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A comparison of ^{99m}Tc -exametazime and ^{123}I -FP-CIT SPECT imaging in the
differential diagnosis of Alzheimer's disease and dementia with Lewy
bodies

Dr. Sean J. Colloby¹, Dr. Michael J. Firbank¹, Dr. Sanjeet Pakrasi¹, Dr. Jim J. Lloyd², Dr. Ian Driver³, Prof. Ian G. McKeith¹, Prof. E. David Williams⁴ and Prof. John T. O'Brien¹.

¹Institute for Ageing and Health, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne. NE4 5PL. UK.

²Regional Medical Physics Department, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne. NE1 4LP. UK.

³Regional Medical Physics Department, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne. NE4 6BE. UK.

⁴Regional Medical Physics Department, Sunderland Royal Hospital, Kayll Road, Sunderland SR4 7TP, UK.

Correspondence to:

Dr. Sean J. Colloby
Institute for Ageing and Health
Newcastle University
Campus for Ageing and Vitality
Newcastle upon Tyne
NE4 5PL
UK
Tel: +44 191 248 1321
Fax +44 191 248 1301
E-mail: s.j.colloby@ncl.ac.uk

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ABSTRACT

Background: To investigate the diagnostic value of perfusion ^{99m}Tc -exametazime single photon emission computed tomography (SPECT) in the diagnosis of dementia with Lewy bodies (DLB) and Alzheimer's disease (AD) in comparison with dopaminergic ^{123}I -2 β -carbomethoxy-3 β -(4-iodophenyl)-n-(3-fluoropropyl) nortropane (FP-CIT) SPECT imaging.

Methods: Subjects underwent ^{99m}Tc -exametazime (39 controls, 36 AD, 30 DLB) and ^{123}I -FP-CIT (33 controls, 33 AD, 28 DLB) scanning. For each scan, 5 raters performed visual assessments blind to clinical diagnosis on selected transverse ^{99m}Tc -exametazime images in standard stereotactic space. Diagnostic accuracy of ^{99m}Tc -exametazime was compared to ^{123}I -FP-CIT results for the clinically relevant subgroups AD and DLB using receiver operating characteristic (ROC) curve analysis.

Results: Inter-rater agreement for categorising uptake was 'moderate' (mean kappa = 0.53) for ^{99m}Tc -exametazime and 'excellent' (mean kappa = 0.88) for ^{123}I -FP-CIT. For AD and DLB, consensus rating matched clinical diagnosis in 56% of cases using ^{99m}Tc -exametazime and 84% using ^{123}I -FP-CIT. In distinguishing AD from DLB, ROC analysis revealed superior diagnostic accuracy with ^{123}I -FP-CIT (ROC curve area 0.83, sensitivity 78.6%, specificity 87.9%) compared to occipital ^{99m}Tc -exametazime (ROC curve area 0.64, sensitivity 64.3%, specificity 63.6%) $p=0.03$.

Conclusion: Diagnostic accuracy was superior with ^{123}I -FP-CIT compared to ^{99m}Tc -exametazime in the differentiation of DLB from AD.

Keywords: Neuroimaging; Visual Rating; Region of Interest; ROC; Perfusion; Dopamine

Introduction

Dementia with Lewy bodies (DLB) is the second most common cause of degenerative dementia after Alzheimer's disease (AD), accounting for 15-20% of cases in older people. Clinically it is characterised by attentional fluctuation, recurrent visual hallucinations and motor features of parkinsonism, while histopathologically by cortical and sub-cortical Lewy bodies (McKeith *et al.*, 1996). However, due to overlapping clinical features and low sensitivity of clinical diagnostic criteria, the differential diagnosis of AD and DLB remains a major problem in clinical practice (McKeith *et al.*, 1994). Accurate detection of DLB is important because of management implications including different prognosis, adverse sensitivity to neuroleptic agents (Aarsland *et al.*, 2005) and positive response of behavioural features to cholinesterase inhibitors (Aarsland *et al.*, 2004). Investigations which could help improve the accuracy of discrimination between DLB and AD would be a major advance.

Numerous studies of cerebral metabolic imaging using positron emission tomography (PET) (Gilman *et al.*, 2005; Ishii *et al.*, 1998; Minoshima *et al.*, 2001), and cerebral perfusion imaging using single photon emission computed tomography (SPECT) (Lobotesis *et al.*, 2001; Pasquier *et al.*, 2002; Shimizu *et al.*, 2005), have suggested that occipital deficits are a distinctive feature of DLB. Other PET and SPECT tracers, namely ^{18}F -fluoro-L-dopa (F-DOPA), ^{123}I -2-beta-carbomethoxy-3-beta-4-fluorophenyl-tropane (β -CIT) and ^{123}I -2 β -carbomethoxy-3 β -(4-iodophenyl)-N-(3-fluoropropyl) nortropane (FP-CIT), which were developed to evaluate various aspects of dopaminergic function, have demonstrated utility in differentiating AD from DLB (Ceravolo *et al.*, 2003; O'Brien

et al., 2004; Walker *et al.*, 2002). In addition, some studies have utilised ¹²³I-metaiodobenzylguanidine (MIBG) SPECT myocardial scintigraphy, which detects early disturbances of the sympathetic nervous system, and have shown promising results in distinguishing DLB from AD (Hanyu *et al.*, 2006a; Oide *et al.*, 2003). Most PET and SPECT uptake studies in AD and DLB have involved group comparisons, whereas fewer studies have investigated the value of imaging when applied to diagnosis of individual cases. Of these studies results have been variable, with some suggesting occipital hypoperfusion is relatively effective (sensitivity 74% - 85%) in diagnosing DLB (Hanyu *et al.*, 2006a; Hanyu *et al.*, 2006b; Shimizu *et al.*, 2005), while others have revealed less accuracy (sensitivity 65%) (Lobotesis *et al.*, 2001; Pasquier *et al.*, 2002), including one study that showed that reduced occipital perfusion on visual inspection was indeterminate for a diagnosis of DLB (Kemp *et al.*, 2007). There have been few studies comparing diagnostic accuracy between different techniques in the same subjects, and no comparisons of FP-CIT and perfusion SPECT.

In the present study, the aim was to investigate the use of perfusion ^{99m}Tc-exametazime SPECT in the classification of normal elderly controls and patients with AD and DLB in accordance with clinical diagnosis as the gold standard. In particular, we wanted to compare the diagnostic accuracy of occipital lobe hypoperfusion with previous dopaminergic ¹²³I-FP-CIT (DaTSCAN) imaging data in the clinically relevant differential diagnosis of AD and DLB.

Methods

Subjects

The study population consisted of 105 subjects (39 elderly controls, 36 AD, 30 DLB). Patients were recruited from a community-dwelling population who had been referred to local old age psychiatry services. Elderly controls were recruited from friends and spouses of patients included in this and other local research studies. The study was approved by the local research ethics committee and UK Department of Health's Administration of Radioactive Substances Advisory Committee (ARSAC). All participants, as well as the nearest relative for patients, gave informed written consent.

Subjects underwent detailed physical, neurological and neuropsychiatric examinations, which included history, mental state and physical examination. This comprised routine haematology and biochemistry screening, thyroid function tests, syphilis serology, vitamin B₁₂ and folate levels, chest X-ray and head CT scan. Other tests included the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975) and the Cambridge Cognitive Examination (CAMCOG) (Roth *et al.*, 1986), while parkinsonism was rated using the motor subsection of the Unified Parkinson's Disease Rating Scale (UPDRS III) (Fahn *et al.*, 1987). Patient diagnosis was carried out by agreement between two experienced consultant old age psychiatrists using the NINCDS-ADRDA criteria for AD (McKhann *et al.*, 1984), and the international workshop criteria for DLB (McKeith *et al.*, 1996). For AD, 33 patients were diagnosed as 'probable' and 3 patients as 'possible' while for DLB, 23 patients were diagnosed as 'probable' and 7 patients as 'possible'. Controls had no signs or symptoms of cognitive disturbance, did not complain of poor

memory and all scored within normal range of cognitive tests (≥ 25 on MMSE and ≥ 85 on CAMCOG). Subsequently all subjects underwent SPECT scanning.

^{99m}Tc-exametazime and ¹²³I-FP-CIT (DaTSCAN) SPECT imaging

All subjects were scanned using a triple-headed rotating gamma camera (Picker 3000XP) fitted with a high resolution fan-beam collimator, approximately 10 minutes after a bolus intravenous injection of 500 MBq of ^{99m}Tc-exametazime (Ceretek, GE Healthcare, also referred to as HMPAO). One hundred and twenty 15 second views over a 360° orbit were acquired on a 128×128 matrix with a pixel and slice thickness of 3.5mm. Imaging time was 30 minutes. Images were reconstructed using ramp-filtered backprojection with a Butterworth filter (order 13, cut-off 0.2 cycles.cm⁻¹), then resampled to a 64×64 matrix containing 4.0mm cubic voxels. Axial resolution was 12mm full width at half maximum (FWHM) and the reconstructed images were corrected for gamma ray attenuation using Chang's algorithm (uniform attenuation coefficient, $\mu = 0.11\text{cm}^{-1}$).

Within 3 months of their ^{99m}Tc-exametazime scan; most patients (Controls (n=33), AD (n=33), DLB (n=28)) underwent ¹²³I-FP-CIT (DaTSCAN, GE Healthcare, UK) SPECT scanning. Acquisition and processing of scans have been previously described (O'Brien *et al.*, 2004).

Pre-processing of ^{99m}Tc-exametazime scans

First, in order that all SPECT scans be visually rated from equivalent slices, each image volume was registered to match a ^{99m}Tc-exametazime SPECT template in standard MNI

(Montreal Neurological Institute, <http://www.bic.mni.mcgill.ca>) space using statistical parametric mapping (SPM2, Wellcome Department of Imaging Neuroscience, London, UK, <http://www.fil.ion.ucl.ac.uk/spm>). The template was constructed from 39 elderly controls (all of whom participated in this study) by spatial normalisation of each scan to the generic SPM2 SPECT template. The transformed images were then visually inspected to ensure registration to the template was successful, and a mean image was created from the registered scans followed by spatial smoothing with an 8mm FWHM 3D Gaussian filter. Next, using the freeware medical image viewer 'MRIcro' (<http://www.sph.sc.edu/comd/rorden/mricro.html>) and Talairach atlas (Talairach and Tournoux, 1988), 12 transverse images as well as a single coronal slice in standard space were selected for visual rating. Images were displayed relative to their maximum voxel count. Figure 1 shows the MRIcro display of the ^{99m}Tc -exametazime SPECT template together with the neuroanatomical landmarks of each slice and colour scale used for visual rating.

Visual rating of ^{99m}Tc -exametazime scans

Visual qualitative assessment of scans were carried out simultaneously by 5 raters of varying experience (low to high), comprising of 2 consultant medical physicists, a consultant old age psychiatrist and 2 imaging research associates. All registered scans were independently randomised and rated blind to clinical diagnosis. All images were displayed using MRIcro on a PC and projected onto a large screen in full view of the rating panel (approximate dimensions: screen size (w x h) 1.8m x 1.35m, screen to panel distance 3.0m). Initially a brief training exercise was performed by the panel on 10

randomly selected images; these allowed raters to discuss uptake patterns of scans and gain experience implementing the study protocol (see below).

For each scan, 4 brain regions i.e., medial temporal/temporal, occipital, parietal and midline parietal (representing cuneus, precuneus, posterior cingulate) were assessed and rated by each panel member. These regions were chosen on the basis of past research suggesting greatest changes in DLB occur in occipital and precuneal areas (Firbank *et al.*, 2003; Ishii *et al.*, 1999b; Lobotesis *et al.*, 2001; Pasquier *et al.*, 2002), while changes in AD are most pronounced in temporal and parietal areas (Imran *et al.*, 1999; Ishii *et al.*, 1999a; Lee *et al.*, 2003; Lobotesis *et al.*, 2001). Rating scores used a dichotomous variable (0 = normal uptake, 1 = reduced uptake) based on the pattern of uptake. Each rater additionally classified every scan as either a control, AD or DLB. Guidelines for diagnosis were:

- CONTROL = global uptake broadly normal, however could contain minor focal deficits.
- AD = reduced uptake and confined largely to temporal, medial temporal, parietal and posterior cingulate regions.
- DLB = reduced uptake and confined largely to occipital, parietal, cuneal and precuneal regions.

Following visual rating, consensus measures (obtained from majority results) were determined for each region in addition to a consensus diagnosis.

Visual rating of ^{123}I -FP-CIT scans

Visual inspection was performed by 5 raters, two of whom participated in the rating of $^{99\text{m}}\text{Tc}$ -exametazime scans. A detailed description of the methodology has been previously reported (O'Brien *et al.*, 2004). Briefly, visual rating used the 4-category grading system for ^{123}I -FP-CIT tracer uptake according to the classification initially proposed by Benamer et al (Benamer *et al.*, 2000):

- Normal, grade 0: Tracer uptake bilateral in caudate nucleus and putamen and largely symmetric.
- Abnormal, grade 1: Asymmetric uptake with normal or almost normal putamen activity in one hemisphere and with a more marked reduction in the contralateral putamen.
- Abnormal, grade 2: Significant bilateral reduction in putamen uptake with activity confined to the caudate nuclei.
- Abnormal, grade 3: Significant bilateral reduction in uptake affecting both the caudate nuclei and putamen.

For the present study consensus scores were used and then reclassified as either normal or abnormal, i.e., (grade 0 = normal; grade 1, 2 and 3 = abnormal). The scores were then used to compare the diagnostic utility with $^{99\text{m}}\text{Tc}$ -exametazime. Figure 2 illustrates transverse views of typical 'normal' (A) and 'abnormal' (B) ^{123}I -FP-CIT scans.

Statistical analyses

Data were analysed using the Statistical Package for Social Sciences software (SPSS version 15.0). Continuous variables were tested for normality of distribution using the Shapiro-Wilk test and visual inspection of variable histograms. As a result, group effects were investigated using one-way analysis of variance ANOVA (F-test). Nominal data (consensus variables, gender) were summarised using cross-tabulation and evaluated for group differences where appropriate with χ^2 tests. Inter-observer agreement between raters was assessed using Cohen's kappa (κ) test. Sensitivity and specificity of ^{99m}Tc -exametazime SPECT in distinguishing AD and DLB was determined from receiver operating characteristic (ROC) curve analysis (Zweig and Campbell, 1993). All statistical tests were reported as significant if $p \leq 0.05$.

Results

Subject demographics

Table 1 shows demographic and clinical characteristics of the study population. Groups were matched for sex ($\chi^2= 1.8$, $df= 2$, $p= 0.4$) and broadly matched for age ($F_{2, 102}= 3.1$, $p= 0.05$), although AD were slightly older than controls ($p= 0.05$). Disease duration was similar between dementia groups ($F_{1,56}= 2.6$, $p= 0.11$). As expected, significant differences were observed between patients and controls in MMSE ($F_{2, 102}= 87.0$, $p<<0.001$) and CAMCOG ($F_{2, 102}= 96.8$, $p<<0.001$), and between DLB and other groups in UPDRS III ($F_{2, 102}= 80.6$, $p<<0.001$) scores. MMSE and CAMCOG results were comparable in AD and DLB. Some patients were receiving medication (for > 3months) at the time of their SPECT scans (AD: donepezil ($n = 7$), rivastigmine ($n = 2$); DLB: donepezil ($n = 9$), L-Dopa ($n = 3$)).

Visual rating of ^{99m}Tc -exametazime and ^{123}I -FP-CIT scans

In each brain region, inter-rater agreement for ^{99m}Tc -exametazime was calculated from the mean kappa score of all pairwise combinations of the 5 panel members. Temporal, occipital, parietal and midline parietal scores were ($\kappa \pm$ standard error) 0.53 ± 0.08 , 0.55 ± 0.08 , 0.63 ± 0.08 and 0.49 ± 0.09 respectively. Global inter-rater agreement (mean of regional kappa scores) was 0.55 ± 0.08 , demonstrating an overall ‘moderate’ concordance between raters in classifying abnormal and normal patterns of regional uptake. Likewise, agreement between raters in categorising the diagnosis of a case was also ‘moderate’ (0.51 ± 0.07).

Table 2 displays a summary of the ^{99m}Tc -exametazime visual rating results, where findings represent consensus variables. In controls, highest incidence of abnormal uptake occurred in temporal and parietal regions (21%), while the lowest was in midline parietal (10%). Figure 3a shows a typical MRicro display of a ^{99m}Tc -exametazime scan of a control with its relatively well preserved perfusion throughout the cerebrum. In AD, abnormal uptake appeared mostly in temporal (86%) and parietal (69%) areas, and was least frequent in occipital and midline parietal (33%). Figure 3b illustrates a representative blood flow image of an AD patient. In DLB, incidence of abnormal uptake was 80% (parietal), 63% (occipital) and 57% (temporal, midline parietal). Figure 3c shows an example of the ^{99m}Tc -exametazime uptake pattern in DLB. Consensus diagnosis from visual rating matched clinical diagnosis in 65% (67/105) of cases. Proportion of correct diagnoses were greatest in controls (77%), followed by DLB (60%) then AD (53%). Complete diagnostic agreement between all 5 raters occurred in 40% of cases.

Inter-rater agreement of ^{123}I -FP-CIT was calculated from mean kappa scores of all pairwise combinations of panel members and was based on the 4-category grading system (O'Brien *et al.*, 2004). The multi-rater kappa statistic was 0.88 ± 0.02 , indicating 'excellent' global agreement between raters in classifying normal and abnormal patterns. Table 2 shows the ^{123}I -FP-CIT results, where the highest frequency of abnormal uptake occurred in DLB (79%), followed by AD (12%) then controls (6%).

ROC curve analysis

Excluding controls, ROC curve analysis was used to assess the diagnostic performance of ^{99m}Tc -exametazime by region in distinguishing DLB from AD (DLB=30, AD=36). In addition, diagnostic accuracy was assessed for dopaminergic ^{123}I -FP-CIT in differentiating DLB from AD and then compared to the optimum ^{99m}Tc -exametazime method for cases who had undergone both investigations (DLB=28, AD=33). Table 3 summarises for each diagnostic test the ROC curve area, optimal sensitivity and specificity, as well as positive and negative likelihood ratios. Diagnostic characteristics (ROC curve area, sensitivity, specificity) for each ^{99m}Tc -exametazime region produced the following range (min – max) of diagnostic values (0.55 - 0.65, 56.7% - 86.1%, 30.6% - 66.7%), indicating ‘poor’ precision when using individual regions as diagnostic markers. For ^{123}I -FP-CIT, greater diagnostic accuracy was achieved in discriminating DLB from AD (0.83 \pm 0.05, 78.6%, 87.9%). The most accurate ^{99m}Tc -exametazime region for differentiating DLB from AD was in the occipital lobe (0.65 \pm 0.07, 63.3%, 66.7%). Figure 4 shows ROC curves for both ^{123}I -FP-CIT and occipital ^{99m}Tc -exametazime, where significant differences were apparent between their ROC curve areas (\sim 0.19 \pm 0.09, $p = 0.03$), demonstrating the superior diagnostic ability of ^{123}I -FP-CIT over ^{99m}Tc -exametazime. In diagnosing AD and DLB assuming clinical diagnosis as the gold standard, prediction success using ^{99m}Tc -exametazime in AD and DLB were 53% and 60% respectively, but using ^{123}I -FP-CIT increased to 88% and 79%.

Autopsies

Autopsy results were available for 9 patients (2 AD, 7 DLB). Table 4 shows selected ^{99m}Tc -exametazime and ^{123}I -FP-CIT SPECT imaging characteristics of the 9 autopsy confirmed cases. Clinical diagnosis agreed with autopsy diagnosis in all but one (case 8), highlighting the strength of clinical diagnostic criteria as rigorously applied in this study. ^{123}I -FP-CIT imaging agreed with autopsy diagnosis in 7/8 cases (88%). Consensus ^{99m}Tc -exametazime visual rating was less accurate and agreed with autopsy diagnosis in 4/9 cases (44%). Lastly, in light of the autopsy data, where 1 case changed diagnosis, data were reanalysed but results reported above were essentially unchanged.

Discussion

We investigated visual inspection of ^{99m}Tc -exametazime SPECT imaging in the differentiation of AD, DLB and age-matched controls. Inter rater agreement was 'moderate' for the evaluation of regional uptake and designation of likely diagnosis based on the imaging findings. Reduced overall uptake was found comparing dementia subjects to controls; in occipital and parietal regions when comparing DLB to AD; and reduced medial temporal uptake when comparing AD to DLB. Consensus imaging diagnosis matched clinical diagnosis in 65% of cases, and was highest in controls (77%), followed by DLB (60%) and AD (53%) groups. The results indicate that a large degree of overlap exists between patient groups in regional uptake patterns and points to the challenge in accurate visual inspection of ^{99m}Tc -exametazime SPECT scans in the assessment of dementia.

The diagnostic value of ^{99m}Tc -exametazime SPECT by region in classifying subjects from the clinically relevant subgroups AD and DLB was performed by ROC curve analysis. Furthermore, diagnostic accuracy of the optimal ^{99m}Tc -exametazime method was directly compared to dopaminergic ^{123}I -FP-CIT. The sensitivity and specificity of occipital ^{99m}Tc -exametazime SPECT was 64.3% and 63.6% respectively, demonstrating modest diagnostic utility. ^{123}I -FP-CIT showed greater diagnostic accuracy (sensitivity 78.6%, specificity 87.9%) than ^{99m}Tc -exametazime imaging in distinguishing DLB from AD. Inter-rater agreement was also superior for ^{123}I -FP-CIT (mean $\kappa = 0.88$) (O'Brien *et al.*, 2004; Walker *et al.*, 2002), than with ^{99m}Tc -exametazime ($\kappa = 0.55$). This may reflect the fact that as distribution of ^{123}I -FP-CIT is confined to basal ganglia its visual

interpretation is relatively straightforward after a brief period of training, whereas ^{99m}Tc -exametazime and similar perfusion tracers are taken up throughout the brain and the rating of multiple regions may require significantly more expertise.

Numerous cerebral perfusion SPECT imaging studies have investigated the diagnostic utility of differentiating between DLB and AD using occipital uptake measures as the discriminatory variable. The analyses showed a range of sensitivities and specificities of 65-85% and 71-87% respectively (Hanyu *et al.*, 2006a; Hanyu *et al.*, 2006b; Lobotesis *et al.*, 2001; Pasquier *et al.*, 2002; Shimizu *et al.*, 2005). One study by Hanyu *et al.*, showed that diagnostic accuracy improved using combined MMSE and SPECT measures, where sensitivity increased from 75% to 81% and specificity from 78% to 85% (Hanyu *et al.*, 2006b). The results appear to be better than results reported from the present study (sensitivity 60.7%, specificity 81.8%). It may be that sensitivity improves when using quantitative rather than qualitative measures associated with visual methods. Studies using ^{18}F -fluorodeoxyglucose (FDG) PET have generally shown greater precision than perfusion SPECT in distinguishing DLB from AD (Ishii *et al.*, 1998; Minoshima *et al.*, 2001). Sensitivity and specificity are quoted as ranging from 86% to 92% and 80% to 92% respectively; although such findings should be treated as tentative due to small sample sizes in these studies. A larger PET study by Gilman *et al.* was less accurate (sensitivity 64%, specificity 65%), however specificity in excluding DLB increased from 65% to 74% with the introduction of MMSE and motor scores (Gilman *et al.*, 2005).

There is now increasing evidence that ^{123}I -FP-CIT SPECT imaging can make a significant contribution to increasing the diagnostic accuracy of DLB. Walker *et al* revealed that an abnormal scan was associated with an autopsy diagnosis of DLB with a sensitivity of 88% and specificity of 100% (Walker *et al.*, 2007). O'Brien *et al* using visual inspection reported a sensitivity of 78% and specificity of 85% in diagnosing ante-mortem cases of DLB from AD (O'Brien *et al.*, 2004). More recently, a large multicentre study was carried out to investigate the sensitivity and specificity in the ante-mortem differentiation of probable DLB from other causes of dementia using ^{123}I -FP-CIT SPECT. The study found a mean sensitivity of 78% for detecting DLB and a mean specificity of 90% for excluding non-DLB, which was predominantly due to AD (McKeith *et al.*, 2007). A revision of the DLB clinical consensus criteria has now been made, where a diagnosis of 'probable DLB' is given on the basis of one of the core features (fluctuations, hallucinations or parkinsonism) supported by an abnormal ^{123}I -FP-CIT scan (McKeith *et al.*, 2005). Another SPECT tracer which has shown potential in the differential diagnosis of DLB is ^{123}I -MIBG; a ligand used in myocardial scintigraphy that detects early disturbances of the sympathetic nervous system. Hanyu *et al*, showed that when using heart to mediastinum ratios, a high diagnostic accuracy was achieved (sensitivity 100%, specificity 92%) in distinguishing ante-mortem cases of DLB from AD (Hanyu *et al.*, 2006a). However, few studies have been reported and further investigations are required to establish the role of ^{123}I -MIBG SPECT in the diagnosis of DLB.

Strengths of the present study include: the relatively large populations, consensus results reducing individual rater bias, rigorous clinical and neuropsychological testing of subjects. Potential weakness was the lack of autopsy confirmed diagnoses and therefore the reliance on clinical diagnosis as the ‘gold standard’. Autopsy data was available for 9 patients (2 AD, 7 DLB). ^{123}I -FP-CIT was shown to have a sensitivity of 80% and specificity 100% in diagnosing DLB according to autopsy, and was largely in agreement with a previous ^{123}I -FP-CIT study of autopsy confirmed DLB cases (Walker *et al.*, 2002; Walker *et al.*, 2007). There was one false negative autopsy case, i.e., DLB with a ‘normal’ ^{123}I -FP-CIT scan. The patient had ‘global’ but mild parkinsonism (UPDRS III = 17) and there was evidence of neuronal loss in substantia nigra. Lewy body pathology was moderate in limbic areas and substantia nigra while mild or absent in other brain stem nuclei and neocortical regions. Alzheimer type pathology was severe in medial temporal lobe, moderately severe in lateral temporal and parietal cortex, and moderate in frontal and occipital lobes (Braak stage 5). The data was suggestive of ‘mixed’ pathology although the case was most likely at the AD end of the spectrum of DLB. $^{99\text{m}}\text{Tc}$ -exametazime was diagnostically less accurate than ^{123}I -FP-CIT in classifying autopsy diagnosed AD and DLB cases, although perfusion SPECT has been shown to have a role in distinguishing AD from vascular dementia (Hanyu *et al.*, 1995). Much larger autopsy confirmed populations are required in order to reveal the true diagnostic utility of $^{99\text{m}}\text{Tc}$ -exametazime and ^{123}I -FP-CIT imaging in AD and DLB.

In summary, the study compared $^{99\text{m}}\text{Tc}$ -exametazime with ^{123}I -FP-CIT in the diagnosis of DLB from AD. Diagnostic accuracy was superior with ^{123}I -FP-CIT compared to $^{99\text{m}}\text{Tc}$ -

exametazime in accordance with clinical diagnosis. Visual inspection demonstrated that the pattern of cerebral perfusion is moderately shared between AD and DLB, and points to the challenge in separating these groups using perfusion SPECT imaging alone. Other tracers are now available that may offer additional diagnostic information in support of an accurate antemortem diagnosis of DLB. Further SPECT studies are required with large autopsy confirmed populations in order to reveal the true extent such tracers have on the differential diagnosis of DLB.

Conflict of interest

None.

Description of author's roles

S. Colloby designed the study, participated in the visual rating of scans, collected data, carried out the statistical analyses and wrote the manuscript. M. Firbank assisted in the study design, participated in the visual rating of scans and assisted in writing the manuscript. S. Pakrasi, J. Lloyd and I. Driver participated in the visual rating of scans and reviewed the manuscript. I. McKeith and ED. Williams reviewed the manuscript. J. O'Brien assisted in the study design and in writing the manuscript.

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Table 1: Demographic and clinical characteristics of subjects.

	Control	AD	DLB	p value
<i>n</i>	39	36	30	
Sex (M: F)	21: 18	15: 21	18: 12	Ns
Age (yrs)	75.1 ± 6.6	78.7 ± 5.5	76.0 ± 6.5	0.05
MMSE (max. 30)	28.2 ± 1.5	17.7 ± 4.9	16.3 ± 5.4	<0.001*
CAMCOG (max. 107)	93.9 ± 3.9	59.5 ± 15.4	60.3 ± 14.4	<0.001*
UPDRS III (max. 108)	1.3 ± 2.0	5.6 ± 5.0	26.4 ± 14.9	<0.001**
Disease Duration (yrs)	Na	3.1 ± 1.5	2.4 ± 1.9	Ns
Medications				
Cholinesterase Inhibitors				
Donepezil	0	7	9	
Rivastigmine	0	2	0	
L-Dopa	0	0	3	

Values expressed as (Mean ± 1 Standard deviation).

* Con > DLB, AD; ** DLB > Con, AD (ANOVA).

AD= Alzheimer's Disease; DLB= Dementia with Lewy Bodies; MMSE= Mini-Mental State Examination; CAMCOG= Cambridge Cognitive Examination; UPDRS III = Unified Parkinson's Disease Rating Scale (motor subsection); Ns= Not significant; Na=Not applicable.

Table 2: Incidence of reduced uptake from consensus visual rating of ^{99m}Tc -exametazime and ^{123}I -FP-CIT SPECT scans in controls, AD and DLB.

		Clinical Diagnosis		
		Control (39)	AD (36)	DLB (30)
^{99m}Tc -exametazime	Reduced temporal uptake	8 (21%)	31 (86%)	17 (57%)
	Reduced occipital uptake	6 (15%)	12 (33%)	19 (63%)
	Reduced parietal uptake	8 (21%)	25 (69%)	24 (80%)
	Reduced midline parietal uptake	4 (10%)	12 (33%)	17 (57%)
	Consensus diagnosis = Clinical diagnosis	30 (80%)	19 (53%)	18 (60%)
Complete concordance in consensus diagnosis		23 (59%)	12 (33%)	7 (23%)
^{123}I -FP-CIT	*Reduced striatal uptake	2 (6%)	4 (12%)	22 (79%)

*Control (n=33), AD (n=33), DLB (n=28)

Table 3: ROC curve visual rating results from ^{99m}Tc -exametazime scores by region and ^{123}I -FP-CIT in distinguishing DLB from AD. Sensitivity, specificity, positive and negative likelihood ratios ($\pm\text{LR}$) are presented.

	ROC Curve Area (Area \pm Standard error)	Sensitivity [†] (%)	Specificity [†] (%)	+LR	-LR
^{99m}Tc -exametazime					
Temporal	0.65 \pm 0.07 [§]	86.1 [§]	43.3 [§]	1.5 [§]	0.3 [§]
Occipital	0.65 \pm 0.07	63.3	66.7	1.9	0.6
	0.64 \pm 0.07 [*]	64.3 [*]	63.6 [*]	1.8 [*]	0.6 [*]
Parietal	0.55 \pm 0.07	80.0	30.6	1.2	0.7
Midline Parietal	0.62 \pm 0.07	56.7	66.7	1.7	0.7
^{123}I -FP-CIT	0.83 \pm 0.05	78.6	87.9	6.5	0.2

^{*} ^{99m}Tc -exametazime cases with a ^{123}I -FP-CIT scan (AD = 33, DLB = 28).

[§]Direction of a positive test result is AD. Others denote positive test result as DLB.

[†]Values corresponding to minimum false-negative and false-positive results.

Table 4: SPECT imaging characteristics of autopsy confirmed cases.

Case	Clinical Diagnosis	Autopsy Diagnosis	FPCIT	^{99m} Tc-exametazime Diagnosis	Temp	Occ	Par	Mid Par
1	DLB	DLB	Abnormal	DLB	R	R	R	N
2	AD	AD	Normal	DLB	N	R	R	N
3	DLB	DLB	Abnormal	DLB	R	N	R	R
4	DLB	DLB	Normal	AD	R	N	N	N
5	DLB	DLB	No Scan	DLB	N	R	N	N
6	AD	AD	Normal	AD	R	R	R	R
7	DLB	DLB	Abnormal	AD	R	R	R	R
8	DLB	AD	Normal	Control	N	N	R	N
9	DLB	DLB	Abnormal	Control	N	N	N	N

Key: =Visual rating diagnosis; Temp=Temporal/medial temporal; Occ=Occipital; Par=Parietal; Mid Par=Midline Parietal; R=Reduced uptake; N=Normal uptake.

Figure 1. MRIcro display of the ^{99m}Tc -exametazime SPECT template in standard space. Schematic shows transverse and coronal views as well as colour scale used for the visual rating of scans. Neuroanatomical landmarks within each slice are also illustrated.

Figure 2. Typical transverse views of normal (a) and abnormal (b) ^{123}I -FPCIT SPECT scans.

Figure 3. Representative axial ^{99m}Tc -exametazime SPECT scans of groups in standard MNI space. (a) Control: perfusion is relatively well preserved in cortical regions. (b) AD: loss of uptake in temporal and medial temporal lobes (white arrows). Observe that occipital binding remains largely unaffected (green arrows). (c) DLB: reduced uptake in occipital lobe (white arrows), while temporal and medial temporal blood flow remains relatively unchanged (green arrows).

Figure 4. ROC curves of occipital rCBF ^{99m}Tc -exametazime and ^{123}I -FPCIT SPECT using visual rating in the classification of AD and DLB in accordance with clinical diagnosis.