



# Clinical imaging in dementia with Lewy bodies

Ajenthnan Surendranathan, John Tiernan O'Brien

Department of Psychiatry, University of Cambridge, Cambridge, UK

**Correspondence to** Dr Ajenthnan Surendranathan, Department of Psychiatry, University of Cambridge, CCB2 0QQ, UK; as2489@medschl.cam.ac.uk

## ABSTRACT

Dementia with Lewy bodies (DLB) is a common neurodegenerative dementia in older people; however, the clinical features, particularly cognitive fluctuations and rapid eye movement sleep disorder, are often hard to elicit, leading to difficulty in making the diagnosis clinically. Here we examine the literature for the evidence behind imaging modalities that could assist in making the diagnosis. Dopamine transporter (DAT) imaging remains the best modality for differentiation from dementia of Alzheimer's type with high sensitivity and specificity reported based on pathological diagnoses. <sup>123</sup>Iodine-metaiodobenzylguanidine myocardial scintigraphy (MIBG) however is rapidly becoming an alternative imaging modality for the diagnosis of DLB, though studies assessing its accuracy with postmortem verification are still awaited. However, there are suggestions that MIBG may be better in the differentiation of vascular parkinsonism from DLB than DAT scans but may have lower sensitivity for detecting DLB compared with the 80% sensitivity seen in DAT imaging. Structural MRI scans have long been used for the diagnosis of dementia; however, their utility in DLB is limited to revealing the presence of coexisting Alzheimer's disease. Fluorodeoxyglucose (FDG) PET is an alternative biomarker that can also differentiate Alzheimer's disease and DLB but lacks the evidence base of both DAT and MIBG scans.

## INTRODUCTION

Dementia with Lewy bodies (DLB) is a common form of dementia in older people characterised by Lewy bodies consisting mainly of alpha-synuclein<sup>1</sup> within the brain at postmortem of patients who had a clinical dementia syndrome. The criteria for DLB has recently been updated<sup>2</sup> to reflect the increasing use of biomarkers, with imaging biomarkers playing a key role (see [table 1](#)).

The frequency of DLB as a proportion of all dementia in postmortem studies (at least 15%)<sup>3,4</sup> exceeds that found in clinical prevalence studies (4%–5%),<sup>5,6</sup> raising the suggestion that detecting the condition clinically is more difficult than other types of dementia. Indeed, a recent meta-analysis of the diagnostic accuracy of the clinical criteria to date found that about 20% of DLB diagnoses were incorrect.<sup>7</sup> The increasing use of imaging biomarkers and their raised prominence in the diagnostic criteria aims to help clinicians bridge the gap between clinical and pathological prevalence rates.

In particular, differentiation of patients with DLB from patients with Alzheimer's dementia (AD) is often difficult for clinicians, especially as Alzheimer's pathology can be present to varying degrees in DLB, affecting the clinical presentation and imaging findings.<sup>8</sup> Nevertheless, differentiating DLB is important for the patient in order to increase vigilance of associated comorbidities such as autonomic dysfunction, to avoid harmful medications such as neuroleptics and to facilitate appropriate

treatment of any movement disorder.<sup>9</sup> Similarly, early identification will prevent delays in management and unnecessary investigations.

Here we study the evidence behind the latest imaging techniques in DLB and their usefulness in making a DLB diagnosis. Given the difficulties in diagnosing DLB clinically, the review focusses mainly on imaging studies where the diagnoses are confirmed pathologically.

## METHODS

A literature search was carried out 29 September 2017 using PubMed. The following results were obtained from searches in the 'Title/Abstract' fields using the stated terms.

- ▶ (Lewy) AND (Myocardial OR MIBG): 149 articles
- ▶ (Lewy) AND (DATS\* OR FP-CIT OR \*Ioflupane OR SPECT): 274 articles
- ▶ (Lewy) AND (MR OR MRI OR Resonance): 465 articles
- ▶ (Lewy) AND (FDG\*): 120 articles
- ▶ (Lewy) AND ((amyloid OR tau) AND PET): 110 articles.

Only English language articles were considered for further review.

A search of the Cochrane library carried out on 29 September 2017 using the terms: 'dementia' or 'Lewy' or 'DLB', revealed three potentially relevant reviews. One is discussed in this review in dopamine uptake imaging. The other two found scarce evidence for the use in the early diagnosis of DLB in persons with mild cognitive impairment of both amyloid PET imaging<sup>10</sup> and fluorodeoxyglucose (FDG) PET,<sup>11</sup> though both reviews were primarily focused on AD.

**Table 1** The latest diagnostic criteria for dementia with Lewy bodies (DLB)

### Diagnostic criteria

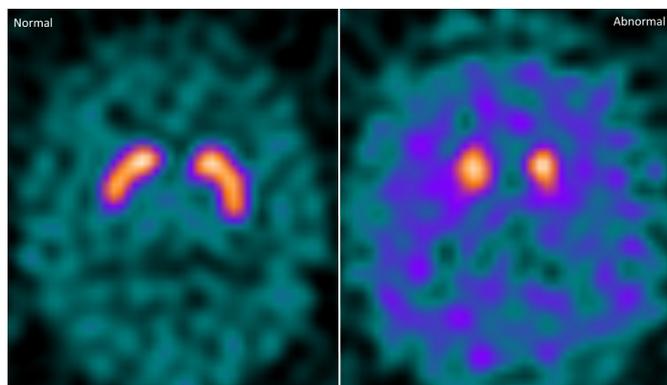
For a patient with dementia (defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions or with activities of daily living):

1. A 'probable' DLB diagnosis requires at least two core features or one core feature and at least one indicative biomarker, whereas
2. a 'possible' DLB diagnosis requires only one of the seven from the list of core features or indicative biomarkers.

Supportive biomarkers are helpful in making the diagnosis, but their specificity to DLB is not clear.

In addition, a patient must have either developed dementia before, or within 1 year, of the onset of any parkinsonian symptoms; hence, if more than a year passes before the onset of dementia following parkinsonism, the alternative diagnosis of Parkinson's disease dementia (PDD) is made.

Core features	Indicative biomarkers	Supportive biomarkers
<ol style="list-style-type: none"> <li>1. recurrent visual hallucinations</li> <li>2. fluctuating cognition</li> <li>3. spontaneous features of parkinsonism</li> <li>4. rapid eye movement (REM) sleep behaviour disorder (RBD).</li> </ol>	<ol style="list-style-type: none"> <li>1. polysomnography confirming RBD by showing REM sleep without atonia</li> <li>2. abnormal dopamine transporter (DAT) imaging revealing reduced DAT uptake in the basal ganglia</li> <li>3. <sup>123</sup>Iodine-metaiodobenzylguanidine myocardial scintigraphy revealing loss of postganglionic sympathetic cardiac innervation.</li> </ol>	<ol style="list-style-type: none"> <li>1. relative preservation of medial temporal lobe structures on CT or MRI</li> <li>2. generalised low uptake on single-photon emission CT/positron emission tomography (PET) perfusion/metabolism scan with reduced occipital activity ± posterior cingulate island sign on fluorodeoxyglucose PET imaging</li> <li>3. prominent posterior slow-wave activity on EEG with periodic fluctuations in the prealpha/theta range.</li> </ol>



**Figure 1** A comparison of a normal DAT scan on the left and an abnormal DAT scan on the right, with the latter showing reduced dopamine uptake in the basal ganglia. Images were provided by Sean Colloby (Newcastle University, UK). DAT, dopamine transporter.

### Dopamine uptake imaging (dopamine transporter (DAT) scans)

<sup>123</sup>I-ioflupane single-photon emission computed tomography (SPECT) assesses DAT uptake in the basal ganglia *in vivo*. SPECT is a nuclear imaging modality that measures radioactivity of gamma rays emitted from radioactive compounds that are bound to tracers. By binding to the DAT, <sup>123</sup>I-ioflupane allows imaging of the presynaptic terminal. The utility of DAT scans particularly in differentiating DLB from AD is based on the reduction of dopamine terminals within the striatum (see figure 1) seen in DLB, compared with their relative preservation in AD.<sup>12</sup> However, DAT imaging can be abnormal in other degenerative disorders where dopaminergic transmission is affected, such as frontotemporal dementia (FTD),<sup>13</sup> corticobasal degeneration (CBD),<sup>14</sup> progressive supranuclear palsy and multiple systems atrophy.<sup>15</sup>

A Cochrane review of DAT imaging for the diagnosis of DLB examined medical literature up until February 2013 for studies that used DAT imaging to diagnose DLB among those with dementia in secondary care and found only one study<sup>16</sup> that verified the results with postmortem examination. Sensitivity was 100% and specificity was 92%, which was more accurate than the clinical diagnoses, hence the reviewers concluded that clinical diagnosis was an unsuitable reference standard. However, the small size of the study (23 participants) and narrow patient group (with moderate dementia, suspected clinically to be AD or DLB and one patient with suspected CBD), led the reviewers to conclude that, though promising, DAT imaging may be less accurate than the results suggested, particularly in patients with mild dementia or with limited symptoms of DLB.<sup>17</sup>

Nevertheless, a further systematic review of the literature up until August 2015 using an established framework for assessing biomarkers found strong evidence for the use of DAT scans in differentiating DLB from AD, including backing for the rationale, as well as specificity of abnormal results for DLB in comparison with AD, together with well-established parameters for the definition of an abnormal scan.<sup>18</sup> The review also highlighted the lack of evidence (at the time) for DAT scans in identifying early or prodromal DLB and minimal comparisons between imaging modalities for the differentiation of DLB from AD.<sup>18</sup>

However, since these two reviews, the evidence for supporting the use of DAT scans in diagnosing DLB has continued to build. A larger postmortem study involving 33 probable DLB cases and 22 AD cases, with eventual confirmation on autopsy of 30 cases of either pure DLB (23) or mixed DLB/AD (7), reported sensitivity of 80% and specificity of 92% for LBD, compared with a sensitivity of 87% and a specificity of 72% for clinical diagnosis when blinded to DAT scan results. Three of the 30 pathologically confirmed DLB subjects however had normal DAT scans, but these patients were found to have minimal pathology in the brain stem (with predominantly neocortical or limbic Lewy bodies) and had presented with fluctuations and visual hallucinations,<sup>19</sup> suggesting

DLB patients with minimal brainstem Lewy bodies and therefore minimal parkinsonism maybe missed. Indeed, a negative correlation between the severity of parkinsonism and DAT uptake in the striatum has been reported in patients with DLB, with no correlation with the other core features of DLB.<sup>20</sup> There were also three false-negative DAT scans in the recent postmortem study, from patients who had AD clinically at the time of their scan, but developed DLB symptoms in the years afterwards, suggesting Lewy body pathology was not present at the time of the scan, but may have developed later, leading to mixed AD/DLB ultimately.<sup>19</sup>

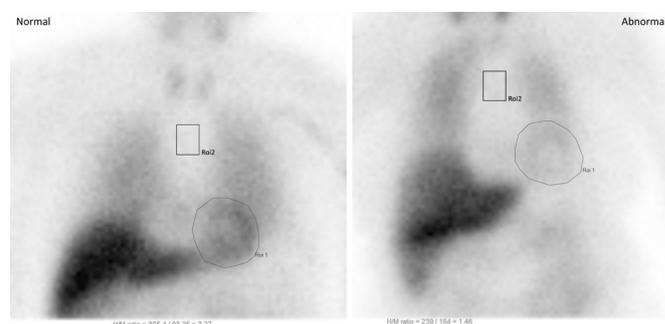
Studies have also assessed the underlying methodology. The 'striatal binding ratio' is used for semiquantitative analysis of DAT scans, but interobserver errors are still seen.<sup>21</sup> Combining semiquantitative analysis with visual rating however increases sensitivity for neurodegenerative dopaminergic diseases<sup>22</sup> including DLB<sup>23</sup>; however, these studies were based on clinical diagnoses only.

A comparison of a 'prodromal' DLB group (defined as having rapid eye movement (REM) sleep behaviour disorder (RBD), olfactory dysfunction, autonomic dysfunction and depression and diffuse occipital hypometabolism on FDG PET), with clinically diagnosed probable DLB as well as AD patients, found both DLB groups to have lower striatal binding ratios than the AD group. In addition, the level of binding in both groups was again negatively correlated with the level of parkinsonism.<sup>24</sup> This suggests that DAT imaging may even be able to distinguish early DLB in those presenting with mild symptoms.

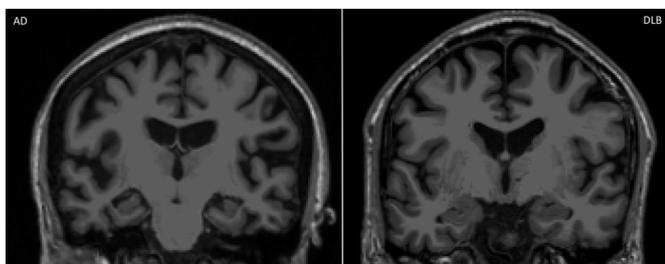
Hence, DAT scans are an excellent measure of an underlying dopaminergic disorder involving the striatum and, in a patient presenting clinically with a dementia syndrome, are a very good means of differentiation from pure Alzheimer's disease, even in early disease.

### Cardiac sympathetic denervation: MIBG

DLB can be associated with cardiac sympathetic denervation, contrasting with relative preservation in AD.<sup>25</sup> The SPECT tracer MIBG allows the detection of early changes in the cardiac sympathetic nervous system non-invasively. The heart-to-mediastinum ratio (commonly referred to as the H/M ratio) of MIBG uptake (see figure 2) is reduced in DLB when compared with healthy adults and in those with AD, providing a useful means of differentiating DLB from other dementias. A meta-analysis in 2010 reviewed eight studies comprising a total of 346 patients with dementia (152 patients with DLB and 194 patients with other dementias) and revealed a pooled sensitivity in the detection of DLB of 98% and a pooled specificity in the differential diagnosis between DLB and other dementias of 94%. The area under the receiver operating characteristic (ROC) curve was a very high 0.99,<sup>26</sup> confirming the utility of MIBG imaging in the diagnosis of DLB. More recently, however, the first large multicentre



**Figure 2** A comparison of a normal MIBG scan on the left and an abnormal MIBG scan on the right. The heart (Roi 1/oval) to mediastinum (Roi 2/rectangle) ratio is lower in the abnormal scan, indicating a loss of sympathetic innervation. Images were provided by Joseph Kane (Newcastle University, UK), Alan Thomas (Newcastle University, UK) and Jim Lloyd (Royal Victoria Infirmary, Newcastle upon Tyne, UK).



**Figure 3** A comparison of coronal T1 MRI scans showing relative atrophy within the hippocampus/temporal lobe in an AD subject (left) compared with a DLB subject (right). Images were provided by Elijah Mak (University of Cambridge, UK). AD, Alzheimer's dementia; DLB, dementia with Lewy bodies.

study including 61 patients with probable DLB, 26 patients with possible DLB and 46 patients with probable AD showed a much lower sensitivity (69%) and also a lower specificity (89%), though this was higher in mild dementia subjects (scoring 22 or more on the mini mental state examination)<sup>27</sup> at 77% and 94%, respectively. However, neither the review nor the multicentre study was supported by postmortem confirmation of DLB diagnoses, raising doubts about the figures reported by each.

Indeed, a recent review of MIBG as a biomarker for DLB revealed that a standardising procedure between operators such as the measurement and quantification of the H/M ratio is yet to be established and also that a correlation between *in vivo* imaging and postmortem tissue sampling is still awaited. In addition, further research is required to identify whether different thresholds are needed for subpopulations of patients, for example, by age group, gender or for those on certain cardiac medications, which can all affect MIBG uptake.<sup>18</sup>

MIBG has also been shown to be useful in the differentiation of parkinsonian symptoms arising from vascular lesions. DAT scans can sometimes be abnormal in vascular parkinsonism, possibly due to inability of the tracer to reach presynaptic receptors as a result of the vascular lesions. Hence, an MIBG scan in such cases aids in the differentiation between a vascular and degenerative cause for the parkinsonism.<sup>28</sup>

Comparison of MIBG and DAT in 30 patients with a clinical diagnosis of probable DLB and 29 patients with non-DLB dementia (13 with AD but also 16 with FTD, which can present with parkinsonism) found MIBG to have better detection rates: MIBG sensitivity of 93% and specificity of 100% and DAT scan sensitivity of 90% and specificity of 76%. Hence, MIBG may be better at detecting DLB in patients with parkinsonism.<sup>29</sup> A comparison in just DLB and AD subjects found DAT scans to be slightly more accurate, sensitivity and specificity 72% and 94% for MIBG, and 88% and 89% for DAT scans.<sup>30</sup> In a comparison with brain perfusion SPECT in DLB subjects alone, sensitivity was the same for both at 79% and better than brain perfusion SPECT (53%).<sup>31</sup> None of the comparison studies were verified with postmortem confirmation of the diagnosis.

### Magnetic resonance imaging

Structural MRI is used extensively in patients presenting with dementia to help with diagnosis. An early literature review highlighted preservation of the hippocampus and medial temporal lobe volume (see figure 3) in DLB in comparison with AD on structural MRI; however, these differences were on a group level between patients with DLB and AD, and sensitivity was found to be a low 40%.<sup>32</sup>

Subsequent studies provided autopsy verification of the diagnosis of DLB and confirmed that medial temporal atrophy on MRI is specific for AD in comparison with DLB (specificity of 94%).<sup>33</sup> Another study found antemortem hippocampal and amygdala volumes increased as you progressed from 'low' to 'intermediate' to 'high' likelihood DLB patients, a means of grading the likelihood that autopsy findings are associated

with typical DLB clinical features based on the distribution of Lewy body pathology and the Braak stage of coexisting Alzheimer's pathology.<sup>8</sup> The reverse was found with dorsal mesopontine volume that decreased as you progressed from 'low' to 'intermediate' to 'high' likelihood DLB patients.<sup>34</sup> Similarly, a further study looking at the impact of coexisting AD pathology, using serial MRIs with postmortem confirmation of diagnosis, showed greater atrophy rates within patients with mixed AD/DLB in the whole brain, temporoparietal cortices, hippocampus and amygdala, similar to patients with AD. However, those without coexisting AD pathology had lower atrophy rates, similar to controls, suggesting global and regional atrophy rates are associated with AD-type pathology in DLB.<sup>35</sup>

The most recent MRI study with autopsy confirmed diagnosis and also the largest with 186 patients (25 DLB, the others with AD or other tauopathies or TDP43 pathology) and 73 controls showed results consistent with previous studies: global atrophy when compared with other dementia subtypes was lower, there was sparing of the hippocampus and regional atrophy was only found bilaterally in the amygdala, though the latter was not significant in comparison with AD subjects.<sup>36</sup>

In addition, there have been reports of insular atrophy in prodromal DLB compared with AD, but once more these studies did not have post-mortem verification.<sup>37,38</sup> More recently, 7 Tesla high-resolution MRI has been used to study dementia; however, so far, there have not been any DLB studies.<sup>39</sup>

Hence, structural MRI is a useful means of assessing for AD pathology, and in a patient presenting with clinical symptoms of DLB, medial temporal atrophy or global atrophy on MRI is likely to indicate a mixed AD/DLB picture. In addition, bilateral atrophy in the amygdala is a specific marker of DLB. Nevertheless, an MRI with minimal atrophy would also be consistent with DLB pathology, with little or no coexisting AD pathology.

### FLUORODEOXYGLUCOSE PET

FDG PET is an *in vivo* marker of metabolism that uses a radioactive analogue of glucose to show areas of hypometabolism consistent with dementia, with the pattern of such areas used to identify the underlying diagnosis.

In DLB, occipital hypometabolism has been confirmed by a number of studies using postmortem verification of diagnoses.<sup>40,41</sup> In the Alzheimer's disease Neuroimaging Initiative study, six patients with pure AD and five with AD/DLB underwent FDG PET prior to autopsy. Those with DLB pathology demonstrated occipital hypometabolism bilaterally when compared with those without (80% sensitivity and 100% specificity for DLB), though other areas of hypometabolism were shared with AD subjects.<sup>40</sup> Another study with 15 DLB or mixed AD/DLB and 10 AD patients found both DLB and AD/DLB patients had reduced metabolism in the occipital cortex, which again distinguished patients with DLB pathology from those with pure AD but with different sensitivity (90%) and specificity (80%).<sup>41</sup>

Kantarci and colleagues' multimodal imaging study<sup>42</sup> assessed clinically diagnosed DLB and AD (21 in each group) and again found hypometabolism in the occipital cortex, but FDG PET had the lowest area under the ROC curve (0.84) when compared with MRI (0.89) and amyloid PET (0.89). Also, increased levels of metabolism were identified in the posterior cingulate compared with the sum of the precuneus and cuneus. The latter has been named the 'Cingulate Island Sign' and has been found to be more specific than occipital hypometabolism for DLB in a separate clinically diagnosed cohort.<sup>43</sup>

In summary, there is good evidence for occipital hypometabolism as a marker of Lewy body pathology in patients with dementia. However, studies have been small and the sensitivity and specificity inconsistent, meaning that the accuracy of this finding is unclear.

### Perfusion SPECT imaging

Perfusion SPECT, similar to FDG PET, uses a surrogate marker of neuronal activity to diagnose dementia, namely cerebral blood flow. It is a well-established technique, with the earliest DLB study in 2001 showing 64% sensitivity and 76% specificity in differentiating 23 DLB subjects from 50 AD subjects (two patients in each cohort had diagnosis verified by autopsy). Reduced perfusion within the occipital lobe in DLB and in the temporal lobe in AD were used as markers.<sup>44</sup> A systematic review of later studies showed a pooled sensitivity and specificity of 70% and 76%, respectively, in the differentiation of AD from DLB in a combined 62 AD and 57 DLB clinically diagnosed patients but noted the small sample sizes in each underlying study.<sup>45</sup> A direct comparison with FDG PET in differentiating 38 AD and 30 DLB subjects found FDG PET to be superior with the area under ROC curve 0.80 for FDG PET against 0.58 for perfusion SPECT, with the authors suggesting increasing availability and reducing costs means FDG PET should be the investigation of choice where both are available.<sup>46</sup>

### Amyloid PET imaging

PET ligands can now identify amyloid burden *in vivo*, but assessing the presence of amyloid is unlikely to accurately differentiate DLB from AD. Indeed, a recent review of amyloid PET imaging found Lewy body disorders had lower cortical amyloid than AD but that there was a subset of patients who had elevated levels compared with controls. However, as there was such a large variation, this limits the use of these scans in the diagnosis of DLB.<sup>47</sup> Furthermore, with the recent introduction of *in vivo* tau PET imaging, which has been found to correlate well with postmortem neurofibrillary tangles,<sup>48</sup> the utility of amyloid imaging even in the diagnosis of AD is likely to diminish.

### Machine learning multivariate methods

Newer techniques involving algorithmic learning of imaging modalities using artificial intelligence have the potential to allow clinicians to apply neuroimaging research at an individual level. Alzheimer's disease has seen the most extensive research, with support vector machines able to differentiate AD subjects from controls using MRI with an accuracy of between 71% and 100%. Machine learning could also be used to predict both conversion of prodromal symptoms to fully fledged disease and potential responses to treatment.<sup>49 50</sup> This is a rapidly evolving field; however, studies in DLB are still awaited.

### CONCLUSION

The evidence base for the use of imaging markers in DLB is still small, especially when compared with AD, with few large studies evaluating the accuracy of imaging biomarkers in pathologically confirmed DLB. Nevertheless, DAT imaging has been shown in two studies to be more specific than clinical diagnostic criteria for DLB and should be the imaging modality of choice in differentiating DLB from pure AD.

The evidence for MIBG imaging continues to build but is hampered by the lack of postmortem verification in studies to date and the relatively select nature of the population studies, largely cohorts from Asia with significant vascular disease. There are signs, however, that it is useful in the differentiation of Lewy body disorders from vascular parkinsonism and non-Lewy body parkinsonian disorders.

Structural MRI is useful for the identification of Alzheimer's type pathology in dementia patients; however, their utility in the diagnosis of DLB is made difficult by the generally lower rates of atrophy seen in DLB, with only bilateral amygdala atrophy the consistent finding. Occipital hypometabolism on FDG PET and occipital hypoperfusion on perfusion SPECT has been found in patients with DLB but only in small sample sizes.

**Acknowledgements** We would like to thank our colleagues for providing the following images: MIBG: Joseph Kane (Newcastle University, UK), Alan Thomas

(Newcastle University, UK) and Jim Lloyd (Royal Victoria Infirmary, Newcastle upon Tyne, UK); DAT scans: Sean Colloby (Newcastle University, UK); and MRI: Elijah Mak (University of Cambridge, UK).

**Funding** National Institute for Health Research (NIHR) Cambridge Dementia Biomedical Research Centre based at the Cambridge Biomedical Campus has supported the writing of the paper but did not have a role in the decision to submit for publication or the design of the review.

**Competing interests** None declared.

**Patient consent** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

doi:10.1136/eb-2017-102848

Received 7 November 2017; Revised 16 January 2018; Accepted 6 March 2018

### REFERENCES

1. **Spillantini MG**, Schmidt ML, Lee VM, *et al.* Alpha-synuclein in lewy bodies. *Nature* 1997;**388**:839–40.
2. **McKeith IG**, Boeve BF, Dickson DW, *et al.* Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology* 2017;**89**:88–100.
3. **Fujimi K**, Sasaki K, Noda K, *et al.* Clinicopathological outline of dementia with Lewy bodies applying the revised criteria: the Hisayama study. *Brain Pathol* 2008;**18**:317–25.
4. **Perry RH**, Irving D, Blessed G, *et al.* Clinically and neuropathologically distinct form of dementia in the elderly. *Lancet* 1989;**1**:166.
5. **Hogan DB**, Fiest KM, Roberts JL, *et al.* The Prevalence and Incidence of Dementia with Lewy Bodies: a Systematic Review. *Can J Neurol Sci* 2016;**43**(Suppl 1):S83–95.
6. **Vann Jones SA**, O'Brien JT. The prevalence and incidence of dementia with Lewy bodies: a systematic review of population and clinical studies. *Psychol Med* 2014;**44**:673–83.
7. **Rizzo G**, Arcuti S, Copetti M, *et al.* Accuracy of clinical diagnosis of dementia with Lewy bodies: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2017;**31**:jnnp-2017-316844.
8. **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**:1863–72.
9. **Galvin JE**. Improving the clinical detection of lewy body dementia with the lewy body composite risk score. *Alzheimers Dement* 2015;**1**:316–24.
10. **Zhang S**, Smailagic N, Hyde C, *et al.* (11)C-PIB-PET for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev* 2014:CD010386.
11. **Smailagic N**, VacanteM HC, Martin S, *et al.* F-FDG-PET for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI) (Review). *Cochrane Database Syst Rev* 2015:1–104.
12. **Perry E**, Court J, Goodchild R, *et al.* Clinical neurochemistry: developments in dementia research based on brain bank material. *J Neurol Transm* 1998;**105**:915–33.
13. **Sedaghat F**, Gotzamani-Psarrakou A, Dedousi E, *et al.* Evaluation of dopaminergic function in frontotemporal dementia using I-FP-CIT single photon emission computed tomography. *Neurodegener Dis* 2007;**4**:382–5.
14. **Klauffke S**, Kuhn AA, Plotkin M, *et al.* Dopamine transporters, D2 receptors, and glucose metabolism in corticobasal degeneration. *Mov Disord* 2006;**21**:1724–7.
15. **Seppi K**, Scherfler C, Donnemiller E, *et al.* Topography of dopamine transporter availability in progressive supranuclear palsy: a voxelwise [123I]beta-CIT SPECT analysis. *Arch Neurol* 2006;**63**:1154–60.
16. **Walker RW**, Walker Z. Dopamine transporter single photon emission computerized tomography in the diagnosis of dementia with Lewy bodies. *Mov Disord* 2009;**24**(Suppl 2):S754–9.
17. **McCleery J**, Morgan S, Bradley KM, *et al.* Dopamine transporter imaging for the diagnosis of dementia with Lewy bodies. *Cochrane Database Syst Rev* 2015;1:CD010633.
18. **Sonni I**, Ratib O, Boccardi M, *et al.* Clinical validity of presynaptic dopaminergic imaging with 123I-ioflupane and noradrenergic imaging with 123I-MIBG in the differential diagnosis between Alzheimer's disease and dementia with Lewy bodies in the context of a structured 5-phase development framework. *Neurobiol Aging* 2017;**52**:228–42.
19. **Thomas AJ**, Attams J, Colloby SJ, *et al.* Autopsy validation of 123I-FP-CIT dopaminergic neuroimaging for the diagnosis of DLB. *Neurology* 2017;**88**:276–83.
20. **Shimizu S**, Hirose D, Namioka N, *et al.* Correlation between clinical symptoms and striatal DAT uptake in patients with DLB. *Ann Nucl Med* 2017;**31**:390–8.
21. **Okizaki A**, Nakayama M, Nakajima K, *et al.* Inter- and intra-observer reproducibility of quantitative analysis for FP-CIT SPECT in patients with DLB. *Ann Nucl Med* 2017;**31**:758–63.
22. **Ueda J**, Yoshimura H, Shimizu K, *et al.* Combined visual and semi-quantitative assessment of (123) I-FP-CIT SPECT for the diagnosis of dopaminergic neurodegenerative diseases. *Neurol Sci* 2017;**38**:1187–91.

23. **Nicastro N**, Garibotto V, Allali G, *et al*. Added value of combined semi-quantitative and visual [123I]FP-CIT SPECT analyses for the diagnosis of dementia with lewy bodies. *Clin Nucl Med* 2017;**42**:e96–e102.
24. **Kasanuki K**, Iseki E, Ota K, *et al*. (123) I-FP-CIT SPECT findings and its clinical relevance in prodromal dementia with Lewy bodies. *Eur J Nucl Med Mol Imaging* 2017;**44**:358–65.
25. **Orimo S**, Amino T, Itoh Y, *et al*. Cardiac sympathetic denervation precedes neuronal loss in the sympathetic ganglia in Lewy body disease. *Acta Neuropathol* 2005;**109**:583–8.
26. **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**:111–7.
27. **Yoshita M**, Arai H, Arai H, *et al*. Diagnostic accuracy of 123I-meta-iodobenzylguanidine myocardial scintigraphy in dementia with Lewy bodies: a multicenter study. *PLoS One* 2015;**10**:e0120540.
28. **Nuvoli S**, Spanu A, Piras MR, *et al*. 123I-ioflupane brain SPECT and 123I-MIBG cardiac planar scintigraphy combined use in uncertain parkinsonian disorders. *Medicine* 2017;**96**:e6967.
29. **Tiraboschi P**, Corso A, Guerra UP, *et al*. (123) I-2 -carbomethoxy-3 -(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. *Ann Neurol* 2016;**80**:368–78.
30. **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**:184–92.
31. **Kobayashi S**, Makino K, Hatakeyama S, *et al*. The usefulness of combined brain perfusion single-photon emission computed tomography, Dopamine-transporter single-photon emission computed tomography, and (123) I-metaiodobenzylguanidine myocardial scintigraphy for the diagnosis of dementia with lewy bodies. *Psychogeriatrics* 2017;**17**:247–55.
32. **Aarsland D**, Kurz M, Beyer M, *et al*. Early discriminatory diagnosis of dementia with Lewy bodies. The emerging role of CSF and imaging biomarkers. *Dement Geriatr Cogn Disord* 2008;**25**:195–205.
33. **Burton EJ**, Barber R, Mukaetova-Ladinska EB, *et al*. Medial temporal lobe atrophy on MRI differentiates Alzheimer's disease from dementia with lewy bodies and vascular cognitive impairment: a prospective study with pathological verification of diagnosis. *Brain* 2009;**132**:195–203.
34. **Kantarci K**, Ferman TJ, Boeve BF, *et al*. Focal atrophy on MRI and neuropathologic classification of dementia with Lewy bodies. *Neurology* 2012;**79**:553–60.
35. **Nedelska Z**, Ferman TJ, Boeve BF, *et al*. Pattern of brain atrophy rates in autopsy-confirmed dementia with Lewy bodies. *Neurobiol Aging* 2015;**36**:452–61.
36. **Harper L**, Bouwman F, Burton EJ, *et al*. Patterns of atrophy in pathologically confirmed dementias: a voxelwise analysis. *J Neurol Neurosurg Psychiatry* 2017;**88**:908–16.
37. **Roquet D**, Noblet V, Anthony P, *et al*. Insular atrophy at the prodromal stage of dementia with lewy bodies: a VBM DARTEL study. *Sci Rep* 2017;**7**:9437.
38. **Blanc F**, Colloby SJ, Cretin B, *et al*. Grey matter atrophy in prodromal stage of dementia with Lewy bodies and Alzheimer's disease. *Alzheimers Res Ther* 2016;**8**:31.
39. **McKiernan EF**, O'Brien JT. 7T MRI for neurodegenerative dementias in vivo: a systematic review of the literature. *J Neurol Neurosurg Psychiatry* 2017;**88**:564–74.
40. **Toledo JB**, Cairns NJ, Da X, *et al*. Clinical and multimodal biomarker correlates of ADNI neuropathological findings. *Acta Neuropathol Commun* 2013;**1**:65.
41. **Minoshima S**, Foster NL, Sima AA, *et al*. Alzheimer's disease versus dementia with lewy bodies: cerebral metabolic distinction with autopsy confirmation. *Ann Neurol* 2001;**50**:358–65.
42. **Kantarci K**, Lowe VJ, Boeve BF, *et al*. Multimodality imaging characteristics of dementia with Lewy bodies. *Neurobiol Aging* 2012;**33**:2091–105.
43. **Lim SM**, Katsifis A, Villemagne VL, *et al*. The 18F-FDG PET cingulate island sign and comparison to 123I-beta-CIT SPECT for diagnosis of dementia with Lewy bodies. *J Nucl Med* 2009;**50**:1638–45.
44. **Lobotesis K**, Fenwick JD, Phipps A, *et al*. Occipital hypoperfusion on SPECT in dementia with lewy bodies but not AD. *Neurology* 2001;**56**:643–9.
45. **Yeo JM**, Lim X, Khan Z, *et al*. Systematic review of the diagnostic utility of SPECT imaging in dementia. *Eur Arch Psychiatry Clin Neurosci* 2013;**263**:539–52.
46. **O'Brien JT**, Firbank MJ, Davison C, *et al*. 18F-FDG PET and perfusion SPECT in the diagnosis of Alzheimer and Lewy body dementias. *J Nucl Med* 2014;**55**:1959–65.
47. **Donaghy P**, Thomas AJ, O'Brien JT. Amyloid PET Imaging in lewy body disorders. *Am J Geriatr Psychiatry* 2015;**23**:23–37.
48. **Hall B**, Mak E, Cervenka S, *et al*. In vivo tau PET imaging in dementia: pathophysiology, radiotracer quantification, and a systematic review of clinical findings. *Ageing Res Rev* 2017;**36**:50–63.
49. **Orrù G**, Pettersson-Yeo W, Marquand AF, *et al*. Using support vector machine to identify imaging biomarkers of neurological and psychiatric disease: a critical review. *Neurosci Biobehav Rev* 2012;**36**:1140–52.
50. **Falahati F**, Westman E, Simmons A. Multivariate data analysis and machine learning in Alzheimer's disease with a focus on structural magnetic resonance imaging. *J Alzheimers Dis* 2014;**41**:685–708.