BMJ open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000380
Article Type:	Research
Date Submitted by the Author:	05-Oct-2011
Complete List of Authors:	Walker, Zuzana; University College London, Mental Health Sciences McKeith, Ian; Institute for Ageing and Health, Newcastle University Rodda, Joanne; University College London, Research Department of Mental Health Sciences Qassem, Tarik; North Essex Partnership Foundation NHS Trust, Mental Health Unit; Ain Shams University, Institute of Psychiatry Tatsch, Klaus; Städtisches Klinikum Karlsruhe, Department of Nuclear Medicine Booij, Jan; Academic Medical Centre, Department of Nuclear Medicine Darcourt, Jacques; University of Nice Sophia-Antipolis, Centre Anoine Lacassagne Department of Nuclear Medicine O'Brien, John; Newcastle University, Institute for Ageing and Health
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Psychiatry
Keywords:	Cognitive disorders, ALZHEIMER'S DISEASE, LEWY BODY, Dementia < NEUROLOGY, SPECT, FUNCTIONAL IMAGING

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No differences in symptom progression between dementia with Lewy bodies and Alzheimer's disease: cohort study

Zuzana Walker MD, Research Department of Mental Health Sciences, University College London, Bloomsbury Campus, London, UK and North Essex Partnership Foundation NHS Trust, Essex, UK

Ian McKeith FMedSci Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, UK

Joanne Rodda MBChB Research Department of Mental Health Sciences, University College London, Bloomsbury Campus, London, UK

Tarik Qassem MBBCh North Essex Partnership Foundation NHS Trust, Essex, UK and Institute of Psychiatry, Ain Shams University, Cairo, Egypt

Klaus Tatsch PhD Department of Nuclear Medicine, Städtisches Klinikum Karlsruhe, Karlsruhe, Germany

Jan Booij PhD Department of Nuclear Medicine, Academic Medical Centre, Amsterdam, Netherlands

Jacques Darcourt PhD Centre Anoine Lacassagne Department of Nuclear Medicine, Medical Faculty, University of Nice Sophia-Antipolis, Nice, France

John O'Brien DM, Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, UK

Correspondence: Zuzana Walker, Mental Health Unit, St. Margaret's Hospital, Epping, Essex, CM16 6TN, UK. email: z.walker@ucl.ac.uk

Contributions to the manuscript

Zuzana Walker: Involved in conception and design of the study as well as being a member of the consensus panel; contributed to statistical analysis and interpretation; co-wrote initial draft of the manuscript.

Ian McKeith: Involved in conception and design of the study as well as being a member of the consensus panel.

Joanne Rodda: Contributed to data analysis and interpretation; co-wrote initial draft of the manuscript; prepared final version of manuscript.

Tarik Qassem: Involved in data processing, analysis and interpretation.

Klaus Tatsch: Involved in conception and design of the study; performed the visual analysis of the SPECT data.

Jan Booij: Involved in conception and design of the study; performed the visual analysis of the SPECT data.

Jacques Darcourt: Involved in conception and design of the study; performed the visual analysis of the SPECT data.

John O'Brien: Involved in conception and design of the study as well as being a member of the consensus panel.

The final version was read and approved by all authors with JR and ZW incoroprating the additional comments.

Study funding and sponsorship:

The data collection was sponsored by GE Healthcare who made data available for further analysis for the present study.

Author disclosure statements:

At the time of the study Zuzana Walker, John O'Brien, Ian McKeith, Klaus Tatsch, Jan Booij and Jacques Darcourt have received consultancy payments from GE Healthcare. Joanne Rodda has received funding for neuroimaging research from GE Healthcare. Tarik Qassem has no disclosures.

Abstract

Background: Dementia with Lewy bodies (DLB) accounts for 10-15% of dementia cases at autopsy and has distinct clinical features associated with earlier institutionalisation and a higher level of carer distress than are seen in Alzheimer's disease (AD). At present, there is ongoing debate as to whether DLB is associated with a more rapid cognitive decline than AD. An understanding of the rate of decline of cognitive and non-cognitive symptoms in DLB may help patients and carers to plan for the future.

Methods: We compared 100 AD and 58 DLB subjects at baseline and 12 month follow-up on cognitive and neuropsychiatric measures including the Cambridge Cognitive Examination and Neuropsychiatric Inventory (NPI). Subjects with mild-moderate dementia from 40 European centres were included. Diagnosis of DLB or AD required agreement between consensus panel clinical diagnosis and visual rating of ^{123}I-FP-CIT (dopamine transporter) SPECT neuroimaging.

Results: The AD and DLB groups did not differ at baseline in terms of age, gender, Clinical Dementia Rating score and use of cholinesterase inhibitors or memantine. NPI and NPI carer distress scores were statistically significantly higher for DLB subjects at baseline and follow-up and there were no differences between AD and DLB in cognitive scores at baseline or follow-up. There was no significant difference in rate of progression of any of the variables analysed.

Conclusions: DLB subjects had more neuropsychiatric features at baseline and follow-up than AD, but we did not find any statistically significant difference in rate of progression between AD and DLB groups on cognitive or neuropsychiatric measures over a 12-month follow-up period.

Article summary

Article focus

- Dementia with Lewy bodies (DLB) has distinct neuropsychiatric features

- At present we do not know whether the poorer prognosis of DLB is due to a more rapid cognitive decline compared to Alzheimer's disease (AD)

Key messages

- In this fairly large cohort of patients with DLB and AD, while there was no difference in level of cognitive impairment (CAMCOG score) at baseline and at 12 months follow-up, DLB patients had significantly higher NPI and NPI carer distress scores both at baseline and 12 months follow-up.
- Therefore the worse prognosis of DLB is likely to be mediated by neuropsychiatric or other symptoms and not by cognitive decline

Strengths of this study

- Inclusion of high number of subjects from 40 European clinical centres
- Well characterised cases with both consensus panel clinical diagnosis (three clinical experts) and dopaminergic transporter SPECT imaging

Limitations of the study

- No autopsy data were available and therefore it is possible that more rapid cognitive decline may be present in pure DLB
- Only one year of follow-up

Introduction

Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia and accounts for approximately 15% of cases of dementia at autopsy [1]. It is characterised by the central feature of a progressive dementia accompanied by one or more core features of fluctuations in cognition, visual hallucinations and spontaneous features of parkinsonism [2].

Awareness of the rate of cognitive decline and also of non-cognitive symptoms can help carers and patients to adjust and plan appropriate lifestyle changes and to make arrangements for the future. This frequently involves making difficult decisions regarding treatment of psychiatric and motor symptoms and utilisation of limited resources available for patients with dementia.

Since its recognition as a neurodegenerative disorder, a body of research has focused on the differentiation of DLB from other dementias, in particular Alzheimer's disease (AD), in terms of both cross-sectional and longitudinal clinical factors. In addition to the clinical syndrome described in the consensus diagnostic criteria, DLB is associated with higher levels of behavioural disturbance and caregiver distress, lower quality of life and greater demand on resources when compared to AD [3;4]. Despite these findings, there is uncertainty within the literature regarding progression and survival in DLB compared to AD. Studies have shown survival in DLB to be either comparable to [5] or shorter [6] than in AD. No differences in decline on global measures (e.g. Clinical Dementia Rating, CDR) have been reported [7]. Studies of the progression of cognitive impairment have generally reported a similar [7;8] or steeper [5] rate of decline in DLB when compared to AD. An exception to this was a study by Stavitsky et al. where AD patients had a steeper decline on cognitive and behavioural measures, although DLB patients had been more impaired at baseline [9].

Comparisons of longitudinal outcomes between DLB and AD to date have generally needed to trade off diagnostic accuracy against prospective study design. Autopsy studies have the benefit of definitive diagnosis, but are usually dependent on retrospective analysis of clinical data. Studies using clinical diagnosis often have the advantage of prospective study design but at the expense of diagnostic accuracy. Overall, the majority of studies of the 1996 clinical consensus criteria for DLB [10] have identified high specificity, with lower estimates of sensitivity. Whilst one study identified 83% sensitivity and 95% specificity, estimates of sensitivity from other studies have been as low as 23% [11;12] with reports of specificity ranging from 8-100%; the most frequent misdiagnosis of DLB is as AD [13].

The development of ^{123}I-FP-CIT SPECT now allows visualisation of striatal dopamine transporters, and consequentially dopaminergic degeneration *in vivo,* and differentiates between AD and DLB with a sensitivity and specificity of 78-88% and 94-100% respectively [14]; an abnormal visual rating on ^{123}I-FP-CIT SPECT was incorporated into the most recent revision of the consensus diagnostic criteria [2]. In the present study, our aim was to compare decline in cognitive, behavioural and global measures over a 12-month period in a prospectively followed cohort of subjects with either AD or DLB confirmed by consensus panel clinical diagnosis and normal (for AD) and abnormal (for DLB) ^{123}I-FP-CIT SPECT imaging.

Methods

Data were collected as part of a phase 3 multicentre imaging study whose methodology is described in detail elsewhere [15;16]. In brief, patients were aged 55–90 years and met the criteria for dementia detailed in DSM-IV and fulfilled at least one of the following: consensus criteria for DLB [10] or NINCDS-ADRDA criteria for probable or possible AD [17], or NINDS/AIREN criteria for probable or possible vascular dementia [18]. A Mini-Mental State Examination (MMSE) score at baseline of 10 or more was required to ensure patients could complete assessments [19]. Patients with dementia who developed parkinsonism more than 1 year before the onset of dementia were deemed to have Parkinson's disease with dementia and were not included [10]. Those with structural imaging findings indicative of infarction in the region of the basal ganglia, including the internal capsule, were excluded. Use of medication known or suspected to interact with striatal binding of ^{123}I-FP-CIT was not permitted [20].

The study was done in accordance with the current revision of the Declaration of Helsinki and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation and applicable to national and local laws and regulations. At every participating site, the study protocol and all amendments were approved by an institutional review board or independent ethics committee. All patients and caregivers gave written informed consent.

Following inclusion in the initial study, participants were invited for clinical and neuropsychological re-assessment at 12 months.

Clinical diagnosis at baseline, as previously reported, was established by an independent consensus panel of three specialist clinicians, who were provided with a patient profile compiled from quality-assured clinical data from the on-site investigators' case record forms and copies of on-site original source data [15]. The same panel reconvened to consider the baseline and the 12-month follow-up data to arrive at a second and final consensus diagnosis. This final consensus diagnosis was used to derive the cohort for the present study.

The following were undertaken at baseline and follow-up: MMSE, Unified Parkinson's Disease Rating Scale (UPDRS) III (motor section) [21], modified Hoehn and Yahr staging [22], clinical assessment of cognitive fluctuation scale [23], the Cambridge Cognitive Examination—revised version (CAMCOG-R) [24], neuropsychiatric inventory with caregiver input (NPI-D) [25], visual object and space perception (VOSP) battery [26] and clinical dementia rating (CDR) [27]. The Cornell Scale for Depression in Dementia [28] and the investigator's estimation of the patient's intelligence quotient level were completed at baseline, but not at follow-up. Results of MRI and CT scans and the on-site investigators' clinical diagnosis before imaging were also available. The consensus panel did not at any stage have access to ^{123}I-FP-CIT SPECT findings and was unaware of the patients' identities, and the names of the centre and the investigators. Before any cases were diagnosed, the consensus panel was asked to diagnose ten patients (separate to the study) for whom autopsy diagnosis was independently available. There was 100% concordance between the diagnoses made by the panel and at autopsy [15]. Individual panel members reviewed each study case, including the baseline consensus panel diagnosis and all subsequent information, before meeting to agree a final clinical diagnosis of probable DLB, possible DLB or non-DLB dementia. Patients in the non-DLB category were further allocated to probable or possible AD, probable or possible vascular dementia or other.

Within a few weeks of the baseline clinical diagnosis, SPECT images were acquired on a 2 or 3 headed gamma camera (SPECT system) 3–6 hours after a single intravenous injection of 111-185 MBq of ^{123}I-FP-CIT [29] (DaTSCAN^{TM}, the radiotracer was supplied by GE Healthcare). See McKeith *et al* for details [15]. Subjects underwent standard thyroid blocking. SPECT imaging was not repeated at follow-up. As previously described, three nuclear medicine physicians assessed scans, blind to diagnosis, using a 4 point scale (0 normal uptake; 1 unilateral putamen loss; 2 bilateral putamen loss; 3 virtually absent uptake) [15], we used only the dichotomous division of normal (0) versus abnormal (1-3) images for analysis.

For the present study, we combined the three independent reads and recorded the result of the scan as normal or abnormal if there was agreement between two or more raters.

For the purposes of the present study, we included only patients with complete data sets from both baseline (T1) and 1 year follow up (T2) assessments and with reliable images from the baseline ^{123}I-FP-CIT SPECT session (n=225). These patients were divided into two diagnostic groups (AD and DLB). Inclusion criteria for the AD group were a consensus diagnosis of possible or probable AD at 12 months follow-up in addition to a negative (normal) ^{123}I-FP-CIT SPECT read (n=100). To be included in the DLB group, patients were required to have a consensus diagnosis of probable DLB at 12 months follow up and to have a positive (abnormal) ^{123}I-FP-CIT SPECT image read (n=58). Patients with a dementia diagnosis other than possible or probable AD or probable DLB were excluded (n=50). Patients with a ^{123}I-FP-CIT SPECT image read that was not in keeping with the consensus clinical diagnosis at 12 months were also excluded (n=14 probable DLB, 3 AD).

Statistical analysis

Data were analysed using SPSS version 18. We compared baseline and 12-month follow-up data and change over time for the AD and DLB groups. χ^2 tests were used to assess differences between the diagnostic groups (AD and DLB) with respect to gender and medication use at baseline. For normally distributed variables, t-tests were used for between-group comparisons of baseline and follow-up variables. Mann Whitney U-tests were used for non-normally distributed baseline and follow-up data. Repeated measures ANOVA was used for analysis of group x time interactions (comparison of change in variables over time in each group). General Linear Models with fixed effect were used to adjust for the difference in NPI scores and the scores on the Cornell Scale for Depression in Dementia at baseline

Results

		AD (*n*=100)	DLB (*n*=58)	P
Gender (M:F)	M	48 [48%]	37 [64%]	0.06
	F	52 [52%]	21 [36%]	
Age in years at ^{123}I-FP-CIT SPECT session		74.9 (7.3)	74.2 (6.1)	0.53
Cornell Scale for Depression in Dementia		3.8 (3.3)	6.6 (3.4)	<0.001
Cholinesterase inhibitor		82 [82%]	45 [76%]	0.50
Memantine		9 [9%]	2 [3%]	0.19
Neuroleptic medication		4 [4%]	9 [16%]	0.01
Clinical Dementia Rating		1.2 (0.69)	1.3 (0.66)	0.3
MMSE score (SD)	Baseline	21.5 (4.5)	21.4 (3.9)	0.85
	Follow-up	19.0 (6.2)	18.5 (6.0)	0.65
	Change	2.6 (4.0)	3.1 (4.3)	0.40
CAMCOG score (SD)	Baseline	66.3 (15.6)	66.0 (13.5)	0.89
	Follow-up	59.5 (20.3)	56.3 (19.7)	0.35
	Change	7.5 (10.6)	9.0 (11.9)	0.429
NPI score (SD)	Baseline	9.7 (10.3)	19.8 (14.6)	<0.001
	Follow-up	12.3 (13.3)	24.2 (17.4)	<0.001
	Change	2.5 (14.8)	3.8 (15.5)	0.59
NPI-carer score (SD)	Baseline	5.8 (6.0)	10.8 (8.0)	<0.001
	Follow-up	5.8 (5.7)	11.8 (8.6)	<0.001
	Change	-0.05 (6.4)	0.8 (7.1)	0.44
Fluctuations	Baseline	0.6 (2.1)	6.0 (4.5)	<0.001
	Follow up	0.4 (1.7)	6.9 (4.1)	<0.001
	Change	-0.2 (2.4)	0.8 (4.1)	0.07
CAMCOG Executive function	Baseline	11.9 (5.2)	11.1 (4.7)	0.33
	Follow-up	10.5 (5.4)	9.4 (5.0)	0.24
	Change	1.5 (3.6)	1.4 (4.0)	0.83

Table: Baseline characteristics and scores on clinical scales and cognitive testing at baseline and 12 month follow-up and change in scores between time points for AD and DLB groups. Data are presented as mean (SD) or number (%).

Baseline and follow-up data for the DLB and AD groups are presented in the table. The groups did not differ in terms of age or gender. There were no between-group baseline differences in terms of CDR or use of cholinesterase inhibitors or memantine. The DLB group had a statistically significant higher mean depression score at baseline and higher scores on the NPI, NPI carer distress and clinical assessment of cognitive fluctuation scales at both baseline and 12-month follow-up ($p<0.001$). There were no differences between the groups on cognitive scores at either baseline or follow-up. No significant differences in change in scores between baseline and 12-month follow-up for any of the variables analysed were identified. Results of analysis did not change when data were stratified according to gender. There was also no statistically significant difference between DLB and AD in the change of CAMCOG score after adjustment for scores on NPI and Cornell Scale for Depression scores. There were numerically greater changes between baseline and follow-up on cognition, fluctuation and on measures of neuropsychiatric symptoms in the DLB patients but this did not reach statistical significance. The lack of a significant difference on the cognitive performance between the DLB and AD groups is unlikely to be due to type II error, as the effect size of that difference was very small (0.02-0.07).

Discussion

In a prospectively-followed sample of patients with clinical consensus panel and dopamine transporter SPECT confirmed diagnosis of AD or DLB, cross-sectional assessments identified expected between-group similarities and differences in cognitive scores and clinical scales in addition to a higher level of carer distress in the DLB group. We identified no differences in rate of progression of cognitive or neuropsychiatric variables over a 12-month follow-up period. Our inclusion of only patients whose consensus clinical diagnosis was in keeping with neuroimaging results make it likely that diagnostic accuracy was very high. Our sample was drawn from 40 different centres in 10 European countries and is thus representative of the clinical population in Europe rather than a single academic centre.

AD and DLB groups were well-matched in terms of age and degree of cognitive impairment at baseline. The findings of higher scores on the NPI, clinician assessment of fluctuation and

Cornell Scale for Depression in dementia were expected given the recognised criteria for diagnosis of DLB [2].

NPI score was higher at both timepoints in DLB, despite similar cognitive and baseline CDR scores; this was associated with higher levels of caregiver distress and is in keeping with other published data [4;30]. Severity of neuropsychiatric symptoms in AD [31] and DLB [32] has been shown to be a predictor of both caregiver distress and nursing home placement. Caregiver distress has also been shown to be an independent risk factor for nursing home placement in dementia [33]. It is possible that the shorter time to nursing home placement that has been reported in DLB compared to AD [34] is related to neuropsychiatric symptoms and associated caregiver distress. Not all studies are consistent, however, and marginal [6] or no differences [8] in time to placement have also been reported. Furthermore, costs of care in DLB and AD have been shown to correlate with impairments in activities of daily living and not NPI scores [4].

Severity of neuropsychiatric symptomatology, and hallucinations in particular, has also been associated with steeper decline in cognitive scores and increased risk of mortality and institutionalisation in AD, independent of antipsychotic drug use [35;36]. These studies have lacked autopsy confirmation of diagnosis and it is possible that AD groups included individuals with undiagnosed DLB, who are more likely to experience hallucinations. We are not aware of any published data related to the impact of neuropsychiatric symptom severity on illness progression and survival in DLB.

We did not identify any between-group differences in change over time of any of the variables examined, i.e. NPI, fluctuations and cognitive performance. It is possible that the lack of detectable difference in decline of NPI and fluctuation scores over time is related to the already high scores at baseline in DLB. The majority of studies of the rate of cognitive decline in DLB vs AD have also reported no differences, e.g. [7;8], although the earliest reports were of more rapid decline in cognition in DLB [37], as were more recent studies [5]. Several studies have reported relatively preserved cognitive scores, particularly in recall, before death in DLB compared to AD [5].

It has been suggested that DLB may be associated with a more rapid decline in global measures of dementia severity or measures of activities of daily living whilst cognitive performance is relatively preserved. However, no significant differences in change in CDR score over time between DLB and AD groups have yet been identified [7]. We did not examine performance on activities of daily living. Cross-sectional assessments of activities of living have reported higher levels of impairment in DLB than AD [9;30], which may be related to extrapyramidal motor symptoms [38]. Longitudinal data, however, suggest no difference or a marginal difference in rate of decline of activities of daily living between AD and DLB [9].

Whilst ours and the majority of studies do not support the idea of a more rapid decline in cognition in DLB, the available literature is split more evenly between findings of either similar or shorter survival in DLB compared to AD. One possibility is that reports of worse outcomes in DLB are related to increased frequency of antipsychotic use as a result of greater severity of neuropsychiatric symptoms. Whilst more DLB than AD participants were prescribed neuroleptics in the present study, no differences in rate of progression were identified. Previous studies of cognitive decline in AD and DLB that have presented data on neuroleptic prescribing did not report any differences between the groups in use of these medications [8;39]. In terms of survival, both early [40] and more recent [6;8] studies have reported shorter survival in DLB vs AD, despite likely changes in neuroleptic prescribing over this time as a result of better understanding of the potentially harmful effects in both DLB [2;10] and dementia as a whole . It therefore seems unlikely that reported differences in survival between DLB and AD can be entirely accounted for by antipsychotic use.

The literature surrounding the differences in longitudinal outcomes in DLB and AD is therefore not easy to interpret. Overall, studies report outcomes in DLB that are either no different from or worse than in AD. Some of the difficulties involved in interpreting and comparing these findings are the differences in study design, use of clinical rather than pathological diagnosis, differing pathological definitions, and retrospective analysis of clinical data. In addition, studies often rely on relative's reports on the onset of dementia, or use as baseline the time of referral, diagnosis or entry into the study. None of these methods necessarily identify equivalent disease stages and these difficulties highlight the complexity of the task of comparing the rate of decline between two disorders with different clinical phenotypes. In DLB, episodic memory is relatively spared in the early stages, but the presence of attentional and visuospatial impairments, visual hallucinations or movement disorder might be more disabling. Comparisons between AD and DLB are therefore not

straightforward, and it is hard to define what is an “equivalent” disease stage. The picture is further complicated by the frequent overlap of AD and DLB neuropathology and the insidious onset of both of these conditions.

Our study would have been improved by a longer duration of follow-up and a more detailed breakdown of cognitive and clinical measures. Exclusion of individuals with severe dementia precluded detection of differences in progression that are present only in later disease stages. Without autopsy diagnosis, we were not able to differentiate patients with pure and combined pathology.

In conclusion, on global cognitive measures, we did not find any difference in rate of progression between AD and DLB groups over a one-year period of observation. Cognitive decline is only one aspect of dementia and other impairments may in fact be more important and disabling.

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STROBE 2007 (v4)Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	9
		(*b*)For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8*
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	9
		(*e*) Describe any sensitivity analyses	9
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n/a
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Comparison of cognitive decline between dementia with Lewy bodies and Alzheimer's disease: a cohort study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000380.R1
Article Type:	Research
Date Submitted by the Author:	28-Nov-2011
Complete List of Authors:	Walker, Zuzana; University College London, Mental Health Sciences McKeith, Ian; Institute for Ageing and Health, Newcastle University Rodda, Joanne; University College London, Research Department of Mental Health Sciences Qassem, Tarik; North Essex Partnership Foundation NHS Trust, Mental Health Unit; Ain Shams University, Institute of Psychiatry Tatsch, Klaus; Städtisches Klinikum Karlsruhe, Department of Nuclear Medicine Booij, Jan; Academic Medical Centre, Department of Nuclear Medicine Darcourt, Jacques; University of Nice Sophia-Antipolis, Centre Anoine Lacassagne Department of Nuclear Medicine O&#65533;Brien, John; Newcastle University, Institute for Ageing and Health
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Mental health
Keywords:	Cognitive disorders, ALZHEIMER'S DISEASE, LEWY BODY, Dementia < NEUROLOGY, SPECT, FUNCTIONAL IMAGING

~~No differences in~~ Comparison of ~~symptom progression~~cognitive decline between dementia with Lewy bodies and Alzheimer's disease: a cohort study

Zuzana Walker MD, Research Department of Mental Health Sciences, University College London, Bloomsbury Campus, London, UK and North Essex Partnership Foundation NHS Trust, Essex, UK

Ian McKeith FMedSci Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, UK

Joanne Rodda MBChB Research Department of Mental Health Sciences, University College London, Bloomsbury Campus, London, UK

Tarik Qassem MBBCh North Essex Partnership Foundation NHS Trust, Essex, UK and Institute of Psychiatry, Ain Shams University, Cairo, Egypt

Klaus Tatsch PhD Department of Nuclear Medicine, Städtisches Klinikum Karlsruhe, Karlsruhe, Germany

Jan Booij PhD Department of Nuclear Medicine, Academic Medical Centre, Amsterdam, Netherlands

Jacques Darcourt PhD Centre Anoine Lacassagne Department of Nuclear Medicine, Medical Faculty, University of Nice Sophia-Antipolis, Nice, France

John O'Brien DM, Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, UK

Correspondence: Zuzana Walker, Mental Health Unit, St. Margaret's Hospital, Epping, Essex, CM16 6TN, UK. email: z.walker@ucl.ac.uk

Contributions to the manuscript

Zuzana Walker: Involved in conception and design of the study as well as being a member of the consensus panel; contributed to statistical analysis and interpretation; co-wrote initial draft of the manuscript, prepared final version of the manuscript

Ian McKeith: Involved in conception and design of the study as well as being a member of the consensus panel, contributed to and approved final version of the manuscript

Joanne Rodda: Involved in conception and design of the study, contributed to data analysis and interpretation; co-wrote initial and subsequent drafts of the manuscript, contributed to and approved final version of the manuscript

Tarik Qassem: Involved in conception and design of the study, data processing, analysis and interpretation, contributed to and approved final version of the manuscript

Klaus Tatsch: Involved in conception and design of the study; performed the visual analysis of the SPECT data, contributed to and approved final version of the manuscript

Jan Booij: Involved in conception and design of the study; performed the visual analysis of the SPECT data, contributed to and approved final version of the manuscript

Jacques Darcourt: Involved in conception and design of the study; performed the visual analysis of the SPECT data, contributed to and approved final version of the manuscript

John O'Brien: Involved in conception and design of the study as well as being a member of the consensus panel, contributed to and approved final version of the manuscript

Study funding and sponsorship:

The data collection was sponsored by GE Healthcare who made data available for further analysis for the present study.

Author disclosure statements:

At the time of the study Zuzana Walker, John O'Brien, Ian McKeith, Klaus Tatsch, Jan Booij and Jacques Darcourt have received consultancy payments from GE Healthcare. Joanne Rodda has received funding for neuroimaging research from GE Healthcare. Tarik Qassem has no disclosures.

Abstract

Objectives: Dementia with Lewy bodies (DLB) accounts for 10-15% of dementia cases at autopsy and has distinct clinical features associated with earlier institutionalisation and a higher level of carer distress than are seen in Alzheimer's disease (AD). At present, there is on-going debate as to whether DLB is associated with a more rapid cognitive decline than AD. An understanding of the rate of decline of cognitive and non-cognitive symptoms in DLB may help patients and carers to plan for the future.

Design: In this cohort study we compared 100 AD and 58 DLB subjects at baseline and 12 month follow-up on cognitive and neuropsychiatric measures.

Setting: Patients were recruited from 40 European centres.

Participants: Subjects with mild-moderate dementia. Diagnosis of DLB or AD required agreement between consensus panel clinical diagnosis and visual rating of 123I-FP-CIT (dopamine transporter) SPECT neuroimaging.

Outcome measures: The Cambridge Cognitive Examination including Mini-Mental State Examination and Neuropsychiatric Inventory (NPI).

Results: The AD and DLB groups did not differ at baseline in terms of age, gender, Clinical Dementia Rating score and use of cholinesterase inhibitors or memantine. NPI and NPI carer distress scores were statistically significantly higher for DLB subjects at baseline and follow-up and there were no differences between AD and DLB in cognitive scores at baseline or follow-up. There was no significant difference in rate of progression of any of the variables analysed.

Conclusions: DLB subjects had more neuropsychiatric features at baseline and follow-up than AD, but we did not find any statistically significant difference in rate of progression between mild-moderate AD and DLB groups on cognitive or neuropsychiatric measures over a 12-month follow-up period.

Article summary

Article focus

- Dementia with Lewy bodies (DLB) has distinct neuropsychiatric features
- At present we do not know whether the poorer prognosis of DLB is due to a more rapid cognitive decline compared to Alzheimer's disease (AD)

Key messages

- In this fairly large cohort of patients with DLB and AD, while there was no difference in level of cognitive impairment (CAMCOG score) at baseline and at 12 months follow-up, DLB patients had significantly higher NPI and NPI carer distress scores both at baseline and 12 months follow-up.
- Therefore the worse prognosis of DLB is likely to be mediated by neuropsychiatric or other symptoms and not only by cognitive decline

Strengths of this study

- Inclusion of high number of subjects from 40 European clinical centres
- Well characterised cases with both consensus panel clinical diagnosis (three clinical experts) and dopaminergic transporter SPECT imaging

Limitations of the study

- No autopsy data were available and therefore it is possible that more rapid cognitive decline may be present in pure DLB
- Only one year of follow-up
- There was higher attrition rate (no-follow-up assessment) in the DLB group and DLB patients that did not return for follow-up were more impaired than AD patients

Introduction

Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia and accounts for approximately 15% of cases of dementia at autopsy [1]. It is characterised by the central feature of a progressive dementia accompanied by one or more core features of fluctuations in cognition, visual hallucinations and spontaneous features of parkinsonism [2].

Awareness of the rate of cognitive decline and also of non-cognitive symptoms can help carers and patients to adjust and plan appropriate lifestyle changes and to make arrangements for the future. This frequently involves making difficult decisions regarding treatment of psychiatric and motor symptoms and utilisation of limited resources available for patients with dementia.

Since its recognition as a neurodegenerative disorder, a body of research has focused on the differentiation of DLB from other dementias, in particular Alzheimer's disease (AD), in terms of both cross-sectional and longitudinal clinical factors. In addition to the clinical syndrome described in the consensus diagnostic criteria, DLB is associated with higher levels of behavioural disturbance and caregiver distress, lower quality of life and greater demand on resources when compared to AD [3;4]. Despite these findings, there is uncertainty within the literature regarding progression and survival in DLB compared to AD. Studies have shown survival in DLB to be either comparable to [5] or shorter [6] than in AD. No differences in decline on global measures (e.g. Clinical Dementia Rating, CDR) have been reported [7]. Studies of the progression of cognitive impairment have generally reported a similar [7;8] or steeper [5] rate of decline in DLB when compared to AD. An exception to this was a study by Stavitsky et al. where AD patients had a steeper decline on cognitive and behavioural measures, although DLB patients had been more impaired at baseline [9].

Comparisons of longitudinal outcomes between DLB and AD to date have generally needed to trade off diagnostic accuracy against prospective study design. Autopsy studies have the benefit of definitive diagnosis, but are usually dependent on retrospective analysis of clinical data. Studies using clinical diagnosis often have the advantage of prospective study design but at the expense of diagnostic accuracy. Overall, the majority of studies of the 1996 clinical consensus criteria for DLB [10] have identified high specificity, with lower estimates of sensitivity. Whilst one study identified 83% sensitivity and 95% specificity, estimates of sensitivity from other studies have been as low as 23% [11;12] with reports of specificity ranging from 8-100%; the most frequent misdiagnosis of DLB is as AD [13].

The development of ^{123}I-FP-CIT SPECT now allows visualisation of striatal dopamine transporters, and consequentially dopaminergic degeneration *in vivo,* and differentiates between AD and DLB with a sensitivity and specificity of 78-88% and 94-100% respectively [14]; an abnormal visual rating on ^{123}I-FP-CIT SPECT was incorporated into the most recent revision of the consensus diagnostic criteria [2]. In the present study, our aim was to compare decline in cognitive, behavioural and global measures over a 12-month period in a prospectively followed cohort of subjects with either AD or DLB confirmed by consensus panel clinical diagnosis and normal (for AD) and abnormal (for DLB) ^{123}I-FP-CIT SPECT imaging.

Methods

Data were collected as part of a phase 3 multicentre imaging study whose methodology is described in detail elsewhere [15;16]. In brief, patients were aged 55–90 years and met the criteria for dementia detailed in DSM-IV and fulfilled at least one of the following: consensus criteria for DLB [10] or NINCDS-ADRDA criteria for probable or possible AD [17], or NINDS/AIREN criteria for probable or possible vascular dementia [18]. A Mini-Mental State Examination (MMSE) score at baseline of 10 or more was required to ensure patients could complete assessments [19]. Patients with dementia who developed parkinsonism more than 1 year before the onset of dementia were deemed to have Parkinson's disease with dementia and were not included [10]. Those with structural imaging findings indicative of infarction in the region of the basal ganglia, including the internal capsule, were excluded. Use of medication known or suspected to interact with striatal binding of ^{123}I-FP-CIT was not permitted [20].

The study was done in accordance with the current revision of the Declaration of Helsinki and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation and applicable to national and local laws and regulations. At every participating site, the study protocol and all amendments were approved by an institutional review board or independent ethics committee. All patients and caregivers gave written informed consent.

Following inclusion in the initial study, participants were invited for clinical and neuropsychological re-assessment at 12 months.

Clinical diagnosis at baseline, as previously reported, was established by an independent consensus panel of three specialist clinicians, who were provided with a patient profile compiled from quality-assured clinical data from the on-site investigators' case record forms and copies of on-site original source data [15]. The same panel reconvened to consider the baseline and the 12-month follow-up data to arrive at a second and final consensus diagnosis. This final consensus diagnosis was used to derive the cohort for the present study.

The following were undertaken at baseline and follow-up: MMSE, Unified Parkinson's Disease Rating Scale (UPDRS) III (motor section) [21], modified Hoehn and Yahr staging [22], clinical assessment of cognitive fluctuation scale [23], the Cambridge Cognitive Examination—

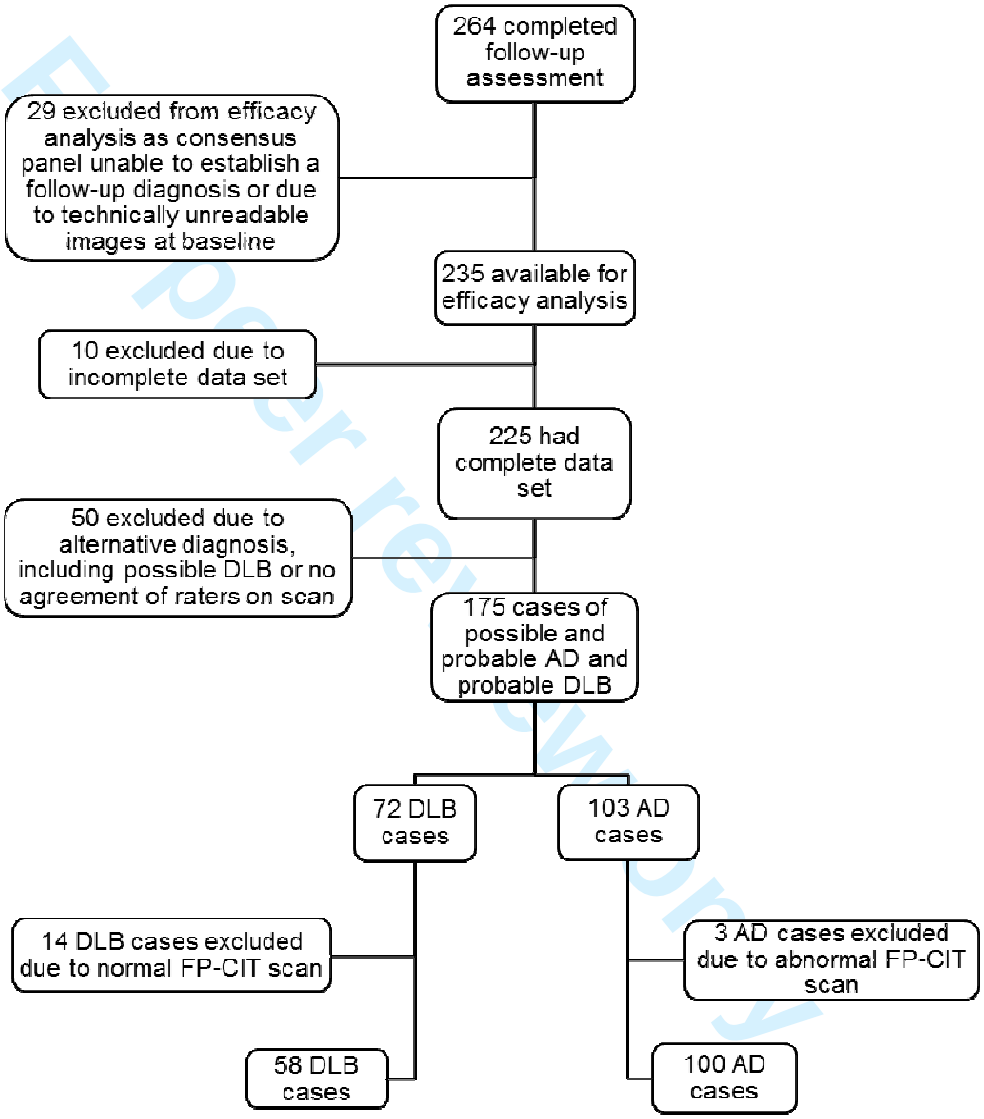
revised version (CAMCOG-R) [24], neuropsychiatric inventory with caregiver input (NPI-D) [25], visual object and space perception (VOSP) battery [26] and clinical dementia rating (CDR) [27]. The Cornell Scale for Depression in Dementia [28] and the investigator's estimation of the patient's intelligence quotient level were completed at baseline, but not at follow-up. Results of MRI and CT scans and the on-site investigators' clinical diagnosis before imaging were also available. The consensus panel did not at any stage have access to ^{123}I-FP-CIT SPECT findings and was unaware of the patients' identities, and the names of the centres and the investigators. Before any cases were diagnosed, the consensus panel was asked to diagnose ten patients (separate to the study) for whom autopsy diagnosis was independently available. There was 100% concordance between the diagnoses made by the panel and at autopsy [15]. Individual panel members reviewed each study case, including the baseline consensus panel diagnosis and all subsequent information, before meeting to agree a final clinical diagnosis of probable DLB, possible DLB or non-DLB dementia. Patients in the non-DLB category were further allocated to probable or possible AD, probable or possible vascular dementia or other.

Within a few weeks of the baseline clinical diagnosis, SPECT images were acquired on a 2 or 3 headed gamma camera (SPECT system) 3–6 hours after a single intravenous injection of 111-185 MBq of ^{123}I-FP-CIT [29] (DaTSCAN™, the radiotracer was supplied by GE Healthcare). See McKeith *et al* for details [15]. Subjects underwent standard thyroid blocking. SPECT imaging was not repeated at follow-up. As previously described, three nuclear medicine physicians assessed scans, blind to diagnosis, using a 4 point scale (0 normal uptake; 1 unilateral putamen loss; 2 bilateral putamen loss; 3 virtually absent uptake) [15], we used only the dichotomous division of normal (0) versus abnormal (1-3) images for analysis. For the present study, we combined the three independent reads and recorded the result of the scan as normal or abnormal if there was agreement between two or more raters.

For the purposes of the present study, we included only patients with complete data sets from both baseline (T1) and 1 year follow up (T2) assessments and with reliable images from the baseline ^{123}I-FP-CIT SPECT session (n=225). These patients were divided into two diagnostic groups (AD and DLB). Inclusion criteria for the AD group were a consensus diagnosis of possible or probable AD at 12 months follow-up in addition to a negative (normal) ^{123}I-FP-CIT SPECT read (n=100). To be included in the DLB group, patients were required to have a consensus diagnosis of probable DLB at 12 months follow up and to have a positive (abnormal) ^{123}I-FP-CIT SPECT image read (n=58). Patients with a dementia diagnosis other than possible or probable AD or probable DLB were excluded (n=50); see

flowchart, Figure. ~~Patients with a ^{123}I FP-CIT SPECT image read that was not in keeping with the consensus clinical diagnosis at 12 months were also excluded (n=14 probable DLB, 3 AD).~~

Figure: Flowchart of subjects included in the study



Statistical analysis

Data were analysed using SPSS version 18. We compared baseline and 12-month follow-up data and change over time for the AD and DLB groups. χ^2 tests were used to assess differences between the diagnostic groups (AD and DLB) with respect to gender and medication use at baseline. For normally distributed variables, t-tests were used for

between-group comparisons of baseline and follow-up variables. Mann Whitney U-tests were used for non-normally distributed baseline and follow-up data. Repeated measures ANOVA was used for analysis of group x time interactions (comparison of change in variables over time in each group). General Linear Models with fixed effect were used to adjust for the difference in NPI scores and the scores on the Cornell Scale for Depression in Dementia at baseline

Results

		AD (*n*=100)	DLB (*n*=58)	P
Gender (M:F)	M	48 [48%]	37 [64%]	0.06
	F	52 [52%]	21 [36%]	
Age in years at ^{123}I-FP-CIT SPECT session		74.9 (7.3)	74.2 (6.1)	0.53
Cornell Scale for Depression in Dementia (baseline)		3.8 (3.3)	6.6 (3.4)	<0.001
Cholinesterase inhibitor		82 [82%]	45 [76%]	0.50
Memantine		9 [9%]	2 [3%]	0.19
Neuroleptic medication		4 [4%]	9 [16%]	0.01
Clinical Dementia Rating (baseline)		1.2 (0.69)	1.3 (0.66)	0.3
MMSE score (SD)	Baseline	21.5 (4.5)	21.4 (3.9)	0.85
	Follow-up	19.0 (6.2)	18.5 (6.0)	0.65
	Change	2.6 (4.0)	3.1 (4.3)	0.40
CAMCOG score (SD)	Baseline	66.3 (15.6)	66.0 (13.5)	0.89
	Follow-up	59.5 (20.3)	56.3 (19.7)	0.35
	Change	7.5 (10.6)	9.0 (11.9)	0.429
NPI score (SD)	Baseline	9.7 (10.3)	19.8 (14.6)	<0.001
	Follow-up	12.3 (13.3)	24.2 (17.4)	<0.001
	Change	2.5 (14.8)	3.8 (15.5)	0.59
NPI-carer score (SD)	Baseline	5.8 (6.0)	10.8 (8.0)	<0.001
	Follow-up	5.8 (5.7)	11.8 (8.6)	<0.001
	Change	-0.05 (6.4)	0.8 (7.1)	0.44
Fluctuations	Baseline	0.6 (2.1)	6.0 (4.5)	<0.001
	Follow up	0.4 (1.7)	6.9 (4.1)	<0.001
	Change	-0.2 (2.4)	0.8 (4.1)	0.07
CAMCOG Executive function	Baseline	11.9 (5.2)	11.1 (4.7)	0.33
	Follow-up	10.5 (5.4)	9.4 (5.0)	0.24
	Change	1.5 (3.6)	1.4 (4.0)	0.83

Table: Baseline characteristics and scores on clinical scales and cognitive testing at baseline and 12 month follow-up and change in scores between time points for AD and DLB groups. Data are presented as mean (SD) or number (%). P= P-values (ANOVA).

Baseline and follow-up data for the DLB and AD groups are presented in the table. The groups did not differ in terms of age or gender. There were no between-group baseline differences in terms of CDR or use of cholinesterase inhibitors or memantine. The DLB

group had a statistically significant higher mean depression score at baseline and higher scores on the NPI, NPI carer distress and clinical assessment of cognitive fluctuation scales at both baseline and 12-month follow-up ($p<0.001$). There were no differences between the groups on cognitive scores at either baseline or follow-up. No significant differences in change in scores between baseline and 12-month follow-up for any of the variables analysed were identified. Results of analysis did not change when data were stratified according to gender. There was also no statistically significant difference between DLB and AD in the change of CAMCOG score after adjustment for scores on NPI and Cornell Scale for Depression scores. There were numerically greater changes (more decline) between baseline and follow-up on cognition, fluctuation and on measures of neuropsychiatric symptoms in the DLB patients but this did not reach statistical significance. The lack of a significant difference on the cognitive performance between the DLB and AD groups is unlikely to be due to lack of power, therefore type II error, as the effect size of that difference was very small (0.02-0.07) and only a sample size of 1685 subjects would have shown a significant difference.

A higher number of DLB patients (25) compared to AD patients (19) did not return for a follow-up visit. DLB patients lost to follow-up were significantly more cognitively impaired than AD patients lost to follow-up at baseline on MMSE (score 17.3 vs 22.2), CAMCOG (score 53.1 vs 66,7) and executive function (score 8.4 vs 13.3).

Discussion

In a prospectively-followed sample of patients with clinical consensus panel and dopamine transporter SPECT confirmed diagnosis of AD or DLB, cross-sectional assessments identified expected between-group similarities and differences in cognitive scores and clinical scales in addition to a higher level of carer distress ~~in the~~relating to the symptoms of DLB patients ~~DLB group~~. We identified no differences in rate of progression of cognitive or neuropsychiatric variables over a 12-month follow-up period. Our inclusion of only patients whose consensus clinical diagnosis was in keeping with neuroimaging results make it likely that diagnostic accuracy was very high. ~~Our sample was drawn from 40 different centres in 10 European countries and is thus representative of the clinical population in Europe rather than a single academic centre.~~

AD and DLB groups were well-matched in terms of age and degree of cognitive impairment at baseline. The findings of higher scores on the NPI, clinician assessment of fluctuation and Cornell Scale for Depression in dementia were expected given the recognised criteria for diagnosis of DLB [2].

NPI score was higher at both time points in DLB, despite similar cognitive and baseline CDR scores; this was associated with higher levels of caregiver distress and is in keeping with other published data [4;30]. Severity of neuropsychiatric symptoms in AD [31] and DLB [32] has been shown to be a predictor of both caregiver distress and nursing home placement. Caregiver distress has also been shown to be an independent risk factor for nursing home placement in dementia [33]. It is possible that the shorter time to nursing home placement that has been reported in DLB compared to AD [34] is related to neuropsychiatric symptoms and associated caregiver distress. Not all studies are consistent, however, and marginal [6] or no differences [8] in time to placement have also been reported. Furthermore, costs of care in DLB and AD have been shown to correlate with impairments in activities of daily living and not NPI scores [4].

Severity of neuropsychiatric symptomatology, and hallucinations in particular, has also been associated with steeper decline in cognitive scores and increased risk of mortality and institutionalisation in AD, independent of antipsychotic drug use [35;36]. These studies have lacked autopsy confirmation of diagnosis and it is possible that AD groups included individuals with undiagnosed DLB, who are more likely to experience hallucinations. We are not aware of any published data related to the impact of neuropsychiatric symptom severity on illness progression and survival in DLB.

We did not identify any between-group differences in change over time of any of the variables examined, i.e. NPI, fluctuations and cognitive performance. It is possible that the lack of detectable difference in decline of NPI and fluctuation scores over time is related to the already high scores at baseline in DLB. The majority of studies of the rate of cognitive decline in DLB vs AD have also reported no differences, e.g. [7;8], although the earliest reports were of more rapid decline in cognition in DLB [37], as were more recent studies [5]. Several studies have reported relatively preserved cognitive scores, particularly in recall, before death in DLB compared to AD [5].

It has been suggested that DLB may be associated with a more rapid decline in global measures of dementia severity or measures of activities of daily living whilst cognitive performance is relatively preserved. However, no significant differences in change in CDR score over time between DLB and AD groups have yet been identified [7]. We did not examine performance on activities of daily living. Cross-sectional assessments of activities of living have reported higher levels of impairment in DLB than AD [9;30], which may be related to extrapyramidal motor symptoms [38]. Longitudinal data, however, suggest no difference or a marginal difference in rate of decline of activities of daily living between AD and DLB [9].

Whilst ours and the majority of studies do not support the idea of a more rapid decline in cognition in DLB, the available literature is split more evenly between findings of either similar or shorter survival in DLB compared to AD. One possibility is that reports of worse outcomes in DLB are related to increased frequency of antipsychotic use as a result of greater severity of neuropsychiatric symptoms. Whilst more DLB than AD participants were prescribed neuroleptics in the present study, no differences in rate of progression were identified. Previous studies of cognitive decline in AD and DLB that have presented data on neuroleptic prescribing did not report any differences between the groups in use of these medications [8;39]. In terms of survival, both early [40] and more recent [6;8] studies have reported shorter survival in DLB vs AD, despite likely changes in neuroleptic prescribing over this time as a result of better understanding of the potentially harmful effects in both DLB [2;10] and dementia as a whole. It therefore seems unlikely that reported differences in survival between DLB and AD can be entirely accounted for by antipsychotic use.

The literature surrounding the differences in longitudinal outcomes in DLB and AD is therefore not easy to interpret. Overall, studies report outcomes in DLB that are either no different from or worse than in AD. Some of the difficulties involved in interpreting and comparing these findings are the differences in study design, use of clinical rather than pathological diagnosis, differing pathological definitions, and retrospective analysis of clinical data. In addition, studies often rely on relative's reports on the onset of dementia, or use as baseline the time of referral, diagnosis or entry into the study. None of these methods necessarily identify equivalent disease stages and these difficulties highlight the complexity of the task of comparing the rate of decline between two disorders with different clinical phenotypes. In DLB, episodic memory is relatively spared in the early stages, but the presence of attentional and visuospatial impairments, visual hallucinations or movement disorder might be more disabling. Comparisons between AD and DLB are therefore not

straightforward, and it is hard to define what is an “equivalent” disease stage. The picture is further complicated by the frequent overlap of AD and DLB neuropathology and the insidious onset of both of these conditions.

Our study would have been improved by a longer duration of follow-up and a more detailed breakdown of cognitive, behavioural and clinical measures. Exclusion of individuals with severe dementia and higher attrition (not returning for follow-up visit) of DLB cases with more severe cognitive impairment precluded detection of differences in progression that are present only in later disease stages. Larger cohorts of patients which could be stratified by stages of severity of dementia are needed to examine this possibility. DLB group had a higher mean depression score at baseline and more patients took a neuroleptic. Both neuroleptics and antidepressants have been shown to have detrimental effect on patients with dementia and could lead to faster progression but this did not seem to be the case over the duration of one year. Without autopsy diagnosis, we were not able to differentiate patients with pure and combined pathology.

In conclusion, on global cognitive measures, we did not find any difference in rate of progression between mild-moderate AD and DLB groups over a one-year period of observation. Cognitive decline is only one aspect of dementia and other impairments may in fact be more important and disabling.

Acknowledgements

GE Healthcare financially supported the collection of data. The study was initiated by the first author. Tim Whitfield provided help during the preparation of the final version of the manuscript.

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Ref Type: Abstract

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Study design	4	Present key elements of study design early in the paper	7
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		(*b*)For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
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Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
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Outcome data	15*	Report numbers of outcome events or summary measures over time	9
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Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ open

Comparison of cognitive decline between dementia with Lewy bodies and Alzheimer's disease: a cohort study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000380.R2
Article Type:	Research
Date Submitted by the Author:	12-Dec-2011
Complete List of Authors:	Walker, Zuzana; University College London, Mental Health Sciences McKeith, Ian; Institute for Ageing and Health, Newcastle University, Rodda, Joanne; University College London, Research Department of Mental Health Sciences Qassem, Tarik; North Essex Partnership Foundation NHS Trust, Mental Health Unit; Ain Shams University, Institute of Psychiatry Tatsch, Klaus; Städtisches Klinikum Karlsruhe, Department of Nuclear Medicine Booij, Jan; Academic Medical Centre, Department of Nuclear Medicine Darcourt, Jacques; University of Nice Sophia-Antipolis, Centre Anoine Lacassagne Department of Nuclear Medicine O&#65533;Brien, John; Newcastle University, Institute for Ageing and Health
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Mental health
Keywords:	Cognitive disorders, ALZHEIMER'S DISEASE, LEWY BODY, Dementia < NEUROLOGY, SPECT, FUNCTIONAL IMAGING

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Comparison of cognitive decline between dementia with Lewy bodies and Alzheimer's disease: a cohort study

Zuzana Walker MD, Research Department of Mental Health Sciences, University College London, Bloomsbury Campus, London, UK and North Essex Partnership Foundation NHS Trust, Essex, UK

Ian McKeith FMedSci Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, UK

Joanne Rodda MBChB Research Department of Mental Health Sciences, University College London, Bloomsbury Campus, London, UK

Tarik Qassem MBBCh North Essex Partnership Foundation NHS Trust, Essex, UK and Institute of Psychiatry, Ain Shams University, Cairo, Egypt

Klaus Tatsch PhD Department of Nuclear Medicine, Städtisches Klinikum Karlsruhe, Karlsruhe, Germany

Jan Booij PhD Department of Nuclear Medicine, Academic Medical Centre, Amsterdam, Netherlands

Jacques Darcourt PhD Centre Anoine Lacassagne Department of Nuclear Medicine, Medical Faculty, University of Nice Sophia-Antipolis, Nice, France

John O'Brien DM, Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, UK

Correspondence: Zuzana Walker, Mental Health Unit, St. Margaret's Hospital, Epping, Essex, CM16 6TN, UK. email: z.walker@ucl.ac.uk

Contributions to the manuscript

Zuzana Walker: Involved in conception and design of the study as well as being a member of the consensus panel; contributed to statistical analysis and interpretation; co-wrote initial draft of the manuscript, prepared final version of the manuscript

Ian McKeith: Involved in conception and design of the study as well as being a member of the consensus panel, contributed to and approved final version of the manuscript

Joanne Rodda: Involved in conception and design of the study, contributed to data analysis and interpretation; co-wrote initial and subsequent drafts of the manuscript, contributed to and approved final version of the manuscript

Tarik Qassem: Involved in conception and design of the study, data processing, analysis and interpretation, contributed to and approved final version of the manuscript

Klaus Tatsch: Involved in conception and design of the study; performed the visual analysis of the SPECT data, contributed to and approved final version of the manuscript

Jan Booij: Involved in conception and design of the study; performed the visual analysis of the SPECT data, contributed to and approved final version of the manuscript

Jacques Darcourt: Involved in conception and design of the study; performed the visual analysis of the SPECT data, contributed to and approved final version of the manuscript

John O'Brien: Involved in conception and design of the study as well as being a member of the consensus panel, contributed to and approved final version of the manuscript

Study funding and sponsorship:

The data collection was sponsored by GE Healthcare who made data available for further analysis for the present study.

Author disclosure statements:

At the time of the study Zuzana Walker, John O'Brien, Ian McKeith, Klaus Tatsch, Jan Booij and Jacques Darcourt have received consultancy payments from GE Healthcare. Joanne Rodda has received funding for neuroimaging research from GE Healthcare. Tarik Qassem has no disclosures.

Abstract

Objectives: Dementia with Lewy bodies (DLB) accounts for 10-15% of dementia cases at autopsy and has distinct clinical features associated with earlier institutionalisation and a higher level of carer distress than are seen in Alzheimer's disease (AD). At present, there is on-going debate as to whether DLB is associated with a more rapid cognitive decline than AD. An understanding of the rate of decline of cognitive and non-cognitive symptoms in DLB may help patients and carers to plan for the future.

Design: In this cohort study we compared 100 AD and 58 DLB subjects at baseline and 12 month follow-up on cognitive and neuropsychiatric measures.

Setting: Patients were recruited from 40 European centres.

Participants: Subjects with mild-moderate dementia. Diagnosis of DLB or AD required agreement between consensus panel clinical diagnosis and visual rating of 123I-FP-CIT (dopamine transporter) SPECT neuroimaging.

Outcome measures: The Cambridge Cognitive Examination including Mini-Mental State Examination and Neuropsychiatric Inventory (NPI).

Results: The AD and DLB groups did not differ at baseline in terms of age, gender, Clinical Dementia Rating score and use of cholinesterase inhibitors or memantine. NPI and NPI carer distress scores were statistically significantly higher for DLB subjects at baseline and follow-up and there were no differences between AD and DLB in cognitive scores at baseline or follow-up. There was no significant difference in rate of progression of any of the variables analysed.

Conclusions: DLB subjects had more neuropsychiatric features at baseline and follow-up than AD, but we did not find any statistically significant difference in rate of progression between mild-moderate AD and DLB groups on cognitive or neuropsychiatric measures over a 12-month follow-up period.

Article summary

Article focus

- Dementia with Lewy bodies (DLB) has distinct neuropsychiatric features
- At present we do not know whether the poorer prognosis of DLB is due to a more rapid cognitive decline compared to Alzheimer's disease (AD)

Key messages

- In this fairly large cohort of patients with DLB and AD, while there was no difference in level of cognitive impairment (CAMCOG score) at baseline and at 12 months follow-up, DLB patients had significantly higher NPI and NPI carer distress scores both at baseline and 12 months follow-up.
- Therefore the worse prognosis of DLB is likely to be mediated by neuropsychiatric or other symptoms and not only by cognitive decline

Strengths of this study

- Inclusion of high number of subjects from 40 European clinical centres
- Well characterised cases with both consensus panel clinical diagnosis (three clinical experts) and dopaminergic transporter SPECT imaging

Limitations of the study

- No autopsy data were available and therefore it is possible that more rapid cognitive decline may be present in pure DLB
- Only one year of follow-up
- There was higher attrition rate (no-follow-up assessment) in the DLB group and DLB patients that did not return for follow-up were more impaired than AD patients

Introduction

Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia and accounts for approximately 15% of cases of dementia at autopsy [1]. It is characterised by the central feature of a progressive dementia accompanied by one or more core features of fluctuations in cognition, visual hallucinations and spontaneous features of parkinsonism [2].

Awareness of the rate of cognitive decline and also of non-cognitive symptoms can help carers and patients to adjust and plan appropriate lifestyle changes and to make arrangements for the future. This frequently involves making difficult decisions regarding treatment of psychiatric and motor symptoms and utilisation of limited resources available for patients with dementia.

Since its recognition as a neurodegenerative disorder, a body of research has focused on the differentiation of DLB from other dementias, in particular Alzheimer's disease (AD), in terms of both cross-sectional and longitudinal clinical factors. In addition to the clinical syndrome described in the consensus diagnostic criteria, DLB is associated with higher levels of behavioural disturbance and caregiver distress, lower quality of life and greater demand on resources when compared to AD [3;4]. Despite these findings, there is uncertainty within the literature regarding progression and survival in DLB compared to AD. Studies have shown survival in DLB to be either comparable to [5] or shorter [6] than in AD. No differences in decline on global measures (e.g. Clinical Dementia Rating, CDR) have been reported [7]. Studies of the progression of cognitive impairment have generally reported a similar [7;8] or steeper [5] rate of decline in DLB when compared to AD. An exception to this was a study by Stavitsky et al. where AD patients had a steeper decline on cognitive and behavioural measures, although DLB patients had been more impaired at baseline [9].

Comparisons of longitudinal outcomes between DLB and AD to date have generally needed to trade off diagnostic accuracy against prospective study design. Autopsy studies have the benefit of definitive diagnosis, but are usually dependent on retrospective analysis of clinical data. Studies using clinical diagnosis often have the advantage of prospective study design but at the expense of diagnostic accuracy. Overall, the majority of studies of the 1996 clinical consensus criteria for DLB [10] have identified high specificity, with lower estimates of sensitivity. Whilst one study identified 83% sensitivity and 95% specificity, estimates of sensitivity from other studies have been as low as 23% [11;12] with reports of specificity ranging from 8-100%; the most frequent misdiagnosis of DLB is as AD [13].

The development of ^{123}I-FP-CIT SPECT now allows visualisation of striatal dopamine transporters, and consequentially dopaminergic degeneration *in vivo,* and differentiates between AD and DLB with a sensitivity and specificity of 78-88% and 94-100% respectively [14]; an abnormal visual rating on ^{123}I-FP-CIT SPECT was incorporated into the most recent revision of the consensus diagnostic criteria [2]. In the present study, our aim was to compare decline in cognitive, behavioural and global measures over a 12-month period in a prospectively followed cohort of subjects with either AD or DLB confirmed by consensus panel clinical diagnosis and normal (for AD) and abnormal (for DLB) ^{123}I-FP-CIT SPECT imaging.

Methods

Data were collected as part of a phase 3 multicentre imaging study whose methodology is described in detail elsewhere [15;16]. In brief, patients were aged 55–90 years and met the criteria for dementia detailed in DSM-IV and fulfilled at least one of the following: consensus criteria for DLB [10] or NINCDS-ADRDA criteria for probable or possible AD [17], or NINDS/AIREN criteria for probable or possible vascular dementia [18]. A Mini-Mental State Examination (MMSE) score at baseline of 10 or more was required to ensure patients could complete assessments [19]. Patients with dementia who developed parkinsonism more than 1 year before the onset of dementia were deemed to have Parkinson's disease with dementia and were not included [10]. Those with structural imaging findings indicative of infarction in the region of the basal ganglia, including the internal capsule, were excluded. Use of medication known or suspected to interact with striatal binding of ^{123}I-FP-CIT was not permitted [20].

The study was done in accordance with the current revision of the Declaration of Helsinki and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation and applicable to national and local laws and regulations. At every participating site, the study protocol and all amendments were approved by an institutional review board or independent ethics committee. All patients and caregivers gave written informed consent.

Following inclusion in the initial study, participants were invited for clinical and neuropsychological re-assessment at 12 months.

Clinical diagnosis at baseline, as previously reported, was established by an independent consensus panel of three specialist clinicians, who were provided with a patient profile compiled from quality-assured clinical data from the on-site investigators' case record forms and copies of on-site original source data [15]. The same panel reconvened to consider the baseline and the 12-month follow-up data to arrive at a second and final consensus diagnosis. This final consensus diagnosis was used to derive the cohort for the present study.

The following were undertaken at baseline and follow-up: MMSE, Unified Parkinson's Disease Rating Scale (UPDRS) III (motor section) [21], modified Hoehn and Yahr staging [22], clinical assessment of cognitive fluctuation scale [23], the Cambridge Cognitive Examination—

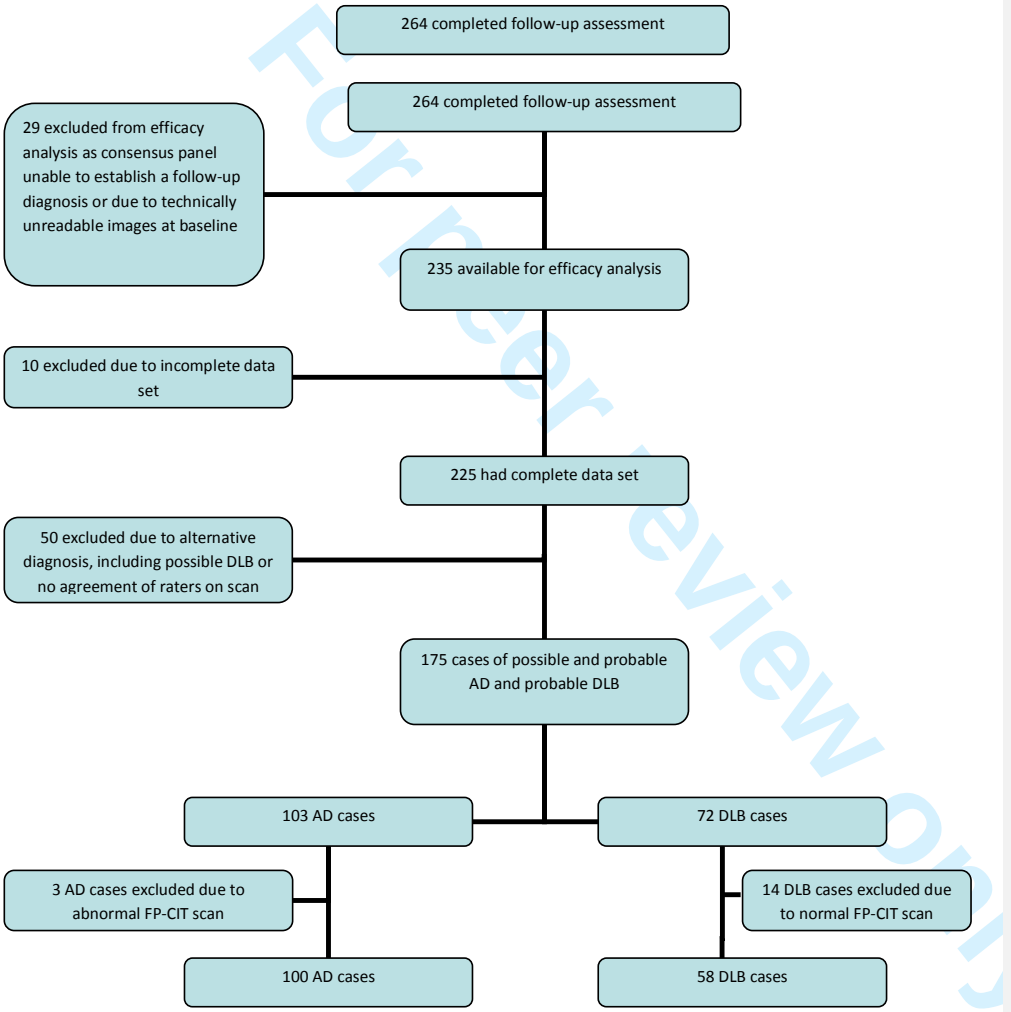
revised version (CAMCOG-R) [24], neuropsychiatric inventory with caregiver input (NPI-D) [25], visual object and space perception (VOSP) battery [26] and clinical dementia rating (CDR) [27]. The Cornell Scale for Depression in Dementia [28] and the investigator's estimation of the patient's intelligence quotient level were completed at baseline, but not at follow-up. Results of MRI and CT scans and the on-site investigators' clinical diagnosis before imaging were also available. The consensus panel did not at any stage have access to ^{123}I-FP-CIT SPECT findings and was unaware of the patients' identities, and the names of the centres and the investigators. Before any cases were diagnosed, the consensus panel was asked to diagnose ten patients (separate to the study) for whom autopsy diagnosis was independently available. There was 100% concordance between the diagnoses made by the panel and at autopsy [15]. Individual panel members reviewed each study case, including the baseline consensus panel diagnosis and all subsequent information, before meeting to agree a final clinical diagnosis of probable DLB, possible DLB or non-DLB dementia. Patients in the non-DLB category were further allocated to probable or possible AD, probable or possible vascular dementia or other.

Within a few weeks of the baseline clinical diagnosis, SPECT images were acquired on a 2 or 3 headed gamma camera (SPECT system) 3–6 hours after a single intravenous injection of 111-185 MBq of ^{123}I-FP-CIT [29] (DaTSCAN^{TM}, the radiotracer was supplied by GE Healthcare). See McKeith *et al* for details [15]. Subjects underwent standard thyroid blocking. SPECT imaging was not repeated at follow-up. As previously described, three nuclear medicine physicians assessed scans, blind to diagnosis, using a 4 point scale (0 normal uptake; 1 unilateral putamen loss; 2 bilateral putamen loss; 3 virtually absent uptake) [15], we used only the dichotomous division of normal (0) versus abnormal (1-3) images for analysis. For the present study, we combined the three independent reads and recorded the result of the scan as normal or abnormal if there was agreement between two or more raters.

For the purposes of the present study, we included only patients with complete data sets from both baseline (T1) and 1 year follow up (T2) assessments and with reliable images from the baseline ^{123}I-FP-CIT SPECT session (n=225). These patients were divided into two diagnostic groups (AD and DLB). Inclusion criteria for the AD group were a consensus diagnosis of possible or probable AD at 12 months follow-up in addition to a negative (normal) ^{123}I-FP-CIT SPECT read (n=100). To be included in the DLB group, patients were required to have a consensus diagnosis of probable DLB at 12 months follow up and to have a positive (abnormal) ^{123}I-FP-CIT SPECT image read (n=58). Patients with a dementia

diagnosis other than possible or probable AD or probable DLB were excluded (n=50); see flowchart, Figure.

Figure: Flowchart of subjects included in the study



N.B. The flowchart details patients who completed both baseline and follow-up assessments. 25 patients with a diagnosis of DLB at baseline, and 19 patients with a diagnosis of AD at baseline did not return for follow-up and are therefore not included in the flowchart.

Statistical analysis

Data were analysed using SPSS version 18. We compared baseline and 12-month follow-up data and change over time for the AD and DLB groups. χ^2 tests were used to assess differences between the diagnostic groups (AD and DLB) with respect to gender and medication use at baseline. For normally distributed variables, t-tests were used for between-group comparisons of baseline and follow-up variables. Mann Whitney U-tests were used for non-normally distributed baseline and follow-up data. Repeated measures ANOVA was used for analysis of group x time interactions (comparison of change in variables over time in each group). General Linear Models with fixed effect were used to adjust for the difference in NPI scores and the scores on the Cornell Scale for Depression in Dementia at baseline

Results

		AD (*n*=100)	DLB (*n*=58)	P
Gender (M:F)	M	48 [48%]	37 [64%]	0.06
	F	52 [52%]	21 [36%]	
Age in years at ^{123}I-FP-CIT SPECT session		74.9 (7.3)	74.2 (6.1)	0.53
Cornell Scale for Depression in Dementia (baseline)		3.8 (3.3)	6.6 (3.4)	<0.001
Cholinesterase inhibitor		82 [82%]	45 [76%]	0.50
Memantine		9 [9%]	2 [3%]	0.19
Neuroleptic medication		4 [4%]	9 [16%]	0.01
Clinical Dementia Rating (baseline)		1.2 (0.69)	1.3 (0.66)	0.3
MMSE score (SD)	Baseline	21.5 (4.5)	21.4 (3.9)	0.85
	Follow-up	19.0 (6.2)	18.5 (6.0)	0.65
	Change	2.6 (4.0)	3.1 (4.3)	0.40
CAMCOG score (SD)	Baseline	66.3 (15.6)	66.0 (13.5)	0.89
	Follow-up	59.5 (20.3)	56.3 (19.7)	0.35
	Change	7.5 (10.6)	9.0 (11.9)	0.429
NPI score (SD)	Baseline	9.7 (10.3)	19.8 (14.6)	<0.001
	Follow-up	12.3 (13.3)	24.2 (17.4)	<0.001
	Change	2.5 (14.8)	3.8 (15.5)	0.59
NPI-carer score (SD)	Baseline	5.8 (6.0)	10.8 (8.0)	<0.001
	Follow-up	5.8 (5.7)	11.8 (8.6)	<0.001
	Change	-0.05 (6.4)	0.8 (7.1)	0.44
Fluctuations	Baseline	0.6 (2.1)	6.0 (4.5)	<0.001
	Follow up	0.4 (1.7)	6.9 (4.1)	<0.001
	Change	-0.2 (2.4)	0.8 (4.1)	0.07
CAMCOG Executive function	Baseline	11.9 (5.2)	11.1 (4.7)	0.33
	Follow-up	10.5 (5.4)	9.4 (5.0)	0.24
	Change	1.5 (3.6)	1.4 (4.0)	0.83

Table: Baseline characteristics and scores on clinical scales and cognitive testing at baseline and 12 month follow-up and change in scores between time points for AD and DLB groups. Data are presented as mean (SD) or number (%). P= P-values (ANOVA).

Baseline and follow-up data for the DLB and AD groups are presented in the table. The groups did not differ in terms of age or gender. There were no between-group baseline differences in terms of CDR or use of cholinesterase inhibitors or memantine. The DLB

group had a statistically significant higher mean depression score at baseline and higher scores on the NPI, NPI carer distress and clinical assessment of cognitive fluctuation scales at both baseline and 12-month follow-up ($p<0.001$). There were no differences between the groups on cognitive scores at either baseline or follow-up. No significant differences in change in scores between baseline and 12-month follow-up for any of the variables analysed were identified. Results of analysis did not change when data were stratified according to gender. There was also no statistically significant difference between DLB and AD in the change of CAMCOG score after adjustment for scores on NPI and Cornell Scale for Depression scores. There were numerically greater changes (more decline) between baseline and follow-up on cognition, fluctuation and on measures of neuropsychiatric symptoms in the DLB patients but this did not reach statistical significance. The lack of a significant difference on the cognitive performance between the DLB and AD groups is unlikely to be due to lack of power, therefore type II error, as the effect size of that difference was very small (0.02-0.07) and only a sample size of 1685 subjects would have shown a significant difference.

A higher number of DLB patients (25) compared to AD patients (19) did not return for a follow-up visit. DLB patients lost to follow-up were significantly more cognitively impaired than AD patients lost to follow-up at baseline on MMSE (score 17.3 vs 22.2), CAMCOG (score 53.1 vs 66,7) and executive function (score 8.4 vs 13.3). Since these patients lost to follow-up were not given a final diagnosis, they were not included in the main analysis.

Discussion

In a prospectively-followed sample of patients with clinical consensus panel and dopamine transporter SPECT confirmed diagnosis of AD or DLB, cross-sectional assessments identified expected between-group similarities and differences in cognitive scores and clinical scales in addition to a higher level of carer distress relating to the symptoms of DLB patients. We identified no differences in rate of progression of cognitive or neuropsychiatric variables over a 12-month follow-up period. Our inclusion of only patients whose consensus clinical diagnosis was in keeping with neuroimaging results make it likely that diagnostic accuracy was very high.

AD and DLB groups were well-matched in terms of age and degree of cognitive impairment at baseline. The findings of higher scores on the NPI, clinician assessment of fluctuation and Cornell Scale for Depression in dementia were expected given the recognised criteria for diagnosis of DLB [2].

NPI score was higher at both time points in DLB, despite similar cognitive and baseline CDR scores; this was associated with higher levels of caregiver distress and is in keeping with other published data [4;30]. Severity of neuropsychiatric symptoms in AD [31] and DLB [32] has been shown to be a predictor of both caregiver distress and nursing home placement. Caregiver distress has also been shown to be an independent risk factor for nursing home placement in dementia [33]. It is possible that the shorter time to nursing home placement that has been reported in DLB compared to AD [34] is related to neuropsychiatric symptoms and associated caregiver distress. Not all studies are consistent, however, and marginal [6] or no differences [8] in time to placement have also been reported. Furthermore, costs of care in DLB and AD have been shown to correlate with impairments in activities of daily living and not NPI scores [4].

Severity of neuropsychiatric symptomatology, and hallucinations in particular, has also been associated with steeper decline in cognitive scores and increased risk of mortality and institutionalisation in AD, independent of antipsychotic drug use [35;36]. These studies have lacked autopsy confirmation of diagnosis and it is possible that AD groups included individuals with undiagnosed DLB, who are more likely to experience hallucinations. We are not aware of any published data related to the impact of neuropsychiatric symptom severity on illness progression and survival in DLB.

We did not identify any between-group differences in change over time of any of the variables examined, i.e. NPI, fluctuations and cognitive performance. It is possible that the lack of detectable difference in decline of NPI and fluctuation scores over time is related to the already high scores at baseline in DLB. The majority of studies of the rate of cognitive decline in DLB vs AD have also reported no differences, e.g. [7;8], although the earliest reports were of more rapid decline in cognition in DLB [37], as were more recent studies [5]. Several studies have reported relatively preserved cognitive scores, particularly in recall, before death in DLB compared to AD [5]. As mentioned in 'Results', patients diagnosed as DLB at baseline who were lost to follow-up were significantly more cognitively impaired than patients diagnosed as AD at baseline who were lost to follow-up. These patients were not included in the final analysis, as the cohort analysed was derived from the final consensus diagnosis made at follow-up. Thus, although patients lost to follow-up appeared to differ cognitively depending on diagnosis, and this could have affected the study's results, their diagnoses

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was not made at the same time point as for the patients included in the final cohort. Reviewing the characteristics of patients lost to follow up must therefore be done tentatively, as their diagnoses were subject to change.

It has been suggested that DLB may be associated with a more rapid decline in global measures of dementia severity or measures of activities of daily living whilst cognitive performance is relatively preserved. However, no significant differences in change in CDR score over time between DLB and AD groups have yet been identified [7]. We did not examine performance on activities of daily living. Cross-sectional assessments of activities of living have reported higher levels of impairment in DLB than AD [9;30], which may be related to extrapyramidal motor symptoms [38]. Longitudinal data, however, suggest no difference or a marginal difference in rate of decline of activities of daily living between AD and DLB [9].

Whilst ours and the majority of studies do not support the idea of a more rapid decline in cognition in DLB, the available literature is split more evenly between findings of either similar or shorter survival in DLB compared to AD. One possibility is that reports of worse outcomes in DLB are related to increased frequency of antipsychotic use as a result of greater severity of neuropsychiatric symptoms. Whilst more DLB than AD participants were prescribed neuroleptics in the present study, no differences in rate of progression were identified. Previous studies of cognitive decline in AD and DLB that have presented data on neuroleptic prescribing did not report any differences between the groups in use of these medications [8;39]. In terms of survival, both early [40] and more recent [6;8] studies have reported shorter survival in DLB vs AD, despite likely changes in neuroleptic prescribing over this time as a result of better understanding of the potentially harmful effects in both DLB [2;10] and dementia as a whole. It therefore seems unlikely that reported differences in survival between DLB and AD can be entirely accounted for by antipsychotic use.

The literature surrounding the differences in longitudinal outcomes in DLB and AD is therefore not easy to interpret. Overall, studies report outcomes in DLB that are either no different from or worse than in AD. Some of the difficulties involved in interpreting and comparing these findings are the differences in study design, use of clinical rather than pathological diagnosis, differing pathological definitions, and retrospective analysis of clinical data. In addition, studies often rely on relative's reports on the onset of dementia, or use as baseline the time of referral, diagnosis or entry into the study. None of these methods

necessarily identify equivalent disease stages and these difficulties highlight the complexity of the task of comparing the rate of decline between two disorders with different clinical phenotypes. In DLB, episodic memory is relatively spared in the early stages, but the presence of attentional and visuospatial impairments, visual hallucinations or movement disorder might be more disabling. Comparisons between AD and DLB are therefore not straightforward, and it is hard to define what is an "equivalent" disease stage. The picture is further complicated by the frequent overlap of AD and DLB neuropathology and the insidious onset of both of these conditions.

Our study would have been improved by a longer duration of follow-up and a more detailed breakdown of cognitive, behavioural and clinical measures. Furthermore, patients' ability to carry out Activities of daily living (ADLs) was not measured, and this can be a useful marker of disease severity and progression. Exclusion of individuals with severe dementia and higher attrition (not returning for follow-up visit) of DLB cases with more severe cognitive impairment precluded detection of differences in progression that are present only in later disease stages. Larger cohorts of patients which could be stratified by stages of severity of dementia are needed to examine this possibility. DLB group had a higher mean depression score at baseline and more patients took a neuroleptic. Both neuroleptics and antidepressants have been shown to have detrimental effect on patients with dementia and could lead to faster progression but this did not seem to be the case over the duration of one year. Without autopsy diagnosis, we were not able to differentiate patients with pure and combined pathology.

In conclusion, on global cognitive measures, we did not find any difference in rate of progression between mild-moderate AD and DLB groups over a one-year period of observation. Cognitive decline is only one aspect of dementia and other impairments may in fact be more important and disabling.

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