^{123}I-2β-Carbomethoxy-3β-(4-Iodophenyl)-*N*-(3-Fluoropropyl) Nortropane Single Photon Emission Computed Tomography and ^{123}I-Metaiodobenzylguanidine Myocardial Scintigraphy in Differentiating Dementia with Lewy Bodies from Other Dementias: A Comparative Study

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Objective: To compare the diagnostic value of striatal ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl) nortropane (^{123}I-FP-CIT) single photon emission computed tomography (SPECT) and ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) myocardial scintigraphy in differentiating dementia with Lewy bodies (DLB) from other dementia types.
Methods: This prospective longitudinal study included 30 patients with a clinical diagnosis of DLB and 29 patients with non-DLB dementia (Alzheimer disease, n = 16; behavioral variant frontotemporal dementia, n = 13). All patients underwent ^{123}I-FP-CIT SPECT and ^{123}I-MIBG myocardial scintigraphy within a few weeks of clinical diagnosis. All diagnoses at each center were agreed upon by the local clinician and an independent expert, both unaware of

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imaging data, and re-evaluated after 12 months. Each image was visually classified as either normal or abnormal by 3 independent nuclear physicians blinded to patients' clinical data.
Results: Overall, sensitivity and specificity to DLB were respectively 93% and 100% for ^{123}I-MIBG myocardial scintigraphy, and 90% and 76% for ^{123}I-FP-CIT SPECT. Lower specificity of striatal compared to myocardial imaging was due to decreased ^{123}I-FP-CIT uptake in 7 non-DLB subjects (3 with concomitant parkinsonism) who had normal ^{123}I-MIBG myocardial uptake. Notably, in our non-DLB group, myocardial imaging gave no false-positive readings even in those subjects (n = 7) with concurrent medical illnesses (diabetes and/or heart disease) supposed to potentially interfere with ^{123}I-MIBG uptake.
Interpretation: ^{123}I-FP-CIT SPECT and ^{123}I-MIBG myocardial scintigraphy have similar sensitivity for detecting DLB, but the latter appears to be more specific for excluding non-DLB dementias, especially when parkinsonism is the only "core feature" exhibited by the patient. Our data also indicate that the potential confounding effects of diabetes and heart disease on ^{123}I-MIBG myocardial scintigraphy results might have been overestimated.

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Once thought to be uncommon, dementia with Lewy bodies (DLB) is currently regarded as the most common form of dementia in the elderly after Alzheimer disease (AD).[1] Besides cognitive impairment, the DLB Consortium originally described 3 core clinical features of DLB (fluctuations, visual hallucinations [VHs], and spontaneous parkinsonism),[2] but because these features may not invariably appear during the disease course[3] or may overlap to some extent with other dementias,[4,5] clinical diagnostic accuracy in clinicopathologic studies has, with one notable exception,[6] been relatively poor.[7–11] Although the subsequent addition of rapid eye movement sleep behavior disorder (RBD) in the diagnostic algorithm[12] has improved DLB identification,[13] its differentiation from other dementias remains a challenge even for experienced clinicians.

In light of the limitations on the level of accuracy that can be achieved by making a diagnosis of DLB only on clinical grounds, great emphasis has recently been placed on imaging methods targeting some of its typical biological alterations, including degeneration of the nigrostriatal dopaminergic system and of postganglionic sympathetic cardiac innervation. Reflecting these pathologic changes, abnormal findings (low uptake) on either dopamine transporter (DAT) single photon emission computed tomography (SPECT), using ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl) nortropane (^{123}I-FP-CIT),[14–16] or myocardial scintigraphy, using ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG),[17] have consistently been reported to be useful markers to support the diagnosis of DLB.[18,19] However, although the diagnostic value of both imaging methods has been acknowledged in the latest formulation of DLB consensus criteria,[12] only abnormalities on DAT imaging have been considered to have enough specificity to be ranked among DLB "suggestive features." DAT SPECT abnormalities have been shown to be highly specific in differentiating DLB from AD because, in the latter condition, the nigrostriatal dopaminergic system is usually intact and, consequently, striatal tracer binding is normal.[14–16] Nonetheless, specificity of DAT imaging is expected to decrease when the differential diagnosis is not between DLB and AD, but between DLB and disorders, such as vascular or frontotemporal dementias, that may also result in loss of nigrostriatal integrity.[20,21] It is also worth highlighting that an abnormal DAT SPECT would not be useful for supporting a hypothetical diagnosis of DLB if parkinsonism is the only "core" feature exhibited by the patient because, in this case, a decrease in striatal tracer binding is expectable (circularity).

Unlike DAT SPECT, ^{123}I-MIBG scintigraphy results are independent of the presence of parkinsonism[17] and integrity of postganglionic sympathetic cardiac innervation is unaffected by dementias other than DLB.[20,22] Conversely, compared to DAT SPECT, ^{123}I-MIBG scintigraphy may have some disadvantages, such as the finding that several common illnesses in the elderly (including heart infarct, heart failure, dilated cardiomyopathy, and autonomic diabetic neuropathy), if severe enough, can interfere with ^{123}I-MIBG uptake.[23,24] Furthermore, although several drugs may reduce the uptake of both tracers,[25,26] and are thus recommended to be temporarily withdrawn before the procedures, the list of medications potentially interfering with ^{123}I-MIBG uptake includes agents of more widespread use (eg, calcium channel blockers, labetalol).

Until now, several studies have evaluated the role of either ^{123}I-FP-CIT SPECT[14–16] or ^{123}I-MIBG scintigraphy[19] in supporting DLB identification, but only 2 cross-sectional studies have compared the diagnostic value of the two methods in concurrent samples.[27,28] To our knowledge, this is the first prospective longitudinal study in the field. Our primary aim was to compare sensitivity and specificity of ^{123}I-FP-CIT SPECT and ^{123}I-MIBG scintigraphy in distinguishing DLB from other dementias. Our secondary aim was to determine positive and negative predictive values, as well as inter-reader agreement for visual assessment of each of the two imaging methods.

Patients and Methods

Subjects

This study included a total of 65 subjects who were referred between July 1 and December 31, 2012 to 5 Italian centers (1 outpatient department specifically focused on DLB and related disorders, 2 memory clinics, and 2 centers with special expertise in early identification of atypical dementias). To be included in the present study, subjects had to fulfill at least 1 of the following: original consensus criteria for DLB,[2] National Institute on Aging–Alzheimer's Association recommendations for diagnosis of AD,[29] revised diagnostic criteria for behavioral variant frontotemporal dementia (bvFTD),[30] or National Institute of Neurological Disorders and Stroke and International Association for Research and Education in Neurosciences criteria for vascular dementia.[31] The diagnosis of DLB was based on more restrictive criteria than those recently recommended by the DLB Consortium.[12] A diagnosis of probable DLB was given to patients with at least 2 of the 3 core features (fluctuations, VHs, and parkinsonism), but not to those with only 1 core and 1 suggestive feature. Original, instead of revised, consensus criteria for DLB were chosen because of the centers' difficulties in accessing a polysomnographic recording for RBD confirmation and the need of excluding ^{123}I-FP-CIT SPECT from the diagnostic process, to avoid the circularity of defining our DLB group based on the construct of interest. To be considered for the present analysis, subjects also had to be at their first clinical examination at the recruiting centers and, to ensure an adequate capacity to comply with the study requirements, had to have a Mini Mental State Examination (MMSE)[32] score of at least 14, a reliable caregiver for the whole study duration, and no disability (blindness, deafness, severe language difficulty) potentially hindering the collection of reliable clinical and neuropsychological data. Another important requirement for subjects' inclusion was their consent to temporarily withdraw any of the drugs known to potentially interfere with the uptake of either of the tracers. Unlike earlier investigations, this study did not exclude subjects with common illnesses in the elderly (including ischemic, hypertensive, dilated cardiomyopathy, and diabetes) that might reduce ^{123}I-MIBG uptake, because we felt it important to estimate the rate of possible false-positive results (due to the concomitance of these medical conditions) in an unselected sample that could more faithfully reflect the "real-life" clinical context.

Clinical Procedures

Before being enrolled in the study, which was approved by the local ethical committees and carried out according to the Declaration of Helsinki and subsequent revisions (Declaration of Helsinki, 1997), all subjects signed written informed consent. Once recruited into the study, all patients underwent detailed clinical, neuropsychological, and neurological examinations. Global tests of cognitive and functional status included the MMSE,[32] the Clinical Dementia Rating (CDR),[33] the Lawton Instrumental Activities of Daily Living Scale,[34] and the Activities of Daily Living Scale.[35] Presence and severity of extrapyramidal signs were rated using the Unified Parkinson Disease Rating Scale–III.[36] Presence and severity of cognitive fluctuations were evaluated using the Clinical Assessment of Fluctuations[37] and the Mayo Fluctuation Scale.[38] Sleep disturbances, neuropsychiatric symptoms, and depression were respectively assessed by the Epworth Sleepiness Scale,[39] the Neuropsychiatric Inventory,[40] and the Cornell Depression Scale.[41] Presence and characteristics of VHs were also evaluated using the North-East Visual Hallucinations Interview.[42] The physical impairment due to comorbid chronic medical illnesses was assessed using the Cumulative Illness Rating Scale (CIRS),[43] which provides for 14 relatively independent areas grouped under body systems. Ratings are made on a 5-point "degree of severity" scale, ranging from "none" to "extremely severe." Two indices were derived from this scale: (1) the severity index, resulting from the mean score of the first 13 categories (thereby, not taking into account the score attributed to the "psychiatric" category); and (2) the comorbidity index, resulting from the number of categories with a score of at least 3 (equivalent to moderate impairment).

In addition to tests of global cognitive status (MMSE and CDR), each subject underwent a comprehensive neuropsychological evaluation, including the Italian version of the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) neuropsychological battery,[44,45] the Digit Cancellation Test, and the Letter Verbal Fluency Test.[46] This battery is composed of measures from each of the cognitive domains that are most often compromised in all types of dementia: verbal and nonverbal long-term memory (Word List Memory, Word List Recall, Word List Recognition, Recall of Constructional Praxis), language (Boston Naming Test, Letter and Semantic Verbal Fluency), constructional and visuospatial abilities (Constructional Praxis, Clock Drawing Test), and attention and executive functions (Digit Cancellation Test and Clock Drawing Test).

According to the local clinical practice at each center, the diagnostic workup could also comprise supplementary exams, including magnetic resonance examination, ^{18}fluorodeoxyglucose positron emission tomography, and lumbar puncture for cerebrospinal fluid analysis.

All clinical diagnoses at each center were agreed upon by 2 assessors, the local clinician and an independent expert (P.T.), and re-evaluated at a 12-month follow-up visit. The assessors did not at any time during the study have access to striatal and myocardial images.

Imaging Procedures

All patients underwent striatal ^{123}I-FP-CIT SPECT and ^{123}I-MIBG myocardial scintigraphy within a few weeks of clinical diagnosis. Two nuclear medicine services took part in the study. Both had well-established expertise in ^{123}I-FP-CIT SPECT and ^{123}I-MIBG myocardial scintigraphy, and were equipped with the same gamma cameras with identical collimators and spatial resolution. Images were acquired and reconstructed according to standardized protocols.[25,26] Patients were given 400mg of sodium perchlorate for thyroid blockade before the injection of each tracer.

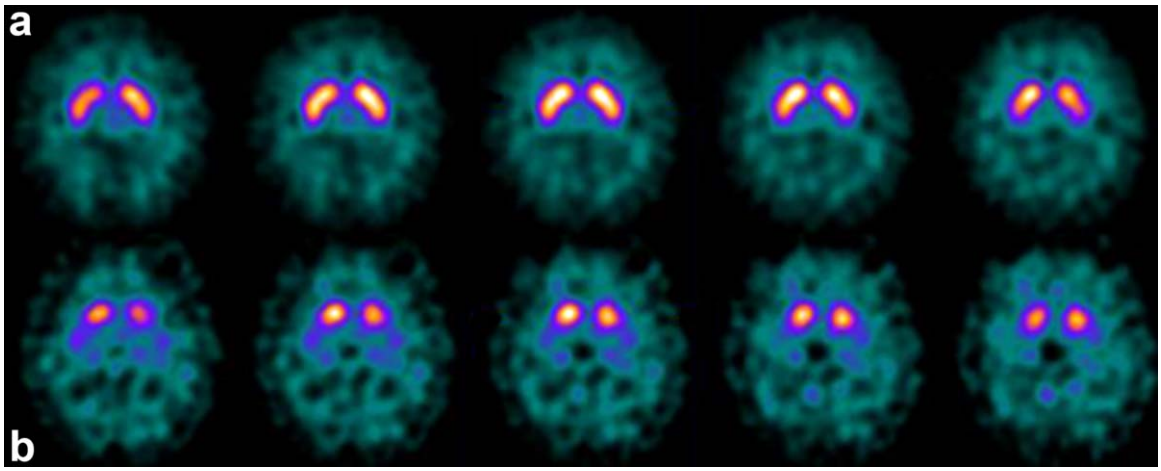

FIGURE 1: (A) Normal and (B) abnormal ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl) nortropane single photon emission computed tomography images. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]

^{123}I-FP-CIT SPECT. Drugs known to interfere with uptake of ^{123}I-FP-CIT[25] were temporarily withdrawn before undergoing SPECT imaging. SPECT acquisition was performed 3 to 4 hours after a single intravenous administration of tracer dose ranging from 111 to 185MBq. Striatal images were visually assessed by 3 independent readers (nuclear physicians with expertise in ^{123}I-FP-CIT SPECT [F.N., U.P.G., D.C.]) who were blinded to all patients' clinical data, except for age. Only a dichotomous classification of normal versus abnormal images was used for visual rating (Fig 1). Images showing evidence of reduced uptake in the putamen and/or in the caudate on the right and/or the left side were classified as abnormal. Apart from visual analysis, which was our main outcome measure, volume of interest (VOI)-based semiquantification of ^{123}I-FP-CIT striatal binding was also performed. Reconstructed images were analyzed using BasGan V2 software,[47] which determines the uptake computation of basal ganglia after drawing automatically a 3-dimensional VOI over caudate and putamen in each hemisphere, and locating occipital VOI for background evaluation. Putamen and caudate nucleus uptake was subtracted by background uptake as follows ([caudate nucleus or putamen uptake − background uptake]/background uptake), and compared to a reference database of 96 healthy subjects for determining the age-adjusted values for each basal nucleus. A scan was considered abnormal when the normalized uptake value of at least 1 of the 4 nuclei (putamen on the right or the left side; caudate on the right or the left side) was more than 2 standard deviations below the mean of controls.

^{123}I-MIBG MYOCARDIAL SCINTIGRAPHY. Drugs known to interfere with uptake of ^{123}I-MIBG[26] were temporarily withdrawn before undergoing myocardial imaging. After intravenous administration of 150 to 200MBq of ^{123}I-MIBG, planar images of the thorax in anterior view were obtained performing static acquisition at 15 minutes (early image) and at 4 hours (delayed image). The total acquisition time was 10 and 15 minutes for the early and delayed images, respectively. Myocardial images were visually assessed by 3 independent readers (nuclear physicians with expertise in ^{123}I-MIBG myocardial scintigraphy [M.L.C., D.V., A.P.]) who were blinded to all patients' clinical data, except for age. Only a dichotomous classification of normal versus abnormal images was used for visual rating (Fig 2). Images showing decreased ^{123}I-MIBG uptake in the heart were classified as abnormal. Apart from visual analysis, which was our main outcome measure, region of interest (ROI)-based semiquantification of MIBG myocardial binding was also performed. ROIs over the left ventricular cavity of the heart and the upper mediastinum were manually drawn on all delayed images by a single tracer (S.C.), blind to diagnoses and the aim of the study. The heart to mediastinum (H/M) ratio was then calculated by dividing the count density of the left ventricular ROI by that of the mediastinal ROI, in keeping with the standard method previously described.[17] According to the local database of either of the nuclear medicine services, an H/M ratio < 1.6 was considered abnormal. This ratio is quite similar to that reported by Yoshita et al.[17] Only the delayed H/M ratios were used for analysis, because the delayed scans reflect the active neuronal uptake of ^{123}I-MIBG.[48]

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (v22.0; Armonk, NY: IBM). Group (DLB vs non-DLB) comparisons with regard to sociodemographic, clinical, and neuropsychological features were performed using Student t test for continuous variables and Pearson chi-square test for dichotomous variables. The significance level was set at $p = 0.05$. Our primary analysis was a comparison of the results of visual assessment (normal or abnormal scan) for each of the two methods between DLB and non-DLB patients. As a secondary analysis, we also made a comparison of semiquantitative results between the two groups. For both visual and semiquantitative analyses, we determined sensitivity (percentage of times the tracer uptake was decreased in patients with a final clinical diagnosis of DLB), specificity (percentage of times the tracer uptake was normal in patients with a final clinical diagnosis of non-DLB

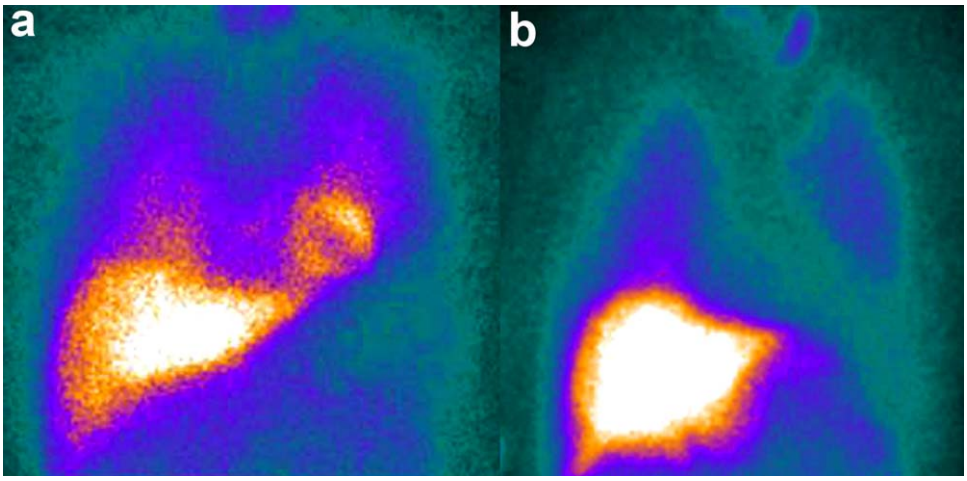

FIGURE 2: (A) Normal and (B) abnormal ^{123}I-metaiodobenzylguanidine myocardial scintigraphy images. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]

dementia), positive predictive value (PPV; the percentage of times that the clinical diagnosis was probable DLB given that the tracer uptake was decreased), and negative predictive value (NPV; the percentage of times that the clinical diagnosis was non-DLB given that the tracer uptake was normal). The PPV and NPV can be calculated for any prevalence as follows: PPV = sensitivity × prevalence/sensitivity × prevalence + (1 − specificity) × (1 − prevalence); NPV = specificity × (1 − prevalence)/(1 − sensitivity) × prevalence + specificity × (1 − prevalence). Ninety-five percent confidence intervals (CIs) for these estimates were calculated with an exact binomial procedure. Sensitivities and specificities of the two imaging techniques were then compared using the exact McNemar test for both visual (overall ratings) and semiquantitative findings.

Sample size calculation was determined assuming that (1) the proportion of DLB patients was approximately 0.5 (owing to intentional oversampling of patients with this disease); and (2) sensitivity and specificity rates of both ^{123}I-FP-CIT SPECT and ^{123}I-MIBG myocardial scintigraphy in identification of DLB and non-DLB cases were in the range of 80 to 90%,[15,16,22] choosing a 95% CI of ± 15%.[49] Based on these estimates, the total number of patients required was 56. A further 10% was planned to be recruited to allow for dropouts and unreadable images.

Inter-reader agreement for visual assessment (normal vs abnormal scan) of each of the two methods was evaluated with Cohen kappa statistic for each pair of independent image readers.

Results

Of the 65 subjects enrolled, 1 with a clinical diagnosis of probable AD did not meet inclusion criteria and 5 (2 with possible AD and 3 with probable DLB) withdrew from the study for personal reasons before undergoing imaging procedures. These 6 subjects were therefore excluded from further analyses. Of the remaining 59 subjects, 32 were clinically diagnosed at baseline as having DLB (probable DLB, n = 27; possible DLB, n = 5) and 27 as having non-DLB dementia (probable AD, n = 8; possible AD, n = 6; probable bvFTD, n = 9; possible bvFTD, n = 3; possible bvFTD + progressive supranuclear palsy, n = 1). At the 12-month follow-up evaluation, a change in diagnostic classification (from possible DLB to probable AD) occurred in 2 subjects; in 7 additional subjects with initial diagnoses of AD (n = 4), DLB (n = 1), or bvFTD (n = 2), the diagnostic shift was only from the possible to the probable category. Thus, according to our final clinical categorization, our two groups were respectively composed of 30 DLB and 29 non-DLB subjects.

Subjects' demographic and clinical features are shown in Table 1 (for more clinical details, also see Supplementary Table 1). The DLB and non-DLB groups were comparable for age at onset, sex, and age and global severity of dementia at first visit. As expected, compared to non-DLB, DLB patients showed a considerably greater frequency of parkinsonism, VHs, and cognitive fluctuations, as well as sleep disturbances and neuropsychiatric symptoms. Neuropsychologically, compared to non-DLB, DLB patients were also characterized by lower scores on tests of visuospatial/constructional and attentional abilities (Table 2).

Sensitivity, specificity, PPV, and NPV for DLB were respectively 93%, 100%, 100%, and 98% for overall visual assessment of myocardial images, and 90%, 76%, 49%, and 97% for striatal images (Supplementary Tables 2 and 3). Similar rates were obtained with semiquantitative assessments (see Supplementary Tables 2 and 3). Of note, whereas sensitivities to DLB between the two techniques were not statistically different ($p = 0.6$), specificity of ^{123}I-MIBG myocardial scintigraphy was significantly greater than that of ^{123}I-FP-CIT SPECT for

TABLE 1. Sociodemographic and Clinical Data

	DLB, n = 30	Non-DLB, n = 29	p^a
Age at onset, yr	69.5 ± 5.5	70.8 ± 8.2	0.490
Age at first visit, yr	73.5 ± 4.8	73.3 ± 7.8	0.934
Sex, female	9 (30%)	12 (41%)	0.361
MMSE	21.3 ± 4.0	22.0 ± 4.7	0.523
CDR 0.5/1/2/3	n = 25; 5/11/9/0	n = 24; 5/12/4/3	0.176
IADL, lost functions			
Female	n = 9, 3.2 ± 3.4	n = 12, 2.4 ± 2.6	0.561
Male	n = 21, 2.2 ± 1.4	n = 17, 2.4 ± 1.5	0.719
ADL, lost functions	0.9 ± 1.5	0.35 ± 0.8	0.101
CIRS Severity	1.2 ± 0.2	1.2 ± 0.1	0.497
CIRS Comorbidity	0.8 ± 1.2	0.5 ± 0.7	0.300
UPDRS-III	23.2 ± 16.2	4.7 ± 9.4	<0.0001
Cornell Depression Scale	7.9 ± 6.6	6.8 ± 4.5	0.494
Epworth Sleepiness Scale	7.8 ± 4.8	5.5 ± 3.6	0.048
Mayo Fluctuation Scale	2.1 ± 1.4	0.4 ± 0.7	<0.0001
Clinical Assessment of Fluctuations	5.0 ± 4.1	1.3 ± 2.7	0.0001
NPI	21.9 ± 18.7	14.3 ± 8.9	0.052
North-East Visual Hallucinations Interview, yes	21 (70%)	1 (3%)	<0.0001

All values are means ± standard deviation or frequencies. Percentages are in parentheses. For all scales, higher scores denote greater disease severity, except for the MMSE, for which higher scores represent better cognitive function.
[a]Two-tailed unpaired *t* test, except for sex, CDR, and North-East Visual Hallucinations Interview, for which chi-square test was used.
ADL = Activities of Daily Living Scale; CDR = Clinical Dementia Rating; CIRS = Cumulative Illness Rating Scale; DLB = dementia with Lewy bodies; IADL = Instrumental Activities of Daily Living Scale; MMSE = Mini Mental State Examination; NPI = Neuropsychiatric Inventory; UPDRS = Unified Parkinson Disease Rating Scale.

both overall visual rating ($p = 0.02$) and semiquantitative results ($p = 0.03$).

As shown in Table 3 (for more details, also see Supplementary Table 4), ^{123}I-FP-CIT SPECT and ^{123}I-MIBG myocardial scintigraphy were discordant in 8 of the 59 (14%) subjects. In the remaining 51 subjects, the two procedures were concordant, although in 2 subjects there was a mismatch between the imaging data (both normal) and the final clinical diagnosis of DLB. More specifically, within the DLB group (n = 30), ^{123}I-FP-CIT SPECT and ^{123}I-MIBG myocardial scintigraphy were concordant in 29 subjects (both abnormal, n = 27; both normal, n = 2) and discordant (reduction in ^{123}I-MIBG uptake but not in ^{123}I-FP-CIT uptake) in only 1 subject. Conversely, within the non-DLB group (n = 29), ^{123}I-FP-CIT SPECT and ^{123}I-MIBG myocardial scintigraphy were concordant (both normal) in 22 (76%) subjects and discordant (reduction in ^{123}I-FP-CIT uptake but not in ^{123}I-MIBG uptake) in 7 (24%) subjects (AD, n = 2; AD with parkinsonism, n = 1; bvFTD, n = 2; bvFTD with parkinsonism, n = 2).

Of note, in the non-DLB group, ^{123}I-MIBG myocardial uptake was invariably normal (specificity of 100%), despite the concomitance of diabetes and/or heart disease in about one-fourth of the patients (see Supplementary Table 1). Of the 7 non-DLB subjects with diabetes, 3 had a CIRS comorbidity index ≥ 3. Conversely, of the 4 non-DLB subjects with heart disease, only 1 had a CIRS comorbidity index ≥ 3 (comparable to New York Heart Association [NYHA] class III), whereas the remaining 3 were only mildly symptomatic (NYHA classes I or II).

Inter-reader agreement for visual assessment of myocardial imaging was excellent (Cohen kappa = 0.89

TABLE 2. Neuropsychological Data

	DLB, n = 30	Non-DLB, n = 29	p^a
CERAD–Verbal Fluency	9.4 ± 4.3	9.1 ± 3.5	0.763
CERAD–Boston Naming Test	11.3 ± 3.9	10.9 ± 3.6	0.714
CERAD–Word List Memory	8.4 ± 3.9	10.4 ± 4.2	0.069
CERAD–Constructional Praxis	6.8 ± 2.6	8.9 ± 1.7	0.0004
CERAD–Word List Recall	1.6 ± 1.2	1.5 ± 2.1	0.874
CERAD–Word List Recognition	14.8 ± 4.3	14.5 ± 4.9	0.791
CERAD–Recall of Constructional Praxis	3.2 ± 2.5	2.5 ± 2.9	0.286
CERAD–Copy a Clock	2.1 ± 1.0	1.5 ± 1.2	0.028
Digit Cancellation Test	25.8 ± 12.3	33.3 ± 14.1	0.034
Verbal fluency (Letters)	15.6 ± 7.4	13.6 ± 8.7	0.335

Raw scores are reported. Values are means ± standard deviation. Higher scores denote a better neuropsychological performance, except for CERAD–Copy a Clock, for which lower scores indicate a better performance.
[a]Two-tailed unpaired *t* test.
CERAD = Consortium to Establish a Registry for Alzheimer's Disease; DLB = dementia with Lewy bodies.

between the independent readers A and B; 0.93 between A and C; 0.96 between B and C). Inter-reader agreement for visual assessment of striatal imaging was also good (Cohen kappa = 0.82 between readers D and E; 0.86 between D and F; 0.82 between E and F), but not as high as for myocardial imaging.

Discussion

In the present study, we compared the diagnostic value of striatal ^{123}I-FP-CIT SPECT and ^{123}I-MIBG myocardial scintigraphy in differentiating DLB from other types of dementia. Consistent with earlier observations,[27] we noted a greater rate of agreement between the two imaging techniques in DLB (93% with reduced uptake of both tracers) than non-DLB patients (76% with normal uptake of both tracers). Of note, in our study, all non-DLB patients with discrepant imaging results had reduced uptake of striatal ^{123}I-FP-CIT but normal uptake of myocardial ^{123}I-MIBG, indicating a full concordance between normality of tracer uptake and a clinical diagnosis of non-DLB exclusively for myocardial imaging. We also found that the agreement for visual assessment among our independent readers was considerably greater for myocardial than for striatal imaging.

Altogether, these results suggest that both striatal ^{123}I-FP-CIT SPECT and ^{123}I-MIBG myocardial scintigraphy can perform equally well in increasing DLB identification, but the latter method appears to be more reliable and accurate for excluding non-DLB dementias, thereby reducing the risk of overdiagnosis. Is avoiding

TABLE 3. Imaging Findings in Relation to Final Clinical Diagnosis

^{123}I-MIBG Myocardial Scintigraphy: Overall Visual Rating	^{123}I-FP-CIT SPECT: Overall Visual Rating	
	Abnormal	Normal
Abnormal	27 DLB (26 probable; 1 possible)	1 probable DLB
Normal	3 probable bvFTD; 1 possible bvFTD+PSP; 2 AD (1 probable; 1 possible); 1 probable AD+CVD	13 AD (12 probable; 1 possible); 9 probable bvFTD; 2 DLB (1 probable; 1 possible)

^{123}I-FP-CIT = ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl) nortropane; ^{123}I-MIBG = ^{123}I-metaiodobenzylguanidine; AD = Alzheimer disease; bvFTD = behavioral variant frontotemporal dementia; CVD = cerebrovascular disease; DLB = dementia with Lewy bodies; PSP = progressive supranuclear palsy; SPECT = single photon emission computed tomography.

overdiagnosing DLB a relevant issue in everyday clinical practice? We feel that it is although, given the high specificity of probable DLB clinical diagnosis against the neuropathological diagnosis reported in most of autopsy controlled studies,[6–11] the issue of DLB overdiagnosis has traditionally received less emphasis in the literature than that of DLB underdiagnosis. Warning clinicians against the risk of DLB overdiagnosis, a more recent autopsy series has, however, questioned the specificity of DLB Consortium clinical criteria for probable DLB, showing a comparable distribution of each of the 3 DLB "core features" between DLB and non-DLB patients.[4] A similar finding was later replicated in another autopsy series,[5] where the overlap of DLB core features between DLB and non-DLB patients appeared to increase with increasing dementia severity. The clinical diagnosis of possible DLB is even more problematic. The only autopsy study to report on the accuracy of a possible DLB clinical diagnosis noted a specificity of only 28%[10]—that is, most had some other pathology accounting for their presentation—further highlighting the importance of diagnostic methods capable of increasing DLB diagnostic accuracy through a proper exclusion of non-DLB dementing disorders.

To our knowledge, no more than 2 studies[27,28] have previously compared the diagnostic value of ^{123}I-FP-CIT SPECT and ^{123}I-MIBG myocardial scintigraphy in differentiating DLB from other types of dementia. However, our experimental design differs from that of these studies in several respects. To prevent selection bias, our patients were enrolled consecutively, without excluding those with concomitant medical conditions potentially interfering with ^{123}I-MIBG uptake; to decrease the risk of misdiagnosis, all clinical diagnoses were agreed upon by 2 assessors and reconsidered after 12 months of follow-up; to guarantee the independence of imaging evaluation, the nuclear physicians who evaluated the basal ganglia and myocardial images were blinded to the patients' clinical information. It is also worth noting that the group of patients studied was skewed toward the inclusion of patients with DLB, who accounted for approximately half of the entire sample. However, this weighting was justified, because one of our purposes was to test how the two imaging methods performed in the positive identification of cases. Also intentional was the selection of recruiting centers particularly skilled in early identification of atypical dementias, which explains the over-representation of FTD patients, generally neglected in this kind of study. Although rarely, delusion and hallucinations have been reported for FTD patients,[20,50] and their presence may sometimes lead to an erroneous diagnosis of DLB, in particular when parkinsonism is also associated.

Several significant points emerge from this study. First, clinical diagnoses appear to have been accurate since the first visit. Should we disregard the shift from the possible to the probable category in 7 patients (1 in the DLB and 6 in the non-DLB group), which merely reflects a greater confidence of the clinician in his/her prior diagnosis, the initial clinical classification has been confirmed at follow-up visit in all but 2 subjects. Compared to non-DLB patients, those with DLB were expectedly characterized by an increased frequency of parkinsonism (and, consequently, by a higher L-dopa prescription), visual hallucinations, and cognitive fluctuations, and greater visuospatial and executive dysfunction.

Second, despite a comparably high sensitivity for identifying DLB (93% vs 90%), ^{123}I-MIBG myocardial scintigraphy appeared to be by far more specific than ^{123}I-FP-CIT SPECT for excluding non-DLB dementias (100% vs 76%). As a result of these similar sensitivities, but significantly different specificities, NPV were similar between the two imaging techniques (98% vs 97%), but ^{123}I-MIBG myocardial scintigraphy had a much greater PPV than ^{123}I-FP-CIT SPECT (100% vs 49%). Of note, because DLB cases were over-represented in our sample (50%), and PPV and NPV depend on the prevalence of the disease (see Statistical Analysis), PPV and NPV were adjusted assuming a DLB prevalence of 20%. Impressively, each of the 3 independent nuclear physicians rated all of the myocardial images of non-DLB subjects as normal (specificity of 100%). A specificity of 100% for excluding non-DLB dementias was also reported earlier,[17] but our result is even more striking when considering that, unlike these investigators, in our "naturalistic" study we also included patients with heart disease and/or diabetes, whose concomitance may theoretically give rise to false-positive results. In our hands, however, more than one-fourth of the non-DLB subjects had a history of diabetes and/or heart disease, and yet their myocardial tracer retention was normal, suggesting that the potential confounding effects of these medical conditions on the accuracy of ^{123}I-MIBG scintigraphy might have been overemphasized.

Third, with specific regard to ^{123}I-FP-CIT SPECT, we had comparable sensitivity to DLB, but lower specificity than that previously reported in prior studies.[14–16] In a recent meta-analysis,[18] the overall sensitivity and specificity of ^{123}I-FP-CIT SPECT to DLB were respectively 86.5% and 93.6%. However, in most of the studies included in this meta-analysis, the comparison with DLB patients was largely limited to AD patients with no or negligible parkinsonism, in whom ^{123}I-FP-CIT uptake

is usually normal. Conversely, in the present study, the non-DLB sample included some patients with bvFTD with variable degrees of parkinsonism, for which the possibility of abnormal ^{123}I-FP-CIT SPECT images has previously been recognized.[20,21] Had we restricted our analyses to AD patients (data not shown), specificity figures (81%) would have been much closer to those previously reported.[18] Therefore, the relatively lower ^{123}I-FP-CIT SPECT specificity seen in this study than in prior studies can largely be explained by a greater heterogeneity of our non-DLB sample.

There are limitations to this study. First, the gold standard for image validation was a clinical rather than a neuropathological diagnosis. However, to minimize the risk of misdiagnosis, all clinical diagnoses were consensually made by 2 assessors and their appropriateness was reviewed after 12 months. Another limitation is that data regarding the possible presence of autonomic dysfunction, and in particular orthostatic hypotension, were not systematically recorded. Due to this omission, the possibility that the high rate of abnormal myocardial imaging (sensitivity of 93%) observed in our DLB group might have been inflated by an overrepresentation of subjects with orthostatic hypotension cannot be excluded. However, sensitivity values of similar magnitude have also been reported by many others,[48] which is not unexpected, because reduced myocardial ^{123}I-MIBG uptake in DLB may also reflect subtle pathologic changes in postganglionic sympathetic cardiac innervation below the threshold of clinical expression. An apparent limitation may be the choice of original[2] instead of revised[12] DLB consensus criteria. However, the exclusion of ^{123}I-FP-CIT SPECT from the diagnostic algorithm was required to avoid the circularity of classifying the DLB subjects using the variable of interest. Moreover, for RBD exclusion, we felt that information based exclusively on the informant interview would have exposed us to the risk of overestimating RBD and, consequently, overdiagnosing DLB. Patients with moderate to severe obstructive sleep apnea can have features (nightmare and behavior) identical to RBD.

Finally, although myocardial imaging was rated as normal in all of our non-DLB patients with heart disease and/or diabetes, such patients were not sufficiently numerous in our sample to definitely exclude any interference of these illnesses on ^{123}I-MIBG uptake.

In summary, in the present study, we compared the diagnostic value of ^{123}I-FP-CIT SPECT and ^{123}I-MIBG myocardial scintigraphy in differentiating DLB from other dementias. We found that the two methods are similarly sensitive to DLB, but ^{123}I-MIBG myocardial scintigraphy may be more reliable and accurate for excluding non-DLB dementias, especially when parkinsonism is the only core feature exhibited by the patient. It is particularly in this case that false-positive (abnormal, low uptake) ^{123}I-FP-CIT SPECT images may be produced and myocardial ^{123}I-MIBG scintigraphy appears to be a more appropriate diagnostic option. Overall, our findings support the view that abnormal (low uptake) ^{123}I-MIBG myocardial scintigraphy should be upgraded from a "supportive" to a "suggestive" DLB feature. The observation that ^{123}I-MIBG myocardial uptake was unaffected by concomitant diabetes and/or heart disease suggests that the potential confounding effects of these medical conditions on ^{123}I-MIBG myocardial scintigraphy results might have been overestimated. This needs to be better elucidated in further studies with larger unselected samples.

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Author Contributions

Concept and study design: P.T., U.P.G., C.M. Data acquisition and analysis: all authors. Drafting the manuscript and figures: P.T., A.C., U.P.G., F.N., M.L.C., D.C., L.A., L.S., C.M.

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Potential Conflicts of Interest

Nothing to report.

References

1. Donaghy PC, McKeith IG. The clinical characteristics of dementia with Lewy bodies and a consideration of prodromal diagnosis. Alzheimers Res Ther 2014;6:46.
2. McKeith IG, Galasko D, Kosaka K, 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;47:1113–1124.
3. Merdes AR, Hansen LA, Jeste DV, et al. Influence of Alzheimer pathology on clinical diagnostic accuracy in dementia with Lewy bodies. Neurology 2003;60:1586–1590.
4. Walker Z, Jaros E, Walker RW, et al. Dementia with Lewy bodies: a comparison of clinical diagnosis, FP-CIT single photon emission computed tomography imaging and autopsy. J Neurol Neurosurg Psychiatry 2007;78:1176–1181.
5. Nelson PT, Jicha GA, Kryscio RJ, et al. Low sensitivity in clinical diagnoses of dementia with Lewy bodies. J Neurol 2010;257:359–366.
6. McKeith IG, Ballard CG, Perry RH, et al. Prospective validation of consensus criteria for the diagnosis of dementia with Lewy bodies. Neurology 2000;54:1050–1058.
7. Mega MS, Masterman DL, Benson DF, et al. Dementia with Lewy bodies: reliability and validity of clinical and pathologic criteria. Neurology 1996;47:1403–1409.
8. Litvan I, MacIntyre A, Goetz CG, et al. Accuracy of the clinical diagnoses of Lewy body disease, Parkinson disease, and dementia with Lewy bodies: a clinicopathologic study. Arch Neurol 1998;55:969–978.
9. Hohl U, Tiraboschi P, Hansen LA, et al. Diagnostic accuracy of dementia with Lewy bodies. Arch Neurol 2000;57:347–351.
10. Verghese J, Crystal HA, Dickson DW, Lipton RB. Validity of clinical criteria for the diagnosis of dementia with Lewy bodies. Neurology 1999;53:1974–1982.
11. Lopez OL, Becker JT, Kaufer DI, et al. Research evaluation and prospective diagnosis of dementia with Lewy bodies. Arch Neurol 2002;59:43–46.
12. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65:1863–1872.
13. Ferman TJ, Boeve BF, Smith GE, et al. Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies. Neurology 2011;77:875–882.
14. Walker Z, Costa DC, Walker RW, et al. Differentiation of dementia with Lewy bodies from Alzheimer's disease using a dopaminergic presynaptic ligand. J Neurol Neurosurg Psychiatry 2002;73:134–140.
15. O'Brien JT, Colloby S, Fenwick J, et al. Dopamine transporter loss visualized with FP-CIT SPECT in the differential diagnosis of dementia with Lewy bodies. Arch Neurol 2004;61:919–925.
16. McKeith I, O'Brien J, Walker Z, et al. Sensitivity and specificity of dopamine transporter imaging with 123I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study. Lancet Neurol 2007;6:305–313.
17. Yoshita M, Taki J, Yokoyama K, et al. Value of 123I-MIBG radioactivity in the differential diagnosis of DLB from AD. Neurology 2006;66:1850–1854.
18. Papathanasiou ND, Boutsiadis A, Dickson J, Bomanji JB. Diagnostic accuracy of 123I-FP-CIT (DaTSCAN) in dementia with Lewy bodies: a meta-analysis of published studies. Parkinsonism Relat Disord 2012;18:225–229.
19. Chung EJ, Kim SJ. (123)I-Metaiodobenzylguanidine myocardial scintigraphy in Lewy body-related disorders: a literature review. J Mov Disord 2015;8:55–66.
20. Novellino F, Bagnato A, Salsone M, et al. Myocardial (123)I-MIBG scintigraphy for differentiation of Lewy bodies disease from FTD. Neurobiol Aging 2010;31:1903–1911.
21. Morgan S, Kemp P, Booij J, et al. Differentiation of frontotemporal dementia from dementia with Lewy bodies using FP-CIT SPECT. J Neurol Neurosurg Psychiatry 2012;83:1063–1070.
22. Hanyu H, Shimizu S, Hirao K, et al. The role of 123I-metaiodobenzylguanidine myocardial scintigraphy in the diagnosis of Lewy body disease in patients with dementia in a memory clinic. Dement Geriatr Cogn Disord 2006;22:379–384.
23. Carrió I, Cowie MR, Yamazaki J, et al. Cardiac sympathetic imaging with mIBG in heart failure. JACC Cardiovasc Imaging 2010;3:92–100.
24. Orimo S, Yogo M, Nakamura T, et al. 123I-meta-iodobenzylguanidine (MIBG) cardiac scintigraphy in α-synucleinopathies. Ageing Res Rev 2016, http://dx.doi.org/10.1016/j.arr.2016.01.001.
25. Darcourt J, Booij J, Tatsch K, et al. EANM procedure guidelines for brain neurotransmission SPECT using (123)I-labelled dopamine transporter ligands, version 2. Eur J Nucl Med Mol Imaging 2010;37:443–450.
26. Flotats A, Carrió I, Agostini D, et al. Proposal for standardization of 123I-metaiodobenzylguanidine (MIBG) cardiac sympathetic imaging by the EANM Cardiovascular Committee and the European Council of Nuclear Cardiology. Eur J Nucl Med Mol Imaging 2010;37:1802–1812.
27. Treglia G, Cason E, Cortelli P, et al. Iodine-123 metaiodobenzylguanidine scintigraphy and iodine-123 ioflupane single photon emission computed tomography in Lewy body diseases: complementary or alternative techniques? J Neuroimaging 2014;24:149–154.
28. Shimizu S, Hirao K, Kanetaka H, et al. Utility of the combination of DAT SPECT and MIBG myocardial scintigraphy in differentiating dementia with Lewy bodies from Alzheimer's disease. Eur J Nucl Med Mol Imaging 2016;43:184–192.
29. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:263–269.
30. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 2011;134:2456–2477.
31. Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993;43:250–260.
32. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
33. Hughes CP, Berg L, Danziger WL, et al. A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566–572.
34. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179–186.
35. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. Gerontologist 1970;10:20–30.
36. Fahn S, Elton RL. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Goldstein M, Calne DB, eds. Recent developments in Parkinson's disease. Florham Park, NJ: MacMillan Healthcare Information, 1987:153–163.
37. Walker MP, Ayre GA, Cummings JL, et al. The Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale. Two methods to assess fluctuating confusion in dementia. Br J Psychiatry 2000;177:252–256.
38. Ferman TJ, Smith GE, Boeve BF, et al. DLB fluctuations: specific features that reliably differentiate DLB from AD and normal aging. Neurology 2004;62:181–187.

39. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 1991;14:540–545.
40. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308–2314.
41. Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell scale for depression in dementia. Biol Psychiatry 1988;23:271–284.
42. Mosimann UP, Collerton D, Dudley R, et al. A semi-structured interview to assess visual hallucinations in older people. Int J Geriatr Psychiatry 2008;23:712–718.
43. Parmalee PA, Thuras PD, Katz IR, Lawton MP. Validation of the Cumulative Illness Rating Scale in a geriatric residential population. J Am Geriatr Soc 1995;43:130–137.
44. Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology 1989;39:1159–1165.
45. Lucca U, Tettamanti M, Quadri P. The Italian version of Consortium to Establish a Registry of Alzheimer's Disease (CERAD). Alzheimers Dement 2008;4:310.
46. Spinnler H, Tognoni G. Standardizzazione e taratura italiana di test neuropsicologici. Ital J Neurol Sci 1987;6(suppl 8):S5–S120.
47. Calvini P, Rodriguez G, Inguglia F, et al. The basal ganglia matching tools package for striatal uptake semi-quantification: description and validation. Eur J Nucl Med Mol Imaging 2007;34:1240–1253.
48. Treglia G, Cason E. Diagnostic performance of myocardial innervation imaging using MIBG scintigraphy in differential diagnosis between dementia with Lewy bodies and other dementias: a systematic review and a meta-analysis. J Neuroimaging 2012;22:111–117.
49. Buderer NM. Statistical methodology: I. Incorporating the prevalence of disease into the sample size calculation for sensitivity and specificity. Acad Emerg Med 1996;3:895–900.
50. Le Ber I, Guedj E, Gabelle A, et al. Demographic, neurological and behavioural characteristics and brain perfusion SPECT in frontal variant of frontotemporal dementia. Brain 2006;129:3051–3065.