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Diagnostic Sensitivity and Symptomatic Relevance of Dopamine Transporter Imaging and Myocardial Sympathetic Scintigraphy in Patients with Dementia with Lewy Bodies

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Abstract.
Background: Dementia with Lewy bodies (DLB) presents with various symptoms, posing challenges for early diagnosis challenging. Dopamine transporter (^{123}I-FP-CIT) single-photon emission tomography (SPECT) and ^{123}I-meta-iodobenzylguanidine (^{123}I-MIBG) imaging are crucial diagnostic biomarkers. Hypothesis about body- and brain-first subtypes of DLB indicate that some DLB may show normal ^{123}I-FP-CIT or ^{123}I-MIBG results; but the characteristic expression of these two subtypes remains unclear.
Objective: This study aimed to evaluate the diagnostic sensitivity of ^{123}I-FP-CIT and ^{123}I-MIBG imaging alone, combined in patients with DLB and explore symptoms associated with the abnormal imaging results.
Methods: Demographic data, clinical status, and imaging results were retrospectively collected from patients diagnosed with possible DLB. Both images were quantified using semi-automated software, and the sensitivity of each imaging modality and their combination was calculated. Demographic data, cognition, and motor and non-motor symptoms were compared among the subgroups based on the imaging results. Symptoms related to each imaging abnormality were examined using binomial logistic regression analyses.
Results: Among 114 patients with DLB, 80 underwent ^{123}I-FP-CIT SPECT (sensitivity: 80.3%), 83 underwent ^{123}I-MIBG imaging (68.2%), and 66 both (sensitivity of either abnormal result: 93.9%). Visual hallucinations differed among the four subgroups based on imaging results. Additionally, nocturia and orthostatic hypotension differed between abnormal and normal ^{123}I-MIBG images.
Conclusions: Overall, ^{123}I-FP-CIT SPECT was slightly higher sensitivity than ^{123}I-MIBG imaging, with combined imaging increasing diagnostic sensitivity. Normal results of a single imaging test may not refute DLB. Autonomic symptoms may lead to abnormal ^{123}I-MIBG scintigraphy findings indicating body-first subtype of patients with DLB.

Keywords: Alzheimer's disease, dementia with Lewy bodies, dopamine transporter imaging, ^{123}I-meta-iodobenzylguanidine myocardial scintigraphy, sensitivity, SPECT

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INTRODUCTION

Dementia with Lewy bodies (DLB) is the second most common form of degenerative dementia after Alzheimer's disease (AD), accounting for 4.2% of all dementia [1]. The pathological feature of DLB is the presence of α-synuclein aggregates, which comprise Lewy bodies and neurites in the cytoplasm of neurons [2]. Symptomatically, DLB is a diverse disease that involves multiple cognitive domains and behavioral and neurological symptoms, including inattention, visuospatial dysfunction, executive dysfunction, hallucinations, Parkinsonism, cognitive fluctuations, rapid eye movement sleep behavior disorder (RBD), and dysautonomia [3]. DLB is a heterogeneous disease presenting with various combinations of symptoms and different severity [4]. The frequency of clinical diagnosis of DLB varies between reports and the prevalence is much lower than expected, which requires standardized diagnostic practice and a robust diagnostic biomarker [5]. The adequate use of dopamine transporter (DAT) imaging and ^{123}I-meta-iodobenzylguanidine (^{123}I-MIBG) scintigraphy supports the diagnosis of DLB [4].

^{123}I-2β-Carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl) nortropane (^{123}I-FP-CIT), or ^{123}I-ioflupan, a radioligand that binds to presynaptic DAT, is clinically used in single-photon emission tomography (SPECT) for diagnosing Parkinsonian syndrome and DLB. ^{123}I-FP-CIT imaging can serve as a clinical tool for detecting nigrostriatal dopaminergic pathway degeneration [6, 7]. Previous studies have demonstrated that ^{123}I-FP-CIT SPECT significantly improves the accuracy of DLB diagnosis and has higher diagnostic accuracy in differentiating patients with DLB from those without DLB [8–10].

In patients with DLB, Lewy bodies are widely distributed throughout the central and peripheral nervous systems, particularly in the sympathetic cardiac plexus [11, 12]. Therefore, ^{123}I-MIBG cardiac scintigraphy is a potential biomarker for DLB in clinical diagnosis and can detect early derangement of the sympathetic nervous system in DLB [13], which strengthens the diagnostic capacity to distinguish DLB from AD [14].

Quantitative evaluation of imaging modalities can reduce inter-observer discrepancies, enable inter- and intra-individual comparisons, and may further improve the diagnosis of DLB [15]. The striatal specific binding ratio (SBR) is a quantitative indicator of radioactive isotope uptake in the striatum relative to the extrastriatal brain region based on ^{123}I-FP-CIT SPECT images [16, 17]. Age-dependent decline in striatal ^{123}I-FP-CIT binding has been reported in human, primate, and rodent brain histochemical studies [18]. This decline led to the z-score transformation of SBR adjusted based on age [19]. This method is currently commercially available with the advent of the DAT VIEW software. The heart-to-mediastinum uptake ratios (HMR) based on early and delayed images and the cardiac washout rate (WR) are quantitative indicators calculated from the planar image of ^{123}I-MIBG scintigraphy [20, 21]. The WR reflects the release of the initial uptake of sympathetic nerve endings and is influenced by the reuptake and sympathetic nerve turnover rates [22]. The delayed-phase HMR represents sympathetic nerve functions, including distribution, density, and activity. HMR is calculated using the semiautomatic region-of-interest (ROI) setting software Smart MIBG [23]. This software also normalizes the HMR between different SPECT cameras and filters.

Practically, only one imaging was performed, leaving the efficacy of the combination unclear. Therefore, to evaluate the diagnostic utility of the ^{123}I-FP-CIT image and ^{123}I-MIBG scintigraphy in detecting DLB, the role of its combination as a diagnostic approach is of both clinical and pathophysiological interest. Emerging evidence suggests that α-synuclein likely propagates between cells in a prion-like manner [24]. In terms of the originating site of α-synuclein aggregation, two subtypes of DLB were hypothesized, namely, the "brain-first" (top-down) and "body-first" (bottom-up) types of DLB, where the abnormal ^{123}I-FP-CIT image and abnormal ^{123}I-MIBG scintigraphy may correspond to the "brain-first" and "body-first," respectively [25]. Horsager and colleagues explored *de novo* Parkinson's disease (PD) by multimodal imaging tests. They hypothesized that PD with RBD may show as a "body-first" subtype, resulting in lower cardiac ^{123}I-MIBG uptake and lower parasympathetic function demonstrated as dysfunction of the gastrointestinal system, compared to PD without RBD [26]. In this report, because of the diagnosis of PD, the neurodegeneration is at least involved in the nigrostriatal system (i.e., Braak stage 3 or above [27]), and showed that presynaptic dopamine imaging was not different between "brain-first" and "body-first" PD subtype. However, based on this assumption, the characteristic expression of the two subtypes in DLB, remains unclear.

This study aimed to calculate the sensitivity of the two imaging modalities in retrospectively col-

lected data from patients with DLB. Second, we used univariate and multivariate statistical approaches to investigate whether cognitive, motor, autonomic, sleep, and sensory symptoms accounted for the abnormal imaging results.

METHODS

Participants

The Institutional Review Board of the Chiba University Graduate School of Medicine approved this retrospective study. All participants received oral explanations of the study orally and by documents and provided written informed consent. All participants were recruited from the outpatient clinic of the Department of Neurology, Chiba University Hospital, which specializes in patients with movement disorders and dementias. The participants were included based on the fourth report of the DLB consortium criteria for possible DLB, which requires the presence of at least one core clinical feature irrespective of the imaging result [28]. The medical records of all patients were reviewed, and data on sex, age at onset, and disease duration from the onset of dementia symptoms were collected. Cognitive function was measured using the Mini-Mental State Examination (MMSE) [29]. The severity of Parkinsonism was examined using the Unified Parkinson's Disease Rating Scale (UPDRS) motor subscore [30]. A board-certified neurologist (SH) assessed non-motor symptoms using structured clinical interviews. Constipation according to the Rome III criteria [31], nocturia is defined as two or more urinations per night [32]. Orthostatic hypotension is defined as Q1-3 of the screening test for suspected neurogenic orthostatic hypotension [33], further confirmed through occasional systolic blood pressure < 100 mmHg. Anosmia is defined as reduced subjective olfactory function reconfirmation by the caregiver. Visual hallucinations are defined as seeing aberrant objects and/or people that do not exist. RBD is defined by single-question screening for RBD [34]. No participants were scanned while taking antidepressants which might interfere with the imaging results.

Nuclear imaging protocols

^{123}*I-FP-CIT SPECT*

Participants were scanned 3 h after the intravenous injection of 167 MBq ^{123}I-FP-CIT using an Infinia+Hawkeye4 (GE Healthcare, Milwaukee, WI, USA) equipped with an extended low-energy general-purpose (ELEGP) collimator. The projection data were acquired over 30 min. The data were reconstructed using the ordered subset expectation maximization method (iterations: 5, subsets: 10). Images were acquired in a 128×128 matrix of 2.95 mm thick axial slices under 4-degree step continuous rotation (8 rotations, 3 min each) and filtered with a Butterworth filter (cutoff frequency 0.5 cycles/cm, order 8) to reconstruct the image. Attenuation was corrected using Chang's technique (factor: 0.07). The striatal SBR was semi-quantitatively calculated based on Bolt's method using DAT VIEW software (version 6.1, AZE Ltd., Kanagawa, Japan) [35, 36], and the age-adjusted z-score was subsequently calculated using 250 normal Japanese databases incorporated in the software [19]. A striatal SBR age-adjusted z-score of less than –2.0 on either side was considered abnormal.

^{123}*I-MIBG myocardial scintigraphy*

Fifteen minutes (early) and 3.5 h (delayed) after intravenous injection of a dose of 111 MBq ^{123}I-MIBG [37], Infinia+Hawkeye4 (GE Healthcare, Milwaukee, WI, USA) equipped with ELEGP collimator was used to capture planar scintigraphy images in the front view. No attenuation or scatter corrections were performed. Standardization was performed using Smart MIBG software (version 3.1.1.0, PD Radiopharma Inc., Tokyo, Japan) and phantom experiments [23]. In the software algorithm, manually pointing to the center of the heart sets the heart ROI as a circle. Simultaneously, a rectangular ROI is determined in the upper mediastinum with a width of 10% of the body and a height of 30% of the mediastinum, which calculates the HMR [38]. To divide the count density of the left ventricular ROI by that of the mediastinal ROI, the HMR and WR were calculated using early and delayed planar images, respectively [39]. Based on a previous report, HMR in delayed images of <2.2 and/or WR > 35% was defined as abnormal [40].

Statistical analysis

The normality of the variables was evaluated using the Kolmogorov–Smirnov test. Categorical and continuous data were compared using the chi-square and Kruskal–Wallis tests, respectively. Subsequently, *post hoc* analyses were performed using the Mann–Whitney *U* test to investigate group

differences in demographic values. To assess the clinical significance of ^{123}I-FP-CIT SPECT and ^{123}I-MIBG image abnormalities, binominal logistic regression tests were conducted using imaging modalities with imaging results (normal/abnormal) as dependent variables, and non-motor symptoms, MMSE total score, and UPDRS part III score as independent variables. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA).

The demographic data of patients with DLB who underwent two imaging procedures were classified into four subgroups as follows: abnormal images, ^{123}I-FP-CIT SPECT normal with ^{123}I-MIBG image abnormal ($DLB^{FP-CIT-MIBG+}$), ^{123}I-FP-CIT SPECT abnormal with ^{123}I-MIBG image normal ($DLB^{FP-CIT+MIBG-}$), and both normal images. The four subgroups were compared using the chi-square test for sex and clinical symptoms. Differences in age at onset, UPDRS part III score, and MMSE total score among the four patient subgroups were analyzed using the Kruskal–Wallis test. The statistical significance threshold of each test was set at $p < 0.05$.

RESULTS

The number of core symptoms, number of imaging procedures and their results, as well as the disposition of the patients with DLB are shown in Fig. 1. Overall, 114 patients with DLB were included in this study. Twenty-one patients with DLB had one core clinical feature, including 15 abnormal results of the 19 ^{123}I-FP-CIT SPECT and 15 abnormal results of the 21 ^{123}I-MIBG images. Ninety-three patients with DLB had two or more core clinical features, including 49 abnormal results of the 61 ^{123}I-FP-CIT SPECT performed and 41 abnormal results of the 62 ^{123}I-MIBG images. Seventeen patients with DLB did not undergo an examination of either image.

Table 1 summarizes the demographic and clinical data of the 114 patients in the entire DLB group, a subgroup of individuals with DLB who underwent ^{123}I-FP-CIT SPECT ($n = 80$) and ^{123}I-MIBG scintigraphy ($n = 83$). In all 114 patients with DLB, the mean age at onset was 74.9 years (standard deviation [SD] = 6.5), slightly predominant in males (58.8%), the mean MMSE total score was 21.4 (SD = 5.6), and the mean UPDRS motor subscore was 19.0 (SD = 16.0). The core clinical symptoms of the 114 patients with DLB were most commonly observed in Parkinsonism (83.3%), followed by cognitive fluctuation (64.0%), visual hallucinations (56.1%), and least frequently in RBD (40.4%). Of the 80 patients who underwent ^{123}I-FP-CIT SPECT, 64 showed abnormal results with a sensitivity of 80.0%. Of the 83 who underwent ^{123}I-MIBG scintigraphy, 56 patients had abnormal results with a sensitivity of 67.5%. The prevalence of core clinical symptoms, MMSE score, and motor severity did not differ between normal and abnormal imaging results on ^{123}I-FP-CIT SPECT or ^{123}I-MIBG scintigraphy.

Non-motor symptoms (autonomic symptoms [constipation, nocturia, and orthostatic hypotension], anosmia, RBD, visual hallucination, and MMSE) and motor symptoms (UPDRS part III) were incorporated into a statistical model to examine which factors predicted the imaging abnormality. On ^{123}I-FP-CIT SPECT, no symptomatic differences were found between patients with DLB with abnormal and normal results (Table 2, left). Between abnormal and normal ^{123}I-MIBG image findings in patients with DLB, differences were observed in nocturia (odds ratio = 0.160, 95% confidence interval: 0.042–0.606, $p = 0.007$) and orthostatic hypotension (odds ratio = 0.165, 95% confidence interval: 0.031–0.879, $p = 0.035$) (Table 2, right).

In the subset of 66 patients with DLB who underwent both ^{123}I-FP-CIT SPECT and ^{123}I-MIBG image, no differences were observed in age at onset, sex, MMSE, or UPDRS between the four subgroups classified based on imaging results, except for visual hallucinations ($p = 0.006$) (Table 3). The 17 $DLB^{FP-CIT+MIBG-}$ and 9 $DLB^{FP-CIT-MIBG+}$ subgroups were specifically compared; however, no demographic differences were observed ($p > 0.1$). Regarding sensitivity, in 66 patients with DLB who underwent two scans, 53 (80.3%) and 45 (68.2%) had abnormal ^{123}I-FP-CIT SPECT and ^{123}I-MIBG images, respectively; the 53 (80.3%) patients who had abnormal ^{123}I-FP-CIT SPECT exhibited higher sensitivity. The combination of ^{123}I-FP-CIT SPECT and ^{123}I-MIBG images, at least one of the images being abnormal, has a sensitivity of 93.9%.

DISCUSSION

This study presents the demographic and clinical data of clinically diagnosed patients with DLB, as well as the sensitivity of ^{123}I-FP-CIT SPECT and ^{123}I-MIBG scintigraphy and their relationship with the symptoms. In DLB, the sensitivity of ^{123}I-FP-CIT SPECT and ^{123}I-MIBG scintigraphy was 80.0%

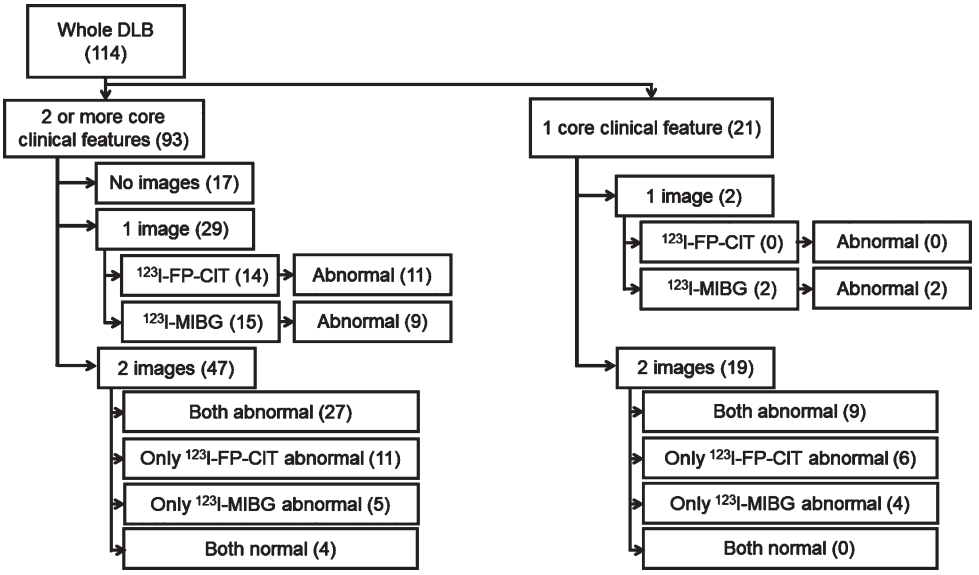

Fig. 1. Imaging assessments and their results: disposition of patients with dementia with Lewy bodies.

Table 1
Demographic and clinical data of the patients with dementia with Lewy bodies (DLB) of whole group and subgroup who underwent dopamine transporter (^{123}I-FP-CIT) image and ^{123}I-meta-iodobenzylguanidine (^{123}I-MIBG) myocardial scintigraphy

	Whole DLB group ($n=114$)	Patients with DLB who underwent ^{123}I-FP-CIT SPECT ($n=80$)		Patients with DLB who underwent ^{123}I-MIBG scintigraphy ($n=83$)	
		^{123}I-FP-CIT abnormal ($n=64$)	^{123}I-FP-CIT normal ($n=16$)	^{123}I-MIBG abnormal ($n=56$)	^{123}I-MIBG normal ($n=27$)
Age at onset (y)	74.9 ± 6.5	74.2 ± 7.1	75.4 ± 5.7	74.5 ± 7.1	73.9 ± 6.6
Sex, female:male	47 : 67	28 : 36	5 : 11	18 : 38	14 : 13
Disease duration (y)	2.2 ± 1.9	1.8 ± 1.8	2.6 ± 2.1	2.2 ± 1.8	2.1 ± 2.3
MMSE	21.4 ± 5.6	22.2 ± 4.5	21.9 ± 7.1	21.9 ± 5.0	20.2 ± 6.9
UPDRS motor subscore	19.0 ± 16.0	17.0 ± 14.8	12.9 ± 10.9	15.3 ± 13.5	16.2 ± 12.7
Cognitive fluctuation, *n* (%)	73 (64.0%)	36 (56.3%)	8 (50.0%)	35 (62.5%)	14 (51.9%)
Parkinsonism, *n* (%)	95 (83.3%)	54 (84.4%)	12 (75.0%)	42(75.0%)	23 (85.2%)
Visual hallucination, *n* (%)	64 (56.1%)	34 (53.1%)	8 (50.0%)	28 (50.0%)	14 (51.9%)
RBD, *n* (%)	46 (40.4%)	26 (40.6%)	7 (43.8%)	23 (41.1%)	7 (25.9%)

Continuous variables are presented as mean ± SD. The two groups were compared using the Mann–Whitney *U* and chi-square tests for continuous and categorical variables, respectively. MMSE, Mini-Mental State Examination; RBD, rapid eye movement behavior disorder; SPECT, single photon emission computed tomography; UPDRS, Unified Parkinson's Disease Rating Scale; SD, standard deviation.

and 67.5%, respectively, and 93.9% when at least one of the images was abnormal by combination. The presence of visual hallucinations differed among the four imaging-based DLB subgroups. Nocturia and orthostatic hypotension are associated with abnormal ^{123}I-MIBG imaging results.

A previous study reported that abnormal DAT images have a sensitivity of 88.8% for detecting clinically probable DLB from AD [41]. However, DAT imaging does not distinguish DLB from other Parkinsonian syndromes [42]. In a meta-analysis, the sensitivity of DAT imaging in clinically diagnosed patients with DLB was 97% (95% confidence interval: 78–100%) [43]. The relatively low sensitivity observed in this study may have resulted from including various patients, the early disease stage examination. A subset of patients has been reported to initially have a normal ^{123}I-FP-CIT SPECT scan, which later converts to abnormal in the follow-up ^{123}I-FP-CIT SPECT scan, indicating that abnormal-

Table 2
The statistical results of the symptomatic predictor of imaging abnormality in 66 patients with dementia with Lewy bodies

	Abnormal ^{123}I-FP-CIT image				Abnormal ^{123}I-MIBG scintigraphy			
	p	Odds ratio	95% CI for odds ratio		*p*	Odds ratio	95% CI for odds ratio	
			Lower	Upper			Lower	Upper
Constipation	0.881	0.905	0.244	3.352	0.339	0.504	0.123	2.056
Nocturia	0.495	0.647	0.185	2.264	0.007*	0.160	0.042	0.606
OH	0.592	1.426	0.390	5.215	0.035*	0.165	0.031	0.879
Anosmia	0.313	0.521	0.147	1.849	0.875	1.118	0.276	4.529
RBD	0.732	1.242	0.359	4.294	0.358	0.539	0.114	2.011
VH	0.562	0.692	0.199	2.402	0.750	1.239	0.332	4.628
MMSE	0.845	1.013	0.893	1.148	0.966	0.998	0.900	1.106
UPDRS	0.536	1.016	0.966	1.069	0.330	0.975	0.928	1.026

Binomial regression analysis results of 83 and 80 patients with dementia and Lewy bodies in dopamine transporter (left) and ^{123}I-meta-iodobenzylguanidine (right) images, respectively. *$p < 0.05$ OH, orthostatic hypotension; RBD, rapid eye movement behavior disorder; VH, visual hallucinations; MMSE, Mini-Mental State Examination; UPDRS, Unified Parkinson's Disease Rating Scale; CI, confidence interval.

Table 3
Demographic and clinical data of the 66 patients with dementia with Lewy bodies (DLB) who underwent both dopamine transporter (^{123}I-FP-CIT) and myocardial sympathetic imaging and four subgroups classified based on the imaging results

	DLB who underwent both ^{123}I-FP-CIT and ^{123}I-MIBG ($n = 66$)	^{123}I-FP-CIT (abnormal) ^{123}I-MIBG (abnormal) ($n = 36$)	^{123}I-FP-CIT (abnormal) ^{123}I-MIBG (normal) ($n = 17$)	^{123}I-FP-CIT (normal) ^{123}I-MIBG (abnormal) ($n = 9$)	^{123}I-FP-CIT (normal) ^{123}I-MIBG (normal) ($n = 4$)	*p*
Age at onset (y)	74.1 ± 7.1	73.8 ± 7.4	73.5 ± 8.0	76.9 ± 5.8	73.3 ± 2.6	0.695
Sex, female:male	25;41	13 : 23	8 : 9	1 : 8	3 : 1	0.125
Disease duration (y)	2.0 ± 1.9	1.7 ± 1.6	3.1 ± 2.2	2.3 ± 2.3	0.67 ± 0.90	0.097
MMSE	21.7 ± 4.8	21.9 ± 4.7	21.8 ± 4.4	22.6 ± 5.0	19.8 ± 9.6	0.971
UPDRS motor sub-score	14.9 ± 12.8	16.2 ± 13.9	14.3 ± 12.1	10.9 ± 8.6	18.8 ± 14.4	0.683
Cognitive fluctuation, *n* (%)	33 (50.0%)	20 (55.6%)	7 (41.2%)	3 (33.3%)	3 (75.0%)	0.396
Parkinsonism, *n* (%)	53 (80.3%)	28 (77.8%)	15 (88.2%)	7 (77.8%)	3 (75.0%)	0.929
Visual hallucination, *n* (%)	31 (47.0%)	21 (58.3%)	4(23.5%)	2 (22.2%)	4 (100.0%)	0.006*
RBD, *n* (%)	23 (34.9%)	14 (48.9%)	5 (29.4%)	3 (33.3%)	1 (25.0%)	0.883
Constipation, *n* (%)	41 (62.1%)	25 (69.4%)	8 (47.1%)	5 (55.6%)	3 (75.0%)	0.406
Nocturia, *n* (%)	34 (51.5%)	23 (63.9%)	4 (23.5%)	5 (55.6%)	2 (50.0%)	0.055
Orthostatic hypotension, *n* (%)	17 (25.8%)	13 (36.1%)	1 (5.9%)	3 (33.3%)	0 (0.0%)	0.066
Anosmia, *n* (%)	38 (57.6%)	24 (66.7%)	8 (47.1%)	4 (44.4%)	2 (50.0%)	0.437

Continuous variables are presented as mean ± SD. Four groups were compared using the Kruskal–Wallis one-way analysis of variance; the post hoc test was conducted using the Mann–Whitney *U* test, adjusted for multiple comparisons for continuous variables, and the chi-square test for categorical variables. *$p < 0.05$. MMSE, Mini-Mental State Examination; RBD, rapid eye movement behavior disorder; UPDRS, Unified Parkinson's Disease Rating Scale; SD, standard deviation.

ity rates may differ based on disease stage [44]. Abnormal DAT imaging is a prerequisite for diagnosing PD, whereas normal ^{123}I-FP-CIT SPECT findings in patients with DLB do not refute the diagnosis of DLB [45].

No association was found among cognitive impairment, core clinical features (including Parkinsonism), and abnormal DAT. DLB has various clinical presentations that differ between cohorts, particularly in the early or prodromal stages of the disease [46]. The lack of a difference in Parkinsonism between abnormal and normal ^{123}I-FP-CIT SPECT was unexpected, as lower striatal DAT binding may reflect more pronounced Parkinsonism of DLB, as demonstrated in previous studies [47, 48]. However, some studies have failed to identify an association between the severity of Parkinsonism and striatal ^{123}I-FP-CIT uptake in patients with DLB, which is consistent with the results of this study [41, 49, 50]. These results demonstrate that even patients with DLB and normal ^{123}I-FP-CIT images may present with Parkinsonism (Table 1). This result demonstrates that the Parkinsonism observed in patients with DLB is somewhat different from that in those with PD, with DLB deficits extending outside of the nigrostriatal system. These differences may be consistent with the dif-

ference in levodopa responsiveness between patients with PD and DLB [51]. Although some studies have demonstrated a relationship between executive dysfunction and striatal DAT binding [47], others have shown no correlation between cognitive function and striatal DAT uptake in patients with DLB [48]. These results indicate that specific cognitive domains, such as executive function, rather than general cognitive function, as well as specific striatal regions, may account for dopaminergic dysfunction in DLB [52]. Cognitive dysfunction in DLB may be multifactorial, including dopaminergic and cholinergic dysfunctions [52]. A previous study showed a significant correlation between reduced DAT uptake in the striatum and visual hallucinations [50]. The degree of visual hallucinations and their presence may differ in pathophysiology; the degree of visual hallucinations may be associated with the striatal dopaminergic system. Another previous study reported that the PD-with-RBD group had more severe striatal dopamine dysfunction than the PD-without-RBD group [53]; however, this was not replicated in this study. To the best of our knowledge, no study has found a correlation between striatal function and cognitive fluctuations, consistent with these results. Most core and non-motor symptoms were examined by asking both patients and caregivers of DLB. In contrast, MMSE and UPDRS were performed only on patients with DLB, which may be influenced by cognitive fluctuation and may vary between the time of examination and scan, leading to no correlation for these scores.

A recent meta-analysis found that the sensitivity of delayed-phase ^{123}I-MIBG image in diagnosing clinical DLB was 93% (95% confidence interval: 81–98%) [43]. Autopsy-confirmed DLB revealed that the sensitivity for delayed HMR of ^{123}I-MIBG scintigraphy was 80.0% (95% confidence interval; 61.4–92.3%) [54]. The sensitivity was slightly lower, possibly resulting from a large number of participants with various initial symptoms. However, it also indicates that DLB can show normal ^{123}I-MIBG image results and normal results may be insufficient to exclude the diagnosis of DLB. A previous neuropathological study reported that DLB with concomitant AD pathology shows relatively preserved cardiac sympathetic function [55], which may account for the lower sensitivity depending on the recruited cohort, where most patients were enrolled from a dementia outpatient clinic.

Similar to the ^{123}I-FP-CIT images, no correlation was observed between ^{123}I-MIBG image results and cognitive impairment, cognitive fluctuation, Parkinsonism, hallucinations, or RBD, which is consistent with a previous report [56]. A previous study showed that the delayed image HMR in the PD-without-RBD group was higher than that in the PD-with-RBD [26], although the situation may differ between PD and DLB. Cardiac autonomic nervous system failure caused by the degeneration of postganglionic sympathetic neurons is also a common feature of DLB [57]. In this study, orthostatic hypotension was associated with abnormal ^{123}I-MIBG image findings. Previous studies have also demonstrated that the average delayed HMR of patients in the DLB group was lower than that of healthy individuals and those in the PD group, corresponding to the high incidence of orthostatic hypotension in the DLB group [58, 59]. To the best of our knowledge, this is the first study to report the relationship between urinary frequency and lower ^{123}I-MIBG HMR in patients with DLB. A hypothesis has been proposed that in the early stages of PD, two different types of neuronal degeneration occur as follows: the dopamine system degenerates first ("brain-first"), and the peripheral autonomic nervous system degenerates first ("body-first") [26]. The orthostatic hypotension and the urinary frequency may be the symptoms of the "body-first" DLB subtype [60, 61]. Although this result did not show any clinical characteristics in 9 patients with DLB$^{FP-CIT-MIBG+}$, it may have resulted from the small number of this specific subgroup. A study has proposed the hypothesis that patients with DLB may be more likely to align with the "body-first" subtype [62].

Regarding the sensitivity of the two detection methods, the sensitivity of ^{123}I-FP-CIT SPECT (80.3%) was slightly higher than that of the ^{123}I-MIBG image (68.2%). However, this does not indicate the superiority or inferiority of the test. When first scanned ^{123}I-FP-CIT SPECT were normal, 69.2% (9/13) were abnormal in ^{123}I-MIBG image and first scanned ^{123}I-MIBG image were normal, 81.0% (17/21) had abnormal ^{123}I-FP-CIT image, both of which helped overlooking the diagnosis of DLB by performing two imaging tests. Both tests should be performed, depending on the likelihood, to narrow down the diagnosis, as each test examines different pathological aspects. A previous pathologically proven DLB study showed that 27 of the 30 (90.0%) DLB cases demonstrated both ^{123}I-FP-CIT SPECT and ^{123}I-MIBG images as abnormal, and two (6.7%) showed normal results [63]. The sensitivities for distinguishing clinically diagnosed

76 DLB cases from 57 AD cases using SBR of ^{123}I-FP-CIT SPECT and HMR of ^{123}I-MIBG scintigraphy were 88.2% and 72.4%, respectively, and it was demonstrated that the sensitivity increased to 96.1% compared with using either of these two methods [41]. This finding is consistent with the results of this study. Visual hallucination was more present in patients with DLB with both imaging abnormalities (58.3%) compared to those with only one abnormality. These findings may indicate that visual hallucinations are likely to appear when pathological involvement is diffuse. Although orthostatic hypotension and nocturia were close to statistical significance, no clinical features distinguished between 17 patients with DLB$^{FP-CIT+MIBG-}$ and 9 patients with DLB$^{FP-CIT-MIBG+}$, probably because of the lack of number of participants. Altogether, 30 out of 66 patients (45.5%) had at least one normal result, probably deviating from Braak's staging framework [27]. RBD and gastrointestinal symptoms shown in the "body-first" PD subtype in the previous study [26] were not replicated in this DLB study, nor was it related to ^{123}I-MIBG abnormality, indicating that some DLB patients exhibit RBD in normal ^{123}I-MIBG image, implying somewhat different progression between PD and DLB. Lifestyle modification or medications may have improved constipation. Depending on the diagnostic certainty, physicians are less likely to refute the diagnosis of DLB based on a single normal scan, and the other scan is needed to accurately diagnose DLB, which mirrors the fact that a single abnormal scan, may be sufficient for diagnosing DLB. We propose that, when autonomic dysfunction was present in DLB, ^{123}I-MIBG cardiac scintigraphy maybe the initial imaging investigation.

The strength of this study lies in the analysis of imaging using semi-automated quantitative methods; however, the diagnosis may differ from the visual inspection. Additionally, this observation was based on real-world data and did not exclude patients based on imaging results. We made an effort not to exclude DLB by imaging results, emphasizing the value of clinical symptoms in diagnosing DLB. The early detection of DLB is crucial in clinical practice, since DLB deteriorates fast, and has high risk of falling, while early intervention by introducing cholinesterase inhibitors and eliminating redundant medications may induce better outcomes. Nevertheless, this study had some limitations. First, the diagnosis was based on clinical criteria, which may include patients without DLB. However, we believe that this study illustrates a real-world clinical situation. Second, the clinical symptoms collected in this study were primarily based on subjective symptoms, which may differ from objective measurements, and may have included common comorbidities, such as nocturia in prostate hypertrophy with male patients. However, the value of patient-oriented reports is increasing in medical research and does not reduce the value of these findings. Third, this study was conducted at a single tertiary dementia center, which may have introduced bias in the cohort. Multicenter studies are needed since the evaluation methods for SBR and HMR used in this study are comparable between different cameras, which increases the number of patients with DLB. Fourth, the cut-off value for each scan was arbitrarily defined, which may have resulted in the under-recognition of near abnormal results and lower sensitivity. Lastly, the number of subgroups in DLB was small (i.e., 17 patients with DLB$^{FP-CIT+MIBG-}$ and 9 patients with DLB$^{FP-CIT-MIBG+}$). Together, there are 26 (39.4%) who had normal imaging results in either test, which we believe it is not a small proportion of DLB, worth reporting, but requires further observation from future studies to draw any conclusion regarding the symptomatic difference, such as orthostatic hypotension and nocturia showing near significance (Table 3). Fifth, specificity was unable to calculate due to lack of control group.

Conclusion

Regarding stand-alone diagnostic methods, the sensitivity of ^{123}I-FP-CIT SPECT was slightly higher than that of ^{123}I-MIBG scintigraphy for DLB diagnosis. However, this does not indicate the superiority of the ^{123}I-FP-CIT image, but when autonomic dysfunction was present, ^{123}I-MIBG may be preferable for initial testing. Both tests should be used to increase the accuracy, since a- single normal imaging result does not refute the diagnosis of DLB. Nocturia and orthostatic hypotension are associated with reduced ^{123}I-MIBG cardiac uptake, demonstrating a "body-first" subtype in patients with DLB.

AUTHOR CONTRIBUTIONS

Shigeki Hirano (Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Resources; Writing – original draft; Writing – review & editing); Zhihui Tang (Data curation; Formal analysis; Investigation; Writing

– original draft); Yume Koizumi (Data curation; Project administration; Writing – review & editing); Michiko Izumi (Data curation; Writing – review & editing); Yoshihisa Kitayama (Data curation; Writing – review & editing); Kosuke Yamagishi (Data curation; Writing – review & editing); Mitsuyoshi Tamura (Data curation; Writing – review & editing); Ai Ishikawa (Data curation; Project administration; Writing – review & editing); Kouichi Kashiwado (Data curation; Project administration; Writing – review & editing); Takashi Iimori (Methodology; Software; Writing – review & editing); Hiroki Mukai (Methodology; Software; Visualization; Writing – review & editing); Hajime Yokota (Software; Visualization; Writing – review & editing); Takuro Horikoshi (Software; Visualization; Writing – review & editing); Takashi Uno (Supervision; Writing – review & editing); Satoshi Kuwabara (Supervision; Writing – review & editing).

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

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

Numbers in the parenthesis indicate the number of participants.

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