BMJ open

[^{123}I]FP-CIT SPECT in suspected dementia with Lewy bodies: a longitudinal case study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-002642
Article Type:	Research
Date Submitted by the Author:	28-Jan-2013
Complete List of Authors:	Siepel, Françoise; Stavanger University Hospital, Centre for Age-Related Medicine Rongve, Arvid; Haugesund Hospital, Department of Psychiatry Buter, Tirza; Stavanger University Hospital, Department of Nuclear Medicine Beyer, Mona; Stavanger University Hospital, Centre for Age-Related Medicine Ballard, Clive; King's College London, Wolfson Centre for Age-Related Diseases Booij, Jan; Academic Medical Center, Department of Nuclear Medicine Aarsland, Dag; Stavanger University Hospital, Centre for Age-Related Medicine
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Radiology and imaging
Keywords:	Dementia < NEUROLOGY, Neuroradiology < NEUROLOGY, Old age psychiatry < PSYCHIATRY

[^{123}I]FP-CIT SPECT in suspected dementia with Lewy bodies: a longitudinal case study

Françoise J. Siepel, MSc[1,2]*; Arvid Rongve[3] MD PhD; Tirza C. Buter[4], MD; Mona K. Beyer[1] MD PhD; Clive G. Ballard[5] Prof MD PhD; Jan Booij[6], Prof MD PhD; Dag Aarsland[1] Prof MD PhD

[1] Centre for Age-Related Medicine, Stavanger University hospital, Stavanger University Hospital, Stavanger, Norway

[2] Department of Clinical Medicine, University of Bergen, Bergen, Norway

[3] Department of Psychiatry, Haugesund Hospital, Haugesund, Norway

[4] Department of Nuclear Medicine, Stavanger University Hospital, Stavanger, Norway

[5] Wolfson Centre for Age-related Diseases, King`s College London, London, UK

[6] Department of Nuclear Medicine, Academic Medical Center, Amsterdam, The Netherlands

*Correspondence and requests for reprints:

Françoise J. Siepel

Stavanger University Hospital, Department of Psychiatry,

Postbox 8100, 4068 Stavanger, Norway.

Phone: +47 51 51 55 78 or +47 51 51 56 19

Fax : +47 51 51 51 61

Email: facois@sus.no

Abbreviated title page

[^{123}I]FP-CIT SPECT in suspected dementia with Lewy bodies: a longitudinal case study

Short title: [^{123}I]FP-CIT SPECT in suspected DLB

Keywords: Single-Photon Emission Computed Tomography, [^{123}I]FP-CIT, Dementia, Lewy Body, Cluster analysis

Paper statistics:

Abstract:	253 words
Paper:	3646 words
References:	42 references
Tables:	3 tables
Images:	1 image

ABSTRACT

Objectives Little is known regarding the "false negative" or "false positive" striatal dopamine transporter binding on SPECT for the diagnosis of dementia with Lewy bodies (DLB). We explore the clinical course in patients fulfilling the criteria for clinical DLB with a normal [^{123}I]FP-CIT SPECT (i.e. SPECT scan negative, clinical features positive (S-CF+)), and patients not fulfilling DLB criteria with a pathological scan (S+CF-).

Design Longitudinal case study over 2-5 years.

Setting Consecutive referrals of patients with mild dementia to dementia clinics in western Norway.

Participants 50 patients (27 men and 23 women; mean age at baseline of 74 (range 52 to 88)) with [^{123}I]FP-CIT SPECT images underwent cluster analyse, and 20 patients allocated to a "DLB" and 8 to a "non-DLB" cluster were included.

Outcome measures were scores on standardized clinical rating scales for hallucination, parkinsonism, fluctuations and REM sleep behaviour disorder; visual rated [^{123}I]FP-CIT SPECT.

Results In the S+CF- group (n=7), frequency and severity of DLB symptoms tended to increase, particularly parkinsonism (7/7) and cognitive fluctuations (7/7), while severity of visual hallucinations and REM sleep behaviour disorder remained stable. The S-CF+ (n=3) fulfilled the operationalized criteria for probable DLB both at baseline and at the end of the follow-up.

Conclusions The findings suggest that systematic visual analyses of [^{123}I]FP-CIT SPECT can detect people with DLB prior to the development of the full clinical syndrome. In addition, the study indicates that some patients fulfilling clinical criteria for probable DLB have a normal scan, and further studies are required to characterize these patients better.

SUMMARY SECTION

Article focus

- [^{123}I]FP-CIT SPECT is an established biomarker for DLB versus AD.
- Little is known about the clinical course of patients with symptoms of DLB having a normal [^{123}I]FP-CIT SPECT and patients not fulfilling the DLB criteria with a pathological scan.
- We performed a detailed clinical follow-up of such patients.

Key Messages

- Patients not fulfilling the DLB criteria with a pathological scan developed full-blown DLB criteria.
- Patients with symptoms of DLB having a normal [^{123}I]FP-CIT SPECT continued to fulfill clinical criteria for DLB, i.e. were false negative according to clinical criteria.
- [^{123}I]FP-CIT SPECT is important in an early stage of DLB.

Strengths and Limitations

- Limitations include the small number of patients included and the lack of autopsy.
- Strengths include the objective clinical classification based on cluster analysis and the long duration and standardized procedures of the study period.

INTRODUCTION

Dementia with Lewy bodies (DLB) is the second most frequent neurodegenerative dementia after Alzheimer's disease (AD). In addition to cognitive decline, frequent clinical symptoms of DLB are parkinsonism, hallucinations and other psychiatric symptoms, fluctuating attention, and autonomous dysfunction including orthostatic hypotension and falls.[1] DLB patients have more reduced quality of life, higher costs, and higher mortality than patients with AD.

DLB is often under-diagnosed especially in the early stages when the frequency of presenting core symptoms is low.[2] Early and accurate diagnosis is however important for informing patient and relatives about key treatment decisions as the disease course and prognosis differ between the dementia types. In addition, diagnosing DLB is meaningful for avoiding antipsychotic drugs due to the sensitivity for side effects in this patient group. Diagnosis is particularly problematic in people who have some symptoms of DLB but do not fulfil the criteria for probable DLB. The clinical diagnosis of DLB has a high specificity (approximately 95%) but low sensitivity (30%) mainly based on the consensus criteria presented in 1996,[3] indicating that the diagnosis is often missed.

Dopaminergic nigrostriatal degeneration is common in DLB and [^{123}I]FP-CIT SPECT imaging is able to detect this dopaminergic deficit. This imaging technique is an established biomarker for the in vivo detection of nigrostriatal degeneration, which is typical feature of Parkinson's disease (PD) also. [^{123}I]FP-CIT SPECT uses a ^{123}I-labeled tracer that binds with high affinity to the dopamine transporter (DAT). A high correlation between abnormal DAT binding and a clinical diagnosis of probable DLB has been shown, and in a pivotal multicentre study, abnormal scans had a mean sensitivity of 78% for distinguishing clinical probable DLB from AD, with specificity of 90% for excluding non-DLB.[4] Decreased striatal DAT binding is listed as one of the suggestive features in the consensus criteria for the clinical diagnosis of DLB.[1]

Very little is known regarding patients fulfilling clinical DLB criteria with a negative [^{123}I]FP-CIT SPECT scan (S-CF+) or patients with an abnormal scan not fulfilling clinical DLB criteria (S+CF-). In contrast, considerable research has been conducted on PD patients with negative DAT scans, i.e. "scans without evidence of dopaminergic deficit" (SWEDD). Repeated DAT imaging showed a normal scan up to 4 year follow up and this group did not benefit from antiparkinson medication.[5] This demonstrates that causes other than nigrostriatal degeneration can cause parkinsonism, such as for example cerebrovascular disease (vascular parkinsonism) and drugs with antidopaminergic activity.[6]

It has been shown in a trial cohort that [^{123}I]FP-CIT SPECT can distinguish DLB from AD even before the full syndrome has emerged. Indeed, this imaging marker is particularly clinically useful in diagnostically uncertain cases, and patients with "S+CF-" may actually represent early cases who will later develop a full DLB syndrome.[7, 8] However, the nosological status and course of the S-CF+ and S+CF- group, in the context of DLB have not been reported in a clinical cohort.

This study aims to explore the clinical characteristics and course of dementia patients who underwent [^{123}I]FP-CIT SPECT imaging. A group of such patients from the Norwegian DemWest cohort was followed according to a standardized and prospective research protocol. We hypothesized that "S+CF-" cases would develop a clinical profile more consistent with the diagnostic criteria for DLB, and that "S-CF+" cases may develop a clinical phenotype that differed from the typical pattern of DLB patients.

MATERIALS AND METHODS

Participants were selected from the DemWest cohort, which includes patients from dementia clinics with a first time diagnosis of mild dementia who are followed annually.[9] Patients were assessed with medical exam and routine blood tests, and standardized clinical assessments and neuropsychological tests were administered, such as the motor subscale of the Unified Parkinson`s Disease Rating Scale (UPDRS) for parkinsonism, Neuropsychiatric Inventory (NPI) to assess psychiatric symptoms including visual hallucinations (VHs) and the Clinician Assessment of Cognitive Fluctuations (COGA)[10] or Mayo fluctuation Questionnaire[11] for cognitive fluctuations. Sleep disturbances including REM sleep behaviour disorder (RBD) were monitored with the Mayo sleep Questionnaire.[12] Neuroleptic sensitivity was classified as previously reported.[13] Exclusion criteria were acute delirium or confusion, terminal illness, recently diagnosed major somatic illness, previous bipolar disorder or psychotic disorder. More details regarding selection and diagnostic procedures are provided elsewhere.[9]

Continuous scores for the core and suggestive DLB features were calculated: for visual hallucinations (frequency x intensity) using the NPI scale item 2 with a range of 0-12; parkinsonism on the UPDRS motor subscale (0-108); fluctuating cognition by the clinician assessment of cognitive fluctuations (0-16) (a subgroup on the Mayo fluctuation questionnaire (0-4)) and combined as previously described.[14] RBD was determined with the Mayo sleep questionnaire (0-4). To select DLB patients we used UPDRS-motor subscale cut-off score of > 9 and at least 1 within other scales.[14]

Imaging

From the DemWest database 50 patients underwent [^{123}I]FP-CIT SPECT imaging on the discretion of the clinician considered DLB to be a differential diagnosis between March 2005 and May 2010 (27 men and 23 women, mean age at baseline of 74 (range 52 to 88). Initial diagnosis of possible or probable DLB was made using clinical judgement.[1] Subsequent classification of patients was undertaken based upon a cluster analysis of symptoms (see analysis section below for details).The average time between initial clinical diagnosis and date of [^{123}I]FP-CIT SPECT imaging was 7 months.

SPECT imaging with the well-validated radiotracer [^{123}I]FP-CIT (N-ω-fluoropropyl-2β-carbomethoxy-3β-[4-iodophenyl] nortropane; DaTscan^{TM}, GE Healthcare) was performed according to clinical routine at each of the three centres. An intravenous injection of about 185 MBq was administered and images were acquired 3-4 h after injection on a multidetector or multiheaded gamma camera with LEHR collimators, a time point at which the specific binding ratio of this tracer to the DAT is stable.[15] Subsequently, images were reconstructed using filtered back projection (FBP) with a Butterworth filter with a 0.55 cutoff and an order of 10. Chang`s attenuation correction was applied with an attenuation coefficient of 0.11 cm^{-1}.[16]

Representative transversal images through the basal ganglia were visually analysed by an external nuclear medicine specialist, experienced in DAT imaging (JB), who did not have access to clinical information. The visual analysis consisted of separate evaluations of the left and right caudate nucleus and putamen divided in normal, abnormal and strongly abnormal.

In addition, magnetic resonance imaging (MRI) was acquired at baseline at the three centres using 1.5 Tesla MRI: a Philips Intera scanner with fast field echo (FFE) protocol (TR/TE/FA= 10 ms/4.6 ms/30°,ST=2.0mm, NEX=2.0, matrix=256x256 or TR/TE/FA=20 ms/4.6 ms/30°,ST=1.0mm, NEX=2.0, matrix=256x256) and GE Signa Excite scanner with fast spoiled gradient recalled (FSPGR) protocol (TR/TE/FA=20 ms/3.1 ms/7°,ST =1.0mm, NEX=1.0, matrix=256x256). Details of the harmonization have been reported previously.[17] Basal ganglia hyperintensities were scored using the basal ganglia part of the Scheltens scale, a semi quantitative rating scale (0-30) including separate assessment (0-6) of the caudate nucleus, putamen, globus pallidus, thalamus and the internal/external capsule.[18] One patient (case 9) did not receive a MRI due to metal prostheses in both ears.

Analysis

For an objective, quantitative classification of cases, cluster analysis was applied based on the scores on the four DLB symptom scales as previously reported.[14] The patients were classified in 4 clusters with help of SPSS version 18. In brief, the two step cluster analysis was performed with four continuous variables (i.e. parkinsonism, hallucinations, cognitive fluctuations and RBD) and log-

likelihood.[14] Missing values analysis with expectation-maximization algorithm was performed when scores at one of the four symptom scales was missing. The four clusters included a “DLB” cluster, with high scores for hallucinations and parkinsonism and cognitive fluctuations, a `non-DLB` cluster with low values on all DLB symptom scales, one cluster included patients with high scores for RBD, and one with high values of cognitive fluctuations. In this study we only considered patients classified in the “DLB” and the “non-DLB” clusters.[14] Based on the [^{123}I]FP-CIT SPECT scan results, patients were classified as S-CF+ (i.e. DLB-cluster and normal scan) or S+CF- (i.e. non-DLB cluster and abnormal scan).

Design

Patients were followed with annual assessments using the same assessment battery at baseline performed by trained research physicians and research nurses. Subsequently, core and suggestive DLB features (parkinsonism, VH, cognitive fluctuations, neuroleptic hypersensitivity, RBD) and their progress were rated by an experienced research clinician (AR), taking into account both research data and transcripts from the medical records, but blinded to all information of [^{123}I]FP-CIT SPECT scan information and clinical diagnosis. The blinding was achieved by actively removing all information about the scans from the transcripts. The rater noted whether symptoms were present and their severity (no, mild-to-moderate, and moderate-to-severe) at baseline, and whether they increased or decreased (mild or marked) or remained stable during the follow-up period.

Ethical approval

The regional ethics committee and the Norwegian authorities approved the DemWest study for collection of medical data. The patients provided written consent to participate in the study after a thorough explanation of the procedure to the patient and caregiver.

RESULTS

There were 20 patients in the DLB cluster, 8 patients in the non-DLB cluster (the remaining 22 patients were included in the other two clusters, with subsequently n=5 with S- and n=7 with S+ in the RBD cluster and n=6 with S- and n=4 with S+ in the cognitive fluctuation cluster). Nine of the 50 patients with [^{123}I]FP-CIT SPECT had one missing value and therefore an estimation was performed.

Scans of 3 patients in the DLB cluster were classified as normal, and these 3 were consequently classified as S-CF+. Seven patients in the non-DLB cluster had a pathological scan, and were classified as S+CF-. An example of the [^{123}I]FP-CIT SPECT scan for the S-CF+ group (left) and S+CF- group (right) is shown in figure 1. Table 1 shows the characteristics of the two groups.

Table 1: Clinical characteristics

Characteristics	False Negative (n=3)	False Positive (n=7)
Gender (M:F)	3:0	4:3
MMSE	22 (20-26)	25 (16-27)
Age at baseline (years)	79 (72-88)	71 (52-80)
Observation time (years)	3.0 (2-4)	3.4 (2-5)
Medication		
Antiparkinson (yes/no)	0:3	1:6
Antipsychotics (yes/no)	2:1	1:6
Antidepressants (yes/no)	1:2	3:4
Antidementia (yes/no)	1:2	6:1

(Numbers represent median (range) or number of patients)

Detailed information about the visual assessment of the [^{123}I]FP-CIT SPECT scans regarding DAT binding in the caudate nucleus bilaterally, and the putamen bilaterally, as well as hyperintensities based on MRI are shown in Table 2.

Table 2: Visual assessment of [^{123}I]FP-CIT SPECT and MRI

	[^{123}I]FP-CIT SPECT					MRI	
	Caudate Left	Caudate Right	Putamen Left	Putamen Right	Final Evaluation	Scheltens score (0-30)	Details
S-CF+							
1	0	0	0	0	normal	3	Right capsula interna/externa
2	0	0	0	0	normal	0	
3	0	0	0	0	normal	8	Left thalamus, right capsula interna/externa
S+CF-							
4	0	0	2	2	abnormal	0	
5	0	2	0	2	abnormal	0	
6	2	2	2	2	abnormal	0	
7	0	1	2	2	abnormal	0	
8	0	0	2	1	abnormal	4	Left caudate, right capsula

							externa
9	2	2	2	2	abnormal	-	Not performed
10	0	1	0	1	abnormal	6	Putamen bilateral, left capsula externa

(0 = normal, 1=abnormal, 2= strongly abnormal on [^{123}I]FP-CIT SPECT). S: [^{123}I]FP-CIT SPECT; CF: clinical features

It can be seen that in the S-CF+ group, the [^{123}I]FP-CIT SPECT scans were normal, by definition, in all studied striatal subareas. In the S+CF- group, putamen DAT binding was abnormal bilaterally in most cases (5/7). None of the cases shows infarcts in the basal ganglia on MR. Some patients had white matter lesions (WML), but these were usually in the low-to-moderate range.

During follow-up, no other diseases were detected which could explain the symptoms. Table 3 shows the core and suggestive symptoms at baseline and their development during follow up.

Table 3: Status of main DLB symptoms at baseline and during follow-up

	Visual hallucinations		REM sleep behaviour disorder		Cognitive fluctuations		Parkinsonism	
	Bsl	Fu	Bsl	Fu	Bsl	Fu	Bsl	Fu
S-CF+								
1	1	0	0	0	1	0	0	2
2	1	-1	1	0	0	1	1	2
3	1	0	1	-1	0	2	0	1
S+CF-								
4	1	0	2	-1	1	2	0	2
5	2	1	0	1	0	2	1	2
6	0	0	0	0	0	1	0	2
7	1	0	0	0	0	2	1	2
8	0	0	0	0	0	2	1	2
9	0	0	0	0	0	1	2	2
10	0	0	0	0	0	2	0	2

(Baseline: 0 = not present, 1 = mild/moderate, 2=moderate/marked; Follow up: -2 = significant decrease, -1 = decrease, 0 = no change, 1 =increase, 2 = significant increase). Bsl: baseline; Fu: follow-up; S: [^{123}I]FP-CIT SPECT; CF: clinical features

In the S+CF- group, it can be seen that some DLB core symptoms were present at baseline in some patients. These were usually of mild-to-moderate severity and did not reach the cut-off values that emerged from the cluster analysis.[14] All 7 had a moderate-to-severe increased parkinsonism during follow-up, although 3/7 had no parkinsonism at baseline. In addition, all 7 S+CF- developed marked worsening in cognitive fluctuations, whereas 6 were without these symptoms at baseline. Less marked changes were noted for VH.

In the S-CF+ group all 3 cases had VH at baseline that remained stable (n=2) or decreased (n=1) in severity during the follow-up period. In contrast, 2 cases showed a moderate-to-severe worsening in parkinsonism and 2 cases had worsening of cognitive fluctuations.

There were no remarkable changes in progression of the severity of RBD that was also rare at baseline. Three patients (2 S-CF+, 1 S+CF-) received antipsychotics but hypersensitivity reactions to these drugs were not observed.

All cases fulfilled the criteria for probable DLB at the end of the follow-up period without taking the [^{123}I]FP-CIT SPECT scan results into account, i.e. they had at least two core features or one core and one clinical suggestive feature.

DISCUSSION

In this study we report longitudinal findings in patients who, based on cluster analysis of symptom scores were classified as “DLB” or “non-DLB”, and who had [^{123}I]FP-CIT SPECT results that were inconsistent with these findings, i.e. “S-CF+” or “S+CF-. Our main findings are that S+CF- patients tend to develop core or suggestive features of DLB, in particular parkinsonism and cognitive fluctuations, i.e. they represent DLB in the early stage. In the S-CF+ group more various DLB symptoms were shown at baseline with mainly a stable or increased severity at follow-up, and all cases fulfilled the criteria for probable DLB at the end of the follow-up period.

Very few longitudinal studies of DLB patients in light of [^{123}I]FP-CIT SPECT have been reported. In contrast, the results of [^{123}I]FP-CIT SPECT imaging and the discrepancy with clinical diagnosis have been extensively studied in PD. The Clinically Uncertain Parkinsonism Syndrome (CUPS) study considered patients with uncertain but clinically suspect PD. [^{123}I]FP-CIT SPECT imaging was inconsistent with initial diagnosis in 36% of the patients with a clinical diagnosis of presynaptic parkinsonism and 54% with non-presynaptic parkinsonism. After two years, however, the clinical diagnosis was established and the rate of agreement between the diagnosis at follow-up and the initial imaging results was 90%, indicating that the initial DAT SPECT scan is of value in the diagnostic follow up of the patients with clinically uncertain PD.[19] This is in line with the current study showing that all 7 FP cases developed increased parkinsonism and cognitive fluctuations consistent with a diagnosis of DLB. Our findings are also consistent with a previous study demonstrating that in cases with “possible DLB”, i.e. not fulfilling criteria for probable DLB, the scan differentiated between those who developed probable DLB and those who did not after one year.[7]

An explanation for this could be that the [^{123}I]FP-CIT SPECT scan detects nigro-striatal degeneration before the full clinical syndrome has been developed. This is supported by the knowledge of PD that 80% of the striatal dopamine neurons need to be lost before PD symptoms are present.[20] In addition, it is shown that by using a radioligand for DAT nigrostriatal damage can be detected years before the onset of motor signs of PD.[21]

Three of our cases (3 out of 50; 6% of all scans) were in the S-CF+ group, and searching for possible explanations is important. It is well known that 10-15% of patients with clinical PD have a normal DAT scan, and it is suggested that this subgroup have no involvement of the dopaminergic nigrostriatal pathway.[6] In the S-CF+ group the cases may have a true negative [^{123}I]FP-CIT SPECT, i.e. they have DLB but without involvement of dopaminergic neurons in the substantia nigra. Some DLB patients indeed do not develop parkinsonism.[22] Pathological classification of DLB identifies three types: brainstem predominant, limbic, and neocortical, assuming the substantia nigra is first affected, following by the amygdalae and limbic cortex and subsequently the neocortex.[23] However, it has been reported that in some cases, Lewy-body pathology can be found in the cortex and higher brain stem but not in the lower brain stem,[24] suggesting that in some patients the pathological process starts in the neocortex, and then progresses towards the brain stem. Our findings in the S-CF+ group are consistent with this hypothesis, in that parkinsonism mainly developed later on. Unfortunately, a follow-up scan or neuropathology was not available to address this hypothesis. Interestingly, a recent clinicopathological study, that included 7 autopsy proven DLB cases, showed that the antemortem [^{123}I]FP-CIT SPECT scan was normal in 2 of these cases. Importantly, in these 2 cases the number of nigrostriatal dopaminergic neurons was also within the normal range.[25] This observation may support the hypothesis that in some patients the pathological process may start in the neocortex.

Another possible explanation for the S-CF+ cases is the pathological heterogeneity in DLB. Whereas some patients have a “pure” DLB, the majority in addition may have AD-type changes such as amyloid plaques and even tangle pathology.[1] 5-10% of patients with clinical dementia have intermediate [^{123}I]FP-CIT SPECT scans, i.e. abnormal DAT binding but not as low as typical of DLB. These intermediate scans could represent cases with mixed DLB/AD pathology.[26] DLB cases with AD pathology have lower prevalence of core DLB symptoms than “pure” DLB.[6, 27] It is possible that mixed cases in an early stage may have subtle or no nigrostriatal dopaminergic pathology leading to a normal DAT scan. In these cases parkinsonism may be caused by Alzheimer-type or even LB-type degeneration in the striatum itself rather than by dopaminergic nigrostriatal neurodegeneration.[28]

Another possible explanation is that S-CF+ cases have another type of dementia than DLB. For example, parkinsonism is not uncommon in AD, particularly in the later stages,[29] and it can be seen

in other conditions such as vascular parkinsonism and frontotemporal dementia. However, both vascular parkinsonism and frontotemporal dementia may have pathological scans, although less common than in DLB.[30, 31] The score for hyperintensities on MRI is in the range from 0-8 (see table 2). These relatively low scores show that cerebrovascular is an unlikely cause of parkinsonism in our cases, also since none of the subjects had lacunar infarcts in the basal ganglia.

Drug-induced parkinsonism is also common,[6] and may take several weeks to resolve after drug discontinuation, and complete resolution may taken over a year.[32] These patients usually have a normal DAT SPECT scan,[33] and thus may be misinterpreted as "S-CF+". In our S-CF+ group, case 1 received antipsychotics during 5 months and discontinued one month before scanning, and in case 3 it was discontinued directly at baseline. However, in both cases, parkinsonism increased during follow-up. Drug-induced parkinsonism is therefore not a likely cause of the "S-CF+" patients in our study.

Finally, several patients were treated with drugs such as antidepressants, antipsychotics, L-DOPA and antidementia drugs, and scanned while on medication, which may influenced the interpretation of the [^{123}I]FP-CIT SPECT scans.[34]

The antidopaminergic effect of antipsychotic drugs may increase the synthesis and release of dopamine in the striatum, leading to a potential competition between the DAT ligand [^{123}I]FP-CIT and synaptic dopamine. Indeed, high doses of the neuropsychotic haloperidol resulted in a reduction in striatal [^{123}I]FP-CIT binding by 25% in rats.[35] However, in another rat study this could not be replicated.[36] Also, it has recently been discussed that even if neuroleptics will induce changes in DAT imaging, such changes will presumably not be large enough to influence the visual assessments of [^{123}I]FP-CIT SPECT studies.[34] Nevertheless, in the present study, 1 patient in the S+CF- group had used an antipsychotic, and we cannot totally exclude that this may have led to a false positive scan.

Although antiparkinsonian medications influence the dopaminergic transmission, they do not seem to affect the visual interpretation and quantification of DAT imaging.[6] The use of Levodopa for example did not significant change the striatal [^{123}I]FP-CIT binding significantly.[37]

The acetylcholinesterase inhibitors, such as donepezil and rivastigmine may reduce striatal dopaminergic transmission, but did not show significant effects on striatal [^{123}I]FP-CIT binding.[38]

Antidepressants such as the selective serotonin reuptake inhibitor (SSRI) paroxetine have been shown to induce a small, but significant increase in striatal [^{123}I]FP-CIT binding ratios.[39] On the other hand, the SSRI citalopram showed a *reduction* in striatal [^{123}I]FP-CIT binding ratios, and blocking of the serotonin transporter (SERT) may lead to high plasma [^{123}I]FP-CIT concentrations.[40] DAT and SERT are important for the termination of dopaminergic and serotonergic transmission, respectively, by reuptake of dopamine and serotonin from the synaptic cleft. FP-CIT binds to DAT and SERT with affinities in the nanomolar range, although the affinity to SERT is lower than that to DAT.[34] Therefore, quantification of [^{123}I]FP-CIT SPECT is susceptible to SERT blocking pharmaceuticals.[40] However, as recently discussed, a small change in the quantification in striatal FP-CIT binding, and with the same change of binding in both the caudate nucleus and putamen, is unlikely to result in false negative and false positive results when a visual assessment is used.[34] One of our S-CF+ and 2 of the S+CF- patients had used an SSRI, but it is unlikely that this has influenced the interpretation of our scan results. Two of the antidepressant users showed a decrease in visual hallucinations during follow-up, cases 2 and 5 (table 3). Nevertheless, more studies are needed to explore how CNS-active drugs frequently used by DLB-patients may influence DAT imaging interpretation.

Some limitations of this study need to be acknowledged. First, the limited number of patients in the S-CF+ and S+CF- group and the difference in follow-up time ranging from 2 to 5 years, dependent on the moment of entrance in the study should be mentioned. Also, no repeat imaging was performed. A prolonged follow-up time in a larger study group with follow-up DAT scan may have provided additional information. Secondly, the NPI item 2 includes hallucinations from different modalities and not only visual. However, we have previously shown that of those with hallucinations in the overall cohort, nearly 80% had visual hallucinations.[41] In addition, we did verify through the medical record transcripts that the patients with hallucinations in fact had visual hallucinations. RBD was diagnosed based only on clinical assessment. Videopolysomnograpphy is the preferred diagnostic method but not widely available, and acceptable sensitivity and specificity has been reported for the Mayo sleep

scale.[42] Finally, scans were only analysed visually. However, in previous studies this approach has shown to be as accurate as semi-quantitative analyses to differentiate normal from abnormal [^{123}I]FP-CIT SPECT scans.[4]

The golden standard for diagnosing DLB is the brain pathology analysis post-mortem. Unfortunately autopsy of the FP and FN cases in this study was not available to confirm diagnosis. However, all 7 available autopsy diagnoses from the DemWest study were consistent with the clinical diagnosis including two AD and five DLB patients. In addition, a relative objective method of cluster analysis was performed based on symptom scores for the main DLB symptoms in this study, and the symptoms of interest were rated by trained research clinicians using standardized and validated instruments.

CONCLUSION

These data support the notion that [^{123}I]FP-CIT SPECT imaging can identify DLB patients before the full syndrome has developed, supporting the usefulness of [^{123}I]FP-CIT SPECT as part of the routine clinical work up in cases with suspect DLB. A minority of patients fulfilling clinical DLB criteria have a normal [^{123}I]FP-CIT SPECT scan, and further studies are needed to characterize such cases.

CONTRIBUTORS

FJS and DA were responsible for the study concept, design, data analysis, writing of the manuscript, and provided input during the whole process of the study. AR was involved in the development of the study concept, clinical patient evaluation and data analysis. TCB was involved in the image selection and reconstruction and provided main input during data acquisition. MKB and JB were responsible for image analysis and interpretation of results. CGB was involved in the concept and evaluation of results. All authors were involved in critical review of the draft and approval of the version to be published.

ACKNOWLEDGMENTS

The authors acknowledge the co-investigators involved in the large dementia study in western Norway and especially K Brønnick for the advice and contribution.

In addition, we thank the National Institute for Health Research (UK) for supporting the work of Clive Ballard through the Biomedical Research Unit for Dementia and the Biomedical Research Centre for Mental Health at King's College London.

COMPETING INTERESTS

JB is consultant of GE Healthcare

FUNDING

This study was supported by GE Healthcare.

Françoise Siepel is supported by a grant from Western Norway regional health authority.

REFERENCES

1. 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**(12):1863-72

2. Tiraboschi P, Salmon DP, Hansen LA, et al. What best differentiates Lewy body from Alzheimer's disease in early-stage dementia? Brain 2006;**129**(Pt 3):729-35

3. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 1996;**47**(5):1113-24

4. McKeith I, O'Brien J, Walker Z, et al. Sensitivity and specificity of dopamine transporter imaging with 123I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study. Lancet Neurol 2007;**6**(4):305-13

5. Marek K, Jennings D, Seibyl J. Long-term folluw-up of patients with scans without evidence of dopaminergic deficit (SWEDD) in the ELLDOPA study [abstract]. Neurology 2005;**64**((1 Suppl)):A274

6. Cummings JL, Henchcliffe C, Schaier S, et al. The role of dopaminergic imaging in patients with symptoms of dopaminergic system neurodegeneration. Brain 2011;**134**(Pt 11):3146-66

7. O'Brien JT, McKeith IG, Walker Z, et al. Diagnostic accuracy of 123I-FP-CIT SPECT in possible dementia with Lewy bodies. Br J Psychiatry 2009;**194**(1):34-9

8. Papathanasiou ND, Boutsiadis A, Dickson J, et al. Diagnostic accuracy of 123I-FP-CIT (DaTSCAN) in dementia with Lewy bodies: a meta-analysis of published studies. Parkinsonism Relat Disord 2012;**18**(3):225-9

9. Aarsland D, Rongve A, Nore SP, et al. Frequency and case identification of dementia with Lewy bodies using the revised consensus criteria. Dement Geriatr Cogn Disord 2008;**26**(5):445-52

10. Walker MP, Ayre GA, Cummings JL, et al. The Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale. Two methods to assess fluctuating confusion in dementia. Br J Psychiatry 2000;**177**:252-6

11. Ferman TJ, Smith GE, Boeve BF, et al. DLB fluctuations: specific features that reliably differentiate DLB from AD and normal aging. Neurology 2004;**62**(2):181-7

12. Boeve BF, TJ; Silber, MH; Smith, GE. Validation of a questionnaire for the diagnosis of REM sleep behavior disorder. Neurology 2002;**58**(Suppl. 3):A509

13. Aarsland D, Perry R, Larsen JP, et al. Neuroleptic sensitivity in Parkinson's disease and parkinsonian dementias. J Clin Psychiatry 2005;**66**(5):633-7

14. Rongve A, Bronnick K, Ballard C, et al. Core and suggestive symptoms of dementia with lewy bodies cluster in persons with mild dementia. Dement Geriatr Cogn Disord 2010;**29**(4):317-24

15. Booij J, Hemelaar TG, Speelman JD, et al. One-day protocol for imaging of the nigrostriatal dopaminergic pathway in Parkinson's disease by [123I]FPCIT SPECT. J Nucl Med 1999;**40**(5):753-61

16. Darcourt J, Booij J, Tatsch K, et al. EANM procedure guidelines for brain neurotransmission SPECT using (123)I-labelled dopamine transporter ligands, version 2. Eur J Nucl Med Mol Imaging 2009;**37**(2):443-50

17. Lebedev AV, Beyer MK, Fritze F, et al. Cortical changes associated with depression in Alzheimer's disease: an MRI surface-based morphometric study [abstract]. European Psychiatry 2012;**27**: p792

18. Scheltens P, Barkhof F, Leys D, et al. A semiquantative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. J Neurol Sci 1993;**114**(1):7-12

19. Tolosa E, Borght TV, Moreno E, et al. Accuracy of DaTSCAN (123I-Ioflupane) SPECT in diagnosis of patients with clinically uncertain parkinsonism: 2-year follow-up of an open-label study. Mov Disord 2007;**22**(16):2346-51

20. Fearnley JM, Lees AJ. Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain 1991;**114 (Pt 5)**:2283-301

21. Ponsen MM, Stoffers D, Booij J, et al. Idiopathic hyposmia as a preclinical sign of Parkinson's disease. Ann Neurol 2004;**56**(2):173-81

22. Ballard CG, Aarsland D, McKeith I, et al. Fluctuations in attention: PD dementia vs DLB with parkinsonism. Neurology 2002;**59**(11):1714-20

23. Braak H, Bohl JR, Muller CM, et al. Stanley Fahn Lecture 2005: The staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered. Mov Disord 2006;**21**(12):2042-51

24. Halliday GM, McCann H. The progression of pathology in Parkinson's disease. Annals of the New York Academy of Sciences 2010;**1184**:188-95

25. Colloby SJ, McParland S, O'Brien JT, et al. Neuropathological correlates of dopaminergic imaging in Alzheimer's disease and Lewy body dementias. Brain 2012;**135**(Pt 9):2798-808

26. Kemp PM, Holmes C. Imaging in dementia with Lewy bodies: a review. Nucl Med Commun 2007;**28**(7):511-9

27. Ballard CG, Jacoby R, Del Ser T, et al. Neuropathological substrates of psychiatric symptoms in prospectively studied patients with autopsy-confirmed dementia with lewy bodies. Am J Psychiatry 2004;**161**(5):843-9

28. Duda JE, Giasson BI, Mabon ME, et al. Novel antibodies to synuclein show abundant striatal pathology in Lewy body diseases. Ann Neurol 2002;**52**(2):205-10

29. Starkstein SE, Merello M, Brockman S, et al. Apathy predicts more severe parkinsonism in Alzheimer's disease. Am J Geriatr Psychiatry 2009;**17**(4):291-8

30. Benitez-Rivero S, Marin-Oyaga VA, Garcia-Solis D, et al. Clinical features and 123I-FP-CIT SPECT imaging in vascular parkinsonism and Parkinson's disease. J Neurol Neurosurg Psychiatry 2012;**84**(2):122-9

31. Morgan S, Kemp P, Booij J, et al. Differentiation of frontotemporal dementia from dementia with Lewy bodies using FP-CIT SPECT. J Neurol Neurosurg Psychiatry 2012;**83**(11):1063-70

32. Lopez-Sendon JL, Mena MA, de Yebenes JG. Drug-induced parkinsonism in the elderly: incidence, management and prevention. Drugs Aging 2012;**29**(2):105-18

33. Diaz-Corrales FJ, Sanz-Viedma S, Garcia-Solis D, et al. Clinical features and 123I-FP-CIT SPECT imaging in drug-induced parkinsonism and Parkinson's disease. Eur J Nucl Med Mol Imaging 2010;**37**(3):556-64

34. Booij J, Kemp P. Dopamine transporter imaging with [(123)I]FP-CIT SPECT: potential effects of drugs. Eur J Nucl Med Mol Imaging 2008;**35**(2):424-38

35. Nikolaus S, Antke C, Kley K, et al. Pretreatment with haloperidol reduces (123)I-FP-CIT binding to the dopamine transporter in the rat striatum: an in vivo imaging study with a dedicated small-animal SPECT camera. J Nucl Med 2009;**50**(7):1147-52

36. Lavalaye J, Knol RJ, de Bruin K, et al. [123I]FP-CIT binding in rat brain after acute and sub-chronic administration of dopaminergic medication. European journal of nuclear medicine 2000;**27**(3):346-9

37. Schillaci O, Pierantozzi M, Filippi L, et al. The effect of levodopa therapy on dopamine transporter SPECT imaging with(123)I-FP-CIT in patients with Parkinson's disease. Eur J Nucl Med Mol Imaging 2005;**32**(12):1452-6

38. Knol RJ, de Bruin K, van Eck-Smit BL, et al. No significant effects of single intravenous, single oral and subchronic oral administration of acetylcholinesterase inhibitors on striatal [123I]FP-CIT binding in rats. Eur J Nucl Med Mol Imaging 2008;**35**(3):598-604

39. Booij J, de Jong J, de Bruin K, et al. Quantification of striatal dopamine transporters with 123I-FP-CIT SPECT is influenced by the selective serotonin reuptake inhibitor paroxetine: a double-blind, placebo-controlled, crossover study in healthy control subjects. J Nucl Med 2007;**48**(3):359-66

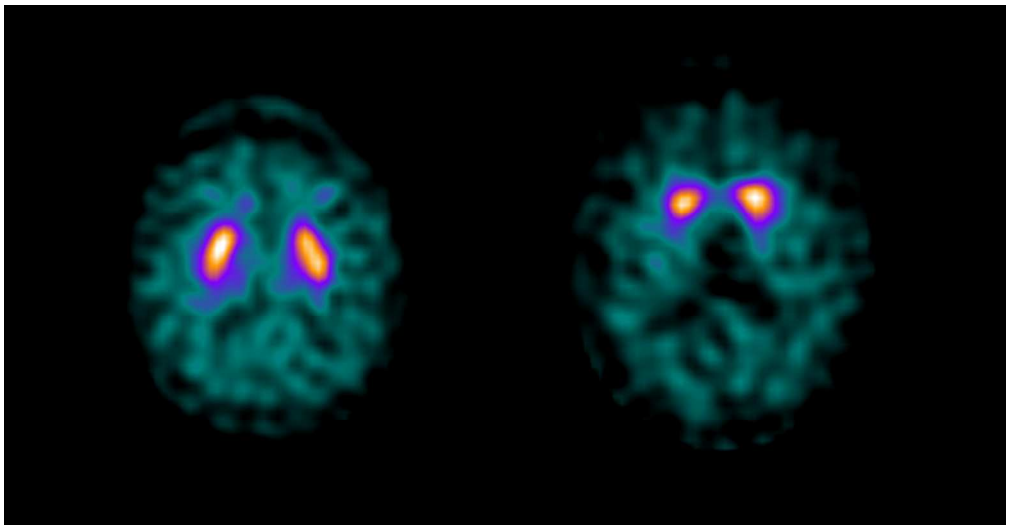
40. Ziebell M, Holm-Hansen S, Thomsen G, et al. Serotonin transporters in dopamine transporter imaging: a head-to-head comparison of dopamine transporter SPECT radioligands 123I-FP-CIT and 123I-PE2I. J Nucl Med 2010;**51**(12):1885-91

41. Bjoerke-Bertheussen J, Ehrt U, Rongve A, et al. Neuropsychiatric symptoms in mild dementia with lewy bodies and Alzheimer's disease. Dement Geriatr Cogn Disord 2012;**34**(1):1-6

42. Boeve BF, Molano JR, Ferman TJ, et al. Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in an aging and dementia cohort. Sleep medicine 2011;**12**(5):445-53

FIGURE LEGENDS

Figure 1: Transversal [^{123}I]FP-CIT SPECT image from a patient in the DLB cluster with a normal scan (left: case 2) and a patient with an abnormal scan in the non-DLB cluster (right: case 4).



Transversal [^{123}I]FP-CIT SPECT image from a patient in the DLB cluster with a normal scan (left: case 2) and a patient with an abnormal scan in the non-DLB cluster (right: case 4).
391x203mm (96 x 96 DPI)

[^{123}I]FP-CIT SPECT in suspected dementia with Lewy bodies: a longitudinal case study

Françoise J. Siepel, MSc[1,2]*; Arvid Rongve[3] MD PhD; Tirza C. Buter[4], MD; Mona K. Beyer[1] MD PhD; Clive G. Ballard[5] Prof MD PhD; Jan Booij[6], Prof MD PhD; Dag Aarsland[1] Prof MD PhD

[1] Centre for Age-Related Medicine, Stavanger University hospital, Stavanger University Hospital, Stavanger, Norway

[2] Department of Clinical Medicine, University of Bergen, Bergen, Norway

[3] Department of Psychiatry, Haugesund Hospital, Haugesund, Norway

[4] Department of Nuclear Medicine, Stavanger University Hospital, Stavanger, Norway

[5] Wolfson Centre for Age-related Diseases, King`s College London, London, UK

[6] Department of Nuclear Medicine, Academic Medical Center, Amsterdam, The Netherlands

*Correspondence and requests for reprints:

Françoise J. Siepel

Stavanger University Hospital, Department of Psychiatry,

Postbox 8100, 4068 Stavanger, Norway.

Phone: +47 51 51 55 78 or +47 51 51 56 19

Fax : +47 51 51 51 61

Email: facois@sus.no

Abbreviated title page

[^{123}I]FP-CIT SPECT in suspected dementia with Lewy bodies: a longitudinal case study

Short title: [^{123}I]FP-CIT SPECT in suspected DLB

Keywords: Single-Photon Emission Computed Tomography, [^{123}I]FP-CIT, Dementia, Lewy Body, Cluster analysis

Paper statistics:

Abstract:	253 words
Paper:	3646 words
References:	42 references
Tables:	3 tables
Images:	1 image

ABSTRACT

Objectives Little is known regarding the "false negative" or "false positive" striatal dopamine transporter binding on SPECT for the diagnosis of dementia with Lewy bodies (DLB). We explore the clinical course in patients fulfilling the criteria for clinical DLB with a normal [^{123}I]FP-CIT SPECT (i.e. SPECT scan negative, clinical features positive (S-CF+)), and patients not fulfilling DLB criteria with a pathological scan (S+CF-).

Design Longitudinal case study over 2-5 years.

Setting Consecutive referrals of patients with mild dementia to dementia clinics in western Norway.

Participants 50 patients (27 men and 23 women; mean age at baseline of 74 (range 52 to 88)) with [^{123}I]FP-CIT SPECT images underwent cluster analyse, and 20 patients allocated to a "DLB" and 8 to a "non-DLB" cluster were included.

Outcome measures were scores on standardized clinical rating scales for hallucination, parkinsonism, fluctuations and REM sleep behaviour disorder; visual rated [^{123}I]FP-CIT SPECT.

Results In the S+CF- group (n=7), frequency and severity of DLB symptoms tended to increase, particularly parkinsonism (7/7) and cognitive fluctuations (7/7), while severity of visual hallucinations and REM sleep behaviour disorder remained stable. The S-CF+ (n=3) fulfilled the operationalized criteria for probable DLB both at baseline and at the end of the follow-up.

Conclusions The findings suggest that systematic visual analyses of [^{123}I]FP-CIT SPECT can detect people with DLB prior to the development of the full clinical syndrome. In addition, the study indicates that some patients fulfilling clinical criteria for probable DLB have a normal scan, and further studies are required to characterize these patients better.

SUMMARY SECTION

Article focus

- [^{123}I]FP-CIT SPECT is an established biomarker for DLB versus AD.
- Little is known about the clinical course of patients with symptoms of DLB having a normal [^{123}I]FP-CIT SPECT and patients not fulfilling the DLB criteria with a pathological scan.
- We performed a detailed clinical follow-up of such patients.

Key Messages

- Patients not fulfilling the DLB criteria with a pathological scan developed full-blown DLB criteria.
- Patients with symptoms of DLB having a normal [^{123}I]FP-CIT SPECT continued to fulfill clinical criteria for DLB, i.e. were false negative according to clinical criteria.
- [^{123}I]FP-CIT SPECT is important in an early stage of DLB.

Strengths and Limitations

- Limitations include the small number of patients included and the lack of autopsy.
- Strengths include the objective clinical classification based on cluster analysis and the long duration and standardized procedures of the study period.

INTRODUCTION

Dementia with Lewy bodies (DLB) is the second most frequent neurodegenerative dementia after Alzheimer's disease (AD). In addition to cognitive decline, frequent clinical symptoms of DLB are parkinsonism, hallucinations and other psychiatric symptoms, fluctuating attention, and autonomous dysfunction including orthostatic hypotension and falls.[1] DLB patients have more reduced quality of life, higher costs, and higher mortality than patients with AD.

DLB is often under-diagnosed especially in the early stages when the frequency of presenting core symptoms is low.[2] Early and accurate diagnosis is however important for informing patient and relatives about key treatment decisions as the disease course and prognosis differ between the dementia types. In addition, diagnosing DLB is meaningful for avoiding antipsychotic drugs due to the sensitivity for side effects in this patient group. Diagnosis is particularly problematic in people who have some symptoms of DLB but do not fulfil the criteria for probable DLB. The clinical diagnosis of DLB has a high specificity (approximately 95%) but low sensitivity (30%) mainly based on the consensus criteria presented in 1996,[3] indicating that the diagnosis is often missed.

Dopaminergic nigrostriatal degeneration is common in DLB and [^{123}I]FP-CIT SPECT imaging is able to detect this dopaminergic deficit. This imaging technique is an established biomarker for the in vivo detection of nigrostriatal degeneration, which is typical feature of Parkinson's disease (PD) also. [^{123}I]FP-CIT SPECT uses a ^{123}I-labeled tracer that binds with high affinity to the dopamine transporter (DAT). A high correlation between abnormal DAT binding and a clinical diagnosis of probable DLB has been shown, and in a pivotal multicentre study, abnormal scans had a mean sensitivity of 78% for distinguishing clinical probable DLB from AD, with specificity of 90% for excluding non-DLB.[4] Decreased striatal DAT binding is listed as one of the suggestive features in the consensus criteria for the clinical diagnosis of DLB.[1]

Very little is known regarding patients fulfilling clinical DLB criteria with a negative [^{123}I]FP-CIT SPECT scan (S-CF+) or patients with an abnormal scan not fulfilling clinical DLB criteria (S+CF-). In contrast, considerable research has been conducted on PD patients with negative DAT scans, i.e. "scans without evidence of dopaminergic deficit" (SWEDD). Repeated DAT imaging showed a normal scan up to 4 year follow up and this group did not benefit from antiparkinson medication.[5] This demonstrates that causes other than nigrostriatal degeneration can cause parkinsonism, such as for example cerebrovascular disease (vascular parkinsonism) and drugs with antidopaminergic activity.[6]

It has been shown in a trial cohort that [^{123}I]FP-CIT SPECT can distinguish DLB from AD even before the full syndrome has emerged. Indeed, this imaging marker is particularly clinically useful in diagnostically uncertain cases, and patients with "S+CF-" may actually represent early cases who will later develop a full DLB syndrome.[7, 8] However, the nosological status and course of the S-CF+ and S+CF- group, in the context of DLB have not been reported in a clinical cohort.

This study aims to explore the clinical characteristics and course of dementia patients who underwent [^{123}I]FP-CIT SPECT imaging. A group of such patients from the Norwegian DemWest cohort was followed according to a standardized and prospective research protocol. We hypothesized that "S+CF-" cases would develop a clinical profile more consistent with the diagnostic criteria for DLB, and that "S-CF+" cases may develop a clinical phenotype that differed from the typical pattern of DLB patients.

MATERIALS AND METHODS

Participants were selected from the DemWest cohort, which includes patients from dementia clinics with a first time diagnosis of mild dementia who are followed annually.[9] Patients were assessed with medical exam and routine blood tests, and standardized clinical assessments and neuropsychological tests were administered, such as the motor subscale of the Unified Parkinson`s Disease Rating Scale (UPDRS) for parkinsonism, Neuropsychiatric Inventory (NPI) to assess psychiatric symptoms including visual hallucinations (VHs) and the Clinician Assessment of Cognitive Fluctuations (COGA)[10] or Mayo fluctuation Questionnaire[11] for cognitive fluctuations. Sleep disturbances including REM sleep behaviour disorder (RBD) were monitored with the Mayo sleep Questionnaire.[12] Neuroleptic sensitivity was classified as previously reported.[13] Exclusion criteria were acute delirium or confusion, terminal illness, recently diagnosed major somatic illness, previous bipolar disorder or psychotic disorder. More details regarding selection and diagnostic procedures are provided elsewhere.[9]

Continuous scores for the core and suggestive DLB features were calculated: for visual hallucinations (frequency x intensity) using the NPI scale item 2 with a range of 0-12; parkinsonism on the UPDRS motor subscale (0-108); fluctuating cognition by the clinician assessment of cognitive fluctuations (0-16) (a subgroup on the Mayo fluctuation questionnaire (0-4)) and combined as previously described.[14] RBD was determined with the Mayo sleep questionnaire (0-4). To select DLB patients we used UPDRS-motor subscale cut-off score of > 9 and at least 1 within other scales.[14]

Imaging

From the DemWest database 50 patients underwent [^{123}I]FP-CIT SPECT imaging on the discretion of the clinician considered DLB to be a differential diagnosis between March 2005 and May 2010 (27 men and 23 women, mean age at baseline of 74 (range 52 to 88). Initial diagnosis of possible or probable DLB was made using clinical judgement.[1] Subsequent classification of patients was undertaken based upon a cluster analysis of symptoms (see analysis section below for details).The average time between initial clinical diagnosis and date of [^{123}I]FP-CIT SPECT imaging was 7 months.

SPECT imaging with the well-validated radiotracer [^{123}I]FP-CIT (N-ω-fluoropropyl-2β-carbomethoxy-3β-[4-iodophenyl] nortropane; DaTscan^{TM}, GE Healthcare) was performed according to clinical routine at each of the three centres. An intravenous injection of about 185 MBq was administered and images were acquired 3-4 h after injection on a multidetector or multiheaded gamma camera with LEHR collimators, a time point at which the specific binding ratio of this tracer to the DAT is stable.[15] Subsequently, images were reconstructed using filtered back projection (FBP) with a Butterworth filter with a 0.55 cutoff and an order of 10. Chang`s attenuation correction was applied with an attenuation coefficient of 0.11 cm^{-1}.[16]

Representative transversal images through the basal ganglia were visually analysed by an external nuclear medicine specialist, experienced in DAT imaging (JB), who did not have access to clinical information. The visual analysis consisted of separate evaluations of the left and right caudate nucleus and putamen divided in normal, abnormal and strongly abnormal.

In addition, magnetic resonance imaging (MRI) was acquired at baseline at the three centres using 1.5 Tesla MRI: a Philips Intera scanner with fast field echo (FFE) protocol (TR/TE/FA= 10 ms/4.6 ms/30°,ST=2.0mm, NEX=2.0, matrix=256x256 or TR/TE/FA=20 ms/4.6 ms/30°,ST=1.0mm, NEX=2.0, matrix=256x256) and GE Signa Excite scanner with fast spoiled gradient recalled (FSPGR) protocol (TR/TE/FA=20 ms/3.1 ms/7°,ST =1.0mm, NEX=1.0, matrix=256x256). Details of the harmonization have been reported previously.[17] Basal ganglia hyperintensities were scored using the basal ganglia part of the Scheltens scale, a semi quantitative rating scale (0-30) including separate assessment (0-6) of the caudate nucleus, putamen, globus pallidus, thalamus and the internal/external capsule.[18] One patient (case 9) did not receive a MRI due to metal prostheses in both ears.

Analysis

For an objective, quantitative classification of cases, cluster analysis was applied based on the scores on the four DLB symptom scales as previously reported.[14] The patients were classified in 4 clusters with help of SPSS version 18. In brief, the two step cluster analysis was performed with four continuous variables (i.e. parkinsonism, hallucinations, cognitive fluctuations and RBD) and log-

likelihood.[14] Missing values analysis with expectation-maximization algorithm was performed when scores at one of the four symptom scales was missing. The four clusters included a “DLB” cluster, with high scores for hallucinations and parkinsonism and cognitive fluctuations, a `non-DLB` cluster with low values on all DLB symptom scales, one cluster included patients with high scores for RBD, and one with high values of cognitive fluctuations. In this study we only considered patients classified in the “DLB” and the “non-DLB” clusters.[14] Based on the [^{123}I]FP-CIT SPECT scan results, patients were classified as S-CF+ (i.e. DLB-cluster and normal scan) or S+CF- (i.e. non-DLB cluster and abnormal scan).

Design

Patients were followed with annual assessments using the same assessment battery at baseline performed by trained research physicians and research nurses. Subsequently, core and suggestive DLB features (parkinsonism, VH, cognitive fluctuations, neuroleptic hypersensitivity, RBD) and their progress were rated by an experienced research clinician (AR), taking into account both research data and transcripts from the medical records, but blinded to all information of [^{123}I]FP-CIT SPECT scan information and clinical diagnosis. The blinding was achieved by actively removing all information about the scans from the transcripts. The rater noted whether symptoms were present and their severity (no, mild-to-moderate, and moderate-to-severe) at baseline, and whether they increased or decreased (mild or marked) or remained stable during the follow-up period.

Ethical approval

The regional ethics committee and the Norwegian authorities approved the DemWest study for collection of medical data. The patients provided written consent to participate in the study after a thorough explanation of the procedure to the patient and caregiver.

RESULTS

There were 20 patients in the DLB cluster, 8 patients in the non-DLB cluster (the remaining 22 patients were included in the other two clusters, with subsequently n=5 with S- and n=7 with S+ in the RBD cluster and n=6 with S- and n=4 with S+ in the cognitive fluctuation cluster). Nine of the 50 patients with [^{123}I]FP-CIT SPECT had one missing value and therefore an estimation was performed.

Scans of 3 patients in the DLB cluster were classified as normal, and these 3 were consequently classified as S-CF+. Seven patients in the non-DLB cluster had a pathological scan, and were classified as S+CF-. An example of the [^{123}I]FP-CIT SPECT scan for the S-CF+ group (left) and S+CF- group (right) is shown in figure 1. Table 1 shows the characteristics of the two groups.

Table 1: Clinical characteristics

Characteristics	False Negative (n=3)	False Positive (n=7)
Gender (M:F)	3:0	4:3
MMSE	22 (20-26)	25 (16-27)
Age at baseline (years)	79 (72-88)	71 (52-80)
Observation time (years)	3.0 (2-4)	3.4 (2-5)
Medication		
Antiparkinson (yes/no)	0:3	1:6
Antipsychotics (yes/no)	2:1	1:6
Antidepressants (yes/no)	1:2	3:4
Antidementia (yes/no)	1:2	6:1

(Numbers represent median (range) or number of patients)

Detailed information about the visual assessment of the [^{123}I]FP-CIT SPECT scans regarding DAT binding in the caudate nucleus bilaterally, and the putamen bilaterally, as well as hyperintensities based on MRI are shown in Table 2.

Table 2: Visual assessment of [^{123}I]FP-CIT SPECT and MRI

	[^{123}I]FP-CIT SPECT					MRI	
	Caudate Left	Caudate Right	Putamen Left	Putamen Right	Final Evaluation	Scheltens score (0-30)	Details
S-CF+							
1	0	0	0	0	normal	3	Right capsula interna/externa
2	0	0	0	0	normal	0	
3	0	0	0	0	normal	8	Left thalamus, right capsula interna/externa
S+CF-							
4	0	0	2	2	abnormal	0	
5	0	2	0	2	abnormal	0	
6	2	2	2	2	abnormal	0	
7	0	1	2	2	abnormal	0	
8	0	0	2	1	abnormal	4	Left caudate,

							right capsula externa
9	2	2	2	2	abnormal	-	Not performed
10	0	1	0	1	abnormal	6	Putamen bilateral, left capsula externa

(0 = normal, 1=abnormal, 2= strongly abnormal on [^{123}I]FP-CIT SPECT). S: [^{123}I]FP-CIT SPECT; CF: clinical features

It can be seen that in the S-CF+ group, the [^{123}I]FP-CIT SPECT scans were normal, by definition, in all studied striatal subareas. In the S+CF- group, putamen DAT binding was abnormal bilaterally in most cases (5/7). None of the cases shows infarcts in the basal ganglia on MR. Some patients had white matter lesions (WML), but these were usually in the low-to-moderate range.

During follow-up, no other diseases were detected which could explain the symptoms. Table 3 shows the core and suggestive symptoms at baseline and their development during follow up.

Table 3: Status of main DLB symptoms at baseline and during follow-up

	Visual hallucinations		REM sleep behaviour disorder		Cognitive fluctuations		Parkinsonism	
	Bsl	Fu	Bsl	Fu	Bsl	Fu	Bsl	Fu
S-CF+								
1	1	0	0	0	1	0	0	2
2	1	-1	1	0	0	1	1	2
3	1	0	1	-1	0	2	0	1
S+CF-								
4	1	0	2	-1	1	2	0	2
5	2	1	0	1	0	2	1	2
6	0	0	0	0	0	1	0	2
7	1	0	0	0	0	2	1	2
8	0	0	0	0	0	2	1	2
9	0	0	0	0	0	1	2	2
10	0	0	0	0	0	2	0	2

(Baseline: 0 = not present, 1 = mild/moderate, 2=moderate/marked; Follow up: -2 = significant decrease, -1 = decrease, 0 = no change, 1 =increase, 2 = significant increase). Bsl: baseline; Fu: follow-up; S: [^{123}I]FP-CIT SPECT; CF: clinical features

In the S+CF- group, it can be seen that some DLB core symptoms were present at baseline in some patients. These were usually of mild-to-moderate severity and did not reach the cut-off values that emerged from the cluster analysis.[14] All 7 had a moderate-to-severe increased parkinsonism during follow-up, although 3/7 had no parkinsonism at baseline. In addition, all 7 S+CF- developed marked worsening in cognitive fluctuations, whereas 6 were without these symptoms at baseline. Less marked changes were noted for VH.

In the S-CF+ group all 3 cases had VH at baseline that remained stable (n=2) or decreased (n=1) in severity during the follow-up period. In contrast, 2 cases showed a moderate-to-severe worsening in parkinsonism and 2 cases had worsening of cognitive fluctuations.

There were no remarkable changes in progression of the severity of RBD that was also rare at baseline. Three patients (2 S-CF+, 1 S+CF-) received antipsychotics but hypersensitivity reactions to these drugs were not observed.

All cases fulfilled the criteria for probable DLB at the end of the follow-up period without taking the [^{123}I]FP-CIT SPECT scan results into account, i.e. they had at least two core features or one core and one clinical suggestive feature.

DISCUSSION

In this study we report longitudinal findings in patients who, based on cluster analysis of symptom scores were classified as "DLB" or "non-DLB", and who had [^{123}I]FP-CIT SPECT results that were inconsistent with these findings, i.e. "S-CF+" or "S+CF-. Our main findings are that S+CF- patients tend to develop core or suggestive features of DLB, in particular parkinsonism and cognitive fluctuations, i.e. they represent DLB in the early stage. In the S-CF+ group more various DLB symptoms were shown at baseline with mainly a stable or increased severity at follow-up, and all cases fulfilled the criteria for probable DLB at the end of the follow-up period.

Very few longitudinal studies of DLB patients in light of [^{123}I]FP-CIT SPECT have been reported. In contrast, the results of [^{123}I]FP-CIT SPECT imaging and the discrepancy with clinical diagnosis have been extensively studied in PD. The Clinically Uncertain Parkinsonism Syndrome (CUPS) study considered patients with uncertain but clinically suspect PD. [^{123}I]FP-CIT SPECT imaging was inconsistent with initial diagnosis in 36% of the patients with a clinical diagnosis of presynaptic parkinsonism and 54% with non-presynaptic parkinsonism. After two years, however, the clinical diagnosis was established and the rate of agreement between the diagnosis at follow-up and the initial imaging results was 90%, indicating that the initial DAT SPECT scan is of value in the diagnostic follow up of the patients with clinically uncertain PD.[19] This is in line with the current study showing that all 7 FP cases developed increased parkinsonism and cognitive fluctuations consistent with a diagnosis of DLB. Our findings are also consistent with a previous study demonstrating that in cases with "possible DLB", i.e. not fulfilling criteria for probable DLB, the scan differentiated between those who developed probable DLB and those who did not after one year.[7]

An explanation for this could be that the [^{123}I]FP-CIT SPECT scan detects nigro-striatal degeneration before the full clinical syndrome has been developed. This is supported by the knowledge of PD that 80% of the striatal dopamine neurons need to be lost before PD symptoms are present.[20] In addition, it is shown that by using a radioligand for DAT nigrostriatal damage can be detected years before the onset of motor signs of PD.[21]

Three of our cases (3 out of 50; 6% of all scans) were in the S-CF+ group, and searching for possible explanations is important. It is well known that 10-15% of patients with clinical PD have a normal DAT scan, and it is suggested that this subgroup have no involvement of the dopaminergic nigrostriatal pathway.[6] In the S-CF+ group the cases may have a true negative [^{123}I]FP-CIT SPECT, i.e. they have DLB but without involvement of dopaminergic neurons in the substantia nigra. Some DLB patients indeed do not develop parkinsonism.[22] Pathological classification of DLB identifies three types: brainstem predominant, limbic, and neocortical, assuming the substantia nigra is first affected, following by the amygdalae and limbic cortex and subsequently the neocortex.[23] However, it has been reported that in some cases, Lewy-body pathology can be found in the cortex and higher brain stem but not in the lower brain stem,[24] suggesting that in some patients the pathological process starts in the neocortex, and then progresses towards the brain stem. Our findings in the S-CF+ group are consistent with this hypothesis, in that parkinsonism mainly developed later on. Unfortunately, a follow-up scan or neuropathology was not available to address this hypothesis. Interestingly, a recent clinicopathological study, that included 7 autopsy proven DLB cases, showed that the antemortem [^{123}I]FP-CIT SPECT scan was normal in 2 of these cases. Importantly, in these 2 cases the number of nigrostriatal dopaminergic neurons was also within the normal range.[25] This observation may support the hypothesis that in some patients the pathological process may start in the neocortex.

Another possible explanation for the S-CF+ cases is the pathological heterogeneity in DLB. Whereas some patients have a "pure" DLB, the majority in addition may have AD-type changes such as amyloid plaques and even tangle pathology.[1] 5-10% of patients with clinical dementia have intermediate [^{123}I]FP-CIT SPECT scans, i.e. abnormal DAT binding but not as low as typical of DLB. These intermediate scans could represent cases with mixed DLB/AD pathology.[26] DLB cases with AD pathology have lower prevalence of core DLB symptoms than "pure" DLB.[6, 27] It is possible that mixed cases in an early stage may have subtle or no nigrostriatal dopaminergic pathology leading to a normal DAT scan. In these cases parkinsonism may be caused by Alzheimer-type or even LB-type degeneration in the striatum itself rather than by dopaminergic nigrostriatal neurodegeneration.[28]

Another possible explanation is that S-CF+ cases have another type of dementia than DLB. For example, parkinsonism is not uncommon in AD, particularly in the later stages,[29] and it can be seen

in other conditions such as vascular parkinsonism and frontotemporal dementia. However, both vascular parkinsonism and frontotemporal dementia may have pathological scans, although less common than in DLB.[30, 31] The score for hyperintensities on MRI is in the range from 0-8 (see table 2). These relatively low scores show that cerebrovascular is an unlikely cause of parkinsonism in our cases, also since none of the subjects had lacunar infarcts in the basal ganglia.

Drug-induced parkinsonism is also common,[6] and may take several weeks to resolve after drug discontinuation, and complete resolution may taken over a year.[32] These patients usually have a normal DAT SPECT scan,[33] and thus may be misinterpreted as "S-CF+". In our S-CF+ group, case 1 received antipsychotics during 5 months and discontinued one month before scanning, and in case 3 it was discontinued directly at baseline. However, in both cases, parkinsonism increased during follow-up. Drug-induced parkinsonism is therefore not a likely cause of the "S-CF+" patients in our study.

Finally, several patients were treated with drugs such as antidepressants, antipsychotics, L-DOPA and antidementia drugs, and scanned while on medication, which may influenced the interpretation of the [^{123}I]FP-CIT SPECT scans.[34]

The antidopaminergic effect of antipsychotic drugs may increase the synthesis and release of dopamine in the striatum, leading to a potential competition between the DAT ligand [^{123}I]FP-CIT and synaptic dopamine. Indeed, high doses of the neuropsychotic haloperidol resulted in a reduction in striatal [^{123}I]FP-CIT binding by 25% in rats.[35] However, in another rat study this could not be replicated.[36] Also, it has recently been discussed that even if neuroleptics will induce changes in DAT imaging, such changes will presumably not be large enough to influence the visual assessments of [^{123}I]FP-CIT SPECT studies.[34] Nevertheless, in the present study, 1 patient in the S+CF- group had used an antipsychotic, and we cannot totally exclude that this may have led to a false positive scan.

Although antiparkinsonian medications influence the dopaminergic transmission, they do not seem to affect the visual interpretation and quantification of DAT imaging.[6] The use of Levodopa for example did not significant change the striatal [^{123}I]FP-CIT binding significantly.[37]

The acetylcholinesterase inhibitors, such as donepezil and rivastigmine may reduce striatal dopaminergic transmission, but did not show significant effects on striatal [^{123}I]FP-CIT binding.[38]

Antidepressants such as the selective serotonin reuptake inhibitor (SSRI) paroxetine have been shown to induce a small, but significant increase in striatal [^{123}I]FP-CIT binding ratios.[39] On the other hand, the SSRI citalopram showed a *reduction* in striatal [^{123}I]FP-CIT binding ratios, and blocking of the serotonin transporter (SERT) may lead to high plasma [^{123}I]FP-CIT concentrations.[40] DAT and SERT are important for the termination of dopaminergic and serotonergic transmission, respectively, by reuptake of dopamine and serotonin from the synaptic cleft. FP-CIT binds to DAT and SERT with affinities in the nanomolar range, although the affinity to SERT is lower than that to DAT.[34] Therefore, quantification of [^{123}I]FP-CIT SPECT is susceptible to SERT blocking pharmaceuticals.[40] However, as recently discussed, a small change in the quantification in striatal FP-CIT binding, and with the same change of binding in both the caudate nucleus and putamen, is unlikely to result in false negative and false positive results when a visual assessment is used.[34] One of our S-CF+ and 2 of the S+CF- patients had used an SSRI, but it is unlikely that this has influenced the interpretation of our scan results. Two of the antidepressant users showed a decrease in visual hallucinations during follow-up, cases 2 and 5 (table 3). Nevertheless, more studies are needed to explore how CNS-active drugs frequently used by DLB-patients may influence DAT imaging interpretation.

Some limitations of this study need to be acknowledged. First, the limited number of patients in the S-CF+ and S+CF- group and the difference in follow-up time ranging from 2 to 5 years, dependent on the moment of entrance in the study should be mentioned. Also, no repeat imaging was performed. A prolonged follow-up time in a larger study group with follow-up DAT scan may have provided additional information. Secondly, the NPI item 2 includes hallucinations from different modalities and not only visual. However, we have previously shown that of those with hallucinations in the overall cohort, nearly 80% had visual hallucinations.[41] In addition, we did verify through the medical record transcripts that the patients with hallucinations in fact had visual hallucinations. RBD was diagnosed based only on clinical assessment. Videopolysomnograpphy is the preferred diagnostic method but not widely available, and acceptable sensitivity and specificity has been reported for the Mayo sleep

scale.[42] Finally, scans were only analysed visually. However, in previous studies this approach has shown to be as accurate as semi-quantitative analyses to differentiate normal from abnormal [^{123}I]FP-CIT SPECT scans.[4]

The golden standard for diagnosing DLB is the brain pathology analysis post-mortem. Unfortunately autopsy of the FP and FN cases in this study was not available to confirm diagnosis. However, all 7 available autopsy diagnoses from the DemWest study were consistent with the clinical diagnosis including two AD and five DLB patients. In addition, a relative objective method of cluster analysis was performed based on symptom scores for the main DLB symptoms in this study, and the symptoms of interest were rated by trained research clinicians using standardized and validated instruments.

CONCLUSION

These data support the notion that [^{123}I]FP-CIT SPECT imaging can identify DLB patients before the full syndrome has developed, supporting the usefulness of [^{123}I]FP-CIT SPECT as part of the routine clinical work up in cases with suspect DLB. A minority of patients fulfilling clinical DLB criteria have a normal [^{123}I]FP-CIT SPECT scan, and further studies are needed to characterize such cases.

CONTRIBUTORS

FJS and DA were responsible for the study concept, design, data analysis, writing of the manuscript, and provided input during the whole process of the study. AR was involved in the development of the study concept, clinical patient evaluation and data analysis. TCB was involved in the image selection and reconstruction and provided main input during data acquisition. MKB and JB were responsible for image analysis and interpretation of results. CGB was involved in the concept and evaluation of results. All authors were involved in critical review of the draft and approval of the version to be published.

ACKNOWLEDGMENTS

The authors acknowledge the co-investigators involved in the large dementia study in western Norway and especially K Brønnick for the advice and contribution.

In addition, we thank the National Institute for Health Research (UK) for supporting the work of Clive Ballard through the Biomedical Research Unit for Dementia and the Biomedical Research Centre for Mental Health at King's College London.

COMPETING INTERESTS

JB is consultant of GE Healthcare

FUNDING

This study was supported by GE Healthcare.

Françoise Siepel is supported by a grant from Western Norway regional health authority.

REFERENCES

1. 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**(12):1863-72

2. Tiraboschi P, Salmon DP, Hansen LA, et al. What best differentiates Lewy body from Alzheimer's disease in early-stage dementia? Brain 2006;**129**(Pt 3):729-35

3. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 1996;**47**(5):1113-24

4. McKeith I, O'Brien J, Walker Z, et al. Sensitivity and specificity of dopamine transporter imaging with 123I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study. Lancet Neurol 2007;**6**(4):305-13

5. Marek K, Jennings D, Seibyl J. Long-term folluw-up of patients with scans without evidence of dopaminergic deficit (SWEDD) in the ELLDOPA study [abstract]. Neurology 2005;**64**((1 Suppl)):A274

6. Cummings JL, Henchcliffe C, Schaier S, et al. The role of dopaminergic imaging in patients with symptoms of dopaminergic system neurodegeneration. Brain 2011;**134**(Pt 11):3146-66

7. O'Brien JT, McKeith IG, Walker Z, et al. Diagnostic accuracy of 123I-FP-CIT SPECT in possible dementia with Lewy bodies. Br J Psychiatry 2009;**194**(1):34-9

8. Papathanasiou ND, Boutsiadis A, Dickson J, et al. Diagnostic accuracy of 123I-FP-CIT (DaTSCAN) in dementia with Lewy bodies: a meta-analysis of published studies. Parkinsonism Relat Disord 2012;**18**(3):225-9

9. Aarsland D, Rongve A, Nore SP, et al. Frequency and case identification of dementia with Lewy bodies using the revised consensus criteria. Dement Geriatr Cogn Disord 2008;**26**(5):445-52

10. Walker MP, Ayre GA, Cummings JL, et al. The Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale. Two methods to assess fluctuating confusion in dementia. Br J Psychiatry 2000;**177**:252-6

11. Ferman TJ, Smith GE, Boeve BF, et al. DLB fluctuations: specific features that reliably differentiate DLB from AD and normal aging. Neurology 2004;**62**(2):181-7

12. Boeve BF, TJ; Silber, MH; Smith, GE. Validation of a questionnaire for the diagnosis of REM sleep behavior disorder. Neurology 2002;**58**(Suppl. 3):A509

13. Aarsland D, Perry R, Larsen JP, et al. Neuroleptic sensitivity in Parkinson's disease and parkinsonian dementias. J Clin Psychiatry 2005;**66**(5):633-7

14. Rongve A, Bronnick K, Ballard C, et al. Core and suggestive symptoms of dementia with lewy bodies cluster in persons with mild dementia. Dement Geriatr Cogn Disord 2010;**29**(4):317-24

15. Booij J, Hemelaar TG, Speelman JD, et al. One-day protocol for imaging of the nigrostriatal dopaminergic pathway in Parkinson's disease by [123I]FPCIT SPECT. J Nucl Med 1999;**40**(5):753-61

16. Darcourt J, Booij J, Tatsch K, et al. EANM procedure guidelines for brain neurotransmission SPECT using (123)I-labelled dopamine transporter ligands, version 2. Eur J Nucl Med Mol Imaging 2009;**37**(2):443-50

17. Lebedev AV, Beyer MK, Fritze F, et al. Cortical changes associated with depression in Alzheimer's disease: an MRI surface-based morphometric study [abstract]. European Psychiatry 2012;**27**: p792

18. Scheltens P, Barkhof F, Leys D, et al. A semiquantative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. J Neurol Sci 1993;**114**(1):7-12

19. Tolosa E, Borght TV, Moreno E, et al. Accuracy of DaTSCAN (123I-Ioflupane) SPECT in diagnosis of patients with clinically uncertain parkinsonism: 2-year follow-up of an open-label study. Mov Disord 2007;**22**(16):2346-51

20. Fearnley JM, Lees AJ. Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain 1991;**114 (Pt 5)**:2283-301

21. Ponsen MM, Stoffers D, Booij J, et al. Idiopathic hyposmia as a preclinical sign of Parkinson's disease. Ann Neurol 2004;**56**(2):173-81

22. Ballard CG, Aarsland D, McKeith I, et al. Fluctuations in attention: PD dementia vs DLB with parkinsonism. Neurology 2002;**59**(11):1714-20

23. Braak H, Bohl JR, Muller CM, et al. Stanley Fahn Lecture 2005: The staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered. Mov Disord 2006;**21**(12):2042-51

24. Halliday GM, McCann H. The progression of pathology in Parkinson's disease. Annals of the New York Academy of Sciences 2010;**1184**:188-95

25. Colloby SJ, McParland S, O'Brien JT, et al. Neuropathological correlates of dopaminergic imaging in Alzheimer's disease and Lewy body dementias. Brain 2012;**135**(Pt 9):2798-808

26. Kemp PM, Holmes C. Imaging in dementia with Lewy bodies: a review. Nucl Med Commun 2007;**28**(7):511-9

27. Ballard CG, Jacoby R, Del Ser T, et al. Neuropathological substrates of psychiatric symptoms in prospectively studied patients with autopsy-confirmed dementia with lewy bodies. Am J Psychiatry 2004;**161**(5):843-9

28. Duda JE, Giasson BI, Mabon ME, et al. Novel antibodies to synuclein show abundant striatal pathology in Lewy body diseases. Ann Neurol 2002;**52**(2):205-10

29. Starkstein SE, Merello M, Brockman S, et al. Apathy predicts more severe parkinsonism in Alzheimer's disease. Am J Geriatr Psychiatry 2009;**17**(4):291-8

30. Benitez-Rivero S, Marin-Oyaga VA, Garcia-Solis D, et al. Clinical features and 123I-FP-CIT SPECT imaging in vascular parkinsonism and Parkinson's disease. J Neurol Neurosurg Psychiatry 2012;**84**(2):122-9

31. Morgan S, Kemp P, Booij J, et al. Differentiation of frontotemporal dementia from dementia with Lewy bodies using FP-CIT SPECT. J Neurol Neurosurg Psychiatry 2012;**83**(11):1063-70

32. Lopez-Sendon JL, Mena MA, de Yebenes JG. Drug-induced parkinsonism in the elderly: incidence, management and prevention. Drugs Aging 2012;**29**(2):105-18

33. Diaz-Corrales FJ, Sanz-Viedma S, Garcia-Solis D, et al. Clinical features and 123I-FP-CIT SPECT imaging in drug-induced parkinsonism and Parkinson's disease. Eur J Nucl Med Mol Imaging 2010;**37**(3):556-64

34. Booij J, Kemp P. Dopamine transporter imaging with [(123)I]FP-CIT SPECT: potential effects of drugs. Eur J Nucl Med Mol Imaging 2008;**35**(2):424-38

35. Nikolaus S, Antke C, Kley K, et al. Pretreatment with haloperidol reduces (123)I-FP-CIT binding to the dopamine transporter in the rat striatum: an in vivo imaging study with a dedicated small-animal SPECT camera. J Nucl Med 2009;**50**(7):1147-52

36. Lavalaye J, Knol RJ, de Bruin K, et al. [123I]FP-CIT binding in rat brain after acute and sub-chronic administration of dopaminergic medication. European journal of nuclear medicine 2000;**27**(3):346-9

37. Schillaci O, Pierantozzi M, Filippi L, et al. The effect of levodopa therapy on dopamine transporter SPECT imaging with(123)I-FP-CIT in patients with Parkinson's disease. Eur J Nucl Med Mol Imaging 2005;**32**(12):1452-6

38. Knol RJ, de Bruin K, van Eck-Smit BL, et al. No significant effects of single intravenous, single oral and subchronic oral administration of acetylcholinesterase inhibitors on striatal [123I]FP-CIT binding in rats. Eur J Nucl Med Mol Imaging 2008;**35**(3):598-604

39. Booij J, de Jong J, de Bruin K, et al. Quantification of striatal dopamine transporters with 123I-FP-CIT SPECT is influenced by the selective serotonin reuptake inhibitor paroxetine: a double-blind, placebo-controlled, crossover study in healthy control subjects. J Nucl Med 2007;**48**(3):359-66

40. Ziebell M, Holm-Hansen S, Thomsen G, et al. Serotonin transporters in dopamine transporter imaging: a head-to-head comparison of dopamine transporter SPECT radioligands 123I-FP-CIT and 123I-PE2I. J Nucl Med 2010;**51**(12):1885-91

41. Bjoerke-Bertheussen J, Ehrt U, Rongve A, et al. Neuropsychiatric symptoms in mild dementia with lewy bodies and Alzheimer's disease. Dement Geriatr Cogn Disord 2012;**34**(1):1-6

42. Boeve BF, Molano JR, Ferman TJ, et al. Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in an aging and dementia cohort. Sleep medicine 2011;**12**(5):445-53

FIGURE LEGENDS

Figure 1: Transversal [^{123}I]FP-CIT SPECT image from a patient in the DLB cluster with a normal scan (left: case 2) and a patient with an abnormal scan in the non-DLB cluster (right: case 4).

BMJ open

[^{123}I]FP-CIT SPECT in suspected dementia with Lewy bodies: a longitudinal case study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-002642.R1
Article Type:	Research
Date Submitted by the Author:	27-Feb-2013
Complete List of Authors:	Siepel, Françoise; Stavanger University Hospital, Centre for Age-Related Medicine Rongve, Arvid; Haugesund Hospital, Department of Psychiatry Buter, Tirza; Stavanger University Hospital, Department of Nuclear Medicine Beyer, Mona; Stavanger University Hospital, Centre for Age-Related Medicine Ballard, Clive; King's College London, Wolfson Centre for Age-Related Diseases Booij, Jan; Academic Medical Center, Department of Nuclear Medicine Aarsland, Dag; Stavanger University Hospital, Centre for Age-Related Medicine
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Radiology and imaging
Keywords:	Dementia < NEUROLOGY, Neuroradiology < NEUROLOGY, Old age psychiatry < PSYCHIATRY

[^{123}I]FP-CIT SPECT in suspected dementia with Lewy bodies: a longitudinal case study

Françoise J. Siepel, MSc[1,2]*; Arvid Rongve[3] MD PhD; Tirza C. Buter[4], MD; Mona K. Beyer[1] MD PhD; Clive G. Ballard[5] Prof MD PhD; Jan Booij[6], Prof MD PhD; Dag Aarsland[1] Prof MD PhD

[1] Centre for Age-Related Medicine, Stavanger University hospital, Stavanger University Hospital, Stavanger, Norway

[2] Department of Clinical Medicine, University of Bergen, Bergen, Norway

[3] Department of Psychiatry, Haugesund Hospital, Haugesund, Norway

[4] Department of Nuclear Medicine, Stavanger University Hospital, Stavanger, Norway

[5] Wolfson Centre for Age-related Diseases, King`s College London, London, UK

[6] Department of Nuclear Medicine, Academic Medical Center, Amsterdam, The Netherlands

*Correspondence and requests for reprints:

Françoise J. Siepel

Stavanger University Hospital, Department of Psychiatry,

Postbox 8100, 4068 Stavanger, Norway.

Phone: +47 51 51 55 78 or +47 51 51 56 19

Fax : +47 51 51 51 61

Email: facois@sus.no

Abbreviated title page

[^{123}I]FP-CIT SPECT in suspected dementia with Lewy bodies: a longitudinal case study

Short title: [^{123}I]FP-CIT SPECT in suspected DLB

Keywords: Single-Photon Emission Computed Tomography, [^{123}I]FP-CIT, Dementia, Lewy Body, Cluster analysis

Paper statistics:

Abstract:	256 words
Paper:	3650 words
References:	42 references
Tables:	3 tables
Images:	1 image

ABSTRACT

Objectives Little is known regarding the "false negative" or "false positive" striatal dopamine transporter binding on SPECT for the diagnosis of dementia with Lewy bodies (DLB). We explored the clinical course in patients fulfilling the criteria for clinical DLB with a normal [^{123}I]FP-CIT SPECT (i.e. SPECT scan negative, clinical features positive (S-CF+)), and patients not fulfilling DLB criteria with an abnormal scan (S+CF-).

Design Longitudinal case study over 2-5 years.

Setting Consecutive referrals of patients with mild dementia to dementia clinics in western Norway.

Participants 50 patients (27 men and 23 women; mean age at baseline of 74 (range 52 to 88)) with [^{123}I]FP-CIT SPECT images underwent cluster analysis: 20/50 patients allocated to a "DLB" and 8 to a "non-DLB" cluster were included.

Outcome measures were scores on standardized clinical rating scales for hallucinations, parkinsonism, fluctuations, REM sleep behaviour disorder and visually rated [^{123}I]FP-CIT SPECT.

Results During the follow-up period, in the S+CF- group (n=7), frequency and severity of DLB symptoms tended to increase, particularly parkinsonism (7/7) and cognitive fluctuations (7/7), while severity of visual hallucinations and REM sleep behaviour disorder remained stable. The S-CF+ (n=3) fulfilled the operationalized criteria for probable DLB both at baseline and at the end of the follow-up.

Conclusions The findings suggest that systematic visual analyses of [^{123}I]FP-CIT SPECT can detect people with DLB prior to the development of the full clinical syndrome. In addition, the study indicates that some patients fulfilling clinical criteria for probable DLB have a normal scan, and further studies are required to characterize these patients better.

SUMMARY SECTION

Article focus

- [^{123}I]FP-CIT SPECT is an established biomarker for DLB versus AD.
- Little is known about the clinical course of patients with symptoms of DLB and a normal [^{123}I]FP-CIT SPECT and patients not fulfilling the DLB criteria with an abnormal scan.
- We performed a detailed clinical follow-up of such patients.

Key Messages

- Patients not fulfilling the DLB criteria with an abnormal scan developed over time typical DLB clinical features.
- Patients with symptoms of DLB and a normal [^{123}I]FP-CIT SPECT continued to fulfil clinical criteria for DLB, i.e. were false negative according to clinical criteria.
- [^{123}I]FP-CIT SPECT is a helpful investigation in an early stage of DLB.

Strengths and Limitations

- Limitations include the small number of patients included and the lack of autopsy.
- Strengths include the objective clinical classification based on cluster analysis and the long duration of follow-up and the use of standardized procedures during the study period.

INTRODUCTION

Dementia with Lewy bodies (DLB) is the second most frequent neurodegenerative dementia after Alzheimer's disease (AD). In addition to cognitive decline, frequent clinical symptoms of DLB are parkinsonism, hallucinations and other psychiatric symptoms, fluctuating attention, and autonomous dysfunction including orthostatic hypotension and falls.[1] DLB patients have more reduced quality of life, higher costs, and higher mortality than patients with AD.

DLB is often under-diagnosed especially in the early stages when the frequency of presenting core symptoms is low.[2] Early and accurate diagnosis is however important for informing patient and relatives about key treatment decisions as the disease course and prognosis differ between the dementia types. In addition, diagnosing DLB is meaningful for avoiding antipsychotic drugs due to the sensitivity for side effects in this patient group. Diagnosis is particularly problematic in people who have some symptoms of DLB but do not fulfil the criteria for probable DLB. The clinical diagnosis of DLB has a high specificity (approximately 95%) but low sensitivity (30%) mainly based on the consensus criteria presented in 1996,[3] indicating that the diagnosis is often missed.

Dopaminergic nigrostriatal degeneration is common in DLB and [^{123}I]FP-CIT SPECT imaging is able to detect this dopaminergic deficit. This imaging technique is an established biomarker for the in vivo detection of nigrostriatal degeneration, which is typical feature of Parkinson's disease (PD) also. [^{123}I]FP-CIT SPECT uses a ^{123}I-labeled tracer that binds with high affinity to the dopamine transporter (DAT). A high correlation between abnormal DAT binding and a clinical diagnosis of probable DLB has been shown, and in a pivotal multicentre study, abnormal scans had a mean sensitivity of 78% for distinguishing clinical probable DLB from AD, with specificity of 90% for excluding non-DLB.[4] Decreased striatal DAT binding is listed as one of the suggestive features in the consensus criteria for the clinical diagnosis of DLB.[1]

Very little is known regarding patients fulfilling clinical DLB criteria with a negative [^{123}I]FP-CIT SPECT scan (S-CF+) or patients with an abnormal scan not fulfilling clinical DLB criteria (S+CF-). In contrast, considerable research has been conducted on PD patients with negative DAT scans, i.e. "scans without evidence of dopaminergic deficit" (SWEDD). Repeated DAT imaging showed a normal scan up to 4 year follow up and this group did not benefit from antiparkinson medication.[5] This demonstrates that causes other than nigrostriatal degeneration can cause parkinsonism, such as for example cerebrovascular disease (vascular parkinsonism) and drugs with antidopaminergic activity.[6]

It has been shown in a trial cohort that [^{123}I]FP-CIT SPECT can distinguish DLB from AD even before the full syndrome has emerged. Indeed, this imaging marker is particularly clinically useful in diagnostically uncertain cases, and patients with "S+CF-" may actually represent early cases who will later develop a full DLB syndrome.[7, 8] However, the nosological status and course of the S-CF+ and S+CF- group, in the context of DLB have not been reported in a clinical cohort.

This study aims to explore the clinical characteristics and course of dementia patients who underwent [^{123}I]FP-CIT SPECT imaging. A group of such patients from the Norwegian DemWest cohort was followed according to a standardized and prospective research protocol. We hypothesized that "S+CF" cases would develop a clinical profile more consistent with the diagnostic criteria for DLB, and that "S-CF+" cases may develop a clinical phenotype that differed from the typical pattern of DLB patients.

MATERIALS AND METHODS

Participants were selected from the DemWest cohort, which includes patients from dementia clinics with a first time diagnosis of mild dementia who are followed annually.[9] Patients were assessed with medical exam and routine blood tests, and standardized clinical assessments and neuropsychological tests were administered, such as the motor subscale of the Unified Parkinson`s Disease Rating Scale (UPDRS) for parkinsonism, Neuropsychiatric Inventory (NPI) to assess psychiatric symptoms including visual hallucinations (VHs) and the Clinician Assessment of Cognitive Fluctuations (COGA)[10] or Mayo fluctuation Questionnaire[11] for cognitive fluctuations. Sleep disturbances including REM sleep behaviour disorder (RBD) were monitored with the Mayo sleep Questionnaire.[12] Neuroleptic sensitivity was classified as previously reported.[13] Exclusion criteria were acute delirium or confusion, terminal illness, recently diagnosed major somatic illness, previous bipolar disorder or psychotic disorder. More details regarding selection and diagnostic procedures are provided elsewhere.[9]

Continuous scores for the core and suggestive DLB features were calculated: for visual hallucinations (frequency x intensity) using the NPI scale item 2 with a range of 0-12; parkinsonism on the UPDRS motor subscale (0-108); fluctuating cognition by the clinician assessment of cognitive fluctuations (0-16) (a subgroup on the Mayo fluctuation questionnaire (0-4)) and combined as previously described.[14] RBD was determined with the Mayo sleep questionnaire (0-4). To select DLB patients we used UPDRS-motor subscale cut-off score of > 9 and at least 1 within other scales.[14]

Imaging

From the DemWest database 50 patients underwent [^{123}I]FP-CIT SPECT imaging on the discretion of the clinician considered DLB to be a differential diagnosis between March 2005 and May 2010 (27 men and 23 women, mean age at baseline of 74 (range 52 to 88). Initial diagnosis of possible or probable DLB was made using clinical judgement.[1] Subsequent classification of patients was undertaken based upon a cluster analysis of symptoms (see analysis section below for details).The average time between initial clinical diagnosis and date of [^{123}I]FP-CIT SPECT imaging was 7 months.

SPECT imaging with the well-validated radiotracer [^{123}I]FP-CIT (N-ω-fluoropropyl-2β-carbomethoxy-3β-[4-iodophenyl] nortropane; DaTscan^{TM}, GE Healthcare) was performed according to clinical routine at each of the three centres. An intravenous injection of about 185 MBq was administered and images were acquired 3-4 h after injection on a multidetector or multiheaded gamma camera with LEHR collimators, a time point at which the specific binding ratio of this tracer to the DAT is stable.[15] Subsequently, images were reconstructed using filtered back projection (FBP) with a Butterworth filter with a 0.55 cutoff and an order of 10. Chang`s attenuation correction was applied with an attenuation coefficient of 0.11 cm^{-1}.[16]

Representative transversal images through the basal ganglia were visually analysed by an external nuclear medicine specialist, experienced in DAT imaging (JB), who did not have access to clinical information. The visual analysis consisted of separate evaluations of the left and right caudate nucleus and putamen divided in normal, abnormal and strongly abnormal.

In addition, magnetic resonance imaging (MRI) was acquired at baseline at the three centres using 1.5 Tesla MRI: a Philips Intera scanner with fast field echo (FFE) protocol (TR/TE/FA= 10 ms/4.6 ms/30°,ST=2.0mm, NEX=2.0, matrix=256x256 or TR/TE/FA=20 ms/4.6 ms/30°,ST=1.0mm, NEX=2.0, matrix=256x256) and GE Signa Excite scanner with fast spoiled gradient recalled (FSPGR) protocol (TR/TE/FA=20 ms/3.1 ms/7°,ST =1.0mm, NEX=1.0, matrix=256x256). Details of the harmonization have been reported previously.[17] Basal ganglia hyperintensities were scored using the basal ganglia part of the Scheltens scale, a semi quantitative rating scale (0-30) including separate assessment (0-6) of the caudate nucleus, putamen, globus pallidus, thalamus and the internal/external capsule.[18] One patient (case 9) did not receive a MRI due to metal prostheses in both ears.

Analysis

For an objective, quantitative classification of cases, cluster analysis was applied based on the scores on the four DLB symptom scales as previously reported.[14] The patients were classified in 4 clusters with help of SPSS version 18. In brief, the two step cluster analysis was performed with four continuous variables (i.e. parkinsonism, hallucinations, cognitive fluctuations and RBD) and log-

likelihood.[14] Missing values analysis with expectation-maximization algorithm was performed when scores at one of the four symptom scales was missing. The four clusters included a “DLB” cluster, with high scores for hallucinations and parkinsonism and cognitive fluctuations, a `non-DLB` cluster with low values on all DLB symptom scales, one cluster included patients with high scores for RBD, and one with high values of cognitive fluctuations. In this study we only considered patients classified in the “DLB” and the “non-DLB” clusters.[14] Based on the [^{123}I]FP-CIT SPECT scan results, patients were classified as S-CF+ (i.e. DLB-cluster and normal scan) or S+CF- (i.e. non-DLB cluster and abnormal scan).

Design

Patients were followed with annual assessments using the same assessment battery at baseline performed by trained research physicians and research nurses. Subsequently, core and suggestive DLB features (parkinsonism, VH, cognitive fluctuations, neuroleptic hypersensitivity, RBD) and their progress were rated by an experienced research clinician (AR), taking into account both research data and transcripts from the medical records, but blinded to all information of [^{123}I]FP-CIT SPECT scan information and clinical diagnosis. The blinding was achieved by actively removing all information about the scans from the transcripts. The rater noted whether symptoms were present and their severity (no, mild-to-moderate, and moderate-to-severe) at baseline, and whether they increased or decreased (mild or marked) or remained stable during the follow-up period.

Ethical approval

The regional ethics committee and the Norwegian authorities approved the DemWest study for collection of medical data. The patients provided written consent to participate in the study after a thorough explanation of the procedure to the patient and caregiver.

RESULTS

There were 20 patients in the DLB cluster, 8 patients in the non-DLB cluster (the remaining 22 patients were included in the other two clusters, with subsequently n=5 with S- and n=7 with S+ in the RBD cluster and n=6 with S- and n=4 with S+ in the cognitive fluctuation cluster). Nine of the 50 patients with [^{123}I]FP-CIT SPECT had a missing value for one of the four symptom scores and therefore the previously mentioned missing value analysis was performed.

Scans of 3 patients in the DLB cluster were classified as normal, and these 3 were consequently classified as S-CF+. Seven patients in the non-DLB cluster had an abnormal scan, and were classified as S+CF-. An example of the [^{123}I]FP-CIT SPECT scan for the S-CF+ group (left) and S+CF- group (right) is shown in figure 1. Table 1 shows the characteristics of the two groups.

Table 1: Clinical characteristics

Characteristics	S-CF+ (n=3)	S+CF- (n=7)
Gender (M:F)	3:0	4:3
MMSE	22 (20-26)	25 (16-27)
Age at baseline (years)	79 (72-88)	71 (52-80)
Observation time (years)	3.0 (2-4)	3.4 (2-5)
Medication		
Antiparkinson (yes/no)	0:3	1:6
Antipsychotics (yes/no)	2:1	1:6
Antidepressants (yes/no)	1:2	3:4
Antidementia (yes/no)	1:2	6:1

(Numbers represent median (range) or number of patients). S: [^{123}I]FP-CIT SPECT; CF: clinical features

Detailed information about the visual assessment of the [^{123}I]FP-CIT SPECT scans regarding DAT binding in the caudate nucleus bilaterally, and the putamen bilaterally, as well as hyperintensities based on MRI are shown in Table 2.

Table 2: Visual assessment of [^{123}I]FP-CIT SPECT and MRI

	[^{123}I]FP-CIT SPECT					MRI	
	Caudate Left	Caudate Right	Putamen Left	Putamen Right	Final Evaluation	Scheltens score (0-30)	Details
S-CF+							
1	0	0	0	0	normal	3	Right capsula interna/externa
2	0	0	0	0	normal	0	
3	0	0	0	0	normal	8	Left thalamus, right capsula interna/externa
S+CF-							
4	0	0	2	2	abnormal	0	
5	0	2	0	2	abnormal	0	
6	2	2	2	2	abnormal	0	
7	0	1	2	2	abnormal	0	

8	0	0	2	1	abnormal	4	Left caudate, right capsula externa
9	2	2	2	2	abnormal	-	Not performed
10	0	1	0	1	abnormal	6	Putamen bilateral, left capsula externa

(0 = normal, 1=abnormal, 2= strongly abnormal on [^{123}I]FP-CIT SPECT). S: [^{123}I]FP-CIT SPECT; CF: clinical features

It can be seen that in the S-CF+ group, the [^{123}I]FP-CIT SPECT scans were normal, by definition, in all studied striatal subareas. In the S+CF- group, putamen DAT binding was abnormal bilaterally in most cases (5/7). None of the cases shows infarcts in the basal ganglia on MR. Some patients had white matter lesions (WML), but these were usually in the low-to-moderate range.

During follow-up, no other diseases were detected which could explain the symptoms. Table 3 shows the core and suggestive symptoms at baseline and their development during follow up.

Table 3: Status of main DLB symptoms at baseline and during follow-up

	Visual hallucinations		REM sleep behaviour disorder		Cognitive fluctuations		Parkinsonism	
	Bsl	Fu	Bsl	Fu	Bsl	Fu	Bsl	Fu
S-CF+								
1	1	0	0	0	1	0	0	2
2	1	-1	1	0	0	1	1	2
3	1	0	1	-1	0	2	0	1
S+CF-								
4	1	0	2	-1	1	2	0	2
5	2	1	0	1	0	2	1	2
6	0	0	0	0	0	1	0	2
7	1	0	0	0	0	2	1	2
8	0	0	0	0	0	2	1	2
9	0	0	0	0	0	1	2	2
10	0	0	0	0	0	2	0	2

(Baseline: 0 = not present, 1 = mild/moderate, 2=moderate/marked; Follow up: -2 = significant decrease, -1 = decrease, 0 = no change, 1 =increase, 2 = significant increase). Bsl: baseline; Fu: follow-up; S: [^{123}I]FP-CIT SPECT; CF: clinical features

In the S+CF- group, it can be seen that some DLB core symptoms were present at baseline in some patients. These were usually of mild-to-moderate severity and did not reach the cut-off values that emerged from the cluster analysis.[14] All 7 had a moderate-to-severe increased parkinsonism during follow-up, although 3/7 had no parkinsonism at baseline. In addition, all 7 S+CF- developed marked

worsening in cognitive fluctuations, whereas 6 were without these symptoms at baseline. Less marked changes were noted for VH.

In the S-CF+ group all 3 cases had VH at baseline that remained stable (n=2) or decreased (n=1) in severity during the follow-up period. In contrast, 2 cases showed a moderate-to-severe worsening in parkinsonism and 2 cases had worsening of cognitive fluctuations.

There were no remarkable changes in progression of the severity of RBD that was also rare at baseline. Three patients (2 S-CF+, 1 S+CF-) received antipsychotics but hypersensitivity reactions to these drugs were not observed.

All cases fulfilled the criteria for probable DLB at the end of the follow-up period without taking the [^{123}I]FP-CIT SPECT scan results into account, i.e. they had at least two core features or one core and one clinical suggestive feature.

DISCUSSION

In this study we report longitudinal findings in patients who, based on cluster analysis of symptom scores were classified as “DLB” or “non-DLB”, and who had [^{123}I]FP-CIT SPECT results that were inconsistent with these findings, i.e. “S-CF+” or “S+CF-. Our main findings are that S+CF- patients tend to develop core or suggestive features of DLB, in particular parkinsonism and cognitive fluctuations, i.e. they represent DLB in the early stage. In the S-CF+ group more various DLB symptoms were shown at baseline with mainly a stable or increased severity at follow-up, and all cases fulfilled the criteria for probable DLB at the end of the follow-up period.

Very few longitudinal studies of DLB patients in light of [^{123}I]FP-CIT SPECT have been reported. In contrast, the results of [^{123}I]FP-CIT SPECT imaging and the discrepancy with clinical diagnosis have been extensively studied in PD. The Clinically Uncertain Parkinsonism Syndrome (CUPS) study considered patients with uncertain but clinically suspect PD. [^{123}I]FP-CIT SPECT imaging was inconsistent with initial diagnosis in 36% of the patients with a clinical diagnosis of presynaptic parkinsonism and 54% with non-presynaptic parkinsonism. After two years, however, the clinical diagnosis was established and the rate of agreement between the diagnosis at follow-up and the initial imaging results was 90%, indicating that the initial DAT SPECT scan is of value in the diagnostic follow up of the patients with clinically uncertain PD.[19] This is in line with the current study showing that all 7 FP cases developed increased parkinsonism and cognitive fluctuations consistent with a diagnosis of DLB. Our findings are also consistent with a previous study demonstrating that in cases with “possible DLB”, i.e. not fulfilling criteria for probable DLB, the scan differentiated between those who developed probable DLB and those who did not after one year.[7]

An explanation for this could be that the [^{123}I]FP-CIT SPECT scan detects nigro-striatal degeneration before the full clinical syndrome has been developed. This is supported by the knowledge of PD that 80% of the striatal dopamine neurons need to be lost before PD symptoms are present.[20] In addition, it is shown that by using a radioligand for DAT nigrostriatal damage can be detected years before the onset of motor signs of PD.[21]

Three of our cases (3 out of 50; 6% of all scans) were in the S-CF+ group, and searching for possible explanations is important. It is well known that 10-15% of patients with clinical PD have a normal DAT scan, and it is suggested that this subgroup have no involvement of the dopaminergic nigrostriatal pathway.[6] In the S-CF+ group the cases may have a true negative [^{123}I]FP-CIT SPECT, i.e. they have DLB but without involvement of dopaminergic neurons in the substantia nigra. Some DLB patients indeed do not develop parkinsonism.[22] Pathological classification of DLB identifies three types: brainstem predominant, limbic, and neocortical, assuming the substantia nigra is first affected, following by the amygdalae and limbic cortex and subsequently the neocortex.[23] However, it has been reported that in some cases, Lewy-body pathology can be found in the cortex and higher brain stem but not in the lower brain stem,[24] suggesting that in some patients the pathological process starts in the neocortex, and then progresses towards the brain stem. Our findings in the S-CF+ group are consistent with this hypothesis, in that parkinsonism mainly developed later on. Unfortunately, a follow-up scan or neuropathology was not available to address this hypothesis. Interestingly, a recent clinicopathological study, that included 7 autopsy proven DLB cases, showed that the antemortem [^{123}I]FP-CIT SPECT scan was normal in 2 of these cases. Importantly, in these 2 cases the number of nigrostriatal dopaminergic neurons was also within the normal range.[25] This observation may support the hypothesis that in some patients the pathological process may start in the neocortex.

Another possible explanation for the S-CF+ cases is the pathological heterogeneity in DLB. Whereas some patients have a “pure” DLB, the majority in addition may have AD-type changes such as amyloid plaques and even tangle pathology.[1] 5-10% of patients with clinical dementia have intermediate [^{123}I]FP-CIT SPECT scans, i.e. abnormal DAT binding but not as low as typical of DLB. These intermediate scans could represent cases with mixed DLB/AD pathology.[26] DLB cases with AD pathology have lower prevalence of core DLB symptoms than “pure” DLB.[6, 27] It is possible that mixed cases in an early stage may have subtle or no nigrostriatal dopaminergic pathology leading to a normal DAT scan. In these cases parkinsonism may be caused by Alzheimer-type or even LB-type degeneration in the striatum itself rather than by dopaminergic nigrostriatal neurodegeneration.[28]

Another possible explanation is that S-CF+ cases have another type of dementia than DLB. For example, parkinsonism is not uncommon in AD, particularly in the later stages,[29] and it can be seen

in other conditions such as vascular parkinsonism and frontotemporal dementia. However, both vascular parkinsonism and frontotemporal dementia may have abnormal scans, although less common than in DLB.[30, 31] The score for hyperintensities on MRI is in the range from 0-8 (see table 2). These relatively low scores show that cerebrovascular is an unlikely cause of parkinsonism in our cases, also since none of the subjects had lacunar infarcts in the basal ganglia.

Drug-induced parkinsonism is also common,[6] and may take several weeks to resolve after drug discontinuation, and complete resolution may taken over a year.[32] These patients usually have a normal DAT SPECT scan,[33] and thus may be misinterpreted as "S-CF+". In our S-CF+ group, case 1 received antipsychotics during 5 months and discontinued one month before scanning, and in case 3 it was discontinued directly at baseline. However, in both cases, parkinsonism increased during follow-up. Drug-induced parkinsonism is therefore not a likely cause of the "S-CF+" patients in our study.

Finally, several patients were treated with drugs such as antidepressants, antipsychotics, L-DOPA and antidementia drugs, and scanned while on medication, which may influenced the interpretation of the [^{123}I]FP-CIT SPECT scans.[34]

The antidopaminergic effect of antipsychotic drugs may increase the synthesis and release of dopamine in the striatum, leading to a potential competition between the DAT ligand [^{123}I]FP-CIT and synaptic dopamine. Indeed, high doses of the neuropsychotic haloperidol resulted in a reduction in striatal [^{123}I]FP-CIT binding by 25% in rats.[35] However, in another rat study this could not be replicated.[36] Also, it has recently been discussed that even if neuroleptics will induce changes in DAT imaging, such changes will presumably not be large enough to influence the visual assessments of [^{123}I]FP-CIT SPECT studies.[34] Nevertheless, in the present study, 1 patient in the S+CF- group had used an antipsychotic, and we cannot totally exclude that this may have led to a false positive scan.

Although antiparkinsonian medications influence the dopaminergic transmission, they do not seem to affect the visual interpretation and quantification of DAT imaging.[6] The use of Levodopa for example did not significant change the striatal [^{123}I]FP-CIT binding significantly.[37]

The acetylcholinesterase inhibitors, such as donepezil and rivastigmine may reduce striatal dopaminergic transmission, but did not show significant effects on striatal [^{123}I]FP-CIT binding.[38]

Antidepressants such as the selective serotonin reuptake inhibitor (SSRI) paroxetine have been shown to induce a small, but significant increase in striatal [^{123}I]FP-CIT binding ratios.[39] On the other hand, the SSRI citalopram showed a *reduction* in striatal [^{123}I]FP-CIT binding ratios, and blocking of the serotonin transporter (SERT) may lead to high plasma [^{123}I]FP-CIT concentrations.[40] DAT and SERT are important for the termination of dopaminergic and serotonergic transmission, respectively, by reuptake of dopamine and serotonin from the synaptic cleft. FP-CIT binds to DAT and SERT with affinities in the nanomolar range, although the affinity to SERT is lower than that to DAT.[34] Therefore, quantification of [^{123}I]FP-CIT SPECT is susceptible to SERT blocking pharmaceuticals.[40] However, as recently discussed, a small change in the quantification in striatal FP-CIT binding, and with the same change of binding in both the caudate nucleus and putamen, is unlikely to result in false negative and false positive results when a visual assessment is used.[34] One of our S-CF+ and 2 of the S+CF- patients had used an SSRI, but it is unlikely that this has influenced the interpretation of our scan results. Two of the antidepressant users showed a decrease in visual hallucinations during follow-up, cases 2 and 5 (table 3). Nevertheless, more studies are needed to explore how CNS-active drugs frequently used by DLB-patients may influence DAT imaging interpretation.

Some limitations of this study need to be acknowledged. First, the limited number of patients in the S-CF+ and S+CF- group and the difference in follow-up time ranging from 2 to 5 years, dependent on the moment of entrance in the study should be mentioned. Also, no repeat imaging was performed. A prolonged follow-up time in a larger study group with follow-up DAT scan may have provided additional information. Secondly, the NPI item 2 includes hallucinations from different modalities and not only visual. However, we have previously shown that of those with hallucinations in the overall cohort, nearly 80% had visual hallucinations.[41] In addition, we did verify through the medical record transcripts that the patients with hallucinations in fact had visual hallucinations. RBD was diagnosed based only on clinical assessment. Videopolysomnograpphy is the preferred diagnostic method but not widely available, and acceptable sensitivity and specificity has been reported for the Mayo sleep

scale.[42] Finally, scans were only analysed visually. However, in previous studies this approach has shown to be as accurate as semi-quantitative analyses to differentiate normal from abnormal [^{123}I]FP-CIT SPECT scans.[4]

The golden standard for diagnosing DLB is the brain pathology analysis post-mortem. Unfortunately autopsy of the FP and FN cases in this study was not available to confirm diagnosis. However, all 7 available autopsy diagnoses from the DemWest study were consistent with the clinical diagnosis including two AD and five DLB patients. In addition, a relative objective method of cluster analysis was performed based on symptom scores for the main DLB symptoms in this study, and the symptoms of interest were rated by trained research clinicians using standardized and validated instruments.

CONCLUSION

These data support the notion that [^{123}I]FP-CIT SPECT imaging can identify DLB patients before the full syndrome has developed, supporting the usefulness of [^{123}I]FP-CIT SPECT as part of the routine clinical work up in cases with suspect DLB. A minority of patients fulfilling clinical DLB criteria have a normal [^{123}I]FP-CIT SPECT scan, and further studies are needed to characterize such cases.

CONTRIBUTORS

FJS and DA were responsible for the study concept, design, data analysis, writing of the manuscript, and provided input during the whole process of the study. AR was involved in the development of the study concept, clinical patient evaluation and data analysis. TCB was involved in the image selection and reconstruction and provided main input during data acquisition. MKB and JB were responsible for image analysis and interpretation of results. CGB was involved in the concept and evaluation of results. All authors were involved in critical review of the draft and approval of the version to be published.

ACKNOWLEDGMENTS

The authors acknowledge the co-investigators involved in the large dementia study in western Norway and especially K Brønnick for the advice and contribution.

In addition, we thank the National Institute for Health Research (UK) for supporting the work of Clive Ballard through the Biomedical Research Unit for Dementia and the Biomedical Research Centre for Mental Health at King's College London.

COMPETING INTERESTS

JB is consultant of GE Healthcare

FUNDING

This study was supported by GE Healthcare.

Françoise Siepel is supported by a grant from Western Norway regional health authority.

DATA SHARING

No additional data available.

REFERENCES

1. 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**(12):1863-72

2. Tiraboschi P, Salmon DP, Hansen LA, et al. What best differentiates Lewy body from Alzheimer's disease in early-stage dementia? Brain 2006;**129**(Pt 3):729-35

3. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 1996;**47**(5):1113-24

4. McKeith I, O'Brien J, Walker Z, et al. Sensitivity and specificity of dopamine transporter imaging with 123I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study. Lancet Neurol 2007;**6**(4):305-13

5. Marek K, Jennings D, Seibyl J. Long-term folluw-up of patients with scans without evidence of dopaminergic deficit (SWEDD) in the ELLDOPA study [abstract]. Neurology 2005;**64**((1 Suppl)):A274

6. Cummings JL, Henchcliffe C, Schaier S, et al. The role of dopaminergic imaging in patients with symptoms of dopaminergic system neurodegeneration. Brain 2011;**134**(Pt 11):3146-66

7. O'Brien JT, McKeith IG, Walker Z, et al. Diagnostic accuracy of 123I-FP-CIT SPECT in possible dementia with Lewy bodies. Br J Psychiatry 2009;**194**(1):34-9

8. Papathanasiou ND, Boutsiadis A, Dickson J, et al. Diagnostic accuracy of 123I-FP-CIT (DaTSCAN) in dementia with Lewy bodies: a meta-analysis of published studies. Parkinsonism Relat Disord 2012;**18**(3):225-9

9. Aarsland D, Rongve A, Nore SP, et al. Frequency and case identification of dementia with Lewy bodies using the revised consensus criteria. Dement Geriatr Cogn Disord 2008;**26**(5):445-52

10. Walker MP, Ayre GA, Cummings JL, et al. The Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale. Two methods to assess fluctuating confusion in dementia. Br J Psychiatry 2000;**177**:252-6

11. Ferman TJ, Smith GE, Boeve BF, et al. DLB fluctuations: specific features that reliably differentiate DLB from AD and normal aging. Neurology 2004;**62**(2):181-7

12. Boeve BF, TJ; Silber, MH; Smith, GE. Validation of a questionnaire for the diagnosis of REM sleep behavior disorder. Neurology 2002;**58**(Suppl. 3):A509

13. Aarsland D, Perry R, Larsen JP, et al. Neuroleptic sensitivity in Parkinson's disease and parkinsonian dementias. J Clin Psychiatry 2005;**66**(5):633-7

14. Rongve A, Bronnick K, Ballard C, et al. Core and suggestive symptoms of dementia with lewy bodies cluster in persons with mild dementia. Dement Geriatr Cogn Disord 2010;**29**(4):317-24

15. Booij J, Hemelaar TG, Speelman JD, et al. One-day protocol for imaging of the nigrostriatal dopaminergic pathway in Parkinson's disease by [123I]FPCIT SPECT. J Nucl Med 1999;**40**(5):753-61

16. Darcourt J, Booij J, Tatsch K, et al. EANM procedure guidelines for brain neurotransmission SPECT using (123)I-labelled dopamine transporter ligands, version 2. Eur J Nucl Med Mol Imaging 2009;**37**(2):443-50

17. Lebedev AV, Beyer MK, Fritze F, et al. Cortical changes associated with depression in Alzheimer's disease: an MRI surface-based morphometric study [abstract]. European Psychiatry 2012;**27**: p792

18. Scheltens P, Barkhof F, Leys D, et al. A semiquantative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. J Neurol Sci 1993;**114**(1):7-12

19. Tolosa E, Borght TV, Moreno E, et al. Accuracy of DaTSCAN (123I-Ioflupane) SPECT in diagnosis of patients with clinically uncertain parkinsonism: 2-year follow-up of an open-label study. Mov Disord 2007;**22**(16):2346-51

20. Fearnley JM, Lees AJ. Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain 1991;**114 (Pt 5)**:2283-301

21. Ponsen MM, Stoffers D, Booij J, et al. Idiopathic hyposmia as a preclinical sign of Parkinson's disease. Ann Neurol 2004;**56**(2):173-81

22. Ballard CG, Aarsland D, McKeith I, et al. Fluctuations in attention: PD dementia vs DLB with parkinsonism. Neurology 2002;**59**(11):1714-20

23. Braak H, Bohl JR, Muller CM, et al. Stanley Fahn Lecture 2005: The staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered. Mov Disord 2006;**21**(12):2042-51

24. Halliday GM, McCann H. The progression of pathology in Parkinson's disease. Annals of the New York Academy of Sciences 2010;**1184**:188-95

25. Colloby SJ, McParland S, O'Brien JT, et al. Neuropathological correlates of dopaminergic imaging in Alzheimer's disease and Lewy body dementias. Brain 2012;**135**(Pt 9):2798-808

26. Kemp PM, Holmes C. Imaging in dementia with Lewy bodies: a review. Nucl Med Commun 2007;**28**(7):511-9

27. Ballard CG, Jacoby R, Del Ser T, et al. Neuropathological substrates of psychiatric symptoms in prospectively studied patients with autopsy-confirmed dementia with lewy bodies. Am J Psychiatry 2004;**161**(5):843-9

28. Duda JE, Giasson BI, Mabon ME, et al. Novel antibodies to synuclein show abundant striatal pathology in Lewy body diseases. Ann Neurol 2002;**52**(2):205-10

29. Starkstein SE, Merello M, Brockman S, et al. Apathy predicts more severe parkinsonism in Alzheimer's disease. Am J Geriatr Psychiatry 2009;**17**(4):291-8

30. Benitez-Rivero S, Marin-Oyaga VA, Garcia-Solis D, et al. Clinical features and 123I-FP-CIT SPECT imaging in vascular parkinsonism and Parkinson's disease. J Neurol Neurosurg Psychiatry 2012;**84**(2):122-9

31. Morgan S, Kemp P, Booij J, et al. Differentiation of frontotemporal dementia from dementia with Lewy bodies using FP-CIT SPECT. J Neurol Neurosurg Psychiatry 2012;**83**(11):1063-70

32. Lopez-Sendon JL, Mena MA, de Yebenes JG. Drug-induced parkinsonism in the elderly: incidence, management and prevention. Drugs Aging 2012;**29**(2):105-18

33. Diaz-Corrales FJ, Sanz-Viedma S, Garcia-Solis D, et al. Clinical features and 123I-FP-CIT SPECT imaging in drug-induced parkinsonism and Parkinson's disease. Eur J Nucl Med Mol Imaging 2010;**37**(3):556-64

34. Booij J, Kemp P. Dopamine transporter imaging with [(123)I]FP-CIT SPECT: potential effects of drugs. Eur J Nucl Med Mol Imaging 2008;**35**(2):424-38

35. Nikolaus S, Antke C, Kley K, et al. Pretreatment with haloperidol reduces (123)I-FP-CIT binding to the dopamine transporter in the rat striatum: an in vivo imaging study with a dedicated small-animal SPECT camera. J Nucl Med 2009;**50**(7):1147-52

36. Lavalaye J, Knol RJ, de Bruin K, et al. [123I]FP-CIT binding in rat brain after acute and sub-chronic administration of dopaminergic medication. European journal of nuclear medicine 2000;**27**(3):346-9

37. Schillaci O, Pierantozzi M, Filippi L, et al. The effect of levodopa therapy on dopamine transporter SPECT imaging with(123)I-FP-CIT in patients with Parkinson's disease. Eur J Nucl Med Mol Imaging 2005;**32**(12):1452-6

38. Knol RJ, de Bruin K, van Eck-Smit BL, et al. No significant effects of single intravenous, single oral and subchronic oral administration of acetylcholinesterase inhibitors on striatal [123I]FP-CIT binding in rats. Eur J Nucl Med Mol Imaging 2008;**35**(3):598-604

39. Booij J, de Jong J, de Bruin K, et al. Quantification of striatal dopamine transporters with 123I-FP-CIT SPECT is influenced by the selective serotonin reuptake inhibitor paroxetine: a double-blind, placebo-controlled, crossover study in healthy control subjects. J Nucl Med 2007;**48**(3):359-66

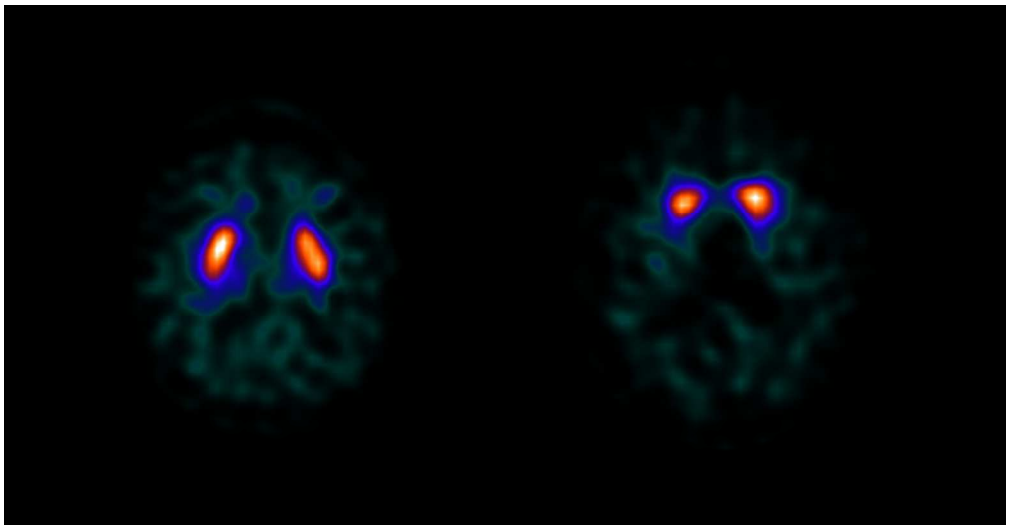
40. Ziebell M, Holm-Hansen S, Thomsen G, et al. Serotonin transporters in dopamine transporter imaging: a head-to-head comparison of dopamine transporter SPECT radioligands 123I-FP-CIT and 123I-PE2I. J Nucl Med 2010;**51**(12):1885-91

41. Bjoerke-Bertheussen J, Ehrt U, Rongve A, et al. Neuropsychiatric symptoms in mild dementia with lewy bodies and Alzheimer's disease. Dement Geriatr Cogn Disord 2012;**34**(1):1-6

42. Boeve BF, Molano JR, Ferman TJ, et al. Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in an aging and dementia cohort. Sleep medicine 2011;**12**(5):445-53

FIGURE LEGENDS

Figure 1: Transversal [^{123}I]FP-CIT SPECT image from a patient in the DLB cluster with a normal scan (left: case 2) and a patient with an abnormal scan in the non-DLB cluster (right: case 4).



Transversal [^{123}I]FP-CIT SPECT image from a patient in the DLB cluster with a normal scan (left: case 2) and a patient with an abnormal scan in the non-DLB cluster (right: case 4).
173x90mm (300 x 300 DPI)

[^{123}I]FP-CIT SPECT in suspected dementia with Lewy bodies: a longitudinal case study

Françoise J. Siepel, MSc[1,2]*; Arvid Rongve[3] MD PhD; Tirza C. Buter[4], MD; Mona K. Beyer[1] MD PhD; Clive G. Ballard[5] Prof MD PhD; Jan Booij[6], Prof MD PhD; Dag Aarsland[1] Prof MD PhD

[1] Centre for Age-Related Medicine, Stavanger University hospital, Stavanger University Hospital, Stavanger, Norway

[2] Department of Clinical Medicine, University of Bergen, Bergen, Norway

[3] Department of Psychiatry, Haugesund Hospital, Haugesund, Norway

[4] Department of Nuclear Medicine, Stavanger University Hospital, Stavanger, Norway

[5] Wolfson Centre for Age-related Diseases, King`s College London, London, UK

[6] Department of Nuclear Medicine, Academic Medical Center, Amsterdam, The Netherlands

*Correspondence and requests for reprints:

Françoise J. Siepel

Stavanger University Hospital, Department of Psychiatry,

Postbox 8100, 4068 Stavanger, Norway.

Phone: +47 51 51 55 78 or +47 51 51 56 19

Fax : +47 51 51 51 61

Email: facois@sus.no

Abbreviated title page

[^{123}I]FP-CIT SPECT in suspected dementia with Lewy bodies: a longitudinal case study

Short title: [^{123}I]FP-CIT SPECT in suspected DLB

Keywords: Single-Photon Emission Computed Tomography, [^{123}I]FP-CIT, Dementia, Lewy Body, Cluster analysis

Paper statistics:

Abstract:	256 words
Paper:	3650 words
References:	42 references
Tables:	3 tables
Images:	1 image

ABSTRACT

Objectives Little is known regarding the "false negative" or "false positive" striatal dopamine transporter binding on SPECT for the diagnosis of dementia with Lewy bodies (DLB). We explored the clinical course in patients fulfilling the criteria for clinical DLB with a normal [^{123}I]FP-CIT SPECT (i.e. SPECT scan negative, clinical features positive (S-CF+)), and patients not fulfilling DLB criteria with an abnormal scan (S+CF-).

Design Longitudinal case study over 2-5 years.

Setting Consecutive referrals of patients with mild dementia to dementia clinics in western Norway.

Participants 50 patients (27 men and 23 women; mean age at baseline of 74 (range 52 to 88)) with [^{123}I]FP-CIT SPECT images underwent cluster analysis: 20/50 patients allocated to a "DLB" and 8 to a "non-DLB" cluster were included.

Outcome measures were scores on standardized clinical rating scales for hallucinations, parkinsonism, fluctuations, REM sleep behaviour disorder and visually rated [^{123}I]FP-CIT SPECT.

Results During the follow-up period, in the S+CF- group (n=7), frequency and severity of DLB symptoms tended to increase, particularly parkinsonism (7/7) and cognitive fluctuations (7/7), while severity of visual hallucinations and REM sleep behaviour disorder remained stable. The S-CF+ (n=3) fulfilled the operationalized criteria for probable DLB both at baseline and at the end of the follow-up.

Conclusions The findings suggest that systematic visual analyses of [^{123}I]FP-CIT SPECT can detect people with DLB prior to the development of the full clinical syndrome. In addition, the study indicates that some patients fulfilling clinical criteria for probable DLB have a normal scan, and further studies are required to characterize these patients better.

SUMMARY SECTION

Article focus

- [^{123}I]FP-CIT SPECT is an established biomarker for DLB versus AD.
- Little is known about the clinical course of patients with symptoms of DLB and a normal [^{123}I]FP-CIT SPECT and patients not fulfilling the DLB criteria with an abnormal scan.
- We performed a detailed clinical follow-up of such patients.

Key Messages

- Patients not fulfilling the DLB criteria with an abnormal scan developed over time typical DLB clinical features.
- Patients with symptoms of DLB and a normal [^{123}I]FP-CIT SPECT continued to fulfil clinical criteria for DLB, i.e. were false negative according to clinical criteria.
- [^{123}I]FP-CIT SPECT is a helpful investigation in an early stage of DLB.

Strengths and Limitations

- Limitations include the small number of patients included and the lack of autopsy.
- Strengths include the objective clinical classification based on cluster analysis and the long duration of follow-up and the use of standardized procedures during the study period.

INTRODUCTION

Dementia with Lewy bodies (DLB) is the second most frequent neurodegenerative dementia after Alzheimer's disease (AD). In addition to cognitive decline, frequent clinical symptoms of DLB are parkinsonism, hallucinations and other psychiatric symptoms, fluctuating attention, and autonomous dysfunction including orthostatic hypotension and falls.[1] DLB patients have more reduced quality of life, higher costs, and higher mortality than patients with AD.

DLB is often under-diagnosed especially in the early stages when the frequency of presenting core symptoms is low.[2] Early and accurate diagnosis is however important for informing patient and relatives about key treatment decisions as the disease course and prognosis differ between the dementia types. In addition, diagnosing DLB is meaningful for avoiding antipsychotic drugs due to the sensitivity for side effects in this patient group. Diagnosis is particularly problematic in people who have some symptoms of DLB but do not fulfil the criteria for probable DLB. The clinical diagnosis of DLB has a high specificity (approximately 95%) but low sensitivity (30%) mainly based on the consensus criteria presented in 1996,[3] indicating that the diagnosis is often missed.

Dopaminergic nigrostriatal degeneration is common in DLB and [^{123}I]FP-CIT SPECT imaging is able to detect this dopaminergic deficit. This imaging technique is an established biomarker for the in vivo detection of nigrostriatal degeneration, which is typical feature of Parkinson's disease (PD) also. [^{123}I]FP-CIT SPECT uses a ^{123}I-labeled tracer that binds with high affinity to the dopamine transporter (DAT). A high correlation between abnormal DAT binding and a clinical diagnosis of probable DLB has been shown, and in a pivotal multicentre study, abnormal scans had a mean sensitivity of 78% for distinguishing clinical probable DLB from AD, with specificity of 90% for excluding non-DLB.[4] Decreased striatal DAT binding is listed as one of the suggestive features in the consensus criteria for the clinical diagnosis of DLB.[1]

Very little is known regarding patients fulfilling clinical DLB criteria with a negative [^{123}I]FP-CIT SPECT scan (S-CF+) or patients with an abnormal scan not fulfilling clinical DLB criteria (S+CF-). In contrast, considerable research has been conducted on PD patients with negative DAT scans, i.e. "scans without evidence of dopaminergic deficit" (SWEDD). Repeated DAT imaging showed a normal scan up to 4 year follow up and this group did not benefit from antiparkinson medication.[5] This demonstrates that causes other than nigrostriatal degeneration can cause parkinsonism, such as for example cerebrovascular disease (vascular parkinsonism) and drugs with antidopaminergic activity.[6]

It has been shown in a trial cohort that [^{123}I]FP-CIT SPECT can distinguish DLB from AD even before the full syndrome has emerged. Indeed, this imaging marker is particularly clinically useful in diagnostically uncertain cases, and patients with "S+CF-" may actually represent early cases who will later develop a full DLB syndrome.[7, 8] However, the nosological status and course of the S-CF+ and S+CF- group, in the context of DLB have not been reported in a clinical cohort.

This study aims to explore the clinical characteristics and course of dementia patients who underwent [^{123}I]FP-CIT SPECT imaging. A group of such patients from the Norwegian DemWest cohort was followed according to a standardized and prospective research protocol. We hypothesized that "S+CF" cases would develop a clinical profile more consistent with the diagnostic criteria for DLB, and that "S-CF+" cases may develop a clinical phenotype that differed from the typical pattern of DLB patients.

MATERIALS AND METHODS

Participants were selected from the DemWest cohort, which includes patients from dementia clinics with a first time diagnosis of mild dementia who are followed annually.[9] Patients were assessed with medical exam and routine blood tests, and standardized clinical assessments and neuropsychological tests were administered, such as the motor subscale of the Unified Parkinson`s Disease Rating Scale (UPDRS) for parkinsonism, Neuropsychiatric Inventory (NPI) to assess psychiatric symptoms including visual hallucinations (VHs) and the Clinician Assessment of Cognitive Fluctuations (COGA)[10] or Mayo fluctuation Questionnaire[11] for cognitive fluctuations. Sleep disturbances including REM sleep behaviour disorder (RBD) were monitored with the Mayo sleep Questionnaire.[12] Neuroleptic sensitivity was classified as previously reported.[13] Exclusion criteria were acute delirium or confusion, terminal illness, recently diagnosed major somatic illness, previous bipolar disorder or psychotic disorder. More details regarding selection and diagnostic procedures are provided elsewhere.[9]

Continuous scores for the core and suggestive DLB features were calculated: for visual hallucinations (frequency x intensity) using the NPI scale item 2 with a range of 0-12; parkinsonism on the UPDRS motor subscale (0-108); fluctuating cognition by the clinician assessment of cognitive fluctuations (0-16) (a subgroup on the Mayo fluctuation questionnaire (0-4)) and combined as previously described.[14] RBD was determined with the Mayo sleep questionnaire (0-4). To select DLB patients we used UPDRS-motor subscale cut-off score of > 9 and at least 1 within other scales.[14]

Imaging

From the DemWest database 50 patients underwent [^{123}I]FP-CIT SPECT imaging on the discretion of the clinician considered DLB to be a differential diagnosis between March 2005 and May 2010 (27 men and 23 women, mean age at baseline of 74 (range 52 to 88). Initial diagnosis of possible or probable DLB was made using clinical judgement.[1] Subsequent classification of patients was undertaken based upon a cluster analysis of symptoms (see analysis section below for details).The average time between initial clinical diagnosis and date of [^{123}I]FP-CIT SPECT imaging was 7 months.

SPECT imaging with the well-validated radiotracer [^{123}I]FP-CIT (N-ω-fluoropropyl-2β-carbomethoxy-3β-[4-iodophenyl] nortropane; DaTscan^{TM}, GE Healthcare) was performed according to clinical routine at each of the three centres. An intravenous injection of about 185 MBq was administered and images were acquired 3-4 h after injection on a multidetector or multiheaded gamma camera with LEHR collimators, a time point at which the specific binding ratio of this tracer to the DAT is stable.[15] Subsequently, images were reconstructed using filtered back projection (FBP) with a Butterworth filter with a 0.55 cutoff and an order of 10. Chang`s attenuation correction was applied with an attenuation coefficient of 0.11 cm^{-1}.[16]

Representative transversal images through the basal ganglia were visually analysed by an external nuclear medicine specialist, experienced in DAT imaging (JB), who did not have access to clinical information. The visual analysis consisted of separate evaluations of the left and right caudate nucleus and putamen divided in normal, abnormal and strongly abnormal.

In addition, magnetic resonance imaging (MRI) was acquired at baseline at the three centres using 1.5 Tesla MRI: a Philips Intera scanner with fast field echo (FFE) protocol (TR/TE/FA= 10 ms/4.6 ms/30°,ST=2.0mm, NEX=2.0, matrix=256x256 or TR/TE/FA=20 ms/4.6 ms/30°,ST=1.0mm, NEX=2.0, matrix=256x256) and GE Signa Excite scanner with fast spoiled gradient recalled (FSPGR) protocol (TR/TE/FA=20 ms/3.1 ms/7°,ST =1.0mm, NEX=1.0, matrix=256x256). Details of the harmonization have been reported previously.[17] Basal ganglia hyperintensities were scored using the basal ganglia part of the Scheltens scale, a semi quantitative rating scale (0-30) including separate assessment (0-6) of the caudate nucleus, putamen, globus pallidus, thalamus and the internal/external capsule.[18] One patient (case 9) did not receive a MRI due to metal prostheses in both ears.

Analysis

For an objective, quantitative classification of cases, cluster analysis was applied based on the scores on the four DLB symptom scales as previously reported.[14] The patients were classified in 4 clusters with help of SPSS version 18. In brief, the two step cluster analysis was performed with four continuous variables (i.e. parkinsonism, hallucinations, cognitive fluctuations and RBD) and log-

likelihood.[14] Missing values analysis with expectation-maximization algorithm was performed when scores at one of the four symptom scales was missing. The four clusters included a “DLB” cluster, with high scores for hallucinations and parkinsonism and cognitive fluctuations, a `non-DLB` cluster with low values on all DLB symptom scales, one cluster included patients with high scores for RBD, and one with high values of cognitive fluctuations. In this study we only considered patients classified in the “DLB” and the “non-DLB” clusters.[14] Based on the [^{123}I]FP-CIT SPECT scan results, patients were classified as S-CF+ (i.e. DLB-cluster and normal scan) or S+CF- (i.e. non-DLB cluster and abnormal scan).

Design

Patients were followed with annual assessments using the same assessment battery at baseline performed by trained research physicians and research nurses. Subsequently, core and suggestive DLB features (parkinsonism, VH, cognitive fluctuations, neuroleptic hypersensitivity, RBD) and their progress were rated by an experienced research clinician (AR), taking into account both research data and transcripts from the medical records, but blinded to all information of [^{123}I]FP-CIT SPECT scan information and clinical diagnosis. The blinding was achieved by actively removing all information about the scans from the transcripts. The rater noted whether symptoms were present and their severity (no, mild-to-moderate, and moderate-to-severe) at baseline, and whether they increased or decreased (mild or marked) or remained stable during the follow-up period.

Ethical approval

The regional ethics committee and the Norwegian authorities approved the DemWest study for collection of medical data. The patients provided written consent to participate in the study after a thorough explanation of the procedure to the patient and caregiver.

RESULTS

There were 20 patients in the DLB cluster, 8 patients in the non-DLB cluster (the remaining 22 patients were included in the other two clusters, with subsequently n=5 with S- and n=7 with S+ in the RBD cluster and n=6 with S- and n=4 with S+ in the cognitive fluctuation cluster). Nine of the 50 patients with [^{123}I]FP-CIT SPECT had a missing value for one of the four symptom scores and therefore the previously mentioned missing value analysis was performed.

Scans of 3 patients in the DLB cluster were classified as normal, and these 3 were consequently classified as S-CF+. Seven patients in the non-DLB cluster had an abnormal scan, and were classified as S+CF-. An example of the [^{123}I]FP-CIT SPECT scan for the S-CF+ group (left) and S+CF- group (right) is shown in figure 1. Table 1 shows the characteristics of the two groups.

Table 1: Clinical characteristics

Characteristics	S-CF+ (n=3)	S+CF- (n=7)
Gender (M:F)	3:0	4:3
MMSE	22 (20-26)	25 (16-27)
Age at baseline (years)	79 (72-88)	71 (52-80)
Observation time (years)	3.0 (2-4)	3.4 (2-5)
Medication		
Antiparkinson (yes/no)	0:3	1:6
Antipsychotics (yes/no)	2:1	1:6
Antidepressants (yes/no)	1:2	3:4
Antidementia (yes/no)	1:2	6:1

(Numbers represent median (range) or number of patients). S: [^{123}I]FP-CIT SPECT; CF: clinical features

Detailed information about the visual assessment of the [^{123}I]FP-CIT SPECT scans regarding DAT binding in the caudate nucleus bilaterally, and the putamen bilaterally, as well as hyperintensities based on MRI are shown in Table 2.

Table 2: Visual assessment of [^{123}I]FP-CIT SPECT and MRI

	[^{123}I]FP-CIT SPECT					MRI	
	Caudate Left	Caudate Right	Putamen Left	Putamen Right	Final Evaluation	Scheltens score (0-30)	Details
S-CF+							
1	0	0	0	0	normal	3	Right capsula interna/externa
2	0	0	0	0	normal	0	
3	0	0	0	0	normal	8	Left thalamus, right capsula interna/externa
S+CF-							
4	0	0	2	2	abnormal	0	
5	0	2	0	2	abnormal	0	
6	2	2	2	2	abnormal	0	
7	0	1	2	2	abnormal	0	

8	0	0	2	1	abnormal	4	Left caudate, right capsula externa
9	2	2	2	2	abnormal	-	Not performed
10	0	1	0	1	abnormal	6	Putamen bilateral, left capsula externa

(0 = normal, 1=abnormal, 2= strongly abnormal on [^{123}I]FP-CIT SPECT). S: [^{123}I]FP-CIT SPECT; CF: clinical features

It can be seen that in the S-CF+ group, the [^{123}I]FP-CIT SPECT scans were normal, by definition, in all studied striatal subareas. In the S+CF- group, putamen DAT binding was abnormal bilaterally in most cases (5/7). None of the cases shows infarcts in the basal ganglia on MR. Some patients had white matter lesions (WML), but these were usually in the low-to-moderate range.

During follow-up, no other diseases were detected which could explain the symptoms. Table 3 shows the core and suggestive symptoms at baseline and their development during follow up.

Table 3: Status of main DLB symptoms at baseline and during follow-up

	Visual hallucinations		REM sleep behaviour disorder		Cognitive fluctuations		Parkinsonism	
	Bsl	Fu	Bsl	Fu	Bsl	Fu	Bsl	Fu
S-CF+								
1	1	0	0	0	1	0	0	2
2	1	-1	1	0	0	1	1	2
3	1	0	1	-1	0	2	0	1
S+CF-								
4	1	0	2	-1	1	2	0	2
5	2	1	0	1	0	2	1	2
6	0	0	0	0	0	1	0	2
7	1	0	0	0	0	2	1	2
8	0	0	0	0	0	2	1	2
9	0	0	0	0	0	1	2	2
10	0	0	0	0	0	2	0	2

(Baseline: 0 = not present, 1 = mild/moderate, 2=moderate/marked; Follow up: -2 = significant decrease, -1 = decrease, 0 = no change, 1 =increase, 2 = significant increase). Bsl: baseline; Fu: follow-up; S: [^{123}I]FP-CIT SPECT; CF: clinical features

In the S+CF- group, it can be seen that some DLB core symptoms were present at baseline in some patients. These were usually of mild-to-moderate severity and did not reach the cut-off values that emerged from the cluster analysis.[14] All 7 had a moderate-to-severe increased parkinsonism during follow-up, although 3/7 had no parkinsonism at baseline. In addition, all 7 S+CF- developed marked

worsening in cognitive fluctuations, whereas 6 were without these symptoms at baseline. Less marked changes were noted for VH.

In the S-CF+ group all 3 cases had VH at baseline that remained stable (n=2) or decreased (n=1) in severity during the follow-up period. In contrast, 2 cases showed a moderate-to-severe worsening in parkinsonism and 2 cases had worsening of cognitive fluctuations.

There were no remarkable changes in progression of the severity of RBD that was also rare at baseline. Three patients (2 S-CF+, 1 S+CF-) received antipsychotics but hypersensitivity reactions to these drugs were not observed.

All cases fulfilled the criteria for probable DLB at the end of the follow-up period without taking the [^{123}I]FP-CIT SPECT scan results into account, i.e. they had at least two core features or one core and one clinical suggestive feature.

DISCUSSION

In this study we report longitudinal findings in patients who, based on cluster analysis of symptom scores were classified as “DLB” or “non-DLB”, and who had [^{123}I]FP-CIT SPECT results that were inconsistent with these findings, i.e. “S-CF+” or “S+CF-. Our main findings are that S+CF- patients tend to develop core or suggestive features of DLB, in particular parkinsonism and cognitive fluctuations, i.e. they represent DLB in the early stage. In the S-CF+ group more various DLB symptoms were shown at baseline with mainly a stable or increased severity at follow-up, and all cases fulfilled the criteria for probable DLB at the end of the follow-up period.

Very few longitudinal studies of DLB patients in light of [^{123}I]FP-CIT SPECT have been reported. In contrast, the results of [^{123}I]FP-CIT SPECT imaging and the discrepancy with clinical diagnosis have been extensively studied in PD. The Clinically Uncertain Parkinsonism Syndrome (CUPS) study considered patients with uncertain but clinically suspect PD. [^{123}I]FP-CIT SPECT imaging was inconsistent with initial diagnosis in 36% of the patients with a clinical diagnosis of presynaptic parkinsonism and 54% with non-presynaptic parkinsonism. After two years, however, the clinical diagnosis was established and the rate of agreement between the diagnosis at follow-up and the initial imaging results was 90%, indicating that the initial DAT SPECT scan is of value in the diagnostic follow up of the patients with clinically uncertain PD.[19] This is in line with the current study showing that all 7 FP cases developed increased parkinsonism and cognitive fluctuations consistent with a diagnosis of DLB. Our findings are also consistent with a previous study demonstrating that in cases with “possible DLB”, i.e. not fulfilling criteria for probable DLB, the scan differentiated between those who developed probable DLB and those who did not after one year.[7]

An explanation for this could be that the [^{123}I]FP-CIT SPECT scan detects nigro-striatal degeneration before the full clinical syndrome has been developed. This is supported by the knowledge of PD that 80% of the striatal dopamine neurons need to be lost before PD symptoms are present.[20] In addition, it is shown that by using a radioligand for DAT nigrostriatal damage can be detected years before the onset of motor signs of PD.[21]

Three of our cases (3 out of 50; 6% of all scans) were in the S-CF+ group, and searching for possible explanations is important. It is well known that 10-15% of patients with clinical PD have a normal DAT scan, and it is suggested that this subgroup have no involvement of the dopaminergic nigrostriatal pathway.[6] In the S-CF+ group the cases may have a true negative [^{123}I]FP-CIT SPECT, i.e. they have DLB but without involvement of dopaminergic neurons in the substantia nigra. Some DLB patients indeed do not develop parkinsonism.[22] Pathological classification of DLB identifies three types: brainstem predominant, limbic, and neocortical, assuming the substantia nigra is first affected, following by the amygdalae and limbic cortex and subsequently the neocortex.[23] However, it has been reported that in some cases, Lewy-body pathology can be found in the cortex and higher brain stem but not in the lower brain stem,[24] suggesting that in some patients the pathological process starts in the neocortex, and then progresses towards the brain stem. Our findings in the S-CF+ group are consistent with this hypothesis, in that parkinsonism mainly developed later on. Unfortunately, a follow-up scan or neuropathology was not available to address this hypothesis. Interestingly, a recent clinicopathological study, that included 7 autopsy proven DLB cases, showed that the antemortem [^{123}I]FP-CIT SPECT scan was normal in 2 of these cases. Importantly, in these 2 cases the number of nigrostriatal dopaminergic neurons was also within the normal range.[25] This observation may support the hypothesis that in some patients the pathological process may start in the neocortex.

Another possible explanation for the S-CF+ cases is the pathological heterogeneity in DLB. Whereas some patients have a “pure” DLB, the majority in addition may have AD-type changes such as amyloid plaques and even tangle pathology.[1] 5-10% of patients with clinical dementia have intermediate [^{123}I]FP-CIT SPECT scans, i.e. abnormal DAT binding but not as low as typical of DLB. These intermediate scans could represent cases with mixed DLB/AD pathology.[26] DLB cases with AD pathology have lower prevalence of core DLB symptoms than “pure” DLB.[6, 27] It is possible that mixed cases in an early stage may have subtle or no nigrostriatal dopaminergic pathology leading to a normal DAT scan. In these cases parkinsonism may be caused by Alzheimer-type or even LB-type degeneration in the striatum itself rather than by dopaminergic nigrostriatal neurodegeneration.[28]

Another possible explanation is that S-CF+ cases have another type of dementia than DLB. For example, parkinsonism is not uncommon in AD, particularly in the later stages,[29] and it can be seen

in other conditions such as vascular parkinsonism and frontotemporal dementia. However, both vascular parkinsonism and frontotemporal dementia may have abnormal scans, although less common than in DLB.[30, 31] The score for hyperintensities on MRI is in the range from 0-8 (see table 2). These relatively low scores show that cerebrovascular is an unlikely cause of parkinsonism in our cases, also since none of the subjects had lacunar infarcts in the basal ganglia.

Drug-induced parkinsonism is also common,[6] and may take several weeks to resolve after drug discontinuation, and complete resolution may taken over a year.[32] These patients usually have a normal DAT SPECT scan,[33] and thus may be misinterpreted as "S-CF+". In our S-CF+ group, case 1 received antipsychotics during 5 months and discontinued one month before scanning, and in case 3 it was discontinued directly at baseline. However, in both cases, parkinsonism increased during follow-up. Drug-induced parkinsonism is therefore not a likely cause of the "S-CF+" patients in our study.

Finally, several patients were treated with drugs such as antidepressants, antipsychotics, L-DOPA and antidementia drugs, and scanned while on medication, which may influenced the interpretation of the [^{123}I]FP-CIT SPECT scans.[34]

The antidopaminergic effect of antipsychotic drugs may increase the synthesis and release of dopamine in the striatum, leading to a potential competition between the DAT ligand [^{123}I]FP-CIT and synaptic dopamine. Indeed, high doses of the neuropsychotic haloperidol resulted in a reduction in striatal [^{123}I]FP-CIT binding by 25% in rats.[35] However, in another rat study this could not be replicated.[36] Also, it has recently been discussed that even if neuroleptics will induce changes in DAT imaging, such changes will presumably not be large enough to influence the visual assessments of [^{123}I]FP-CIT SPECT studies.[34] Nevertheless, in the present study, 1 patient in the S+CF- group had used an antipsychotic, and we cannot totally exclude that this may have led to a false positive scan.

Although antiparkinsonian medications influence the dopaminergic transmission, they do not seem to affect the visual interpretation and quantification of DAT imaging.[6] The use of Levodopa for example did not significant change the striatal [^{123}I]FP-CIT binding significantly.[37]

The acetylcholinesterase inhibitors, such as donepezil and rivastigmine may reduce striatal dopaminergic transmission, but did not show significant effects on striatal [^{123}I]FP-CIT binding.[38]

Antidepressants such as the selective serotonin reuptake inhibitor (SSRI) paroxetine have been shown to induce a small, but significant increase in striatal [^{123}I]FP-CIT binding ratios.[39] On the other hand, the SSRI citalopram showed a *reduction* in striatal [^{123}I]FP-CIT binding ratios, and blocking of the serotonin transporter (SERT) may lead to high plasma [^{123}I]FP-CIT concentrations.[40] DAT and SERT are important for the termination of dopaminergic and serotonergic transmission, respectively, by reuptake of dopamine and serotonin from the synaptic cleft. FP-CIT binds to DAT and SERT with affinities in the nanomolar range, although the affinity to SERT is lower than that to DAT.[34] Therefore, quantification of [^{123}I]FP-CIT SPECT is susceptible to SERT blocking pharmaceuticals.[40] However, as recently discussed, a small change in the quantification in striatal FP-CIT binding, and with the same change of binding in both the caudate nucleus and putamen, is unlikely to result in false negative and false positive results when a visual assessment is used.[34] One of our S-CF+ and 2 of the S+CF- patients had used an SSRI, but it is unlikely that this has influenced the interpretation of our scan results. Two of the antidepressant users showed a decrease in visual hallucinations during follow-up, cases 2 and 5 (table 3). Nevertheless, more studies are needed to explore how CNS-active drugs frequently used by DLB-patients may influence DAT imaging interpretation.

Some limitations of this study need to be acknowledged. First, the limited number of patients in the S-CF+ and S+CF- group and the difference in follow-up time ranging from 2 to 5 years, dependent on the moment of entrance in the study should be mentioned. Also, no repeat imaging was performed. A prolonged follow-up time in a larger study group with follow-up DAT scan may have provided additional information. Secondly, the NPI item 2 includes hallucinations from different modalities and not only visual. However, we have previously shown that of those with hallucinations in the overall cohort, nearly 80% had visual hallucinations.[41] In addition, we did verify through the medical record transcripts that the patients with hallucinations in fact had visual hallucinations. RBD was diagnosed based only on clinical assessment. Videopolysomnograpphy is the preferred diagnostic method but not widely available, and acceptable sensitivity and specificity has been reported for the Mayo sleep

scale.[42] Finally, scans were only analysed visually. However, in previous studies this approach has shown to be as accurate as semi-quantitative analyses to differentiate normal from abnormal [^{123}I]FP-CIT SPECT scans.[4]

The golden standard for diagnosing DLB is the brain pathology analysis post-mortem. Unfortunately autopsy of the FP and FN cases in this study was not available to confirm diagnosis. However, all 7 available autopsy diagnoses from the DemWest study were consistent with the clinical diagnosis including two AD and five DLB patients. In addition, a relative objective method of cluster analysis was performed based on symptom scores for the main DLB symptoms in this study, and the symptoms of interest were rated by trained research clinicians using standardized and validated instruments.

CONCLUSION

These data support the notion that [^{123}I]FP-CIT SPECT imaging can identify DLB patients before the full syndrome has developed, supporting the usefulness of [^{123}I]FP-CIT SPECT as part of the routine clinical work up in cases with suspect DLB. A minority of patients fulfilling clinical DLB criteria have a normal [^{123}I]FP-CIT SPECT scan, and further studies are needed to characterize such cases.

CONTRIBUTORS

FJS and DA were responsible for the study concept, design, data analysis, writing of the manuscript, and provided input during the whole process of the study. AR was involved in the development of the study concept, clinical patient evaluation and data analysis. TCB was involved in the image selection and reconstruction and provided main input during data acquisition. MKB and JB were responsible for image analysis and interpretation of results. CGB was involved in the concept and evaluation of results. All authors were involved in critical review of the draft and approval of the version to be published.

ACKNOWLEDGMENTS

The authors acknowledge the co-investigators involved in the large dementia study in western Norway and especially K Brønnick for the advice and contribution.

In addition, we thank the National Institute for Health Research (UK) for supporting the work of Clive Ballard through the Biomedical Research Unit for Dementia and the Biomedical Research Centre for Mental Health at King's College London.

COMPETING INTERESTS

JB is consultant of GE Healthcare

FUNDING

This study was supported by GE Healthcare.

Françoise Siepel is supported by a grant from Western Norway regional health authority.

REFERENCES

1. 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**(12):1863-72

2. Tiraboschi P, Salmon DP, Hansen LA, et al. What best differentiates Lewy body from Alzheimer's disease in early-stage dementia? Brain 2006;**129**(Pt 3):729-35

3. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 1996;**47**(5):1113-24

4. McKeith I, O'Brien J, Walker Z, et al. Sensitivity and specificity of dopamine transporter imaging with 123I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study. Lancet Neurol 2007;**6**(4):305-13

5. Marek K, Jennings D, Seibyl J. Long-term folluw-up of patients with scans without evidence of dopaminergic deficit (SWEDD) in the ELLDOPA study [abstract]. Neurology 2005;**64**((1 Suppl)):A274

6. Cummings JL, Henchcliffe C, Schaier S, et al. The role of dopaminergic imaging in patients with symptoms of dopaminergic system neurodegeneration. Brain 2011;**134**(Pt 11):3146-66

7. O'Brien JT, McKeith IG, Walker Z, et al. Diagnostic accuracy of 123I-FP-CIT SPECT in possible dementia with Lewy bodies. Br J Psychiatry 2009;**194**(1):34-9

8. Papathanasiou ND, Boutsiadis A, Dickson J, et al. Diagnostic accuracy of 123I-FP-CIT (DaTSCAN) in dementia with Lewy bodies: a meta-analysis of published studies. Parkinsonism Relat Disord 2012;**18**(3):225-9

9. Aarsland D, Rongve A, Nore SP, et al. Frequency and case identification of dementia with Lewy bodies using the revised consensus criteria. Dement Geriatr Cogn Disord 2008;**26**(5):445-52

10. Walker MP, Ayre GA, Cummings JL, et al. The Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale. Two methods to assess fluctuating confusion in dementia. Br J Psychiatry 2000;**177**:252-6

11. Ferman TJ, Smith GE, Boeve BF, et al. DLB fluctuations: specific features that reliably differentiate DLB from AD and normal aging. Neurology 2004;**62**(2):181-7

12. Boeve BF, TJ; Silber, MH; Smith, GE. Validation of a questionnaire for the diagnosis of REM sleep behavior disorder. Neurology 2002;**58**(Suppl. 3):A509

13. Aarsland D, Perry R, Larsen JP, et al. Neuroleptic sensitivity in Parkinson's disease and parkinsonian dementias. J Clin Psychiatry 2005;**66**(5):633-7

14. Rongve A, Bronnick K, Ballard C, et al. Core and suggestive symptoms of dementia with lewy bodies cluster in persons with mild dementia. Dement Geriatr Cogn Disord 2010;**29**(4):317-24

15. Booij J, Hemelaar TG, Speelman JD, et al. One-day protocol for imaging of the nigrostriatal dopaminergic pathway in Parkinson's disease by [123I]FPCIT SPECT. J Nucl Med 1999;**40**(5):753-61

16. Darcourt J, Booij J, Tatsch K, et al. EANM procedure guidelines for brain neurotransmission SPECT using (123)I-labelled dopamine transporter ligands, version 2. Eur J Nucl Med Mol Imaging 2009;**37**(2):443-50

17. Lebedev AV, Beyer MK, Fritze F, et al. Cortical changes associated with depression in Alzheimer's disease: an MRI surface-based morphometric study [abstract]. European Psychiatry 2012;**27**: p792

18. Scheltens P, Barkhof F, Leys D, et al. A semiquantative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. J Neurol Sci 1993;**114**(1):7-12

19. Tolosa E, Borght TV, Moreno E, et al. Accuracy of DaTSCAN (123I-Ioflupane) SPECT in diagnosis of patients with clinically uncertain parkinsonism: 2-year follow-up of an open-label study. Mov Disord 2007;**22**(16):2346-51

20. Fearnley JM, Lees AJ. Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain 1991;**114 (Pt 5)**:2283-301

21. Ponsen MM, Stoffers D, Booij J, et al. Idiopathic hyposmia as a preclinical sign of Parkinson's disease. Ann Neurol 2004;**56**(2):173-81

22. Ballard CG, Aarsland D, McKeith I, et al. Fluctuations in attention: PD dementia vs DLB with parkinsonism. Neurology 2002;**59**(11):1714-20

23. Braak H, Bohl JR, Muller CM, et al. Stanley Fahn Lecture 2005: The staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered. Mov Disord 2006;**21**(12):2042-51

24. Halliday GM, McCann H. The progression of pathology in Parkinson's disease. Annals of the New York Academy of Sciences 2010;**1184**:188-95

25. Colloby SJ, McParland S, O'Brien JT, et al. Neuropathological correlates of dopaminergic imaging in Alzheimer's disease and Lewy body dementias. Brain 2012;**135**(Pt 9):2798-808

26. Kemp PM, Holmes C. Imaging in dementia with Lewy bodies: a review. Nucl Med Commun 2007;**28**(7):511-9

27. Ballard CG, Jacoby R, Del Ser T, et al. Neuropathological substrates of psychiatric symptoms in prospectively studied patients with autopsy-confirmed dementia with lewy bodies. Am J Psychiatry 2004;**161**(5):843-9

28. Duda JE, Giasson BI, Mabon ME, et al. Novel antibodies to synuclein show abundant striatal pathology in Lewy body diseases. Ann Neurol 2002;**52**(2):205-10

29. Starkstein SE, Merello M, Brockman S, et al. Apathy predicts more severe parkinsonism in Alzheimer's disease. Am J Geriatr Psychiatry 2009;**17**(4):291-8

30. Benitez-Rivero S, Marin-Oyaga VA, Garcia-Solis D, et al. Clinical features and 123I-FP-CIT SPECT imaging in vascular parkinsonism and Parkinson's disease. J Neurol Neurosurg Psychiatry 2012;**84**(2):122-9

31. Morgan S, Kemp P, Booij J, et al. Differentiation of frontotemporal dementia from dementia with Lewy bodies using FP-CIT SPECT. J Neurol Neurosurg Psychiatry 2012;**83**(11):1063-70

32. Lopez-Sendon JL, Mena MA, de Yebenes JG. Drug-induced parkinsonism in the elderly: incidence, management and prevention. Drugs Aging 2012;**29**(2):105-18

33. Diaz-Corrales FJ, Sanz-Viedma S, Garcia-Solis D, et al. Clinical features and 123I-FP-CIT SPECT imaging in drug-induced parkinsonism and Parkinson's disease. Eur J Nucl Med Mol Imaging 2010;**37**(3):556-64

34. Booij J, Kemp P. Dopamine transporter imaging with [(123)I]FP-CIT SPECT: potential effects of drugs. Eur J Nucl Med Mol Imaging 2008;**35**(2):424-38

35. Nikolaus S, Antke C, Kley K, et al. Pretreatment with haloperidol reduces (123)I-FP-CIT binding to the dopamine transporter in the rat striatum: an in vivo imaging study with a dedicated small-animal SPECT camera. J Nucl Med 2009;**50**(7):1147-52

36. Lavalaye J, Knol RJ, de Bruin K, et al. [123I]FP-CIT binding in rat brain after acute and sub-chronic administration of dopaminergic medication. European journal of nuclear medicine 2000;**27**(3):346-9

37. Schillaci O, Pierantozzi M, Filippi L, et al. The effect of levodopa therapy on dopamine transporter SPECT imaging with(123)I-FP-CIT in patients with Parkinson's disease. Eur J Nucl Med Mol Imaging 2005;**32**(12):1452-6

38. Knol RJ, de Bruin K, van Eck-Smit BL, et al. No significant effects of single intravenous, single oral and subchronic oral administration of acetylcholinesterase inhibitors on striatal [123I]FP-CIT binding in rats. Eur J Nucl Med Mol Imaging 2008;**35**(3):598-604

39. Booij J, de Jong J, de Bruin K, et al. Quantification of striatal dopamine transporters with 123I-FP-CIT SPECT is influenced by the selective serotonin reuptake inhibitor paroxetine: a double-blind, placebo-controlled, crossover study in healthy control subjects. J Nucl Med 2007;**48**(3):359-66

40. Ziebell M, Holm-Hansen S, Thomsen G, et al. Serotonin transporters in dopamine transporter imaging: a head-to-head comparison of dopamine transporter SPECT radioligands 123I-FP-CIT and 123I-PE2I. J Nucl Med 2010;**51**(12):1885-91

41. Bjoerke-Bertheussen J, Ehrt U, Rongve A, et al. Neuropsychiatric symptoms in mild dementia with lewy bodies and Alzheimer's disease. Dement Geriatr Cogn Disord 2012;**34**(1):1-6

42. Boeve BF, Molano JR, Ferman TJ, et al. Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in an aging and dementia cohort. Sleep medicine 2011;**12**(5):445-53

FIGURE LEGENDS

Figure 1: Transversal [^{123}I]FP-CIT SPECT image from a patient in the DLB cluster with a normal scan (left: case 2) and a patient with an abnormal scan in the non-DLB cluster (right: case 4).