Cognitive decline in dementia with Lewy bodies: a 5-year prospective cohort study

A Rongve, H Soennesyn, Ragnhild Skogseth, Ragnhild Oesterhus, T Hortobágyi, Clive Ballard, B H Auestad, D Aarsland

ABSTRACT

Objectives: We report the cognitive decline in persons diagnosed with mild dementia with Lewy bodies (DLB) and mild Alzheimer’s disease (AD) during 5 years of annual follow-ups.

Methods: Patients were recruited into the study from geriatric, psychiatric and neurology clinics in Western Norway during 2005–2013. They were diagnosed according to clinical consensus criteria, based on standardised clinical rating scales. Autopsy-based diagnoses were available for 20 cases. Cognitive decline for up to 5 years was assessed using the Clinical Dementia Rating (CDR) scale and the Mini-Mental State Examination (MMSE). Survival analysis including Cox regression (time to reach severe dementia) and linear mixed-effects (lme) modelling were used to model the decline on MMSE.

Results: At least one follow-up assessment was available for 67 patients with DLB and 107 patients with AD, with a median follow-up time of 4.3 years. The time to reach severe dementia was significantly shorter in DLB (median 1793 days) compared with AD (1947 days; p=0.033), and the difference remained significant in the multiple Cox regression analysis (HR=2.0, p<0.02). In the adjusted lme model, MMSE decline was faster in DLB (annual decline 4.4 points) compared with AD (3.2 points; p<0.008).

Conclusions: Our findings show that from the mild dementia stage, patients with DLB have a more rapid cognitive decline than in AD. Such prognostic information is vital for patients and families and crucial for planning clinical trials and enabling health economic modelling.

INTRODUCTION

Few longitudinal cohort studies of dementia with Lewy bodies (DLB) exist compared with in other neurodegenerative diseases. Accordingly, the long-term course and prognostic factors in DLB are not known. Early observations suggested that patients with DLB had a faster cognitive decline as compared with Alzheimer’s disease (AD), but subsequent studies have reported contradictory results. In a recent meta-analysis, we found no significant difference in the rate of decline on Mini-Mental State Examination (MMSE) in DLB and AD. However, this conclusion was based on few studies with small sample sizes and short follow-up time. Understanding the disease course is vital to give patients and families a better understanding of prognosis and is also essential to underpin accurate design and powering of clinical trials and to enable health economic models for cost-effectiveness. We therefore aimed to assess the rate of decline for up to 5 years in DLB in comparison to AD. In addition to the MMSE, which may be less sensitive to the cognitive changes in DLB compared with AD, we used a broader assessment of cognition and function, the Clinical Dementia Rating (CDR) scale, using time to reach severe dementia, CDR stage 3, as a coprimary outcome.

METHODS

Design
We used a prospective design, and patients with DLB were diagnosed clinically using extensive and standardised diagnostic investigations and also recruiting for postmortem
confirmation. Our aim was to allow for long follow-up time from the time of diagnosis with annual assessment points. There is yet no consensus regarding the best cognitive scale to track cognitive decline in DLB, and thus we used CDR as our measure of cognitive functioning.

Participants and inclusion

In the Dementia Study of western Norway (DemVest-study) all referrals to geriatric and psychiatric clinics in Hordaland and Rogaland counties (with 448 345 (13.4% aged 67 or higher) and 393 104 (11.5%, 67+) inhabitants, respectively) underwent a full medical examination for a first-time diagnosis of mild dementia during 2005–2007, and consecutively invited to participate if inclusion and exclusion criteria were fulfilled. All neurology clinics in the region were invited to refer patients with suspected dementia to the study. The referral pattern varies among general practitioners (GPs), but most dementia patients are diagnosed by their local GP. To reduce risk for referral bias, GPs in the area were therefore contacted by letter prior to study start and invited to refer all patients with suspect dementia to one of the participating centres. Subsequently we included DLB cases selectively from 2007 until 2013 to increase sample size. Patients were followed annually with a structured interview, caregiver interview and cognitive tests. Drug treatment was provided as clinically indicated by the treating physician, but it was recommended that patients with AD and DLB should receive treatment with cholinesterase inhibitor, and most patients were treated from inclusion in the study.

Inclusion and exclusion criteria

To select patients with mild dementia only, a MMSE score of at least 20 or a CDR global score=1 was required for inclusion. Patients without dementia or with acute delirium or confusion, terminal illness, recently diagnosed with a major somatic illness which according to the clinician would significantly impact on cognition, function or study participation, previous bipolar disorder or psychotic disorder were excluded. Patients were recruited for brain donation and subsequent pathological diagnosis. Only patients with probable or definite DLB and AD were included in this study.

Diagnostic and clinical baseline examination

A research clinician performed a structured clinical interview of patients and caregivers regarding demographics, previous diseases and drug history. The assessment procedure included a detailed history using a semistructured interview, clinical examination including physical, neurological, psychiatric and a detailed neuropsychological test battery, routine of blood and brain MRI. Dopamine transporter SPECT scans were available for 34 patients with DLB, and was clearly abnormal in 26 and borderline in 2 cases. The final clinical diagnosis was made by two of the study clinicians based on all available information, including pathological diagnosis when available, according to the consensus criteria for DLB and AD. The diagnoses were re-evaluated several times during the study period, and a final diagnosis was made in 2014 (see ref. for further details of the inclusion and diagnostic and baseline procedures). A pathological diagnosis was available in 20 patients (see below).

Structured rating scales for detecting the DLB core features were systematically administered to all patients by dedicated study physicians or research nurses. Annual meetings between study clinicians were held to maintain similar procedures. Fluctuating cognition was rated using the Clinician Assessment of Cognitive Fluctuations and the Mayo Fluctuation Questionnaire. REM sleep behaviour disorder (RBD) was diagnosed if there was a history of recurrent nocturnal dream enactment behaviour recorded from the Mayo Sleep Questionnaire (MSQ). The Unified Parkinson’s Rating Scale item 3 (UPDRS-3) was used to measure parkinsonian symptoms. Activities of daily living were assessed using the Rapid Disability Rating Scale-2. The Neuropsychiatric Inventory (NPI) was applied to assess visual hallucinations and other psychiatric symptoms. The Cumulative Illness Rating Scale (CIRS) was applied to measure the total burden of all other diseases.

Cognitive decline

Cognitive decline was measured using the CDR scale. The CDR examines six different areas in dementia: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. All six items are scored from 0 to 3, with 0 corresponding to no dementia, 0.5 mild cognitive impairment, 1 mild dementia, 2 moderately severe dementia and 3 severe dementia. A global score 0–3 was calculated based on an available online algorithm. The time from baseline to the first assessment with an overall CDR score of 3, that is, severe dementia, was recorded. The CDR was scored by a trained research physician, and the scoring was made independent of the other cognitive tests, by the same clinician at every occasion to the extent possible. In addition, cognition was also measured using the MMSE, administered by a trained research nurse. Decline was calculated from baseline to study end, death or first assessment with MMSE score equal to 0.

Pathological diagnosis and APOE genotyping

Brain dissection, regional sampling, and tissue processing and staining are done following standard protocols including BrainNet Europe and Brains for Dementia Research UK. Specific stain for identification of AD-type and LB pathologies (modified Bielschowsky), and immune histochemical procedures were used for detection of hyperphosphorylated τ (pretangles, tangles, dystrophic neurites and neuropil threads), amyloid β (diffuse and classical plaques and amyloid angiopathy), and α-synuclein (LB and Lewy neurites), according to standard immunohistochemical protocols. Each case was assessed by an experienced neuropathologist (TH) who
was blinded to clinical data. Pathological diagnosis was made according to international consensus criteria for DLB and AD. The presence of possible coexisting TAR DNA-binding protein 43 (TDP-43) proteinopathy was assessed according to guidelines, and microscopic vascular lesions considered and recorded. A neuropathological diagnosis was available for a total 20 of the included patients.

APOE genotyping was performed in 125 patients, and the proportion with at least one e4 allele was 64% in both groups.

Statistics
Baseline characteristics are presented and group comparisons made using t test, Mann-Whitney or χ² tests as appropriate. We applied Kaplan-Meier survival analysis and the log-rank test. Time to CDR=3 was analysed and compared between the groups using Cox regression analysis, and clinical predictors of course were identified. These data have some indication of non-proportional hazards at about 5 years which may lead to unreliable results. To avoid problems caused by this, we partitioned the time axis by censoring at 5 years as suggested in chapter 6 of Therneau and Grambsch. The cox regression was performed using these extra censored data. This removed signs of possible non-proportional hazards according to tests based on scaled Schoenfeldt residuals. We also analysed time to CDR=3 or death as a clinically relevant outcome. Longitudinal analysis with linear mixed-effects (lme) model, adjusting for age, sex, CIRS, duration and baseline MMSE, and CDR was applied using random intercept and slope model. This produced an adequate model for the data according to analyses of the residuals and random effects. Need for interaction terms in the model was checked with clear non-significant results. Possible non-linear patterns in decline were checked by adding a time squared term to the model. This was also clearly insignificant. It may be argued that the more frequent drop-out in the DLB group due to death as compared with the AD group occur at random and thus the lme modelling approach adjusts for this in an appropriate way in this situation. To study the impact of different death rates on longitudinal outcome, we also tried joint modelling where the lme model is linked to a cox proportional hazards model for survival. Although a significant correlation between death rates and longitudinal outcome was registered, this death rate-adjusted lme analysis showed practically the same results as the ordinary lme analysis. All statistical analyses were performed using the program packages SPSS and R. (Team RC. A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2013. URL http://www R-project org).

RESULTS
Follow-up data were available for 107 patients with probable or definite (n=8) DLB (see figure 1). Demographic and clinical baseline characteristics are shown in table 1. Patients with DLB were more commonly males, had slightly longer disease duration, and as expected higher NPI and UPDRS motor scores. Patients with DLB also had higher CIRS scores than the AD group. Duration of follow-up varied according to time of study inclusion and time of death. One hundred and eleven of the patients died, but there were no drop-outs for other reasons. Median follow-up time was 1577 days (4.3 years), and the number of person-years was 292 for DLB and 479 for AD. Seventy-one (40.8%) patients reached a global CDR score of 3, 28 (41.8%) diagnosed with DLB and 43 (40.2%) diagnosed with AD (p=0.834).

The median time to severe dementia, defined as CDR=3, was 1947 days in AD and 1793 days in DLB (p=0.033; see figure 2). The mortality rates were significantly higher in DLB than in AD. As can be seen in figure 3, there were large variability in the cognitive decline, some having a short time to reach the severe dementia stage whereas others remained at the mild or moderate stage for several years. The unadjusted and adjusted Cox models (table 2) show that a diagnosis of DLB was associated with shorter time to severe dementia.

Figure 1 Flowchart showing screening and inclusions. AD, Alzheimer’s disease; DLB, dementia with Lewy bodies; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.
Median time until CDR=3 or death was 1861 days in probable AD and 1210 days in probable DLB (p<0.0005; see figure 4). In the fully adjusted Cox regression model, higher baseline age, longer duration of symptoms and higher CDR global scores predicted shorter time until CDR=3 or death in addition to having a DLB diagnosis (p=0.039; see online supplementary material).

The progression of MMSE is shown in figure 3. There is a significant decline in MMSE score over time. The diagnosis X time (years) interaction is significant (p=0.008; table 3), indicating that the decline over time differs between the two groups. In the adjusted linear mixed model, taking into account potential confounders (see table 3), MMSE is reduced on average by 3.2 points per year in the AD group, whereas in the DLB group, the decrease is more rapid; on average 4.4 points per year. The slope is also significantly affected by baseline MMSE level and baseline CDR global scores. The individual and mean group MMSE scores over the study period are shown in figure 3. Figure 3 also illustrates the variability in the rate of decline, which is slightly higher in DLB (SD of annual decline 2.2, range −5.9 to 4.1) compared with AD (SD 1.6, range −4.1 to 3.3). We conducted the lme analysis also including antidementia drug use in the model, which was not associated with decline and did not change the main findings (results not included).

Among the 20 patients with neuropathological analysis, seven of the nine with a clinical diagnosis of DLB had their diagnosis confirmed neuropathologically, whereas two were changed to AD. In addition, one patient with a clinical diagnosis of AD was changed to DLB. Coexisting moderate or severe AD pathology was present in most of these cases. Ten of the 11 patients with clinical diagnosis of AD had their diagnosis confirmed with severe AD pathology (Braak τ stage 6), although some degree of coexisting DLB pathology was noted in 4, and 3 patients had mild TDP-43 pathology limited to the amygdala.

### Table 1 Baseline characteristics of the cohort

<table>
<thead>
<tr>
<th></th>
<th>Probable AD (n=107)</th>
<th>Probable DLB (n=67)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>75.1 (7–9)</td>
<td>76.1 (7–2)</td>
<td>0.598</td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>80 (74.8)</td>
<td>32 (47.8)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Education, years, mean, SD</td>
<td>9.8 (3.0)</td>
<td>9.5 (2.7)</td>
<td>0.512</td>
</tr>
<tr>
<td>CDR global score, median, IQR</td>
<td>1.00 (0.50)</td>
<td>1.00 (0.50)</td>
<td>0.217</td>
</tr>
<tr>
<td>MMSE total score, mean, SD</td>
<td>23.6 (2.3)</td>
<td>23.5 (3.0)</td>
<td>0.870</td>
</tr>
<tr>
<td>Duration of symptoms before baseline, years, mean, SD</td>
<td>2.0 (2.0)</td>
<td>2.6 (1.9)</td>
<td>0.011</td>
</tr>
<tr>
<td>NPI total scores, mean, SD</td>
<td>15.7 (16.9)</td>
<td>22.8 (19.1)</td>
<td>0.006</td>
</tr>
<tr>
<td>CIRS score, mean, SD</td>
<td>5.1 (2.1)</td>
<td>6.3 (2.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>UPDRS III scores, mean, SD</td>
<td>15.2 (2.3)</td>
<td>14.2 (13.0)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Antipsychotics, N (%)</td>
<td>4 (3.7)</td>
<td>10 (14.9)</td>
<td>0.008</td>
</tr>
<tr>
<td>Antiparkinsonian medication, N (%)</td>
<td>0 (0)</td>
<td>9 (13.4)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Antidementia medication, N (%)</td>
<td>68 (63.6)</td>
<td>38 (56.7)</td>
<td>0.436</td>
</tr>
<tr>
<td>Death during follow-up, N (%)</td>
<td>59 (55.1)</td>
<td>52 (77.6)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

AD, Alzheimer’s dementia; CDR, Clinical Dementia Rating; CIRS, Cumulative Illness Rating Scale; DLB, Dementia with Lewy bodies; MMSE, Mini-Mental State Examination; N, number; NPI, Neuropsychiatric Inventory; UPDRS, Unified Parkinson’s Disease Rating Scale-motor subscale.

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**Figure 2** Survival until severe dementia in dementia with Lewy bodies (DLB) and Alzheimer’s disease (AD).

**Figure 3** Longitudinal declines on individual MMSE scores and estimated lme-results. AD, Alzheimer’s disease; DLB, dementia with Lewy bodies; MMSE, Mini-Mental State Examination.
DISCUSSION

In the largest prospective longitudinal long-term cohort study in DLB to date, the time to reach severe dementia was shorter, and the rate of cognitive decline was faster, in DLB than in AD. This adds to previous findings that patients with DLB have a particularly severe prognosis, including more reduced quality of life, higher health-related costs, shorter time to nursing home admission, more severe caregiver burden and shorter survival than patients with AD, all factors which are also crucial for health economic modelling. However, compared with these outcome measures, the difference in cognitive decline is less striking, suggesting that aspects other than the rate of cognitive decline are more important for clinical milestones such as nursing home admission and death. Finally, unlike other studies, we used a different outcome (time to CDR=3) also in applying a more sophisticated statistical approach.

Previous studies comparing the cognitive course in DLB and AD have shown inconsistent results. In a recent systematic review, we identified 18 longitudinal studies. Some studies reported no difference in the rate of cognitive decline, whereas some reported faster decline in DLB and others a faster decline in AD. In addition, there seemed to be differential decline of the different cognitive domains, with more rapid memory decline in AD, and more rapid executive (verbal fluency) in DLB. In a meta-analysis including the six studies reporting decline on MMSE, no significant differences were found between AD and DLB. However, these 18 studies were based on small DLB groups and had a short follow-up period, which may lead to insecure estimates of decline. In addition, several studies included patients who were already at a moderate or severe degree of dementia, which may also influence the rate of subsequent decline.

Although our cohort is the largest prospectively studied DLB cohort, the number of patients is nevertheless small and thus statistical power to detect differences is limited. In addition, the relatively high mortality in DLB leads to few patients completing the full 5-year observation period. DLB is a heterogeneous disease and patients may thus be referred to clinics of different medical specialties, including psychiatry, neurology, geriatric medicine and sleep medicine. Since it is possible that the symptom profile may be related to rate of decline, findings from different studies may vary according to recruitment procedures. The inclusion of referrals compared with community-based patients likely lead to

Table 2 Factors associated with time to reach severe dementia

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted HRs</th>
<th>p Value</th>
<th>Adjusted HRs</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline, years</td>
<td>1.00 (0.97 to 1.04)</td>
<td>0.781</td>
<td>2.35 (1.39 to 3.99)</td>
<td>0.002</td>
</tr>
<tr>
<td>Diagnoses, DLB vs AD</td>
<td>0.6 (0.35 to 1.02)</td>
<td>0.057</td>
<td>0.83 (0.45 to 1.53)</td>
<td>0.556</td>
</tr>
<tr>
<td>Education in years</td>
<td>1.01 (0.92 to 1.10)</td>
<td>0.907</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of symptoms in years</td>
<td>1.13 (1.00 to 1.27)</td>
<td>0.048</td>
<td>1.15 (1.01 to 1.29)</td>
<td>0.030</td>
</tr>
<tr>
<td>MMSE total scores</td>
<td>0.79 (0.71 to 0.89)</td>
<td>&lt;0.0005</td>
<td>0.82 (0.73 to 0.93)</td>
<td>0.002</td>
</tr>
<tr>
<td>CIRS total scores</td>
<td>1.02 (0.90 to 1.16)</td>
<td>0.745</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDR global scores</td>
<td>3.26 (1.80 to 5.89)</td>
<td>&lt;0.0005</td>
<td>2.42 (1.26 to 4.65)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Cox regression, time until CDR=3. HRs presented with 95% CI.
AD, Alzheimer’s dementia; CDR, Clinical Dementia Rating; CIRS, Cumulative Illness Rating Scale; DLB, Dementia with Lewy bodies; MMSE, Mini-Mental State Examination.

Table 3 Factors associated with the rate of decline on MMSE

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up time in years</td>
<td>−3.20 (−3.69, −2.7)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>1.63 (0.3, 3.27)</td>
<td>0.050</td>
</tr>
<tr>
<td>Sex</td>
<td>0.41 (−1.01, 1.83)</td>
<td>0.571</td>
</tr>
<tr>
<td>Age in years</td>
<td>0.04 (−0.05, 0.13)</td>
<td>0.402</td>
</tr>
<tr>
<td>CIRS scores at baseline</td>
<td>−0.01 (−0.3, 0.29)</td>
<td>0.957</td>
</tr>
<tr>
<td>Duration of symptoms before baseline in years</td>
<td>−0.10 (−0.41, 0.21)</td>
<td>0.524</td>
</tr>
<tr>
<td>MMSE scores at baseline</td>
<td>0.83 (0.58, 1.08)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>CDR at baseline</td>
<td>−2.48 (−4.16, −0.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>Diagnosis x year</td>
<td>−1.24 (−2.15, −0.32)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Linear mixed effects analysis, covariate adjusted.
CDR, Clinical Dementia Rating; CIRS, Cumulative Illness Rating Scale; MMSE, Mini-Mental State Examination.

Figure 4 Survival until severe dementia or death in Alzheimer’s disease (AD) and dementia with Lewy bodies (DLB).
more complex AD and DLB cases to be included which may have influenced the findings, and thus our conclusions may not be valid for community-based patients. Furthermore, we took care to include patients from a variety of specialist sources; the main recruitment was from old age psychiatry and geriatric medicine clinics. Neurology clinics were recommended to refer patients to the study, but patients with more severe motor symptoms may still be under-represented, and no patients were referred from internal medicine or sleep clinics. Thus, patients with DLB with primary sleep or autonomous symptoms may not have been included.

We used time to severe dementia as measured by CDR in addition to MMSE as outcome measure. MMSE is less sensitive to the cognitive impairment associated with DLB, although may still be sensitive to the rate of change in these patients. In contrast, the CDR captures the full range of functional deficits due to cognition as judged by a trained clinician after interviewing patients and caregivers, and is likely a more accurate and comprehensive measure of severity. However, the CDR was developed for use in AD and has not yet been adequately tested in DLB.

Finally, for the majority of patients, a clinical diagnosis was used, which is not 100% accurate. However, we used DaTSCAN/CIT-SPECT to help in the differentiation between DLB and AD, as well as standardised rating scales for the core and suggestive clinical features of DLB. The longitudinal assessment by the same clinician also increases the diagnostic accuracy. In addition, neuropsychological analysis was available for 20 (11%) cases which confirmed the clinical diagnosis in most cases. Antideementia medications like cholinesterase inhibitors and memantine improve cognition in both DLB and AD, but this effect may be longer lasting in DLB as compared with in AD, and the cognitive decline in DLB therefore may be underestimated in our study. Parkinsonism in DLB might influence the CDR scores and increase these scores independent of cognition. To conclude, we found that time to reach severe dementia is shorter in DLB compared with AD. This, together with the high mortality and institutionalisation rate and caregiver burden in DLB, underlines the severe prognosis of this common disease. Future studies should explore the course of other key clinical symptoms, including motor and psychiatric symptoms. Detailed prognostic information is vital for patients and families and is essential to underpin accurate design and powering of clinical trials, and is also essential to enable the development of more accurate health economic models for cost-effectiveness, which depend on conversion between different stages of dementia severity.

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Data sharing statement Data collection is ongoing, and data sharing is currently limited to members of the study group.

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