Utility of early imaging of myocardial innervation scintigraphy in the diagnosis of Lewy body dementia

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ABSTRACT

The importance of accurate and early diagnosis of dementia with Lewy bodies (DLB) lies in its pharmacological management. Delayed imaging of cardiac 123I-MIBG scintigraphy allows differentiation between DLB and other neurodegenerative diseases with cognitive impairment.

The aim of this study was to assess the utility of early imaging of cardiac 123I-MIBG scintigraphy for differentiating DLB from others neurodegenerative disease with cognitive impairment.

Material and methods: We assess retrospectively 106 patients (51 men, mean age 78 years) with cognitive impairment that underwent a cardiac 123I-MIBG study. Planar images were acquired in anterior view of the thorax 15 min (early) and 4 h (delayed) after tracer administration. The heart-to-mediastinum ratios (HMR) at 15 min (HMR15m) and at 4 h (HMR4h) were obtained.

Results: After four years, 52 patients were diagnosed of DLB. HMR15m and HMR4h were significantly inferior in DLB respect to the others neurodegenerative diseases (1.27 ± 0.15 vs 1.76 ± 0.15, p < 0.05) and (1.14 ± 0.13 vs 1.68 ± 0.19, p < 0.01), respectively. The ROC analysis showed a HMR15m cut-off point of 1.56 to differentiated DLB from the other dementias with a sensitivity and a specificity of 98%.

Conclusions: Early imaging of cardiac 123I-MIBG scintigraphy can help to differentiate DLB from other neurodegenerative diseases with cognitive impairment.

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Utility of the early imaging of the gammagrama in the differential diagnosis of Dementia with Cerebros of Lewy

RESUMEN

La realización de un correcto diagnóstico inicial ayuda al manejo clínico de los pacientes con Demencia con Cerebros de Lewy (DCLw). La imagen tardía de la gammagrama cardíaca con 123I-MIBG permite diferenciar entre DCLw y otro tipo de demencias.

El objetivo del estudio es valorar la utilidad de la imagen precoz de la gammagrama cardíaca con 123I-MIBG para el diagnóstico diferencial entre DCLw y otras demencias neurodegenerativas.

Material y métodos: Estudio retrospectivo de 106 pacientes (51 hombres, edad media 78 años) a los que se les realizó una gammagrama de inervación miocárdica por estudio de demencia. Se obtuvieron imágenes planares en proyección anterior a los 15 min (precoz) y a las 4 h (tardía) de la administración del trazador. La captación miocárdica de 123I-MIBG se semicuantificó mediante la obtención del índice de captación (ICM) a los 15 min (ICM15m) y a las 4 h (ICM4h).

Resultados: El diagnóstico clínico a los 4 años fue de 52 pacientes con DCLw. El ICM15m para los pacientes con DCLw fue significativamente inferior al de los otros pacientes (1.27 ± 0.15 vs 1.76 ± 0.15, p < 0.05), así como el ICM4h (1,14 ± 0,13 vs 1,68 ± 0,19, p = 0,01). A partir del análisis ROC se obtuvo un punto de corte del ICM15m de 1,56 con un área bajo la curva del 0,99, para poder diferenciar DCLw respecto a los otros tipos de demencia, con una sensibilidad y especificidad del 98%.

Conclusión: La imagen precoz de la gammagrama de inervación miocárdica con 123I-MIBG, puede ser útil para diferenciar la DCLw de otro tipo de demencias neurodegenerativas.

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Introduction

Lewy body dementia (LBD) is the second cause of degenerative dementia in the elderly following Alzheimer dementia (AD), being observed in 10–15% of autopsies.1 Definitive diagnosis of LBD is postmortem since the application of the International Consensus Criteria allows in vivo diagnosis with a high specificity but with limited sensitivity,2 thereby making differential diagnosis among dementias, especially AD, difficult. The importance of early
In LBD, Parkinson disease (PD) and pure autonomic failure. It has been demonstrated that the diagnosis of LBD lays in its pharmacological management due to the good response to cholinesterase inhibitors presented by these patients, albeit with secondary effects to the neuroleptics.1-3 Metiodobenzylguanidine (123I-MIBG) is an analog of noradrenaline with which it shares the same mechanisms of uptake and storage. Myocardial innervation scintigraphy with 123I-MIBG allows non-invasive evaluation of the sympathetic nervous system.4 This study consists in the acquisition of planar images of the thorax at 15 min (early image) and at 4 h (delayed image) after the administration of the tracer, with posterior semiquantification of myocardial uptake of the tracer using the heart/mediastinum (H/M) ratio. Early images reflect the integrity of the presynaptic nerve terminals while delayed images reflect the integrity of neuronal function.5,6 In LBD, Parkinson disease (PD) and pure autonomic failure, a reduction is observed in the cardiac uptake of 123I-MIBG in both the early and the delayed images secondary to the presence of Lewy bodies in the cardiac plexus.5,7 It has been demonstrated that delayed images in cardiac scintigraphy with 123I-MIBG allow differential diagnosis between LBD and other neurodegenerative diseases associated with dementia, especially AD.8-11 However, there is no evidence of the utility of early imaging for this diagnosis.

Taking into account the short duration of the test as well as its comfortability compared to other functional tests, the aim of this study was to evaluate the utility of early imaging of cardiac scintigraphy with 123I-MIBG in the differential diagnosis between LBD and other neurodegenerative dementias.

Material and methods

All the patients undergoing myocardial innervation scintigraphy for LBD from January 2003 to January 2008 were retrospectively evaluated. A total of 106 patients were included over these 5 years (51 men and 55 women) with a mean age of 78 years (range 61–89). The patients were visited by a neurologist with experience in neurodegenerative diseases in the Memory Unit of the Hospital de la Santa Creu i Sant Pau in Barcelona, Spain. Patients with diseases or taking medication known to interfere with the uptake of 123I-MIBG were excluded.12

Myocardial innervation scintigraphy

Thirty minutes after thyroid blockade with 500 mg of oral potassium perchlorate 370 MBq (10 mCi) of 123I-MIBG were endovascularly administered. The scintigraphic studies were obtained at 15 min (early image) and at 4 h (delayed image) after the administration of the tracer. The acquisition of the studies was performed in a gamma camera (General Electric Millenium Hawkeye V3) equipped with parallel hole collimators for general purposes and centered in the photopeak of the 123I (159 keV) with an energy window of 20%. Planar images of the thorax were obtained in anterior projection and a 128 × 128 matrix. The early image was acquired for a fixed number of counts (1000 K) while the delayed image, was acquired for the same time duration as the early image.

Myocardial uptake of 123I-MIBG was semiquantified using the H/M ratio at 15 min (H/M15m) and at 4 h (H/M4h). To obtain the H/M ratio, areas of interest were drawn over the cardiac area and the mediastium, the average counts/pixel of each of the regions drawn and the following formula was applied.

\[
\text{H/M ratio} = \frac{(\text{counts/pixel})_{\text{heart}}}{(\text{counts/pixel})_{\text{mediastinum}}}
\]

Table 1

<table>
<thead>
<tr>
<th>Type of Dementia</th>
<th>H/M15m</th>
<th>H/M4h</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBD</td>
<td>1.26 ± 0.14</td>
<td>1.14 ± 0.12</td>
</tr>
<tr>
<td>AD</td>
<td>1.77 ± 0.15</td>
<td>1.66 ± 0.21</td>
</tr>
<tr>
<td>Parkinson Plus</td>
<td>1.72 ± 0.16</td>
<td>1.65 ± 0.17</td>
</tr>
<tr>
<td>FD</td>
<td>1.75 ± 0.08</td>
<td>1.72 ± 0.13</td>
</tr>
<tr>
<td>Vascular D</td>
<td>1.77 ± 0.13</td>
<td>1.74 ± 0.11</td>
</tr>
<tr>
<td>NT hydrocephalus</td>
<td>1.64</td>
<td>1.73</td>
</tr>
<tr>
<td>MACD</td>
<td>1.81 ± 0.16</td>
<td>1.68 ± 0.17</td>
</tr>
</tbody>
</table>

LBD: Lewy body dementia; AD: Alzheimer dementia; FD: frontal dementia; Vascular D: vascular dementia; NT hydrocephalus: normotensive hydrocephalus; MACD: mild amnestic cognitive decline.

Statistical analysis

The “Statistical Package for Social Sciences” (SPSS) (v. 18) was used for statistical analysis. The H/M15m followed a normal distribution in the whole sample. The qualitative results are expressed as percentages and the quantitative results as means ± standard deviation. To determine the significance of the differences between the variables, analysis of variance (ANOVA) was performed. The differences between the means were calculated using the T test for independent samples. ROC (receiver operating curve) analysis was done to calculate the cut off of the H/M15m to differentiate between LBD and other neurodegenerative diseases. Results with p < 0.05 were considered significant.

Results

At 4 years the final clinical diagnosis was made based on the International Clinical Consensus Criteria with 52 (4 with 52 (49.1%) patients with LBD, 31 (29.2%) with AD, 9 (8.5%) with Parkinson Plus (4 progressive supranuclear palsy, 4 multisystemic atrophy and 1 corticobasal degeneration), 6 (5.7%) with frontotemporal dementia, 5 (4.7%) with vascular dementia, 1 (0.9%) normotensive hydrocephalus and 2 (1.9%) with mild amnestic-type cognitive deterioration.

No statistically significant differences were observed between the age and the sex among the different groups of dementias (p > 0.05).

Table 1 shows the H/M15m and H/M4h for each type of dementia. The H/M15m of the patients with LBD was significantly lower than that of those diagnosed with another type of dementia (1.27 ± 0.15 vs 1.76 ± 0.15, p < 0.05). Likewise, the same occurred with the H/M4h (1.14 ± 0.13 vs 1.68 ± 0.19, p < 0.01). All the patients with a reduction in the H/M15m, also presented a reduction in the H/M4h (Figs. 1 and 2).

A cut off of the H/M15m of 1.56 was obtained with the ROC analysis, with an area under the curve of 0.99 and with a sensitivity and specificity of 98% to differentiate between LBD and other types of neurodegenerative dementias.

Discussion

The initial diagnosis of LBD should take into account the specific symptoms such as visual hallucinations, falls and sleep alterations which these patients present and are generally not considered in other types of dementia. When the grade of dementia is similar, it has been observed that patients diagnosed with LBD have greater functional alteration and worse quality of life than those with AD.13 Moreover, patients with LBD present good response to cholinesterase inhibitors but with elevated secondary effects to neuroleptic drugs.1,13 Therefore, a correct initial diagnosis helps not only the clinical management but also the evaluation of the prognosis of dementia in these patients.
The last International Clinical Consensus Criteria 

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To the contrary, the present study aimed to 

One of the histopathological characteristics which Lewy body diseases present, including LBD, PD and pure autonomic failure, is an alteration in cardiac sympathetic innervation because the presence of Lewy bodies produces a reduction in the cardiac uptake of $^{123}$I-MIBG.\textsuperscript{5,14} The last International Clinical Consensus Criteria considered an alteration in sympathetic innervation demonstrated with $^{123}$I-MIBG as clinical criteria supporting the disease.\textsuperscript{2} On the other hand, the 4th International Workshop of LBD and PD associated with dementia proposed the inclusion of an alteration in myocardial sympathetic innervation scintigraphy as criteria suggestive of LBD.\textsuperscript{15}

In the last International Clinical Consensus Criteria a reduction in basal lymph nodes observed by SPECT or PET appeared as suggestive criteria.\textsuperscript{2} Recently, our center studied the relationship between myocardial innervation scintigraphy and dopamine transporter SPECT in 28 patients diagnosed with LBD and found an reduction in the $H/M_{4h}$ and an alteration in the cerebral SPECT in 23 of these patients, with a significant correlation between the two tests ($p < 0.05$). We therefore concluded that both an alteration in cardiac sympathetic innervation and an alteration in the presynaptic nigrostriatal occur in parallel in patients with probable LBD.\textsuperscript{16}

Treglia et al.\textsuperscript{17} recently reviewed the utility of myocardial scintigraphy with $^{123}$I-MIBG in 8 studies including a total of 346 patients (152 diagnosed with LBD and 194 with other types of dementia). The results obtained indicated that the $H/M_{4h}$ presented a sensitivity of 98% and a specificity of 94% (both with a confidence interval of 95%, 94–100%) to differentiate between LBD and other dementias and concluded that scintigraphy with $^{123}$I-MIBG allows precise differential diagnosis.

To date, the studies undertaken to evaluate the utility of scintigraphy with $^{123}$I-MIBG in LBD are based on the $H/M_{4h}$ as a specific marker for the assessment of myocardial sympathetic innervation.\textsuperscript{8,9,18} To the contrary, the present study aimed to evaluate the utility of early imaging ($H/M_{15m}$) in the differential diagnosis between degenerative dementias with the aim of reducing the duration of the study and thereby increase the comfortability of the patients. The results obtained show a significant reduction in the $H/M_{15m}$ of patients with LBD compared with those with other types of dementia, with a cut off of 1.56 providing a sensitivity and specificity of 98%.

Although the $H/M_{4h}$ reflects the specific neuronal uptake of $^{123}$I-MIBG, the $H/M_{15m}$ reflects the integrity of the myocardial sympathetic system and the distribution of the myocardial sympathetic neurones. No previous study has compared these two ratios, but similar to the $H/M_{4h}$, it has been described\textsuperscript{9,19} that the $H/M_{15m}$ also presents statistically significant differences in patients with LBD compared to patients with other neurodegenerative dementias. Orimo et al.\textsuperscript{14} have histopathologically demonstrated a marked reduction in the myocardial sympathetic terminations in 11 patients with LBD independently of the age, sex, disease duration or the presence of orthostatic hypotension, with cardiac sympathetic denervation being a histopathological characteristic of Lewy body diseases. Thus, a reduction in the myocardial sympathetic terminations in patients with LBD may explain the alteration in cardiac sympathetic innervation observed in the early images, with a consequent reduction in the $H/M_{15m}$. Although further studies are necessary, the result obtained indicated the possibility of not performing the delayed images in patients presenting an important reduction in the $H/M_{15m}$, since in our study no patient with an $H/M_{15m}$ lower than 1.56 presented a normal $H/M_{4h}$. Not undertaking the delayed images would shorten the study time, increasing the comfortability of both the patients and the care providers.

The most important limitation of this study, as in most of the studies on neurological diseases, is the lack of histological confirmation of the disease since the gold pattern considered in this study is the clinical evolution. Another limitation may be the elderly age of the patients since the older the age the lower the myocardial uptake of $^{123}$I-MIBG. Nonetheless, this limitation has been obviated by the absence of statistically significant differences in the age of the patients in the two groups of dementias. Finally, the limitation related to possible false positives due to diseases and medications which may interfere with the cardiac uptake of $^{123}$I-MIBG was also obviated with the exclusion of these patients from the study.

![Fig. 1](http://www.elsevier.es) Patient diagnosed with Lewy body dementia. Both the early image (A) and the delayed image (B) show an important reduction in the myocardial uptake of $^{123}$I-MIBG. $H/M_{15m}$: 1.20, $H/M_{4h}$: 1.10.

![Fig. 2](http://www.elsevier.es) Patient diagnosed with Alzheimer dementia. The early image (A) and the delayed image (B) show correct myocardial uptake of $^{123}$I-MIBG. $H/M_{15m}$: 1.75, $H/M_{4h}$: 1.64.
Conclusion

Patients with LBD present a reduced H/M_{15m} compared to those with another type of neurodegenerative dementia. Thus, early imaging of myocardial innervation scintigraphy with $^{123}$I-MIBG with obtention of the H/M_{15m} may be useful to differentiate between patients with LBD and those with other types of dementias and reduce the length of the study and increase the comfortability.

Conflict of interests

The authors declare no conflict of interests.

References