

## SHORT REPORT

## Reliability of MIBG myocardial scintigraphy in the diagnosis of Parkinson's disease

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*J Neurol Neurosurg Psychiatry* 2005;76:249–251. doi: 10.1136/jnnp.2004.037028

**Aim:** To evaluate the reliability of [<sup>123</sup>I]meta-iodobenzylguanidine (MIBG) myocardial scintigraphy for diagnosing Parkinson's disease (PD).

**Patients/Methods:** A series of 391 outpatients showing one or more parkinsonian-like symptoms was longitudinally followed up for accurate clinical diagnosis. MIBG scintigraphy was performed in the patients and 10 normal controls of similar age. The heart to mediastinum uptake ratio was calculated in each person, and the values were considered abnormal if they were greater than two standard deviations below the control mean.

**Results:** MIBG uptake was decreased in most patients with PD (87.7%), and was seen in all advanced cases with Hohen-Yahr stage III or more; the sensitivity and specificity of scintigraphy for detecting PD were 87.7% and 37.4%, respectively. Surprisingly, over half of the patients without PD (66.5%) also exhibited low uptake, resulting in considerable overlap in the ratios between PD and the other disorders.

**Conclusion:** MIBG scintigraphy is a sensitive, but not specific, test for PD. Low MIBG uptake does not necessarily indicate PD, but is essential for diagnosing advanced PD.

Parkinson's disease (PD) is characterised by several cardinal symptoms, including resting tremor, rigidity, bradykinesia, and postural instability, and because there are no absolute indicators the clinical diagnosis of PD is based on a combination of these symptoms.<sup>1</sup> Because the initial symptoms of PD may change with age at onset,<sup>2</sup> the clinical diagnosis is sometimes difficult, particularly for general physicians.

In addition to the salient symptoms, autonomic abnormalities have frequently been noted in PD.<sup>3</sup> Recently, [<sup>123</sup>I]meta-iodobenzylguanidine (MIBG) myocardial scintigraphy has been used for visual assessment of the sympathetic nerve terminals, based on the fact that MIBG, a noradrenaline storage analogue,<sup>4</sup> shares the same metabolic pathways as noradrenaline. MIBG uptake is reportedly decreased in nearly all patients with PD,<sup>5–12</sup> regardless of orthostatic hypotension,<sup>5,9,11,12</sup> suggesting that MIBG scintigraphy can be a useful tool for detecting PD. However previous studies of scintigraphy in PD have involved relatively small numbers of patients. Moreover, low MIBG uptake has been shown in various conditions other than PD,<sup>8,13–15</sup> and cardiac sympathetic tone possibly alters with aging.<sup>16</sup> Thus, the clinical usefulness of this test should be confirmed in a large and aged population, because patients with PD are mostly of advanced age.<sup>17</sup>

In our present study, we performed MIBG scintigraphy in a relatively large and aged population with one or more parkinsonian-like symptoms, and compared MIBG uptake

with the final clinical diagnosis to clarify the usefulness and limitations of scintigraphy for diagnosing PD.

## PATIENTS AND METHODS

From the outpatients visiting our service between May 1995 and November 1999, 483 patients showing one or more parkinsonian-like symptoms were enrolled in our present study. The symptoms included tremor (resting, postural, action, or intention), abnormal muscle tone (rigidity or spasticity), postural and gait disorders (pulsion, festinating gait, or *démarche a petits pas*), and kinetic disorders (bradykinesia or hesitation). Patients with a previous history of stroke were primarily excluded. Of the 483 patients, 82 with ischaemic heart disease, chronic heart failure, diabetes mellitus, or antipsychotic treatments were excluded based on electrocardiogram, chest *x* ray photograph, blood glucose (or glycated haemoglobin) concentration, and current medication history, because these conditions may influence MIBG uptake.<sup>13–15</sup> The remaining 391 patients (mean age, 75.5; SD, 7.5 years) were finally analysed after longitudinal follow up for accurate diagnosis. Ten healthy volunteers of a similar age (mean, 75.2; SD, 9.2 years) also participated in our study. The clinical diagnosis of PD was made based on two or more cardinal symptoms according to Calne's criteria,<sup>1</sup> and responsiveness to levodopa, by two or more neurologists certified by the Japanese Society of Neurology.

MIBG scintigraphy was performed after informed consent from each patient. Data were collected for three minutes, four hours after injection of 111 MBq of [<sup>123</sup>I]MIBG (Daichi Radioisotope Laboratories, Tokyo, Japan) using a dual head  $\gamma$  camera ZLC-7500 (Siemens, Munich, Germany), and a static image was obtained with a 128  $\times$  128 matrix. Regions of interest were manually drawn around the heart and mediastinum, and tracer uptake was measured within each region of interest to calculate the heart to mediastinum (H/M) ratio. Values were considered abnormal if they were more than 2 SDs below the control mean. Patients were categorised as either "normal" or "decreased" according to their H/M ratios, and then the sensitivity and specificity of MIBG scintigraphy for diagnosing PD were calculated in the patient series.

Statistical analyses were performed using StatView 5.0 on a Macintosh computer. The  $\chi^2$  test, Fisher's exact test, or Mann-Whitney U test was used to compare sex, prevalence of patients with low H/M ratio, age, and H/M ratio between the groups. A Mantel extension method was used to evaluate correlations between H/M ratio and Hohen-Yahr (HY) stage in patients with PD. Values were expressed as mean (SD), and  $p < 0.05$  was considered significant.

**Abbreviations:** CVD, cerebrovascular disease; DLB, dementia with Lewy bodies; H/M, heart to mediastinum; HY, Hohen-Yahr; MIBG, meta-iodobenzylguanidine; MSA, multiple system atrophy; PD, Parkinson's disease; PSP, progressive supranuclear palsy; SDAT, senile dementia of Alzheimer type

**Table 1** H/M ratio and clinical diagnosis

Diagnosis	N	Decreased patients		Mean (SD) H/M ratio
		N	%	
PD	122	107	87.7	1.38 (0.29)
Hohen-Yahr stage I	18	7	38.9	1.81 (0.33)
Hohen-Yahr stage II	27	23	85.2	1.48 (0.30)
Hohen-Yahr stage III	29	29	100.0	1.31 (0.01)
Hohen-Yahr stage IV	32	32	100.0	1.22 (0.01)
Hohen-Yahr stage V	16	26	100.0	1.20 (0.01)
MSA	14	3	21.4	2.00 (0.39)
DLB	5	5	100.0	1.17 (0.06)
PSP	7	6	85.7	1.69 (0.29)
SDAT	15	12	80.0	1.40 (0.29)
CVD	129	87	64.3	1.66 (0.35)
Other disorders (total)	81	53	65.4	1.70 (0.39)
Unknown cases	18	13	72.2	1.55 (0.35)

CVD, cerebrovascular disease; DLB, dementia with Lewy bodies; H/M, heart to mediastinum; MSA, multiple system atrophy; PD, Parkinson's disease; PSP, progressive supranuclear palsy; SDAT, senile dementia of Alzheimer type.

## RESULTS

The clinical diagnosis was available in 373 of the 391 patients, and 122 were diagnosed as having PD (mean HY stage, 3.0; SD, 1.3; mean age, 75.5; SD, 7.1 years). Of the remaining 251 patients, 14 had multiple system atrophy (MSA), five had dementia with Lewy bodies (DLB), seven had progressive supranuclear palsy (PSP), 15 had senile dementia of Alzheimer type (SDAT), 129 had cerebrovascular disease (CVD), and 81 had other disorders (table 1). None of the patients with PSP had taken amantadine. All the patients with SDAT fulfilled the probable clinical criteria except for the presence of motor signs. The patients with CVD included those with multiple lacunar state, Binswanger-type subcortical encephalopathy, and old small haemorrhage.

None of the patients showed a focal defect in MIBG uptake. The mean (SD) H/M ratio in control subjects was 2.10 (0.13), and the lower normal limit of the ratio was set at 1.84. Of the 391 enrolled patients, 286 had low H/M ratios.

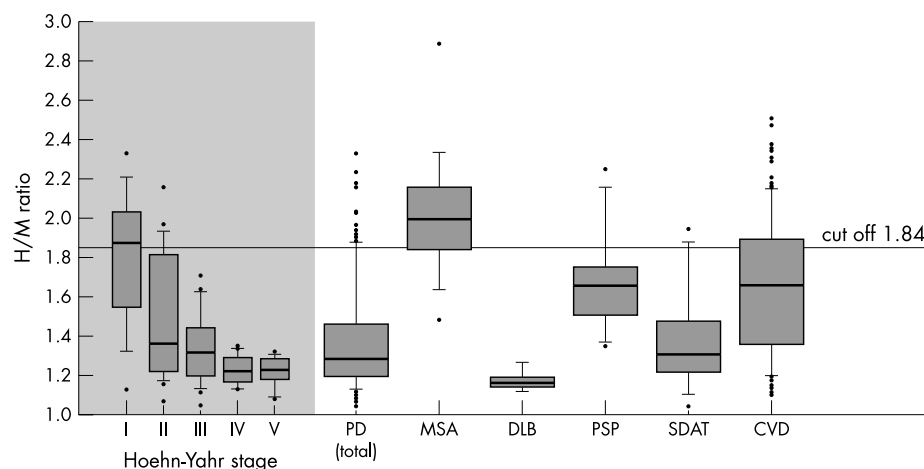
There were no significant differences in either age or sex between patients with and without PD, or with each HY stage among the patients with PD. The H/M ratio was decreased in 107 of the 122 patients with PD; it was decreased in all advanced patients with HY stage III or more, and the sensitivity and specificity of MIBG scintigraphy for diagnosing PD were 87.7% and 37.4%, respectively. Moreover, the H/M ratio had a strong negative correlation with disease severity ( $p < 0.0001$ ; fig 1).

Although 179 of the 269 patients without PD had low H/M ratios (mean, 1.66; SD, 0.37), a low ratio was seen more frequently in the PD population than in the non-PD population ( $p < 0.0001$ ; table 1). There was a significant difference in the prevalence of a low H/M ratio in PD compared with MSA ( $p < 0.0001$ ) and CVD ( $p = 0.0001$ ), but not DLB ( $p = 0.99$ ), PSP ( $p = 0.99$ ), or SDAT ( $p = 0.42$ ). Compared with PD, the H/M ratio was significantly higher in MSA ( $p < 0.0001$ ), PSP ( $p = 0.0047$ ), and CVD ( $p < 0.0001$ ), but was significantly lower in DLB ( $p = 0.024$ ). The H/M ratio was not significantly different between PD and SDAT ( $p = 0.61$ ).

## DISCUSSION

Our present study showed that most patients with PD had a low MIBG uptake, confirming previous observations.<sup>5-12</sup> However, nearly 70% of the patients without PD also had low uptake, and there were considerable overlaps in the H/M ratios between PD and the other disorders (fig 1), indicating that MIBG scintigraphy cannot necessarily distinguish PD from other disorders.

Our study revealed extremely low MIBG uptake in DLB and relatively preserved uptake in MSA and PSP, consistent with previous studies.<sup>8</sup> Interestingly, we found that nearly half of the patients with SDAT had low MIBG uptake, although previous observations have shown normal uptake in SDAT.<sup>18,19</sup> The patients with SDAT studied here were



**Figure 1** Heart to mediastinum (H/M) ratio of disorders. The box plots show the median values (centre line of box), the 25th (lower line of box), 75th (upper line of box), 10th (lower T bar), and 90th centiles (upper T bar) in each group. The cutoff line is set at 1.84—2 SD below the control mean. The correlation between the H/M ratio and disease severity in patients with Parkinson's disease is shown in the grey zone. CVD, cardiovascular disease; DLB, dementia with Lewy bodies; MSA, multiple system atrophy; PD, Parkinson's disease; PSP, progressive supranuclear palsy; SDAT, senile dementia of Alzheimer type.

diagnosed because of the presence of motor signs. A recent pathological study revealed that the sensitivity and specificity of the SDAT clinical criteria<sup>20</sup> used in our present study were low, and that several patients with clinically possible SDAT displayed additional pathological features, including Lewy body pathology, in addition to the Alzheimer pathology.<sup>21</sup> Thus, the present SDAT population might have Lewy body disorder, resulting in low MIBG uptake. In addition, the more severely reduced H/M ratio seen in DLB compared with PD and the strong negative correlation between H/M ratio and HY stage in PD suggest that Lewy body pathology itself may cause low MIBG uptake.

Our present data showed that the prevalence of a low H/M ratio was high even in patients with CVD, who are not likely to have autonomic involvement, suggesting additional factors for low MIBG uptake. Because CVD is one form of vascular accident, latent cardiac disorders might be responsible for the low uptake. In addition, the daily medications that these patients were taking might have influenced MIBG uptake.

Our results clearly show that MIBG scintigraphy is a sensitive, but not specific, test for PD. Furthermore, low MIBG uptake does not necessarily indicate PD, but is essential for the disorder, especially for the advanced form. Because no objective examinations are available for diagnosing PD, the high sensitivity of scintigraphy is clinically useful as a co-diagnostic method.

#### ACKNOWLEDGEMENTS

We thank Drs C Nito, S Amemiya, and S Okubo from the Second Department of Internal Medicine, Nippon Medical School, Japan for their clinical assistance, and Dr Y Morcos from the Department of Neurology, University of Tennessee Health Science Center, USA for her editorial assistance.

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Competing interests: none declared

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Received 20 January 2004  
 In revised form 25 March 2004  
 Accepted 28 April 2004

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