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ORIGINAL ARTICLE

^{123}I-MIBG Myocardial Scintigraphy in the Diagnosis of Lewy Body Dementia

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MIBG myocardial scintigraphy;
Heart-to-mediastinum ratio

Abstract
Introduction: Lewy body dementia (LBD) is the second most common cause of neurodegenerative dementia after Alzheimer's disease (AD). A cardiac post-ganglionic sympathetic denervation has been described in this condition which can be quantified by MIBG (metaiodobenzylguanidine) myocardial scintigraphy. The aim of our work was to retrospectively evaluate cardiac MIBG uptake (expressed as the heart-to-mediastinum ratio at 4h (HMR) in patients with suspected LBD, and to examine its relationship with clinical and para-clinical data.
Material and methods: A total of 77 patients with clinical suspicion of LBD evaluated at our centre between September 2005 and June 2008 to whom a MIBG myocardial scintigraphy has been performed were retrospectively reviewed. International Consensus Criteria of LBD were applied to divide the sample into probable LBD, possible LBD and non-LBD. HMR values and their relationships with clinical and neuropsychological data were analyzed. A subgroup of patients had FP-CIT (fluoropropyl-carbomethoxy-3β-4-iodophenyltropane) SPECT as a part of the evaluation.
Results: Mean HMR values were significantly lower in probable LBD group than in possible LBD and non-LBD groups. Low HMR values were associated only with reduced FP-CIT uptake in the striatum, but not with any clinical or neuropsychological item.
Conclusions: Low MIBG myocardial scintigraphy uptake is a robust measure in LBD, and it is not largely affected by medical conditions, or by the stage of the disease. In LBD reduced MIBG myocardial uptake is associated with nigrostriatal degeneration.

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PALABRAS CLAVE
Demencia con cuerpos de Lewy;
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Índice corazón/mediastino a las 4h;
FP-CIT SPECT

Gammagrafía miocárdica con ^{123}I-MIBG en el diagnóstico de la demencia con cuerpos de Lewy

Resumen
Introducción: La demencia con cuerpos de Lewy (DCLw) es la segunda causa más frecuente de demencia degenerativa tras la demencia tipo Alzheimer (DTA). En esta entidad se ha descrito una denervación simpática cardíaca posganglionar, que puede cuantificarse mediante la gammagrafía miocárdica con MIBG (metayodobencilguanidina). El objetivo de nuestro trabajo fue evaluar retrospectivamente la captación miocárdica de MIBG, expresada cuantitativamente como el índice corazón/mediastino a las 4h (ICM) en pacientes con sospecha clínica de DCLw, y examinar su relación con los datos clínicos y paraclínicos.
Pacientes y métodos: Se revisaron retrospectivamente datos de 77 pacientes con sospecha clínica de DCLw evaluados entre septiembre de 2005 y junio de 2008 en nuestro hospital a los que se les había realizado una gammagrafía miocárdica con MIBG. Se aplicaron los criterios internacionales de consenso para dividir la muestra en DCLw probable, DCLw posible y sin DCLw. Se analizaron el ICM en cada grupo y su relación con variables clínicas y neuropsicológicas. A un subgrupo de pacientes se le había realizado además un SPECT con FP-CIT (fluoropropil-carbometoxi-3β-4-yodofeniltropano) como parte de la evaluación.
Resultados: Los valores medios de ICM fueron significativamente menores en el grupo de DCLw probable que en los grupos de DCLw posible y sin DCLw. Valores disminuidos de ICM solamente se asociaron a una captación disminuida en el estriado en el FP-CIT SPECT, pero no a ninguna variable clínica ni neuropsicológica.
Conclusiones: La captación miocárdica reducida de MIBG es una medida robusta en la DCLw, y no se ve afectada por condiciones médicas o el estadio de la enfermedad. Una disminución en la captación miocárdica de MIBG se asocia a la degeneración nigroestriada en la DCLw.

Introduction

Lewy body dementia (LBD) is part of a spectrum of degenerative disorders having some features in common, for example, the deregulation and aggregation of alpha-synuclein.[1] It is characterised pathologically by Lewy bodies and intraneuronal neurites in the limbic and neocortical areas, but also in the brainstem in varying degrees.[2] The clinical manifestations of Lewy body diseases include LBD, Parkinson's disease (PD), PD with dementia (PDD) and pure autonomic failure (PAF).[1]

Lewy body dementia is the second leading cause of degenerative dementia after Alzheimer's disease (AD) in the elderly population.[3] Its clinical features include fluctuating cognition, recurrent visual hallucinations and spontaneous parkinsonism,[2] and cognitive deficits focus on memory, attention and executive and visuospatial functions.[1] Its early differentiation from other dementias, particularly Alzheimer-type dementia (ATD), is important because LBD has a different course and prognosis; not only that, early differentiation is also important to prevent iatrogenic pharmacological interventions (in particular, marked deteriorations have been reported after treatment with neuroleptics that involve a significant increase in mortality).[1] International consensus criteria[2] make diagnosis of LBD in life possible with high specificity but poor sensitivity, and its main differential diagnosis is with ATD. Almost 60% of patients with ATD may suffer mild to moderate parkinsonism during the course of the disease,[4] which further complicates the differential diagnosis between the two entities.

We have investigated the usefulness of various diagnostic techniques used to differentiate LBD from ATD and other dementias, including structural and functional neuroimaging. However, the sensitivity of these tests is very variable, and only SPECT with fluoropropyl-2β-(carbomethoxy-3β-(4-iodophenyl)tropane (FP-CIT) is accepted as a "suggestive" criterion in international consensus standards.[2]

In LBD as well as in PD, PDD and PAF, there is a dysfunction of the autonomic cardiovascular system at a postganglionic level.[5-7] This cardiac dysfunction occurs early in the evolution of the disease, even preceding neuronal loss in sympathetic ganglia, and is due to the presence of Lewy bodies in the sympathetic system. It can be quantified by myocardial scintigraphy with metaiodobenzylguanidine (MIBG), and is associated with a decreased uptake of this radiotracer in the myocardium, expressed as a reduced heart/mediastinum (H/M) ratio. A physiological analogue of noradrenaline, MIBG is stored in sympathetic nerve terminals. Decreased myocardial MIBG uptake is not specific to LBD, as several cardiac diseases (such as acute myocardial ischemia, dilated

and hypertrophic cardiomyopathies, heart failure and severe arrhythmias) and diabetes mellitus can also present a similar pattern.[8-13] A physiological decline of the tracer can also be detected with normal aging.[8] Some drugs, such as tricyclic antidepressants, sympathomimetics, and antihypertensives may also alter the results.[14,15]

Several studies have investigated the role of myocardial scintigraphy with MIBG in the diagnosis of LBD[4-7,16-22] and have demonstrated a marked reduction of the H/M ratio in LBD, comparing ATD patients with cognitively healthy subjects. Patients with PD, PDD or PAF have similar results to those of patients with LBD, with a reduced H/M ratio, while patients with other parkinsonian syndromes, such as multisystem atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), show normal or only slightly diminished myocardial uptake of the tracer.[16,23,24] The new international consensus criteria for the diagnosis of LBD[2] mention MIBG myocardial scintigraphy as a technique that supports the diagnosis. However, the clinical correlations of reduced myocardial uptake of MIBG in LBD have not been adequately defined yet.

In this study, we evaluated the use of MIBG myocardial scintigraphy in patients with clinical suspicion of LBD. We also examined the relationship between myocardial uptake of MIBG and the typical symptoms of LBD, the results of FP-CIT SPECT and the neuropsychological profile of these patients.

Patients and Methods

Patients

We retrospectively reviewed data from 77 patients with clinical suspicion of LBD visited at the Memory Unit of the Hospital de la Santa Creu i Sant Pau between September 2005 and June 2008. All patients were examined by a neurologist with expertise in neurodegenerative diseases and met the criteria for dementia outlined in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV).[25] The neurologist who visited the patient in the clinic established the clinical suspicion of LBD if the patient presented, in addition to dementia, some of the characteristic signs or symptoms of the entity. The demographic data collected included age, gender, arterial hypertension, diabetes mellitus, dyslipidemia, stroke and heart disease, family history of dementia and treatment. The main criterion for inclusion in the study was having undergone an MIBG myocardial scintigraphy due to clinical suspicion of LBD.

Most patients underwent a neuropsychological study as part of their evaluation that included Mini-Mental State Examination (MMSE)[26,27] (adjusted score), Blessed dementia scale,[28] Boston naming test,[29] semantic and phonetic verbal fluency,[30] Global Deterioration Scale (GDS),[31] and Interview for Deterioration in Daily Life in Dementia (IDDD).[32] Only those neuropsychological studies conducted more than 12 months before or after the scintigraphy scan were reviewed.

To analyse the results, 2 neurologists applied international consensus criteria for LBD[2] independently and classified the cases into probable LBD, possible LBD and without LBD. The kappa correlation coefficient between them was 0.63. In cases where there was discordance between the 2 neurologists in the classification of a patient, a diagnosis was carried out after a consensus review and discussing the case in detail. Briefly, probable LBD was considered when the patient had two of the three essential criteria of the disease (cognitive fluctuations, structured visual hallucinations and spontaneous symptoms of parkinsonism) or when the patient presented an essential criterion and one or more of the suggestive criteria (REM sleep behaviour disorders, severe neuroleptic sensitivity or reduced uptake of the basal ganglia demonstrated through PET or SPECT).

Finally, we evaluated the relationship of the H/M ratio with characteristic LBD symptoms (spontaneous parkinsonism, visual hallucinations, fluctuations in the level of consciousness and autonomic dysfunction) and clinical history, results of striatal uptake in FP-CIT SPECT, drugs and data from the neuropsychological examination.

Myocardial Scintigraphy with MIBG

Thirty minutes after thyroid blockade with oral administration of 500 mg of potassium perchlorate, 370 MBq of MIBG (GE Healthcare Biosciences) were administered intravenously. Planar thorax images were acquired 4 h after the tracer injection. A gamma camera (GE Millennium Hawkeye V3) equipped with a high-resolution collimator for low energies was used. The energy window of the gamma camera was 20% centred on the ^{123}I (159 keV) photopeak. Planar images were obtained from an anterior view of the thorax and stored in a 128?128 matrix. Myocardial activity of the MIBG tracer was semi-quantified to obtain the H/M ratio. This was calculated after drawing regions of interest on the superior mediastinum and the left ventricle in the planar images obtained at 4 h. The formula used was H/M ratio=average activity/pixel in the region of interest in the heart / average activity/pixel in the region of interest in the mediastinum. In our centre, the normal H/M ratio for patients over 65 years was >1.56.[33]

FP-CIT SPECT

In order to minimise radiation on the thyroid gland, we first proceeded to block it with potassium perchlorate (500 mg, 20 min before injection). Each subject was injected with 5 mCi (185 MBq) of intravenous ^{123}I-FP-CIT. Image acquisition was initiated 3 h after the injection. The equipment used was a 2-head gamma camera (GE Hawkeye) equipped with a parallel-opening, general purpose collimator, of high resolution and for low energy, connected to a dedicated computer for the image acquisition. The energy window of the gamma camera was 20% centred on the ^{123}I (159 keV) photopeak. SPECT was carried out to obtain 120 images of 20 s each, throughout a range of 360° in a circular orbit in "stop-shot" mode. All the projections were stored using a 128?128 matrix and processed with a Butterworth filter. Following the image acquisition, we proceeded to obtain axial, oblique, coronal and sagittal tomographic sections, which were then quantified. Images were evaluated visually.

Table 1 Clinical features and H/M ratio in each diagnostic category after applying the international consensus criteria for LBD2

	Age (years)	Males/females (%M)	MMSE	Delay (months)	H/M ratio
Probable LBD (n=55)	74.9±6.5	31/24 (56.4%)	21.6±5.6	42.1±23.7	1.35±0.27
Possible LBD (n=18)	72.4±6.1	5/13 (27.8%)	18.6±5.3	41.9±43.8	1.59±0.24[a]
Without LBD (n=4)	74±8.8	2/2 (50%)	25.7±1.3	42±14.8	1.82±0.28[b]
Total (n=77)	74.3±6.5	38/39 (49.4%)	21.2±5.6	42±28.94	1.43±0.29

%M: Percentage of males; Delay: time from onset of symptoms until the performance of myocardial scintigraphy; H/M ratio: heart/mediastinum ratio; LBD: Lewy body dementia; MMSE: score on the Mini-Mental State Examination[26,27]

[a]Statistical significance (P=.004) between the H/M ratio of the group with probable LBD and possible LBD.

[b]Statistical significance (P=.004) between the H/M ratio of the group with probable LBD and without LBD. The data express mean ± standard deviation, unless indicated otherwise.

Statistical Analysis

We used the Statistical Package for Social Sciences (SPSS) (v.17) for all the analyses. The H/M ratio followed a normal distribution throughout the sample. An analysis of covariance (ANCOVA) was carried out, with the H/M ratio as an independent variable in all diagnostic groups and with Scheffe's F *post hoc* test. The Student t test was performed to assess the relationship between the H/M ratio and variables such as gender, the results of striatal uptake in the FP-CIT SPECT, the personal and family history and characteristic LBD symptoms. We performed a Pearson correlation analysis to assess the relationship of the H/M ratio with age and neuropsychological variables. The results were expressed as a percentage for qualitative variables and as mean ± standard deviation for quantitative data. Probability values $P<.05$ were considered significant. The kappa correlation coefficient was calculated to determine the agreement between the 2 neurologists when independently implementing the international consensus criteria for LBD.[2]

Results

We collected data from 77 patients (38 men and 39 women). The mean age of the entire sample was 74.3±6.5 years.

The patient sample was classified into probable LBD (n=55), possible LBD (n=18) or without LBD (n=4) according to international consensus criteria for LBD.[2] Table 1 shows the clinical characteristics and the H/M ratio after applying these criteria. There were no statistically significant differences between groups with respect to age, gender, MMSE score and duration of symptoms at the time of the scintigraphy. The average H/M ratio was significantly lower in the group with probable LBD with respect to the group with possible LBD (1.35±0.27 vs 1.59±0.24 respectively; $P=.004$) and also with respect to the group without LBD (1.35±0.27 vs 1.82±0.28 respectively; $P=.004$) (fig. 1). No significant differences in the H/M ratio were found between the groups with possible LBD and without LBD. Among patients classified as with probable LBD, 13 presented an H/M ratio >1.56 (considered as a normal value in our laboratory[33]). The 4 patients classified as without LBD were clinically diagnosed as suffering AD (n=3) and mixed dementia (n=1).

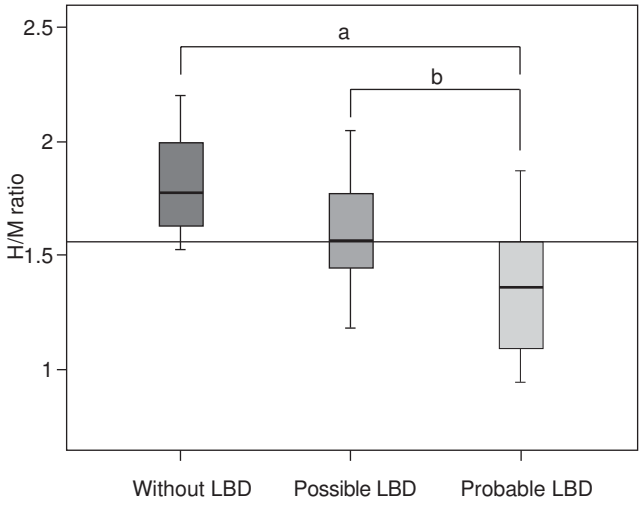

Figure 1 Relationship of the heart/mediastinum (H/M) ratio with the diagnosis according to international consensus criteria for Lewy body dementia (LBD).2 The cut-off point was set at 1.56 (normal H/M ratio value for patients over 60 years according to our laboratory).[33]
Statistical significance (p=0.004) among groups with probable DCLw without DCLw. Statistical significance (p=0.004) among group with possible DCLw and probable DCLw.

We also studied the relationship between the H/M ratio and gender, the characteristic symptoms of LBD and the personal or family history of the patient (table 2). A significant association was found only between low H/M ratio values and low striatal uptake in FP-CIT SPECT ($P=.002$). Patients with Parkinsonism had a lower H/M ratio than patients without Parkinsonism, although the difference did not reach statistical significance. Neither prior pathological history nor the use of drugs influenced the results of myocardial scintigraphy. Table 3 specifies in detail the drugs being taken by patients at the time of myocardial scintigraphy.

Lastly, no relationship was found for the H/M ratio with any neuropsychological test, or with age or duration of symptoms at the time of myocardial scintigraphy (table 4).

Table 2 Relationship between the H/M ratio and clinical and demographic characteristics

	Patients (n)	Mean±SD	t	df	P
Gender					
Males	38	1.37±0.29	−1.733	75	0.087
Females	39	1.48±0.28			
Spontaneous parkinsonism					
No	27	1.54±0.27	2.47	75	0.16
Yes	50	1.37±0.29			
Visual hallucinations					
No	40	1.47±0.33	1.24	70.383	0.220
Yes	37	1.39±0.24			
Cognitive fluctuations					
No	62	1.44±0.3	0.945	73	0.348
Yes	13	1.36±0.26			
Dysautonomia					
No	44	1.4±0.32	−0.943	74.999	0.349
Yes	33	1.46±0.24			
Diseases that may interfere with myocardial uptake of MIBG[8-13]					
No	53	1.39±0.31	−1.931	75	0.057
Yes	24	1.52±0.23			
Drugs that may interfere with myocardial uptake of MIBG[14,15]					
No	46	1.4±0.33	−1.003	74.957	0.319
Yes	31	1.47±0.23			
Alteration of the FP-CIT SPECT					
No	16	1.62±0.26	3.226	57	0.002*
Yes	43	1.35±0.3			
Stroke					
No	72	1.43±0.3	−0.296	75	0.768
Yes	5	1.47±0.26			
Arterial hypertension					
No	30	1.45±0.35	0.554	48.358	0.582
Yes	47	1.41±0.25			
Diabetes mellitus					
No	58	1.39±0.3	−1.548	75	0.126
Yes	19	1.52±0.24			
Dyslipidemia					
No	52	1.42±0.3	−0.434	75	0.666
Yes	25	1.45±0.27			
Cardiopathy					
No	52	1.42±0.31	−0.615	75	0.540
Yes	25	1.46±0.26			
Family history of dementia					
No	42	1.47±0.29	1.303	75	0.197
Yes	35	1.38±0.29			

df: degrees of freedom; H/M ratio: heart/mediastinum ratio; SD: standard deviation.
*Statistical significance (P=.002) between reduced H/M ratio values and alteration of striatal uptake in FP-CIT SPECT.

Discussion

In this study, we analysed the correlations of MIBG myocardial scintigraphy in a sample of patients with clinical suspicion of LBD. Given that the clinical diagnosis of these patients may have been partly influenced by the outcome of the examination itself, 2 neurologists applied the international consensus criteria for LBD retrospectively and independently.[2] With this evidence, the sample of patients was divided into those with probable LBD, possible LBD and without LBD, and it was found that average H/M ratio differed significantly between these groups. The group with probable LBD presented the lowest values, with a statistically significant difference compared to the groups with possible LBD and without LBD, as was expected. The average H/M ratio of the group without LBD was lower than that of the group with possible LBD, although this difference did not reach statistical significance. This finding could be explained by the small size of the group without LBD (n=4), which would require a greater magnitude of difference between the H/M ratio values from both groups to find significant differences (whereas they can be found when comparing its H/M ratio with that of the group with probable LBD).

These data are consistent with those of other studies evaluating the results of myocardial scintigraphy in patients with LBD.[4,16-22] In a previous study carried out at our centre, Estorch et al[22] demonstrated, in a group of 56 dementia patients, with a 4-year clinical follow-up, that MIBG myocardial scintigraphy performed during the first visit could help to distinguish LBD from other degenerative diseases, using a H/M ratio cut-off point of 1.36, with a sensitivity of 94%, specificity of 96% and accuracy of 95%.

Several previously-published studies have focused mainly on the value of MIBG myocardial scintigraphy as a diagnostic tool for LBD, although its association with clinical and neuropsychological factors is still not well established. Only a recently published work[34] has correlated the results of MIBG myocardial scintigraphy with clinical signs of patients with probable LBD; significant differences were found only in the H/M ratio, based on the presence or absence of orthostatic hypotension. In our study, we retrospectively evaluated if there was any relationship between the values

Table 3 Patient treatment when MIBG myocardial scintigraphy was performed

Drugs	Patients, n (%)
Anti-dementia	
None	17 (22.1)
Rivastigmine	36 (46.8)
Donepezil	4 (5.2)
Galantamine	5 (6.5)
Memantine	5 (6.5)
Rivastigmine + memantine	1 (1.3)
Rivastigmine + donepezil	5 (6.5)
Rivastigmine + galantamine	2 (2.6)
Others	2 (2.6)
Anti-parkinsonians	
None	48 (32.3)
Levodopa	29 (37.7)
Neuroleptic	
None	51 (66.2)
Quetiapine	19 (24.7)
Risperidone	4 (5.2)
Olanzapine	1 (1.3)
Others	2 (2.6)
Antidepressants	
None	32 (41.6)
Fluoxetine	4 (5.2)
Sertraline	6 (7.8)
Citalopram	9 (11.7)
Escitalopram	8 (10.4)
Trazodone	8 (10.4)
Other SSRIs	3 (3.9)
SNRIs	4 (5.2)
Amitriptyline	2 (2.6)
Others	1 (1.3)
Others	
Antihypertensive	27 (29.9)
Sympathomimetics	1 (1.3)
Opioids	1 (1.3)

SNRIs: serotonin and norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

Table 4 Correlation between H/M ratio and age, duration of symptoms and results of neuropsychological assessment

	n	P	Pearson correlation
Age (years)	77	0.547	—0.7
Delay* (months)	77	0.138	—0.17
MMSE	59	0.642	—0.062
Blessed rest	32	0.224	—0.221
IDDD	39	0.39	—0.142
Semantic verbal fluency (results at 60 s)	49	0.629	0.178
Phonemic verbal fluency (results at 60 s)	48	0.226	0.178
Boston denomination test	52	0.456	0.106
GDS	46	0.233	—0.18

GDS: Global Deterioration Scale[31]; H/M ratio: heart/mediastinum ratio; IDDD: Interview for Deterioration in Daily Life in Dementia[32]; MMSE: Mini-Mental State Examination[26,27].

*Time from onset of symptoms until the completion of myocardial scintigraphy.

of the H/M ratio and demographic, clinical or neuropsychological factors. We found no relationship between reduced MIBG uptake and clinical variables such as age, gender, medical history or drug treatment. This probably means that cardiac sympathetic denervation is an early, robust occurrence in LBD, and is not influenced by clinical or demographic variables.

According to international consensus criteria,[2] FP-CIT SPECT is the only imaging technique considered as an indicative criterion of LBD. Decreased striatal uptake in FP-CIT SPECT reflects the degeneration of the nigrostriatal pathway in the caudate and putamen. Taking advantage of the fact that 59 (77%) patients in our sample had undergone a FP-CIT SPECT and a MIBG myocardial scintigraphy as part of their clinical evaluation, we analysed their results and found a significant association between reduced striatal uptake in FP-CIT SPECT and diminished values of H/M ratio in MIBG myocardial scintigraphy. The strong association between the results of myocardial scintigraphy and the FP-CIT SPECT in our study highlights the fact that myocardial sympathetic denervation is associated with nigrostriatal degeneration in LBD.

The limitations of this study include its retrospective nature, the small sample size, the limitations of the neuropsychological study (with no tests that assessed the visual-perceptive, visual-constructive and executive functions more specifically), the absence of pathological confirmation of the diagnosis and the lack of a control group. However, the data reflect the daily experience in a reference memory unit.

In summary, the data in our study supports the usefulness of MIBG myocardial scintigraphy in the diagnosis of LBD. We conclude that myocardial sympathetic denervation is a robust feature in LBD, independent of demographic and clinical data, which is associated with the nigrostriatal degeneration observed in this disease.

Presentation

Part of this work was presented at the 60th Annual Meeting of the Spanish Society of Neurology, in Barcelona in 2008.

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This study has not received funding.

Conflict of interests

The authors declare no conflict of interests.

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