Efficacy of Single Photon Emission Computed Tomography in Differentiating Dementia with Lewy Bodies – A Review of Neurotransmitter and Perfusion Imaging

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Abstract

The accuracy of the clinical diagnosis of dementia with Lewy bodies continues to be relatively poor. Several neuroimaging techniques have been used to facilitate a more accurate diagnosis. Thus far, functional neuroimaging has provided the most help. This article concentrates on the use of single photon emission computed tomography (SPECT) and reports on the efficacy data available from studies investigating cerebral perfusion, cardiac scintigraphy and dopaminergic neurotransmission. The results from perfusion studies are inconsistent. Cardiac scintigraphy shows more promise, but it is not yet known whether co-morbid cardiac conditions, which are common in the elderly, will limit the clinical use of this method. The radioligand ^{123}I–FP-CIT binds to dopamine transporters in nigrostriatal nerve terminals and provides a way of assessing the neurodegeneration caused by Lewy body pathology. Abnormal ^{123}I–FP-CIT has been shown to have high sensitivity and specificity in an autopsy study and a large multicentre trial. This article aims to give an overview of the topic.

Dementia with Lewy bodies (DLB) is a common form of dementia. The characteristic features are: progressive dementia particularly affecting attention, visuo-spatial and executive ability; fluctuating cognition; spontaneous parkinsonian symptoms; persistent vivid visual hallucinations; hypersensitivity to neuroleptic medication; and rapid eye movement (REM) sleep behavioural disorder.[1] Patients with DLB frequently have mixed pathology, and the presence of Alzheimer's disease (AD) pathology modifies the clinical features of DLB.[2] It is often hard to distinguish DLB from AD clinically during life, and AD is the main differential diagnosis. Clinical diagnostic criteria for DLB[3] applied at presentation can fail to identify up to 50% of cases.[4] An accurate diagnosis is important for carers in order for them to be aware of the symptomatology of the illness, the course and the prognosis, and also for professionals in order for them to provide appropriate management of motor, cognitive, psychiatric, sleep and autonomic symptoms and to avoid neuroleptic medication, which frequently leads to worsening of parkinsonian symptoms and alterations in consciousness,[5] as well as being associated with increased morbidity and mortality.[6,7] Furthermore, patients with DLB have a profound cholinergic deficit and may well benefit from treatment with cholinesterase inhibitors. Failure to diagnose DLB affects AD treatment trials, making it more difficult to develop and test drugs that specifically target the different underlying pathologies of DLB and AD.

At present there are several imaging techniques that can improve the identification of DLB during life. Whole-brain atrophy, rate of atrophy over time[8] and white matter lesions on magnetic resonance imaging (MRI) are not helpful in differential diagnosis. Hippocampal and medial temporal lobe atrophy can detect differences between AD and DLB at a group level, but have limited sensitivity and therefore utility for individual patients.[9–11]

Much more promising are techniques that can detect the functional integrity of the brain. This article will concentrate on single photon emission computed tomography (SPECT), which is easily accessible to clinicians. An alternative method, positron emission tomography (PET), is at present mainly available in research centres and therefore plays only a limited role in everyday practice in the majority of countries. SPECT can measure perfusion and assess the neurotransmitter system with a variety of specific ligands, as listed in *Table 1*.

Dopamine Transporter Imaging

Decreased concentrations of dopamine and dopamine transporters in DLB were first described in histopathological studies.[12] Pre-synaptic dopamine transporter (DAT) reduction, particularly in the striatum (caudate and putamen), and changes in post-synaptic D2 receptor binding led to the development of new imaging ligands. Compared with patients with DLB, those with AD have a well-preserved nigrostriatal pathway and therefore no changes in the uptake of specific radiotracers that target this pathway. The significance of the pronounced pre-synaptic dopaminergic deficit in the striatum in DLB compared with AD has been reflected in the revised clinical criteria

Table1: Radioactive Ligands Used with Single Photon Emission Computed Tomography

Function	Ligand – Common Abbreviation	Ligand – Full Chemical Name	Quantity	Time to Scan
Dopamine imaging	^{123}I-β-CIT	[123I]2β,-carboxymethoxy-3β,-(4- iodophenyl) tropane	145–185MBq	18–24 hours
	^{123}I-FP-CIT	[123I]N- (3-fluoropropyl)-2β,-carbometoxy-3β,-(4-iodophenyl) nortropane	185MBq	3–6 hours
	^{123}I-IBZM	[123I]iodobenzamide	185MBq	1.5–2 hours
Perfusion	99mTc-HMPAO	Technetium-99m-hexamethylpropylene amine oxime	500MBq	10 minutes
	99mTc-ECD	Technetium-99m-ethyl cysteinate dimer	555MBq	15 minutes
	^{123}I-IMP	N-isopropyl-p-[123I]iodoamphetamine	222MBq	15 minutes
Myocardial scintigraphy	^{123}I-MIBG	[123I]metaiodobenzylguanidine	111MBq	15 minutes
Cholinergic imaging	[123]I-5IA-85380 (nicotinic)	[123I]-5-Iodo-3-[2(S)-2-azetidinylmethoxy] pyridine	185MBq	2 hours
	^{123}I-QNB (muscarinic)	[123I]-iodo-quinuclidinyl-benzilate	185MBq	5 hours

for the diagnosis of DLB,[1] which now include "low dopamine transporter uptake in the basal ganglia demonstrated by SPECT imaging" as a "suggestive feature" for DLB.

Efficacy of Pre-synaptic Dopamine Imaging

Initial semi-quantitative studies with [123I]-2β-carbomethoxy-3β-(4-iodophenyl) tropane (b-CIT) and [123I]-N-(3-fluoropropyl)-2β,-carbometoxy-3β,-(4-iodophenyl) nortropane (FP-CIT) demonstrated reduced striatal dopamine transporter binding in DLB compared with AD[13–16] and a more marked symmetrical reduction of dopamine transporter compared with early Parkinson's disease (PD).[17,18]

At present, the most studied technique for assessing dopaminergic pathways is FP-CIT SPECT. FP-CIT has the advantage of a shorter period of delay between the injection of the ligand and imaging (three to six hours) compared with b-CIT SPECT (18–24 hours; see *Figure 1*).

O' Brien et al.[19] reported both semi-quantitative and visual analysis of FP-CIT SPECT of a large cohort of 164 subjects (23 DLB, 34 AD, 36 PD dementia [PDD], 38 PD and 33 healthy controls). When comparing AD and DLB, the semi-quantitative analysis had a sensitivity of 78% and specificity of 85%, and visual rating had a sensitivity of 78% and specificity of 94%. However, DAT loss did not provide good diagnostic separation between DLB, PD and PDD.

In a cohort with subsequent autopsy confirmation of diagnosis, FP-CIT SPECT substantially enhanced the accuracy of diagnosis of DLB in comparison with clinical criteria alone.[4] The sensitivity of an

In a cohort with subsequent autopsy confirmation of diagnosis, FP-CIT single photon emission computed tomography substantially enhanced the accuracy of diagnosis of dementia with Lewy bodies in comparison with clinical criteria alone.

initial clinical diagnosis of DLB was 75% and the specificity was 42%. The sensitivity for the diagnosis of DLB of an abnormal FP-CIT scan, defined as total (bilateral) posterior putamen binding less than two standard deviations below the mean of controls, was 88%, and the specificity was 100%. Visual assessment of scans had a sensitivity of 88% and specificity of 83%. When an abnormal scan was

Figure 1: FP-CIT Labels Dopamine Transporter in Nigrostriatal Nerve Terminals in the Striatum
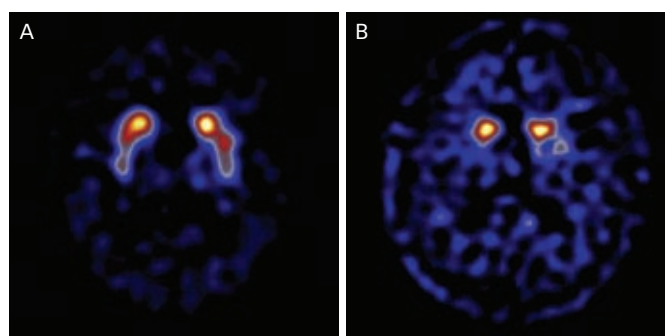
a. Normal FP-CIT uptake in a patient with Alzheimer's disease.
b. Reduced FP-CIT uptake in a patient with dementia with Lewy bodies.

defined as reduced DAT binding in the posterior putamen on one side, the sensitivity increased to 100% at the expense of some loss of specificity, 92%.

Important data come from a large European multicentre study[20] in which participants were scanned with FP-CIT SPECT after a consensus diagnosis was made by a panel of experts. Of the 288 patients included in the efficacy analysis, 88 were diagnosed with probable DLB, 56 with possible DLB and 144 with non-DLB. The scans were visually rated by three independent nuclear medicine specialists. When probable DLB patients were compared with non-DLB patients, the sensitivity of scanning was 77.7% and the specificity was 90.4%. Only 38% of possible DLB cases had an abnormal FP-CIT SPECT image. One-year follow-up of the possible DLB cases showed that FP-CIT SPECT at baseline had a sensitivity of 63% and a specificity of 100% for probable DLB diagnosis.[21] These studies are summarised in *Table 2*.

In a review article, Booji and Kemp[22] discussed the observed 10% increase of striatal FP-CIT binding ratios in patients using selective serotonin re-uptake inhibitors (SSRIs) and serotonin and norepinephrine re-uptake inhibitors (SNRIs).[23] They considered that this increase is too small to be misinterpreted on a visually rated scan. However, there is a possibility that SSRIs and SNRIs could significantly affect semi-quantitative analysis; this needs to be taken into account in research settings when a semi-quantitative analysis may be performed in addition to visual rating.

Efficacy of Post-synaptic Dopamine Imaging

The only study[24] specifically designed to investigate the post-synaptic dopamine D2 neuroreceptor availability in the striatum in DLB used [123I]-iodobenzamide (IBZM) SPECT and showed reduced radioactivity

Table 2: Dopaminergic Scan Studies

Study	Ligand	Number of Participants	MMSE (mean±SD)	SPECT Analysis and Efficacy	Comments
Donnemiller et al., 1997[13]	^{123}I-β-CIT	DLB (n=7) AD (n=6)	DLB (20.1±5.2) AD (12.8±8.8)	Semi-quantitative: ↓ DAT binding compared with AD	Occipital hypoperfusion also found on HMPAO SPECT
Ransmayr et al., 2001[17]	^{123}I-β-CIT	DLB (n=20) PD (n=24) Controls (n=10)	Not reported	Semi-quantitative: ↓ DAT binding in the DLB group compared with controls, DLB dopaminergic loss more marked and less asymmetrical compared with PD	No efficacy data available
Walker et al., 2002[15]	^{123}I-FP-CIT	DLB (n=27) AD (n=17) PD (n=19 Controls (n=16)	DLB (16.2±6.2) AD (21.5±5.3) PD (27.7) Controls (28.9)	Semi-quantitative: ↓ dopaminergic uptake in the caudate, anterior and posterior putamen compared with controls and AD	Consensus of 91% (κ 0.82) between ROIs and the visual assessment
Ceravolo et al., 2003[16]	^{123}I-FP-CIT	DLB (n=24) AD (n=24)	DLB (21.0±1.8) AD (20.6±2.3)	Lower ratio of specific (striatal) to non-specific binding	No efficacy data
O'Brien et al., 2004[19]	^{123}I-FP-CIT	DLB (n=23) PDD (n=36) PD (n=38) AD (n=34) Controls (n=33)	DLB (16.3±5.8) PDD (19.1±5.6) PD (26.5±2.1) AD (17.3±4.9)	Visual analysis: Sensitivity 78%, specificity 85%, PPV 78% Semi-quantitative: Sensitivity 78%, specificity 94%, PPV 89%	Consensus panel diagnosis
McKeith et al., 2007[20]	^{123}I-FP-CIT	Probable DLB (n=88) Possible DLB (n=56) Non-DLB (n=144)	Probable DLB (20.0±4.5) Possible DLB (20.9±4.2) Non-DLB (21.5±4.4)	Visual analysis: Sensitivity 77.7%, specificity 90.4%, PPV 82.4%, NPV 87.5%	Consensus panel diagnosis
Walker et al., 2007[4]	^{123}I-FP-CIT	DLB (n=8) Non-DLB (n=12) Controls (n=16)	DLB (17.0±5.6) AD (16.6±8.8)	Visual analysis: Sensitivity 88%, specificity 83% Semi-quantitative (total posterior putamen): Sensitivity 88%, specificity 100% Semi-quantitative (unilateral posterior putamen): Sensitivity 100%, specificity 92% Clinical diagnosis: Sensitivity 75%, specificity 42%	Pathologically confirmed diagnoses
O'Brien et al., 2008[21]	^{123}I-FP-CIT	Probable DLB (n=72) Possible DLB (n=46) Non-DLB (n=129) No initial diagnosis (n=17)	Baseline: Probable DLB (20.9±4.3) Possible DLB (20.8±4.4) Non-DLB (21.7±4.3) Follow-up: Probable DLB (17.4±6.5) Possible DLB (19.0±7.1) Non-DLB (19.4±6.1)	Visual analysis: Possible DLB: Sensitivity 63%, specificity 100%. Overall diagnostic accuracy in the whole sample: Sensitivity 78%, specificity 93%	Consensus panel diagnosis diagnoses at one-year follow-up

MMSE = mini-mental state examination; SPECT = single photon emission computed tomography; SD = standard deviation; DLB = dementia with Lewy bodies; AD = Alzheimer's disease; DAT = dopamine transporter binding; PD = Parkinson's disease; ROIs = regions of interest; PDD = Parkinson's disease dementia; PPV = positive predictive value; NPV = negative predictive value; HMPAO = Tc-hexamethylpropyleneamine oxime.

uptake in the caudate and increased activity in the putamen, giving a reduced caudate/putamen ratio. This was a small study and there was overlap between DLB and AD, making it unlikely that ^{123}I–IBZM would be of much use in clinical practice. A study investigating FP-CIT and IBZM SPECT in parkinsonian syndromes[25] found no abnormalities of the post-synaptic D2 receptor in six patients who were later diagnosed with DLB. Direct comparisons between these two studies cannot be made as they differ significantly in their aims and methodology.

Cerebral Perfusion Imaging

Perfusion SPECT studies (see *Table 3*) have assessed regional cerebral blood flow, a marker of brain function, using ^{99m}Tc-hexamethylpropylene amine oxime (HMPAO),[13,26–29] ^{99m}Tc-ethyl cysteinate dimer (ECD)[13,16,30] or to N-isopropyl-p-[^{123}I] iodoamphetamine (IMP).[31–36] Donnemiller et al.,[13] in a study of six AD and seven DLB patients, described a "horse-shoe-like pattern" of bilateral parieto-occipital hypoperfusion on SPECT in six out of seven DLB patients compared with only one out of six AD cases. By contrast, the finding of a larger study[26] of 20 AD and 20 DLB patients was diffuse cortical hypoperfusion with significant frontal deficits in DLB and no occipital deficit (sensitivity 90% and specificity 80% using a factorial discriminant analysis with 15 perfusion parameters and mini-mental state examination [MMSE] score). However, a later study[27] reported occipital hypoperfusion in 15 of 23 DLB patients (65%) compared with only nine of 50 AD cases (18%) (sensitivity 64% and specificity 86% using stepwise discriminant analysis with left occipital perfusion and right temporal perfusion as dependent variables). Other studies have also shown occipital hypoperfusion to be more common in DLB than in AD,[16,30,32–36] with varying sensitivities and specificities. A few studies also showed relatively preserved medial temporal perfusion in DLB compared with AD.[28,30,32,36] Sato et al.[36] reported that DLB patients more frequently have occipital hypoperfusion (16 of 22 DLB patients versus three of 25 AD patients) and also hyperperfusion in striatum/thalamus (18 of 22 DLB patients versus eight of 25 AD patients) compared with AD. Combining these two measures gave good sensitivity of 95% and modest specificity of 65% (see *Table 3*).

More recently, Kemp et al.[29] reported occipital hypoperfusion in only 11 of 39 DLB subjects (28%) and in 14 of 45 non-DLB dementia cases (31%), and concluded that occipital hypoperfusion was not

Table 3: Perfusion Scan Studies

Study	Ligand	Number of Participants	MMSE (mean±SD)	Hypoperfusion Deficits	Efficacy	Comments
Donnemiller et al., 1997[13]	99mTc-HMPAO or 99mTc ECD	DLB[a] (n=7) AD (n=6)	Not reported	Bilateral parieto-occipital hypoperfusion deficits in 6 DLB and 1 AD cases	None reported	Described a 'horse-shoe like pattern' of bilateral parieto-occipital hypoperfusion
Defebvre et al., 1999[26]	99mTc-HMPAO	AD (n=20) DLB[a] (n=20)	DLB (16±6) AD (18±7)	10 (hand-drawn) ROIs DLB: diffuse cortical, significant frontal and no occipital deficits	FDA used: Sensitivity 80% Specificity 80%	Global deficits attributed to a lower mean MMSE
Ishii et al., 1999[31]	123I-IMP	DLB[a] (n=7) Normal (n=20)	DLB (19.9±4.1)	Occipital and parietal hypoperfusion	None reported	Glucose metabolism more superior to 123I-IMP
Lobotesis et al., 2001[27]	99mTc-HMPAO	DLB[b] (n=23) AD (n=50) Controls (n=50)	DLB (16±6.1) AD (17.3±5.5)	19 ROIs and visual assessment DLB: occipital AD: frontal and medial temporal Occipital hypoperfusion in DLB (39%) and AD (20%)	Sensitivity 64% Specificity 86%	Large study
Pasquier et al., 2002[30]	99mTc-ECD	DLB[a] (n=34) AD (n=28)	DLB (17.1±6.7) AD (15.8±6.5)	Occipital hypoperfusion in DLB group	Sensitivity 65% Specificity 71%	
Shimizu et al., 2005[33]	123I-IMP	AD (n=75) DLB[a] (n=20) Controls (n=28)	DLB (19.5±4.6) AD (19.4±4.0)	3D SSP, SEE DLB and AD: temporoparietal, frontal and posterior cingulate DLB: medial and lateral occipital	Sensitivity 85% Specificity 85%	3D SSP more reliable and objective than other analysis
Hanyu et al., 2006[34]	123I-IMP	DLB[a] (n=19) AD (n=39) Controls (n=28)	DLB (21.8±4.6) AD (20.1± 4.1)	3D SSP Medial occipital lobe deficits DLB n=14 (73%) and AD n=7 (39%)	Sensitivity 74% Specificity 82%	Myocardial scintigraphy performed better
Hanyu et al., 2006[35]	123I-IMP	DLB[a] (n=36) AD (n=96)	DLB (20.7±3.9) AD (20.3±3.9)	3D SSP, SEE DLB: medial occipital lobe, including cuneus and lingual gyrus	SPECT: Sensitivity 75% Specificity 78% SPECT/MMSE index:[c] Sensitivity 81% Specificity 85%	Some AD (n=28) and DLB (n=10) were analysed previously by Shimizu et al. 2005[33]
Sato et al., 2007[36]	123I-IMP	DLB[a] (n=22) AD (n=25)	DLB (20.1±3.8) AD (19.6±4.4)	DLB: Occipital hypoperfusion (16/22) Striatum/thalamus hyperperfusion (18/22)	Either finding: Sensitivity of 95% Specificity of 65%	
Kemp et al., 2007[29]	99mTc-HMPAO	DLB[d] (n=39) Non-DLB (n=45)	Not reported	Visual and SPM 99 Occipital deficits DLB n=11 (28%), non-DLB n=14 (31%)	PPV 44%	Diagnosis: Visual assessment 123FP-CIT

MMSE = mini-mental state examination; SD = standard deviation; DLB = dementia with Lewy bodies; AD = Alzheimer's disease; SPECT = single photon emission computed tomography; ROIs = regions of interest; FDA = factorial discriminant analysis; SSP = stereotactic surface projections;[52] SEE = stereotactic extraction estimation; SPM = statistical parametric mapping 99; PPV = positive predictive value. a. 1996 Consensus Criteria;[3] b. Study also included possible DLBs; c. SPECT/MMSE index= (z-score in the medial occipital lobe) / (AD/DLB score+10), derived by; d. Only study to use FP-CIT SPECT (DLB defined as abnormal uptake throughout the striata) to diagnose DLB.

helpful in differentiating DLB from other dementias. A possible explanation for these discrepancies would be the difference in the criteria used to diagnose DLB. Older studies used the 1996 DLB consensus criteria;[3] the diagnostic accuracy of these criteria has varied, as evidenced by *post mortem* studies (sensitivity 22–83% and specificity 79–100%). Kemp et al.[29] used FP-CIT SPECT as the gold standard for the diagnosis of DLB, since the diagnostic accuracy of this method has been shown to be superior to that of the 1996 consensus criteria.[4,37]

Different perfusion studies have generally demonstrated a variety of deficits in DLB. This could be due to differences in methodology, including variations in sample sizes, ligands, scanners and methods of analysis. Particular problems associated with qualitative and semi-quantitative studies include increased subjectivity, poor reproducibility and acquisition of information only in pre-selected regions of interest. The newer statistical brain mapping techniques of

statistical parametric mapping (SPM) and 3D stereotactic surface projections (SSP), which allow pixel-by-pixel analysis of cerebral blood flow, result in more objective evaluation of the severity, extent and localisation of regional abnormalities, but have not yet been validated by large multicentre or *post mortem* studies. Thus, currently the usefulness of perfusion SPECT in DLB diagnosis has not been established.

Cholinergic Receptor Imaging

Acetylcholine has important roles in attention, memory and cognition.[38] Changes in cholinergic function have been described in neuropathological studies of DLB.[38–42] SPECT radiotracers are now available for muscarinic acetylcholine receptors (123I-quinuclidinyl-benzylate) and nicotinic acetylcholine receptors (123I-5IA-85380) and for acetylcholine vesicular transporter, which correlates well with choline acetyltransferase. In DLB, increases in both nicotinic and muscarinic receptor binding in the occipital lobe have been shown

with [123]I-5IA-85380[43] and ^{123}I-quinuclidinyl-benzylate,[44] suggesting that this increase could relate to visual hallucinations. In addition, DLB patients had a reduced uptake of [123]I-5IA-85380[43] in frontal, striatal, temporal and cingulate regions compared with controls.

Myocardial Scintigraphy

Patients with DLB have pronounced cardiovascular autonomic dysfunction due to Lewy body degeneration in the cardiac plexus. Using [^{123}I]-metaiodobenzylguanidine (MIBG) cardiac scintigraphy,[45–47] there is reduced cardiac uptake in DLB in comparison with AD even in the absence of autonomic symptoms. This investigation has excellent sensitivity (95–100%) and specificity (87–100%),[48–50] is superior to perfusion SPECT in differentiating DLB from AD[34] and has been shown to be useful in combination with IMP SPECT in possible DLB cases.[51] The main drawback is that abnormal scans are difficult to interpret in the elderly as diseases common in this age group – such as diabetes, myocardial infarction, ischaemic heart disease and cardiomyopathy – can all lead to abnormal scans, thus increasing the risk of a false-positive diagnosis.

Conclusion

In this article we have discussed several imaging techniques available to clinicians to help in the diagnosis of DLB. These techniques are now widely available, but the cost and the exposure to radioactive ligands means that most patients undergo only one scan to facilitate diagnosis.

The most important factors in choosing an investigation are the diagnostic efficacy of the scan, the comfort and wellbeing of the patient and the local availability of a particular method. Studies with HMPAO SPECT looking for occipital hypoperfusion with relative preservation of medial temporal perfusion have not given consistent results. MIBG is a non-invasive technique that has shown promise, but co-morbid medical conditions are likely to lead to abnormal scans and make MIBG more difficult to interpret.

At present, the most studied technique for assessing dopaminergic pathways is FP-CIT SPECT. Following a number of single-centre studies of FP-CIT SPECT using both semi-quantitative and visual analysis, there is now good evidence from an autopsy study and a European multicentre study that FP-CIT SPECT has high sensitivity and specificity for distinguishing probable DLB from non-DLB dementia.[4,20] The autopsy study[4] is ongoing, and additional results continue to support the published data. One-year follow-up data from the European trial[21] also suggest that FP-CIT SPECT is diagnostically helpful in less clinically clear cases of possible DLB. ■
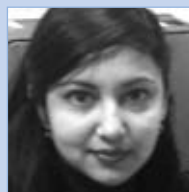
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