SHORT REPORT

Cardiac ^{123}I -meta-iodobenzylguanidine (MIBG) uptake in dementia with Lewy bodies: comparison with Alzheimer's disease

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Abstract

Cardiac ^{123}I -meta-iodobenzylguanidine (MIBG) uptake was measured in 11 patients with dementia with Lewy bodies (DLB), 10 patients with Alzheimer's disease (AD), and 10 age matched control subjects. The severity of cognitive impairment and duration of symptoms in patients with DLB matched that in the patients with AD. The heart/mediastinum (H/M) ratio of MIBG uptake in the patients with AD was indistinguishable from that in the control subjects. However, the H/M ratio in all patients with DLB was significantly lower than that in the patients with AD and control subjects ($p < 0.001$). These findings indicate that local myocardial sympathetic nerves are affected in DLB and that cardiac ^{123}I -MIBG scintigraphy may provide a means of differentiating DLB from AD.

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Dementia with Lewy bodies (DLB) is a common cause of degenerative, senile dementia and is associated with distinctive clinical features of fluctuations in cognitive function, visual hallucinations, and parkinsonism.¹ Dementia with Lewy bodies accounts for 15% to 25% of cognitively impaired elderly people, most of whom have received a diagnosis of Alzheimer's disease during life.²

Autonomic failure is recognised as one of the clinical features of DLB³⁻⁴ and may be present more often than previously thought if carefully looked for, but relatively little attention has been paid to it.⁵ Because it is difficult to obtain information about autonomic symptoms with reproducibility from some demented patients, objective autonomic tests are needed. Meta-iodobenzylguanidine (MIBG) is a physiological analogue of noradrenaline (norepinephrine)⁶ and cardiac ^{123}I -MIBG scintigraphy is a useful and non-invasive tool for estimating local myocardial sympathetic nerve damage, not only in primary heart disease, but also in

neurological disorders, with or without clinically manifested autonomic failure.⁶⁻¹⁰ In patients with Parkinson's disease, ^{123}I -MIBG cardiac scintigraphy is a more useful method of detecting autonomic nerve disturbances than a head up tilt test, sympathetic skin response, coefficient of variation in R-R interval, or plasma catecholamine concentrations.¹⁰⁻¹¹ The aim of this study was to assess cardiac sympathetic nerve damage by measuring ^{123}I -MIBG uptake in patients with DLB and to compare these findings with those from patients with AD.

Patients and methods

Eight patients with probable and three with definite, DLB, 10 patients with probable AD, and 10 healthy control subjects were enrolled. All patients and control subjects were instructed about the study, and all gave their informed consent. The diagnosis of DLB was based on the Consortium on DLB International Workshop criteria,¹ and the diagnosis of probable AD was based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association.¹² The order of onset of mental and motor symptoms of DLB was variable. When the initial presentation was parkinsonism, we included only those patients who developed the other mental symptoms within 12 months or in whom the diagnosis was established pathologically. There were no differences between groups for age, sex, duration of symptoms, and best mini mental state examination (MMSE) score (DLB group 66 (8) years; six men and five women; 3.3 (1.6) (1-6) years; 11.8 (8.8) v AD group 68 (8) years old; five men and five women; 3.5 (2.1) (1-7) years; 12.5 (5.9)). Data were compared with age matched control subjects (70 (5) years old; five men and five women; MMSE 28.6 (2.2)). Orthostatic hypotension was defined as a fall of 30 mm Hg in systolic blood pressure or 15 mm Hg in diastolic pressure on standing up from a recumbent position. All patients with DLB and those with AD were examined by routine laboratory tests (brain MRI, ECG, EEG, and cerebral blood

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Figure 1 Examples of cardiac ^{123}I -MIBG uptake in a patient with AD (left) and a patient with DLB (right). The regions of interest consisted of the left ventricle (1) and mediastinum (2). (B) Comparison of the H/M ratio among controls and disease groups. The mean ^{123}I -MIBG heart/mediastinum ratio (H/M ratio) was lower in patients with DLB than in patients with AD or control subjects ($p < 0.001$). Early scan was performed at 30 minutes (early H/M ratio), and delayed scan was performed at 4 hours (delayed H/M ratio) after ^{123}I -MIBG was given. DLB=Dementia with Lewy bodies; AD=Alzheimer's disease; MIBG=meta-iodobenzylguanidine

flow images by single photon emission computed tomography (SPECT)), and these results were incorporated into the diagnosis. No patients had diabetes, heart disease, or hypothyroidism. None of the patients were taking a tricyclic antidepressant, sympathomimetic drugs, or any other drugs except levodopa, reported to interfere with MIBG uptake.

^{123}I -MIBG 111 mBq (MyoMIBG-I123 for injection; Daiichi Radioisotope Laboratories Co, Tokyo, Japan) was given intravenously in Lugol's solution (200 mg iodine) to block thyroid uptake. Planar images of the thorax in anterior view over 5 minutes and SPECT images with a 180 degree rotation were performed at 30 minutes (early scan) and 4 hours (delayed scan). Uptake of MIBG was quantified by comparing regions of interest in the heart and mediastinum. Based on the

regions of interest, cardiac MIBG uptake was expressed as a heart/mediastinum ratio (H/M ratio, fig 1 A). When deficits in cardiac MIBG uptake were found, ^{201}Tl myocardial scintigraphy was performed to exclude impaired myocardial perfusion.

Statistical analyses were by Mann-Whitney U test and differences with $p < 0.05$ were taken as significant.

Results

Clinical data of the patients with DLB are summarised in table 1. The initial symptoms were cognitive decline in four cases, orthostatic dizziness in two, and parkinsonism in five. The best MMSE score decreased by variable degrees from 0 to 22, cognition fluctuated in nine patients. Ten patients with DLB showed features of parkinsonism to a variable extent,

Table 1 Demographics, clinical features, and ^{123}I -MIBG cardiac scintigraphy in patients with DLB

Patients	Age/sex	Initial symptom	Duration (y)	MMSE	Fluctuation in cognition	Hallucination	Parkinsonism	OH	^{123}I -MIBG	
									H/M ratio (E)	H/M ratio (D)
1	68/M	P	3	20	+	+	+	-	1.3	1.2
2	63 / M	C	1	22	+	+	+	-	1.5	1.3
3	66/F	P	3	15	+	+	+	+	1.2	1.1
4	49/F	P	2	12	+	+	+	+	1.5	1.2
5	65/F	P	3	0	+	+	+	-	1.7	1.5
6	61/M	C	1	22	+	+	+	+	1.2	1.1
7	71/M	C	5	2	+	-	+	+	1.5	1.2
8	78/F	P	6	0	-	+	+	-	1.3	1.3
9	70/M	C	3	4	-	+	+	+	1.2	1.1
10	60/M	L	4	19	+	+	+	+	1.3	1.2
11	75/F	L	5	14	+	+	-	+	1.1	1.1

MIBG=Metaiodobenzylguanidine; DLB=dementia with Lewy bodies; MMSE=mini mental state examination; OH=orthostatic hypotension; H/M=ratio of heart/mediastinum in ^{123}I -MIBG uptake; E=early scan; D=delayed scan; +=abnormality present; -=abnormality absent; * syncopal episode was noted; P=parkinsonism; C=cognitive decline; L=loss of consciousness.

orthostatic hypotension with blunting of the pressor responses was present in seven patients, and syncope occurred in four. Four patients (3, 4, 7, and 9) were taking levodopa at the time of the MIBG scans. None of the patients with AD fulfilled criteria for probable DLB.

The median early and delayed cardiac ^{123}I -MIBG uptake was markedly decreased in patients with DLB (H/M ratio 1.4 (0.2) (early scan) and 1.2 (0.2) (delayed scan)) compared with controls (H/M ratio 2.4 (0.1) and 2.4 (0.2), $p < 0.001$; fig 1 B). Examples of cardiac ^{123}I -MIBG uptake in patients with AD and those with DLB are shown in figure 1 A. The reduction in cardiac ^{123}I -MIBG uptake was evident even in the patients not presenting clinical signs and symptoms of autonomic failure. Thallium imaging at rest was normal in all 11 patients with DLB. All patients with AD had normal early and delayed cardiac ^{123}I -MIBG uptake (H/M ratio 2.3 (0.2) and 2.4 (0.2)). Thus, the mean early and delayed cardiac ^{123}I -MIBG uptake was significantly lower in the patients with DLB than in the patients with AD ($p < 0.001$).

Discussion

Uptake of ^{123}I -MIBG reflects myocardial sympathetic nerve function.⁶ We detected low cardiac ^{123}I -MIBG uptake in all patients with DLB even in the early stage with or without orthostatic hypotension and parkinsonism. There was no evidence of thallium perfusion deficit, ECG abnormality, and no substances interfering with neuronal uptake of MIBG. Taken together, low myocardial MIBG uptake was due to disturbance of the postganglionic cardiac sympathetic nerve.

In Parkinson's disease, low cardiac ^{123}I -MIBG uptake is a consistent finding, which is seen at an early disease stage.^{10–13} A decreased cardiac MIBG uptake was also found in a mouse model treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.¹³ Histopathological studies showed that Lewy bodies and Lewy neurites are present in the cardiac plexuses not only in Parkinson's disease but also in incidental Lewy body disease, which is considered to be the presymptomatic phase of Parkinson's disease.¹⁴ These findings strongly suggest that cardiac sympathetic nerve is affected in the early stage of Parkinson's disease. In patients with DLB, vulnerability of sympathetic ganglionic neurons have also been reported.^{3–4} Taken together, our findings suggest that cardiac sympathetic dysfunction developed selectively even in the early stage of DLB, as it does in Parkinson's disease.

An accurate diagnosis of DLB in an early stage is essential for prescribing appropriate neuroleptic medication, counselling of patients, design of future therapeutic trials, and a possibly better response to cholinesterase inhibitors. When the initial presentation is impaired cognition, it is difficult to differentiate DLB from AD during early stages of the illness. Although the presence of autonomic failure has

been considered to be an important feature in making a clinical diagnosis of DLB, autonomic dysfunction is common in elderly patients, even in patients with AD.^{15–16} Ballard *et al* reported that orthostatic hypotension and asystolic responses to carotid sinus massage were often present in patients with DLB, whereas these autonomic indices did not sufficiently differentiate between DLB and AD.¹⁶ By contrast, as demonstrated in this study, the pattern of cardiac ^{123}I -MIBG uptake was markedly different in DLB and AD even in the early stage of illness, and all patients with AD had normal cardiac ^{123}I -MIBG uptake. Clinical features and functional brain imaging and MRI have failed to clearly differentiate between DLB and AD.¹⁷ The specificity of a clinical diagnosis of probable DLB, using consensus criteria, is generally high (>85%), but the sensitivity of case detection, particularly in the early stage, is lower and more variable.¹⁷ Although further studies are needed, ^{123}I -MIBG cardiac scintigraphy could provide a means of distinguishing DLB from AD.

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