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A prospective study of dementia with Lewy bodies

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Abstract

Background: little is known about the longitudinal course of dementia with Lewy bodies (DLB) and how this differs from Alzheimer's disease (AD).
Method: standardized baseline and annual assessments of cognitive and non-cognitive symptoms are reported in a cohort of 72 patients with DLB or AD. AD was diagnosed using the NINCDS ADRDA criteria and DLB was diagnosed with the criteria of McKeith *et al.* Cognitive assessment was undertaken using the MMSE schedule and operationalized definitions were used to diagnose non-cognitive symptoms.
Results: 42 patients with DLB and 30 patients with AD were assessed. Of the 19 on whom *post mortem* examinations have been performed, 18 (95%) have had the clinical diagnosis confirmed. DLB patients were significantly more likely to experience visual hallucinations, disturbances of consciousness and parkinsonism at both baseline and at annual assessments. Of DLB patients exposed to neuroleptics, 33% developed sensitivity reactions. The magnitude and pattern of cognitive decline was similar in both groups.
Conclusion: the importance of the core features highlighted in the newly proposed consensus DLB criteria is supported. These features appear to be stable over time.

Keywords: *Alzheimer's disease, dementia with Lewy bodies, prospective study*

Introduction

Lewy bodies are intraneuronal, eosinophilic inclusion bodies which are seen in the brainstem of patients with Parkinson's disease and occur in cortical areas in some patients with dementia. Recent *post mortem* [1–3] and clinical [4–6] studies have suggested that Dementia with Lewy bodies (DLB) accounts for 10–20% of dementia cases in clinical settings.

Several independent research groups have shown that such patients have a characteristic clinical profile, which includes fluctuating confusion, disturbances of consciousness, parkinsonism, visual hallucinations, delusions and frequent falls [2]. These symptoms form the basis of three sets of clinical diagnostic criteria [2, 7, 8]. Clinical identification of DLB is important, particularly as serious and often fatal neuroleptic sensitivity reactions can occur. These reactions are characterized by extrapyramidal symptoms and features of the neuroleptic malignant syndrome [9]. However, the symptom profile of DLB patients has been identified by retrospective case note examination and there are few prospectively collected longitudinal data on cognitive and non-cognitive symptoms.

The current study provides annual follow-up information for a cohort of patients with DLB or Alzheimer's disease (AD). We hypothesized that visual hallucinations, disturbances of consciousness, significant parkinsonism and falls would be significantly more common in patients with DLB patients than in AD at both the baseline assessment and at 1-year follow-up.

Methods

All patients who were clinically diagnosed as having DLB by a consultant old age psychiatrist in Newcastle were referred to a specialist research clinic [10]. Patients with a clear-cut clinical diagnosis of AD were also referred. These patients were assessed with a

standardized battery, which used an informant interview to collect demographic data as well as detailed information about the presenting symptoms and the course of the illness. The assessment protocol, which is described in detail elsewhere [10], included detailed sections on severity of fluctuation, impairment of consciousness, visual hallucinations, other psychotic symptoms, falls, mood disturbance and sensitivity to neuroleptic drugs. Sensitivity to neuroleptic drugs was defined as marked extrapyramidal symptoms following the administration of neuroleptic drugs, beyond what would usually be experienced by a patient suffering from dementia, together with a step of decline in cognitive functioning or symptoms suggestive of the neuroleptic malignant syndrome [9]. The assessment also incorporated a standardized physical examination which included the Unified Parkinson's Disease Rating Scale [11]. Cognitive assessment, undertaken using the Mini-Mental State Examination (MMSE [12]), was reported as total score and sub-scores for orientation, registration, attention/calculation, recall, expression and praxis. A full dementia blood screen was completed for all patients and a computed tomography or magnetic resonance imaging scan was performed in most cases. The same schedules were completed at 6- and 12-month follow-up.

DLB was diagnosed clinically according to the criteria of McKeith *et al.* [2] and AD was diagnosed using the NINCDS ADRDA criteria [13]. Autopsy examination has been undertaken for 19 (83%) of the 23 patients who have died so far (14 in the DLB group, five in the AD group). Depression was diagnosed according to the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revised, criteria [14], psychotic symptoms were diagnosed using the criteria of Burns *et al.* [15] and parkinsonism was defined as stage 2 or greater on the Hoehn and Yahr system [16]. Falls were defined using the description of Tinnetti *et al.* [17]. A minimum of two falls had to occur within 1 year to be considered clinically significant. Disturbances of consciousness were diagnosed using expert clinical judgement from an informant history and mental state examination.

Statistical evaluation

Descriptive demographic data are presented at baseline and 1-year follow-up. The number of patients with visual hallucinations, auditory hallucinations, delusions, depression, disturbed consciousness, falls and parkinsonism were compared between the two dementias at baseline and 1-year follow-up using odds ratios (ORs) with confidence intervals (CIs). Baseline MMSE scores and the decline of MMSE scores over 1 year were compared between the two groups using the Mann-Whitney U test. The MMSE sub-scores and the decline of sub-scores over 1 year were compared between DLB and AD patients with baseline MMSE scores >10 using logistic regression. All statistics were undertaken with the SPSS [18] package.

Results

Seventy-three patients were examined. Forty-two had a diagnosis of DLB and 30 had a clinical diagnosis of probable ($n = 24$) or possible ($n = 6$) AD. One patient was initially diagnosed as having possible AD but later had a stroke and was excluded from the study. Of the 19 autopsies, 18 (95%) confirmed the clinical diagnosis. The single discrepant case was clinically diagnosed as having possible AD but had Lewy bodies at neuropathological examination. Twenty-four (57%) of the 42 patients with DLB were female and 19 were male. Their mean age at the time of the first assessment was 73.6 and the mean MMSE score was 14.9. Twenty-one (70%) of the patients with AD were female, their mean age was 81.7 and their mean MMSE score was 13.9. There were no significant differences in any of the MMSE sub-scores between the DLB and AD groups (orientation Wald 3.6 $P = 0.06$, registration Wald 0.7 $P = 0.4$, attention/calculation Wald 0.1 $P = 0.7$, recall Wald 1.2 $P = 0.3$, expression Wald 1.5 $P = 0.2$, praxis Wald 0.8 $P = 0.4$). The AD groups were significantly older (Mann-Whitney U test $z = 2.49$, $P = 0.01$).

Baseline symptoms

All of the symptoms identified as common by previous retrospective studies occurred frequently, although only visual hallucinations, auditory hallucinations, delusions, disturbed consciousness and parkinsonism were significantly more common in patients with DLB than those with AD (Table 1). Six (33%) of the 18 patients with DLB exposed to neuroleptic agents had neuroleptic sensitivity reactions. Two of these patients were taking risperidone and four were taking thioridazine. The mean doses in chlorpromazine equivalents were 42 mg per day. Five of the six patients improved markedly within 1 month of stopping neuroleptic drugs, the other patient died. None of the seven patients with AD exposed to neuroleptic drugs experienced a sensitivity reaction. Because of small numbers, this was not a significant difference (Fisher's exact test $P = 0.10$).

Follow-up assessment

Fifty-six patients (33 with DLB, 23 with AD) were examined at 1-year follow-up. Sixteen patients died during the first year of follow-up (nine in the DLB group and seven in the AD group), therefore annual assessments have been completed for all surviving patients. Of the patients who were followed-up after 1 year, 69% were female, their mean age at baseline assessment was 78.8 and their mean baseline MMSE score was 15.1.

Table 1. Baseline assessment in patients with dementia of Lewy body type (DLB) and Alzheimer's disease (AD)

	Disease		
	DLB ($n=42$)	AD ($n=30$)	Significance
Visual hallucinations	39 (92.9%)	8 (26.7%)	OR 35.8 (8.7, 148.4)
Auditory hallucinations	24 (57.1%)	3 (10.0%)	OR 12.0 (8.6, 122.7)
Delusions	25 (59.5%)	6 (20.0%)	OR 5.9 (2.0, 17.3)
Major depression/dysthymia	8 (19.0%)	3 (10.0%)	NS
Two or more falls	16 (38.1%)	9 (30.0%)	NS
Mean MMSE	14.9	13.9	NS
Mean UPDRS factor 2	6.7	2.8	$P=0.002$[a]
Parkinsonism	23 (65.7%)	2 (6.7%)	OR 16.9 (3.6, 80.6)
Neuroleptic sensitivity	6/19 (31.6%)	0/7 (0%)	$P=0.1$ [b]

OR, odds ratio, NS, not significant, MMSE, Mini-Mental State Examination; UPDRS, Unified Parkinson's Disease Rating Scale.
[a]Mann-Whitney U test.
[b]Fisher's exact test.

At follow-up, DLB patients were still significantly more likely to experience visual hallucinations (OR 28.5; 95% CI 6.6, 122.7), disturbed consciousness (OR 3.4; 95% CI 1.02, 9.4) and significant parkinsonism (OR 4.4; 95% CI 1.4, 13.9), but not delusions (OR 0.8; 95% CI 0.3, 2.3) or auditory hallucinations (OR 4.6; 95% CI 0.9, 9.1). The decline in cognitive function as assessed by MMSE was similar in the DLB and AD groups (3.9 *versus* 4.1; Mann-Whitney U test $z=0.09$, $P=0.93$) and there were no significant differences comparing sub-scores (orientation Wald 2.9 $P=0.9$, registration Wald 1.0 $P=0.3$, attention/calculation Wald 1.5 $P=0.2$, recall Wald 1.8 $P=0.2$, expression Wald 1.5 $P=0.2$, praxis Wald 0.1 $P=0.7$).

Overall, DLB patients experienced visual hallucinations in 98 out of 123 (79.7%) interviews compared with 17 out of 97 (18%) interviews with AD patients (OR 18.4; 95% CI 9.2, 35.9). Visual hallucinations were significantly more likely to resolve in patients with AD (OR 40.5; 95% CI 3.8, 428.4). Although the numbers are too small to permit meaningful statistical analysis, the proportions of resolved and incident cases of delusions and depression appeared similar in the two disorders.

Surprisingly, only one new case of parkinsonism emerged in the DLB group, while there were four among the AD patients. One of the AD patients had been newly prescribed a neuroleptic agent, the other four patients had been receiving neuroleptics for at least 1 year. In all of the subjects, parkinsonism remained at the same severity on the Hoehn and Yahr scale at 1-year follow-up (two at stage 2, two at stage 2.5, 11 at stage 3, two at stage 4 and two at stage 5). One patient who had been rated as Hoehn and Yahr stage 3 experienced resolution of parkinsonian symptoms during the year of follow-up. The patient was taking neuroleptic drugs which were discontinued.

Point prevalence rates of the symptoms at baseline and at 1-year follow-up, 1-year prevalence of symptoms and the incidence and resolution rates for the patients who completed at least 1 year of follow-up assessments are presented in Table 2.

Discussion

Visual hallucinations, disturbances of consciousness and significant parkinsonism were significantly more common in patients with DLB than in those with AD at baseline and at 1-year follow-up. Neuropathological validation demonstrated that 18 (95%) of the 19 cases coming to *post mortem* have been diagnosed correctly. Although the DLB patients were representative of patients diagnosed as having DLB within a hospital setting, the AD patients were selected on the basis of a clear-cut clinical diagnosis and were hence not a consecutive series. When operationalized criteria were applied, most but not all of the clinically diagnosed AD cases met the NINCDS ADRDA criteria for probable AD.

Central features

These findings accord with previous clinical studies using standardized instruments in suggesting that more than 80% of patients with DLB have visual hallucinations. Although this is somewhat tautological as visual hallucinations are included as part of the standardized diagnostic criteria [2], it is also likely that neuropathological studies which have relied upon retrospective examination of casenotes have underestimated the frequency of visual hallucinations. Two previous

Table 2. Patients followed-up for 1 year

	Baseline point prevalence	1-year follow-up Symptoms Resolved	Incident	Point prevalence	Prevalence
Alzheimer's disease ($n = 23$)					
Hallucinations					
Auditory	3 (13%)	1	0	2 (9%)	3 (13%)
Visual	7 (30%)	6	2	3 (13%)	9 (39%)
Delusions	6 (26%)	3	8	11 (47%)	14 (60%)
Delusional misidentification	1 (4%)	1	4	4 (17%)	5 (22%)
Depression/dysthymia	3 (13%)	2	2	3 (13%)	5 (22%)
Parkinsonism	2 (8%)	0	4	6 (26%)	6 (26%)
Impaired consciousness	5 (21%)	3	3	5 (21%)	8 (35%)
Falls					
≥2	8 (34%)	4	1	3 (13%)	9 (39%)
≥5	1 (4%)	1	0	0 (0%)	1 (4%)
Dementia of Lewy body type ($n = 33$)					
Hallucinations					
Auditory	22 (67%)	15	3	10 (30%)	25 (76%)
Visual	31 (94%)	4	1	28 (85%)	32 (97%)
Delusions	21 (64%)	12	5	14 (42%)	26 (79%)
Delusional misidentification	11 (33%)	6	1	6 (18%)	12 (36%)
Depression/dysthymia	6 (18%)	3	4	7 (21%)	10 (30%)
Parkinsonism	20 (61%)	1	1	20 (61%)	21 (64%)
Impaired consciousness	15 (46%)	7	8	16 (49%)	23 (70%)
Falls					
≥2	16 (49%)	7	5	14 (42%)	21 (64%)
≥5	4 (12%)	1	0	3 (9%)	4 (12%)

studies [19, 20] have examined the persistence of visual hallucinations, both agreeing with our findings that visual hallucinations were significantly more likely to persist in patients with DLB than those with AD. This supports the distinction made in the newly proposed consensus criteria for DLB [8] which suggest that visual hallucinations are typically persistent or recurrent.

In the study of Byrne and co-workers [1] only nine of the 15 patients had parkinsonism at presentation but all developed parkinsonism during the course of the illness. The current data support previous work in highlighting parkinsonism as a core feature of DLB. Patients with DLB are more likely to have parkinsonism than patients with AD at baseline and 1-year follow-up. The current data also suggest that parkinsonism rarely becomes more severe in DLB patients over a 12-month period and that AD patients may also develop parkinsonism in the later stages of the dementia.

McKeith *et al.* [9] reported that 54% of patients taking neuroleptics developed a severe neuroleptic sensitivity reaction characterized by marked parkinsonism, cognitive deterioration, drowsiness and myoclonus. Two of their patients had features very suggestive of a neuroleptic malignant syndrome. The neuroleptic dose did not seem to explain this phenomenon. In the current series, six out of 18 patients exposed to neuroleptics had a sensitivity reaction, including two patients taking risperidone. The symptoms were similar but much less severe and only one of the six patients died. The mean doses of neuroleptics received by these patients were much smaller. Although neuroleptic dose may not explain the occurrence of the phenomena, it may contribute to the severity. 'Neuroleptic sensitivity' has not been well operationalized. In the current study reactions were only diagnosed when they were clear-cut and pronounced and so some milder reactions may have been missed. Some of the individual cases have been described previously [21].

Disturbed consciousness in DLB patients had a 1-year prevalence of 70% compared with 35% in AD patients. The true prevalence is probably higher as the symptom is often difficult to recognize. Further work needs to be undertaken to improve the identification of disturbed consciousness and to characterize differences between the pattern of disturbed consciousness in DLB and AD. Until this is achieved, it is better to focus upon marked fluctuation in day-to-day severity as a core feature of DLB [8]. As this feature is mandatory

within the criteria of McKeith *et al.*, it would have been of little value to describe fluctuation in this paper. Perhaps most importantly, the current prospective study demonstrates that the core symptoms experienced by DLB sufferers are stable over 1 year of follow-up.

Supportive features

Three out of seven comparative studies have found both auditory hallucinations and delusions to occur significantly more frequently in patients with DLB than those with AD [22]. In the current study, auditory hallucinations and delusions were significantly more common in DLB patients at baseline but not at 1-year follow-up. In addition, they often appeared to be secondary to visual hallucinations. The current data therefore support the consensus criteria [8] which record both phenomena as supportive of a diagnosis of DLB, without being core features of the disease.

Depression has been reported in 12-16% of DLB patients [22] and occurred in 19% of DLB patients in the current study. Only three out of eight series have found depression to occur significantly more often in patients with DLB than those with AD [22]. Our finding that depression does not effectively distinguish the two diagnostic groups is hence consistent with previous work. It is nevertheless important to recognise depression as it is an important cause of excess disability in dementia patients [20]. Falls were only found to be significantly more common in DLB than AD in two out of six comparative studies [22]; our finding that falls are common in DLB sufferers but do not discriminate between DLB and AD was in accordance with this trend. This is also consistent with the direction taken by the consensus diagnostic criteria [8] which describe frequent falls as a supporting rather than a core feature of DLB.

Cognitive assessment

The MMSE scores declined by a similar magnitude in DLB and AD patients over 1 year of follow-up. This contrasts with the only previous study that examined cognitive decline, which suggested that DLB patients declined more rapidly [23]. In the previous report, DLB patients declined more rapidly on tests of frontal lobe function (which are not tested in detail by the MMSE). DLB patients may have greater impairment of attention [24] and visuospatial functioning [25] than AD patients. Test batteries that are more sensitive to these areas of cognitive functioning will be necessary to tease out any differential pattern of progression.

Key points

- Visual hallucinations, disturbances of consciousness and parkinsonism were significantly more common in patients with dementia of Lewy body type (DLB) than in patients with Alzheimer's disease.
- Falls did not occur significantly more often in patients with DLB.
- Even with judicious prescribing, 33% of DLB sufferers exposed to neuroleptics experienced sensitivity reactions.
- The core symptom profile of patients with DLB is stable over 1 year of follow-up.

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