when brain perfusion SPECT images show parietal lobe hypoperfusion since PD patients manifest a non-specific pattern of decreased cerebral blood flow. In fact, as shown in Fig. 2, of the 11 PD patients, we identified 7 (64 %) as without DLB when we used 1.85 as the cut-off value for parietal lobe hypoperfusion.

On the other hand, despite their decreased early H/M ratio, 4 patients with probable DLB (15 %) did not present with parietal lobe hypoperfusion on $^{123}$I-IMP brain perfusion SPECT images. We attribute this to pure autonomic failure (LBD-P: Lewy body disease parkinsonism) due to autonomic neuropathy as the main condition. There were 3 patients with probable DLB (12 %) who manifested parietal lobe hypoperfusion although $^{123}$I-MIBG cardiac scintigraphy showed no abnormality. We think that in these patients cognitive impairment resulted in a diagnosis of Lewy body disease dementia (LBD-D) and that treatment reversed their autonomic dysfunction. In patients with probable DLB, factors such as parkinsonism, cognitive impairment, and autonomic neuropathy, and their main symptoms may result in different findings on $^{123}$I-MIBG cardiac scintigraphy and $^{123}$I-IMP brain perfusion SPECT images.
123I-MIBG cardiac scintigraphy and 123I-IMP brain perfusion SPECT can yield false-positive as well as false-negative results in patients with diabetes mellitus, heart failure, and in patients taking medications (scintigraphy) and in patients with cerebral vascular disorders and atrophy (SPECT). To compensate for these shortcomings, we recommend the acquisition of both 123I-MIBG cardiac scintigraphy- and 123I-IMP brain perfusion SPECT studies.

We attribute the high diagnostic performance in our study in part to the superiority of 123I-IMP brain perfusion SPECT for the discrimination between DLB and PD and to the superior performance of 123I-MIBG cardiac scintigraphy in the discrimination between DLB and AD.

**Limitations**

Our study has some limitations. First, the diagnoses were not confirmed by autopsy but based on the careful interpretation of clinical and imaging findings. While we are carrying out follow-up imaging studies, postmortem findings are needed to confirm the presence of pathological changes in abnormally perfused areas. Second, in patients treated for autonomic dysfunction, the results of 123I-MIBG cardiac scintigraphy may fluctuate. We encountered 3 patients with probable DLB (12 %) in whom 123I-MIBG cardiac scintigraphy showed no abnormality; however, we did not have pre- and post-treatment 123I-MIBG cardiac scintigraphy studies to evaluate the potential effects of treatment. Third, although 123I-MIBG cardiac scintigraphy indicates autonomic dysfunction that is likely in DLB and PD, it is necessary to verify that it is superior to far less expensive clinical tests. In our retrospective study, the results of autonomic function tests were not useful for a differential diagnosis of probable and without DLB. Since not all patients had undergone these tests prior to their treatment, the number of evaluable patients was limited, and accurate comparisons were not possible.

Finally, the use of both 123I-MIBG cardiac scintigraphy and 123I-IMP brain perfusion SPECT raises economic and radiation exposure concerns. Either test can yield a positive result in the early stages of DLB as there are various pathogenic forms, and false-positive and false-negative results are shown by scintigraphy. Therefore, we recommend the combination of both imaging modalities to improve diagnostic performance at least in patients whose conventional tests lead to the suspicion of DLB.

**Conclusion**

DLB has been reported to be the second most common type of degenerative dementia. However, it is often under-diagnosed and its discrimination from other types of dementia is very difficult, especially at its early stages. Since DLB results in specific impairments and functional disabilities, its early and accurate diagnosis is very important for a better prognosis and neuroimaging- and MIBG myocardial scintigraphy studies play important roles. Further research is needed to establish their clinical usefulness.

**References**

1. McKeith I, Mintzer J, Aarsland D, Burn D, Chiu H, Cohen-Mansfield J, et al. Dementia with Lewy bodies. Lancet Neurol. 2004;3(1):19–28.
2. Burgio L. Interventions for the behavioral complications of Alzheimer’s disease: behavioral approaches. Int Psychogeriatr. 1996;8(Suppl 1):45–52.
3. Kaufer DI, Cummings JL, Christine D, Bray T, Castellon S, Masterman D, et al. Assessing the impact of neuropsychiatric symptoms in Alzheimer’s disease: the Neuropsychiatric Inventory Caregiver Distress Scale. J Am Geriatr Soc. 1998;46(2):210–5.
4. Luis CA, Barker WW, Gagarai K, Harwood D, Petersen R, Kashuba A, et al. Sensitivity and specificity of three clinical criteria for dementia with Lewy bodies in an autopsy-verified sample. Int J Geriatr Psychiatry. 1999;14(7):526–33.
5. McKeith IG, Ballard CG, Perry RH, Ince PG, O’Brien JT, Neill D, et al. Prospective validation of consensus criteria for the diagnosis of dementia with Lewy bodies. Neurology. 2000;54(5):1050–8.
6. Holmes C, Cairns N, Lants P, Mann A. Validity of current clinical criteria for Alzheimer’s disease, vascular dementia and dementia with Lewy bodies. Br J Psychiatry. 1999;174:45–50.
7. Mega MS, Masterman DL, Benson DF, Vinters HV, Tomiyasu U, Craig AH, et al. Dementia with Lewy bodies: reliability and validity of clinical and pathologic criteria. Neurology. 1996;47(6):1403–9.
8. Firbank MJ, Burn DJ, McKeith IG, O’Brien JT, Longitudinal study of cerebral blood flow SPECT in Parkinson’s disease with dementia, and dementia with Lewy bodies. Int J Geriatr Psychiatry. 2005;20(8):776–82.
9. Hanyu H, Shimizu S, Hirao K, Kanetaka H, Iwamoto T, Chikamori T, et al. Comparative value of brain perfusion SPECT and [(123)I]MIBG myocardial scintigraphy in distinguishing between dementia with Lewy bodies and Alzheimer’s disease. Eur J Nucl Med Mol Imaging. 2006;33(3):248–53.
10. Tateno M, Kobayashi S, Shirasaka T, Furukawa Y, Fuji K, Mori H, et al. Comparison of the usefulness of brain perfusion SPECT and MIBG myocardial scintigraphy for the diagnosis of dementia with Lewy bodies. Dement Geriatr Cogn Disord. 2008;26(5):453–7.
11. McKeith IG. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the Consortium on DLB International Workshop. J Alzheimers Dis. 2006;9(3 Suppl):417–23.
12. Hattori N, Schwaiger M. Metaiodobenzylguanidine scintigraphy of the heart: what have we learnt clinically? Eur J Nucl Med. 2000;27(1):1–6.
13. Minoshima S, Berger KL, Lee KS, Mintun MA. An automated method for rotational correction and centering of three-dimensional functional brain images. J Nucl Med. 1992;33(8):1579–85.
14. Minoshima S, Frey KA, Koepp RA, Foster NL, Kuhl DE. A diagnostic approach in Alzheimer’s disease using three-dimensional stereotactic surface projections of fluorine-18-FDG PET. J Nucl Med. 1995;36(7):1238–48.

15. Mizumura S, Kumita S, Cho K, Ishihara M, Nakajo H, Toba M, et al. Development of quantitative analysis method for stereotactic brain image: assessment of reduced accumulation in extent and severity using anatomical segmentation. Ann Nucl Med. 2003;17(4):289–95.

16. Horimoto Y, Matsumoto M, Akatsu H, Ikari H, Kojima K, Yamamoto T, et al. Autonomic dysfunctions in dementia with Lewy bodies. J Neurol. 2003;250(5):530–3.

17. Lobotesis K, Fenwick JD, Phipps A, Ryman A, Swann A, Ballard C, et al. Occipital hypoperfusion on SPECT in dementia with Lewy bodies but not AD. Neurology. 2001;56(5):643–9.

18. Pasquier J, Michel BF, Brenot-Rossi I, Hassan-Sebbag N, Sauvan R, Gastaut JL. Value of (99m)Tc-ECD SPET for the diagnosis of dementia with Lewy bodies. Eur J Nucl Med Mol Imaging. 2002;29(10):1342–8.

19. Yoshita M, Taki J, Yamada M. A clinical role for [(123)I]MIBG myocardial scintigraphy in the distinction between dementia of the Alzheimer’s-type and dementia with Lewy bodies. J Neurol Neurosurg Psychiatry. 2001;71(5):583–8.

20. Estorch M, Camacho V, Paredes P, Rivera E, Rodriguez-Revuelto A, Flotats A, et al. Cardiac (123)I-metaiodobenzylguanidine imaging allows early identification of dementia with Lewy bodies during life. Eur J Nucl Med Mol Imaging. 2008;35(9):1636–41.

21. McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology. 1996;47(5):1113–24.

22. Orimo S, Takahashi A, Uchihara T, Mori F, Kakita A, Wakabayashi K, et al. Degeneration of cardiac sympathetic nerve begins in the early disease process of Parkinson’s disease. Brain Pathol. 2007;17(1):24–30.

23. Lippa CF, Duda JE, Grossman M, Hurtig HI, Aarsland D, Boeve BF, et al. DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers. Neurology. 2007;68(11):812–9.