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A new visual rating scale for Ioflupane imaging in Lewy body disease

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ABSTRACT

Background: Dopaminergic loss on ^{123}I-Ioflupane brain imaging is a recognised biomarker for dementia with Lewy bodies. It is usually assessed using a visual rating scale developed for Parkinson's disease, which may not be optimal for dementia with Lewy bodies, as patterns of dopaminergic loss can be different.
Objectives: We aimed to develop a new visual rating scale for ^{123}I-Ioflupane brain images in Lewy body disease that encompasses appearances seen in dementia with Lewy bodies, and validate this against autopsy diagnosis.
Methods: Four experienced observers developed and tested a new scale consisting of two metrics, reflecting overall loss and heterogeneity of loss. 66 subjects were used during development including clinical diagnoses of Alzheimer's disease (n = 14), Parkinson's disease (n = 9), Parkinson's disease dementia (n = 9), dementia with Lewy bodies (n = 15) and normal controls (n = 19). The scale was then tested on an independent group of 46 subjects with autopsy confirmed diagnosis: Alzheimer's disease (n = 11), Parkinson's disease (n = 3), Parkinson's disease dementia (n = 15), dementia with Lewy bodies (n = 12), normal controls (n = 4) and Frontotemporal dementia (n = 1).
Results: In the autopsy validation the sensitivity and specificity of the new scale for Lewy body disease was 97% and 100% respectively, compared with the standard scale which had the same sensitivity (97%), but lower specificity (80%). The new scale had excellent inter rater reliability (intra-class correlation coefficient 0.93).
Conclusion: A new robust and reliable rating scale is described that straightforwardly captures the visual appearance of ^{123}I-Ioflupane brain images. It demonstrated high accuracy in autopsy confirmed cases and offers advantages over the existing visual rating scale.

1. Introduction

Dementia with Lewy bodies (DLB) is the second commonest cause of degenerative dementia after Alzheimer's disease (AD) (Vann Jones and O'Brien, 2014). Although clinical criteria for DLB have high accuracy in specialist centres (sensitivity and specificity both > 80%) (McKeith et al., 2005), it may be low in non-specialist centres. Correct diagnosis of dementia is vital to communicate prognosis to patients and carers and to avoid unnecessary and potentially harmful treatments. Visualisation of nigrostriatal dopaminergic integrity using ^{123}I-Ioflupane (FP-CIT, DaTSCAN, GE Healthcare) brain SPECT imaging has been reported to improve sensitivity in probable DLB (McKeith et al., 2007), to increase certainty of diagnosis in possible DLB (Walker et al., 2015) and is included as an "indicative biomarker" in recent diagnostic criteria (McKeith et al., 2017).

Clinical reporting ^{123}I-Ioflupane scans for DLB is most often by primary visual read which may be supported by semi-quantification. It is helpful to have a systematic robust method to do this visual assessment. A visual rating scale was introduced by Benamer (Benamer et al., 2000) and developed and validated for Parkinson's disease (PD). When applied in DLB (e.g. (McKeith et al., 2007)), this scale has limitations, in particular the scale does not include a pattern of uniform reduction which may be more common in DLB (O'Brien et al., 2004; Walker et al., 2004). Anecdotally, within our centre it was apparent that observers were having to force images into Benamer categories, even though the image did not fit the strict definition.

Kahraman et al. (2012) and Davidsson et al. (2014) employed a system of visual assessment which was similar to Benamer, except that different image categories were defined. Those studies found some success with this system to distinguish PD from atypical PD syndromes, although they did not directly compare with the Benamer method. The application in those papers was different to ours and so unlikely to be

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directly applicable, particularly as they did not include a category of moderate generalised loss which may be seen in DLB.

Visual reading is likely to remain a principal mode of assessment due to difficulties in image quantification. Absolute quantification of ^{123}I-FP-CIT SPECT is extremely difficult (Bailey and Willowson, 2013) and therefore semi-quantitative regional analysis is usually employed. Although useful, there are several limitations to this approach. Different methods of semi-quantification exist with no standard approach (Koch et al., 2005; Morton et al., 2005a, 2005b; Poli et al., 2013; Slomka et al., 2001; Tossici-Bolt et al., 2006, 2011, 2017; Varrone et al., 2013). Depending on the method used, specific binding ratios may be sensitive to changes in acquisition and processing (Dickson et al., 2010; Koch et al., 2013, 2014; Tossici-Bolt et al., 2011; Tossici-Bolt et al., 2017). Deriving a suitable local normal range for binding ratios can be problematic (Dickson et al., 2017). Image warping and registration may not fully account for anatomical variations in striatal shape. Quantification may give misleading answers in cases where background is low due to atrophy or artefactually high due to scalp uptake.

Our aim in the current work was to develop a new visual rating scale in Lewy body disease (LBD) that encompasses the pattern and distribution of dopaminergic loss seen in DLB. We wished the new scale to be reproducible, straightforward to implement, capture both the overall uptake and its distribution and be highly accurate in separating LBD from non-LBD cases in a mixed group of cases including a significant proportion with DLB. Our aim was to devise a system that did not rely on assigning images to pre-defined categories, but that would be applicable across the full range of conditions for which 123I-FP-CIT SPECT is used, including DLB. The scale was developed using a group of subjects with robust clinical diagnoses and then tested using independent cases that additionally had proceeded to autopsy confirmation of diagnosis. The new scale was compared to the existing Benamer scale.

2. Materials and methods

Based on our expertise in rating Ioflupane scans and in particular the need to capture balanced loss in DLB we devised a new rating method which we will refer here to as the “Newcastle scale”. Data from well characterised subjects (O'Brien et al., 2004) were used for the development and testing of the scale in two phases. Phase one consisted of applying it to cases with clinical diagnoses and setting a threshold for detection of Lewy body disease. In phase two the scale was tested using an independent group of subjects with autopsy diagnosis.

All procedures performed in studies involving human participants were in accordance with NHS and Newcastle Brain Bank ethical approvals and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

2.1. Subjects

Image data was drawn from subjects involved in a previous study (O'Brien et al., 2004) as shown in Tables 1 and 2. Patients were obtained from a community-dwelling population referred to local old age psychiatry and neurology services. Normal controls were recruited from among friends and spouses of patients included in this and other research studies.

Subjects underwent detailed physical, neurological and neuropsychiatric examinations, including the Mini-Mental State Examination (MMSE) (Roth et al., 1986), and the motor subsection of the Unified Parkinson's Disease Rating Scale (UPDRS III) (Fahn, 1987). Diagnosis was made by a consensus panel of experienced dementia clinicians using the NINCDS/ADRDA criteria for AD (McKhann et al., 1984), the consensus criteria for DLB and PDD (Parkinson's disease dementia) (McKeith et al., 1996) and the UK Parkinson's Disease Society Brain Bank criteria for PD (Gibb and Lees, 1988). All AD subjects met criteria for probable AD, 23 DLB subjects fulfilled probable and 4 possible DLB. No subject was on any medication which may affect ^{123}I-Ioflupane uptake.

Forty-six subjects underwent autopsy and neuropathological assessment which was performed blind to clinical diagnoses and ^{123}I-Ioflupane findings. The mean (sd) time between scan and autopsy was 5.74 (3.74) years. Neuropathological findings in these cases have been described previously (Thomas et al., 2017). Six cases fulfilled the neuropathological criteria for both AD and DLB (mixed dementia). In these cases clinical notes were reviewed at baseline and all follow up (blinded to any ^{123}I-Ioflupane results) and the most likely clinical diagnosis at the time of scan was chosen to validate the ^{123}I-Ioflupane results.

In phase one Lewy body disease refers to cases with a clinical diagnosis of PD, PDD or DLB. In phase two this term refers to subjects with Lewy body disease meeting neuropathological criteria (Thomas et al., 2017). This includes subjects with a previous clinical diagnosis of PD, PDD or DLB and who had significant Lewy body pathology at autopsy. Since PD, PDD and DLB may be indistinguishable pathologically, we have classified these subjects according to their final combined clinicopathological diagnoses where LBD is confirmed at autopsy.

2.2. Imaging

Subjects were imaged using a triple-detector rotating gamma camera (Picker 3000XP) fitted with a high resolution fan-beam collimator, 4 h after injection of 150 MBq of ^{123}I-Ioflupane. One hundred and twenty 15 s views over a 360° orbit were acquired on a 128 × 128 matrix with a square pixel dimension of 3.5 mm. Imaging time was 30 min. Image reconstruction was performed without attenuation correction using filtered back projection with a Butterworth filter (order 13, cut-off 0.3 cycles.cm^{-1}) to produce transverse sections with an axial resolution of 10 mm full width at half maximum (FWHM).

Table 1
Subjects used in phase 1 (clinical diagnoses).

	n	Sex (M:F)	Age	MMSE	UPDRS III
Controls	19	11:8	73.1 ± 6.0	28.4 ± 1.3	0.5 ± 0.8
AD	14	5:9	80.9 ± 5.3	17.1 ± 5.2	6.1 ± 6.3
DLB	15	9:6	75.2 ± 7.1	14.7 ± 5.6	31.1 ± 10.9
PD	9	7:2	75.2 ± 5.2	25.9 ± 2.3	25.3 ± 10.2
PDD	9	7:2	73.0 ± 7.7	19.9 ± 6.2	42.0 ± 14.3
Group tests, statistic, p-value		$\chi^2 = 5.8$, 0.2	$F_{4,61} = 3.7$, 0.009	$F_{4,61} = 26.9$, < 0.001	$H_4 = 53.0$, < 0.001
Pair wise tests			Gabriel's post-hoc tests:	Gabriel's post-hoc tests:	Mann-Whitney post-hoc tests:
ns = not significant ($p > 0.05$).			AD > con, $p < 0.04$ AD > PDD, $p < 0.04$ Otherwise ns	Con, PD > AD, DLB, PDD ($p < 0.04$); Otherwise ns.	Con, AD < DLB, PD, PDD ($p < 0.02$); Otherwise ns