ORIGINAL ARTICLE

Validation of the Neuropathologic Criteria of the Third Consortium for Dementia With Lewy Bodies for Prospectively Diagnosed Cases

Hiroshige Fujishiro, MD, PhD, Tanis J. Ferman, PhD, Bradley F. Boeve, MD, Glenn E. Smith, PhD, Neill R. Graff-Radford, MBBS, FRCP, Ryan J. Uitti, MD, Zbigniew K. Wszolek, MD, David S. Knopman, MD, Ronald C. Petersen, MD, Joseph E. Parisi, MD, and Dennis W. Dickson, MD

Abstract

There is limited information on the validity of the pathologic criteria of the Third Consortium on Dementia with Lewy bodies (CDLB), and none are based on prospectively diagnosed cases. In this study, the core clinical features of dementia with Lewy bodies (DLB) and the suggestive clinical feature of rapid eye movement sleep behavior disorder were assessed using a battery of standardized clinical instruments in 76 patients with the clinical diagnosis of either DLB or Alzheimer disease. At autopsy, 29 patients had high-likelihood, 17 had intermediate-likelihood, and 6 had low-likelihood DLB pathology. The frequency of core clinical features and the accuracy of the clinical diagnosis of probable DLB were significantly greater in high-likelihood than in low-likelihood cases. This is consistent with the concept that the DLB clinical syndrome is directly related to Lewy body pathology and inversely related to Alzheimer pathology. Thus, the Third Consortium on DLB neuropathologic criteria scheme performed reasonably well and are useful for estimating the likelihood of the premortem DLB syndrome based on postmortem findings. In view of differences in the frequency of clinically probable DLB in cases with Braak neurofibrillary tangle stages V (90%) and VI (20%) and diffuse cortical Lewy bodies, a possible modification of the scheme is to consider cases with neurofibrillary tangle stage VI to be low-likelihood DLB.

Key Words: Alzheimer disease, α-synuclein, Clinicopathologic correlation, Diagnostic criteria, Dementia with Lewy bodies, Prospective study, REM behavior disorder.

INTRODUCTION

Dementia with Lewy bodies (DLB) is the second most common neurodegenerative disorder after Alzheimer disease (AD) in some series. Accurate clinical diagnosis of DLB is important because of the differences in prognosis and management compared with other dementing disorders (1). There is limited information regarding the validity of the Third Consortium on DLB (CDLB) pathologic criteria, and none are based exclusively on prospectively diagnosed patients (2). The First CDLB pathologic criteria for DLB only required the presence of some Lewy bodies in brainstem or cortex (Fig. 1) regardless of the extent or severity of concurrent AD pathology (3). The Third CDLB criteria recommend that the neuropathologic diagnosis should be in the form of a probability statement related to the likelihood that the pathology would be associated with the DLB clinical syndrome and that the probability is positively correlated with the distribution of Lewy bodies and negatively correlated with the severity of Alzheimer-type pathologic features (4). This recommendation was based on prevailing evidence that the greater extent of Alzheimer-type pathology, the less likely the patient would have presented with the DLB clinical syndrome, even if widespread cortical Lewy bodies were present at autopsy (5–8).

To assess the validity of this recommendation, we applied the Third CDLB neuropathologic criteria to the analysis of 76 patients with dementia and the clinical diagnosis of either DLB or AD. All patients were prospectively and longitudinally evaluated with a battery of clinical instruments that assess the core clinical features of DLB in a standardized manner. At autopsy, the brains of these patients were evaluated using semiquantitative methods, including immunohistochemistry for α-synuclein.

MATERIALS AND METHODS

Subjects and Clinical Evaluation

Participants were recruited from outpatient clinics of the Department of Neurology at the Mayo Clinic in Rochester, MN, and Jacksonville, FL. Inclusion criteria required that the clinical evaluation had been completed within 3 years of death and that the following quantitative
measures had been completed within 4 years before death: Mayo Fluctuations Scale (9), Neuropsychiatric Inventory (10), Mayo Sleep Questionnaire (11), Global Deterioration Scale (12), Mini-Mental State Examination (13), and the Unified Parkinson’s Disease Rating Scale (UPDRS) (14). Patients were excluded if their clinical evaluations predated the implementation of the fluctuations and sleep questionnaires. This degree of restrictiveness was enforced to be certain that the revised DLB clinical diagnostic criteria, including quantitative data on the core features of fluctuations, visual hallucinations, and parkinsonism and the suggestive clinical feature of a rapid eye movement (REM) sleep behavior disorder (RBD), could be applied.

The subjects included 43 patients with probable DLB, 9 with possible DLB, and 24 with probable AD. All had standardized assessments that included validated clinical instruments, and all had brain autopsies between 1999 and 2006. Demographic and clinical features are summarized in Table 1. A clinical diagnosis of DLB was made according to Third CDLB criteria (4), and a clinical diagnosis of probable AD was made according to the National Institute for Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association criteria (15). For each patient, the clinical diagnosis was made at a consensus conference that included neurologists, neuropsychologists, and geriatricians after each annual evaluation. The diagnosis of dementia was made according to the Diagnostic and Statistical Manual for Mental Disorders, Third Edition, Revised (16). Fluctuations were assessed using the Mayo Fluctuations Questionnaire (9), which asks the informants to mark the answer that best described the patient within the past month. Information regarding visual hallucinations was obtained via informant interview and the Neuropsychiatric Inventory. The presence or absence of fully formed visual hallucinations and information regarding sleep behavior (11) were obtained from the patient and his or her informant. The presence or absence of RBD was assessed according to formal published criteria (17) and included both patient/informant interviews and the Mayo Sleep Questionnaire (11). Of those patients with the clinical diagnosis of RBD, 47% also had undergone formal overnight polysomnography, which confirmed the presence of dream enactment behavior or lack of atonia during REM sleep. Parkinsonism was assessed by neurologic examination, and the UPDRS was used to quantify the extent of extrapyramidal motor signs. The Global Deterioration Scale afforded a noncognitive rating of dementia severity, and Mini-Mental State Examination provided a cognitive measure of dementia severity. The average interval (±SD) from final assessment to death for Neuropsychiatric Inventory and UPDRS was 1.2 ± 0.9 and 2.0 ± 1.3 years, respectively. There was no difference in this interval between DLB and AD groups.

Neuropathologic Evaluation

All cases underwent a standardized neuropathologic assessment, with evaluation of gross and microscopic findings and quantitative analysis of Alzheimer-type pathology. Sections were taken from 6 regions of the cortex, hippocampus, amygdala, basal ganglia, thalamus, midbrain,pons, medulla, and cerebellum. Counts of senile plaques and neurofibrillary tangles (NFTs) were made in 6 cortical sections, 4 sectors of the hippocampus, 2 regions of the amygdala, and the basal nucleus of Meynert with thioflavin-S fluorescent microscopy. The presence and severity of amyloid angiopathy (CAA) were assessed on a 4-point scale (none, mild, moderate, and severe) in each cortical area; an average of each region represented the final CAA score. Senile plaques and NFTs were counted at 10 and 400, respectively, in cortex, hippocampus, and amygdala; the average lesion densities were calculated for each region. A Braak NFT stage (18) was assigned to all cases based on the distribution of NFTs with thioflavin-S fluorescent microscopy, as previously described (19–22). The severity of senile plaque pathology was also assessed using the Consortium to Establish a Registry for Alzheimer Disease guidelines (23). All cases underwent immunostaining with a monoclonal antibody to phospho-tau (CP13 [24]; Peter Davies, Albert

TABLE 1. Demographics and Clinical Features of Patients

<table>
<thead>
<tr>
<th>Probable DLB (n = 43)</th>
<th>Possible DLB (n = 9)</th>
<th>Probable AD (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at death, years</td>
<td>76 (71, 81)</td>
<td>73 (60, 85)</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>7 (5, 8)</td>
<td>8 (7, 10)</td>
</tr>
<tr>
<td>Sex ratio (female/male)</td>
<td>12:31</td>
<td>5:4</td>
</tr>
<tr>
<td>Dementia</td>
<td>43 (100%)</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>MMSE closest to death</td>
<td>17 (11, 24)</td>
<td>12 (9, 20)</td>
</tr>
<tr>
<td>GDS closest to death</td>
<td>6 (5, 7)</td>
<td>6 (6, 7)</td>
</tr>
<tr>
<td>Visual hallucination</td>
<td>35 (81%)†</td>
<td>6 (66%)*</td>
</tr>
<tr>
<td>NPI closest to death</td>
<td>12 (8, 18)</td>
<td>17 (7, 24)</td>
</tr>
<tr>
<td>Extrapyramidal signs</td>
<td>40 (93%)†</td>
<td>3 (33%)*</td>
</tr>
<tr>
<td>UPDRS motor score closest to death</td>
<td>16 (10, 20)†</td>
<td>1 (0, 10)</td>
</tr>
<tr>
<td>Fluctuating alertness/ cognition</td>
<td>34 (79%)†</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>REM sleep behavior disorder</td>
<td>38 (88%)†</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*, p < 0.05 compared with probable AD.
†, p < 0.05 compared with both possible DLB and probable AD.
Einstein College of Medicine, Bronx, NY) and a polyclonal antibody to α-synuclein (25) using immunostaining with a DAKO Autostainer. The subtypes of Lewy body pathology (i.e. brainstem, limbic-transitional, or diffuse [26]) were determined based on Lewy body counts in 5 cortical sections and the amygdala. Semiquantitative grading of Lewy body pathology and assignment of Lewy body type were also determined according to the Third CDLB recommendations (4). The 2 methods gave similar results. The Lewy body density was determined at 200× magnification from the following regions: middle frontal (Brodmann area [BA] 46), superior temporal (BA38), inferior parietal (BA39), anterior cingulate (BA24), and parahippocampal gyri (BA35).

Cerebrovascular pathology was assessed on all cases using a semiquantitative scale similar to that previously reported (27). Briefly, cases with no cerebrovascular lesions were scored 0, those with minimal cerebrovascular pathology (including 1 to 2 small lacunes, mild CAA, or mild leukoencephalopathy) were scored 1, those with moderate lesions (including more than 2 lacunes, severe CAA, or diffuse leukoencephalopathy) were scored as 2, and those with marked cerebrovascular pathology (including old cortical infarcts, multiple microinfarcts, or hippocampal sclerosis) were scored 3.

The final neuropathologic diagnosis was made according to the Third CDLB criteria and the National Institute on Aging-Reagan criteria for AD (4, 28). For the sake of discussion, cases that fell into the high- and intermediate-likelihood DLB categories were considered to have the pathologic diagnosis of DLB.

Statistical Analysis

Data were analyzed with SigmaStat 3.0 (Systat Software, Inc, Point Richmond, CA), and the significance level was set at p < 0.05. For the comparison of cases with respect to demographic and pathologic features, 1-way analysis of variance or Kruskal-Wallis analysis of variance on ranks was used, as appropriate. If there was a significant difference, Fisher least significant difference method or Dunn method was performed for pairwise comparisons. For the comparison of categorical variables, the Fisher exact or χ² test was used, as appropriate.

RESULTS

Summary of Clinical Findings

This study focused on patients with dementia and the clinical diagnosis of either DLB or AD because these are the most common disorders in patients recruited from the neurology outpatient clinics to have the complete battery of standardized tests that were developed to evaluate the neuropsychology of DLB (National Institutes of Health R01-AG15866). They also represent the most common disorders in the elderly cohort under investigation and are needed to address the interplay of Alzheimer and Lewy body pathology that is at the crux of the Third CDLB neuropathologic criteria of DLB. Less common clinical diagnoses were intentionally excluded from this study; however, at autopsy, several other pathologic processes were detected (e.g. progressive supranuclear palsy [PSP], frontotemporal lobar degeneration with ubiquitin inclusions, and cortico-basal degeneration). Patients with a primary clinical diagnosis of Parkinson disease, with or without cognitive complaints, were excluded as recommended by the Third CDLB criteria (4).

The demographics and clinical features of DLB and AD cases are summarized in Table 1. All patients had dementia using DSM-III-R criteria and did not differ in the severity of dementia as assessed by Mini-Mental State Examination and Global Deterioration Scale. The prospective DLB cohort included 43 patients with clinically probable DLB and 9 patients with clinically possible DLB. By definition, clinically probable AD with extrapyramidal signs or visual hallucinations fulfill the criteria for possible DLB. Of the 43 clinically probable DLB patients, 38 had 2 or more core features, and 5 patients had 1 core feature plus RBD. Although the study design did not include matching for age at death, disease duration, or male-to-female ratio, patients with clinically probable DLB, clinically possible DLB, or clinically probable AD did not differ with respect to any of these variables. As expected, the frequency of visual hallucinations and extrapyramidal signs was significantly greater in clinically probable DLB than clinically probable AD, with intermediate values for clinically possible DLB. Clinically probable DLB had a higher median UPDRS motor score than both clinically probable AD and clinically possible DLB. Fluctuating level of alertness or consciousness and RBD were also more frequent in clinically probable DLB than in clinically possible DLB and clinically probable AD.

Neuropathologic Diagnosis

Of the 43 clinically probable DLB patients, 40 had intermediate- or high-likelihood DLB pathology. More than 80% of the cases with clinically probable DLB had diffuse cortical Lewy bodies. One clinically probable DLB patient had PSP with concurrent Alzheimer-type pathology (Braak NFT stage V1), but no Lewy bodies. This patient had 2 core clinical features as well as RBD. The dementia in this patient was probably related to AD and the parkinsonism to PSP. Cases with combined PSP and AD are extremely uncommon (3% of 588 PSP cases in the CurePSP brain bank—D. W. Dickson, unpublished observation, 2008). There were only 2 cases with low-likelihood DLB pathology; both had advanced Alzheimer-type pathology (Braak NFT stages V–VI) with limbic Lewy bodies. One of these cases had cerebrovascular pathology, including basal ganglia infarcts, which might have modified the clinical presentation. In general, cerebrovascular pathology was absent to mild in most cases of DLB.

Only 2 of 9 clinically possible DLB cases had intermediate- or high-likelihood DLB pathology. The other 7 cases had intermediate- or high-likelihood AD according to NIA neuropathologic criteria for AD (28), and 2 of the 7 had Lewy bodies confined to amygdala (Fig. 2). Lewy bodies relatively confined to the amygdala typifies α-synuclein pathology in approximately 20% of cases of advanced AD (22). Both cases of AD with amygdala Lewy bodies fit...
pathologic criteria for DLB using the First CDLB criteria (3), but not Third CDLB criteria (4). It is worth noting, however, that the Third CDLB criteria do not specifically address this increasingly recognized and distinct form of Lewy body pathology (22). Both cases had visual hallucinations as the only core DLB clinical feature. In this series of demented individuals with clinical diagnoses of probable DLB and possible DLB, none had brainstem predominant Lewy bodies.

Of the 24 cases with clinically probable AD, 21 had NIA-Reagan intermediate- or high-likelihood AD pathology (28). The 3 cases that did not have Alzheimer pathology included 2 cases of frontotemporal lobar degeneration with ubiquitinated inclusions and 1 corticobasal degeneration, none of which had Lewy bodies. Of the remaining 21 cases with clinically probable AD, 8 had Lewy bodies, including 4 with low-likelihood (1 brainstem predominant and 3 limbic Lewy bodies) and 4 with intermediate-likelihood (all with diffuse Lewy bodies) DLB pathology.

For comparison of neuropathologic findings between clinically probable DLB and clinically probable AD (Table 2), cases with other degenerative diseases (1 PSP in clinically probable DLB; 2 frontotemporal lobar degeneration with ubiquitinated inclusions and 1 corticobasal degeneration in clinically probable AD) were excluded. Not surprisingly, clinically probable AD cases had more severe AD pathology as assessed by the density of cortical and amygdala senile plaques as well as the density of cortical, limbic, and nucleus basalis of Meynert NFTs compared with clinically probable DLB. As expected, clinically probable DLB had more Lewy body pathology as assessed by density of cortical, limbic, and amygdala Lewy bodies compared with clinically probable AD. Cerebrovascular pathology, as assessed by the average CAA score and an overall cerebrovascular score (27), was greater in clinically probable AD than in clinically probable DLB.

Application of Third CDLB Criteria to Clinically Probable DLB

Excluding the case with mixed PSP and AD, 42 of 43 cases with clinically probable DLB had low-, intermediate-, or high-likelihood DLB pathology (Table 3A). More than 95% of clinically probable DLB cases met pathologic criteria of intermediate- (12 cases; 29%) or high-likelihood DLB (28 cases; 67%). The most frequent category (20 cases) was diffuse Lewy body disease with Braak NFT stages III and IV. The second most frequent category (10 cases) was diffuse Lewy body disease with Braak NFT stages V and VI. Only 1 of these 10 cases with clinically probable DLB had Braak NFT stage VI. Two clinically possible DLB cases had intermediate- or high-likelihood DLB pathology.

Of the 8 clinically probable AD cases with Lewy bodies, all of which had Braak NFT stages V and VI; none had

| TABLE 2. Pathologic Features of Clinically Probable DLB and Clinically Probable AD |
|-------------------------------|-------------------------------|
|                              | Probable DLB (n = 42) | Probable AD (n = 21) |
| Neurofibrillary tangles       |                              |                              |
| Braak stage                   | IV (III, V) | VI (IV, VI)* |
| Cortical                      | 0 (0, 1) | 5 (1, 9)* |
| Limbic                        | 4 (2, 6) | 10 (5, 14)* |
| Amygdala                      | 2 (0, 3) | 5 (3, 10)* |
| nbM                           | 1 (0, 3) | 5 (2, 11)* |
| Senile plaques                |                              |                              |
| CERAD score                   | 2 (1, 2) | 3 (2, 3)* |
| Cortical                      | 33 (12, 45) | 46 (27,50)* |
| Limbic                        | 8 (3, 14) | 13 (5, 17) |
| Amygdala                      | 17 (9, 28) | 33 (16, 43)* |
| Lewy bodies                   |                              |                              |
| Cortical                      | 6 (3, 10)* | 0 (0, 1) |
| Limbic                        | 13 (9, 20)* | 0 (0, 4) |
| Amygdala                      | 50 (21, 67)* | 0 (0, 38) |
| Vascular                      |                              |                              |
| Amyloid angiopathy            | 1 (0, 1) | 1 (1, 3)* |
| Cerebrovascular score         | 0.5 (0, 1) | 1 (1, 2)* |

*p < 0.05.

AD, Alzheimer disease; CERAD, Consortium to Establish a Registry for Alzheimer Disease (0 = none, 1 = sparse, 2 = moderate, 3 = frequent); DLB, dementia with Lewy bodies; nbM, nucleus basalis of Meynert.
high-likelihood DLB (Table 3B). Of the 4 cases with intermediate-likelihood DLB and diffuse cortical Lewy bodies, 3 had Braak NFT stage VI. Similarly, 2 of the 3 cases with transitional/limbic Lewy bodies had Braak NFT stage VI. The single brainstem predominant case also had Braak NFT stage VI. These findings suggest that when Alzheimer pathology is advanced, especially in cases with Braak NFT stage VI, the clinical syndrome is likely to be that of AD rather than DLB, regardless of the density or distribution of Lewy bodies.

Comparison of Clinical Findings Among DLB Pathologic Categories

In this prospective series of demented patients with clinical diagnoses of DLB or AD, 52 cases had Lewy bodies, excluding 2 cases with Lewy bodies confined to the amygdala. These cases were pathologically stratified into 29 cases of high-likelihood, 17 intermediate-likelihood, and 6 with low-likelihood DLB pathology. Comparisons of demographic and clinical features in the 3 groups are summarized in Table 4. All of the core clinical features of DLB, except for visual hallucinations, were significantly greater in high-likelihood than low-likelihood cases, with intermediate-likelihood DLB falling in the middle. Although no difference in the overall frequency of visual hallucinations was noted, if timing of hallucinations was taken into consideration, there was a significant difference between the 3 groups with respect to visual hallucinations that had onset within 3 years of disease onset. The accuracy of clinical diagnosis of probable DLB in each group was significantly greater in high-likelihood DLB than in low-likelihood DLB, with intermediate-likelihood in the

### Table 3. Application of the Third CDLB Criteria to Clinically Probable DLB and Clinically Probable AD

<table>
<thead>
<tr>
<th></th>
<th>NIA Low (Braak Stage 0–II)</th>
<th>NIA Intermediate (Braak Stage III–IV)</th>
<th>NIA High (Braak Stage V–VI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) Probable DLB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brainstem CDLB low</td>
<td>CDLB low</td>
<td>CDLB low</td>
</tr>
<tr>
<td></td>
<td>Limbic CDLB high</td>
<td>CDLB intermediate</td>
<td>CDLB low</td>
</tr>
<tr>
<td></td>
<td>Diffuse CDLB high</td>
<td>CDLB high</td>
<td>CDLB high</td>
</tr>
<tr>
<td></td>
<td>(14%)</td>
<td>CDLB intermediate</td>
<td>0 (5%)</td>
</tr>
<tr>
<td>(B) Probable AD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brainstem CDLB low</td>
<td>CDLB low</td>
<td>CDLB low</td>
</tr>
<tr>
<td></td>
<td>Limbic CDLB high</td>
<td>CDLB intermediate</td>
<td>CDLB low</td>
</tr>
<tr>
<td></td>
<td>Diffuse CDLB high</td>
<td>CDLB high</td>
<td>CDLB high</td>
</tr>
<tr>
<td></td>
<td>0 (19%)</td>
<td>CDLB intermediate</td>
<td>0 (5%)</td>
</tr>
</tbody>
</table>

Each box shows the number of clinically probable DLB (A) or probable AD (B) in the category and the percentage of all clinically probable DLB or probable AD in that category. One mixed progressive supranuclear palsy/AD case with clinically probable DLB, 2 cases of frontotemporal lobar degeneration with ubiquitinated inclusion, and 1 case of corticobasal degeneration with clinically probable AD are not included. The total for AD does not equal 100% because most probable AD cases did not have Lewy bodies.

### Table 4. Comparison of 52 Prospectively Diagnosed Cases With Lewy Bodies at Autopsy

<table>
<thead>
<tr>
<th></th>
<th>High-Likelihood DLB (n = 29)</th>
<th>Intermediate-Likelihood DLB (n = 17)</th>
<th>Low-Likelihood DLB (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of probable DLB, %</td>
<td>96*</td>
<td>76</td>
<td>33</td>
</tr>
<tr>
<td>Age at death, years</td>
<td>77 ± 7</td>
<td>64 ± 8</td>
<td>38</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>7 (5, 8)</td>
<td>8 (6, 8)</td>
<td>11 (10, 6)†</td>
</tr>
<tr>
<td>Sex ratio (female/male)</td>
<td>8:21</td>
<td>5:12</td>
<td>4:2</td>
</tr>
<tr>
<td>Brain weight, g</td>
<td>1,260 ± 175</td>
<td>1,260 ± 150</td>
<td>1,060 ± 175†</td>
</tr>
<tr>
<td>Visual hallucinations (VH), %</td>
<td>76</td>
<td>65</td>
<td>33</td>
</tr>
<tr>
<td>VH within 3 years of disease onset, %</td>
<td>62*</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>Extrapyramidal signs (EPS), %</td>
<td>93†</td>
<td>65</td>
<td>33</td>
</tr>
<tr>
<td>EPS within 3 years of disease onset, %</td>
<td>83†</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>Fluctuating alertness/cognition, %</td>
<td>83†</td>
<td>29</td>
<td>16</td>
</tr>
<tr>
<td>REM sleep behavior disorder, %</td>
<td>90†</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>

* p < 0.05 compared with low-likelihood DLB.
† p < 0.05 compared with both intermediate- and high-likelihood DLB.
‡ p < 0.05 compared with both intermediate- and low-likelihood DLB.

DLB, dementia with Lewy bodies.

AD, Alzheimer disease; CDLB, Consortium on dementia with Lewy bodies; DLB, dementia with Lewy bodies; NIA, National Institute on Aging.
DISCUSSION

This report describes neuropathologic findings in a prospective and longitudinal study of a cohort of patients with dementia, some of whom had an antemortem clinical diagnosis of DLB. Clinical assessments used standardized methods for assessing all the major clinical features of DLB; this is one of the first studies of this type. Based on the Third CDLB criteria, 29 had high-, 17 had intermediate-, and 6 had low-likelihood DLB pathology according to the distribution of Lewy bodies and the severity of Alzheimer-type pathology. All of those with high-likelihood DLB pathology had clinically probable DBL, except for one with clinically possible DLB. The frequency of core clinical features and the accuracy of the clinical diagnosis of probable DBL were significantly greater in high-likelihood cases than in low-likelihood cases, consistent with the hypothesis that the DLB clinical syndrome is related to distribution of Lewy bodies, but inversely related to the severity of Alzheimer-type pathology. Thus, the scheme for assessing the neuropathology in the Third CDLB criteria performs reasonably well, at least in this select research cohort. The findings suggest that the CDLB criteria are a practical method for estimating the likelihood of the DLB clinical syndrome based solely on postmortem findings.

Clinical Evaluation

Of the core clinical features, fluctuating cognition with pronounced variation in attention and alertness has often been difficult to evaluate, especially in retrospective studies (29, 30). We made an effort to assess this feature reliably and systematically through the use of a validated informant questionnaire administered at their annual evaluation (11). In addition to ascertainment of the presence of each of the core DBL features, we also determined whether RBD, one of the suggestive features recommended by the Third CDLB, was present in each patient at initial presentation and then annually until death. Of those with RBD diagnosed by interview and questionnaire, 47% underwent polysomnography, and REM sleep without atonia was confirmed in all but 2 who did not go into REM sleep. This provides evidence of the validity of our clinical assessment of RBD, even if polysomnography was not carried out. In this series, RBD antedated the diagnosis of DLB in almost all cases in which RBD was noted. These findings are consistent with previous reports of a high frequency of α-synucleinopathy in patients with RBD (31–33).

For all cases in this series, a clinical diagnosis of probable DBL was made before autopsy, whereas in many previous studies, raters have assessed clinical records to make the diagnosis of DLB after death, but before pathologic evaluation (34). This type of analysis might underestimate the frequency of fluctuations and RBD. Some reported studies include cases diagnosed before 1996, before the First CDLB criteria were published, and before some aspects of the disease, such as RBD, were more widely recognized and added as the supportive feature for a clinical diagnosis of DBL in 1999 (2, 30, 31, 35, 36). Most published clinicopathologic studies of DLB do not provide details on the number of core features in the cohort and might have included some with possible DBL. The present report describes neuropathologic findings of patients with prospective diagnoses all made after 1996 and focused on only those patients with clinically probable DBL, with the use of standardized assessments of fluctuations, parkinsonism, visual hallucinations, and RBD.

Neuropathologic Evaluation

Most of the cases in this prospective series of clinically probable DBL had diffuse cortical Lewy bodies (86%), whereas no brainstem-predominant Lewy body cases were found. In a previous study of 24 prospectively diagnosed DLB cases, McKeith et al (34) reported that 71% had diffuse cortical Lewy bodies, 25% had limbic Lewy bodies, and 4% had brainstem-predominant Lewy bodies. In a more recent study of clinically diagnosed DBL, Weisman et al (2) reported that 55% had diffuse cortical Lewy bodies and 45% had limbic Lewy bodies, but none had brainstem-predominant Lewy bodies. The explanation for the higher frequency of brainstem predominant Lewy bodies in the report by McKeith et al (34) compared with the current study and that of Weisman et al is not clear. All studies are based on relatively small numbers of cases, and the difference could be due to chance. It is also possible that differences in pathologic methods may explain the difference. In the study by McKeith et al, Lewy bodies were assessed with ubiquitin immunohistochemistry (34), whereas the current study used α-synuclein immunohistochemistry, which is the recommended method for detecting Lewy bodies (4). The use of α-synuclein immunohistochemistry may have revealed more limbic and cortical Lewy bodies than ubiquitin immunohistochemistry and thus shifted brainstem-predominant cases into limbic or diffuse categories.

Application of Third CDLB Pathologic Scheme

Weisman et al (2) have recently reported a validation study of Third CDLB neuropathologic criteria, in which they suggest that the degree of Alzheimer-type pathology is the major determinant of the clinical syndrome. It should be noted, however, that they classified cases with diffuse cortical Lewy bodies with Braak NFT stages V and VI as “low probability DLB,” which is incorrect (37). According to the Third CDLB criteria (4), such cases should be classified as intermediate-likelihood DBL. The frequency of the DBL clinical syndrome in this group was 33%, which was the same as in the other intermediate-likelihood group (limbic Lewy bodies with Braak NFT stages III and IV; 33%); lower in frequency than those considered to have a high probability of the DBL syndrome (40%–63%); and greater than those considered to have a low probability of the DBL syndrome (0%–13%) (2). It would thus seem that the Third CDLB criteria are valid in their series and that the likelihood of the DBL syndrome is a function of both the distribution of Lewy

middle. These results support the hypothesis that the DLB clinical syndrome is positively correlated with Lewy body pathology and negatively correlated with Alzheimer-type pathology.

Fujishiro et al

J Neuropathol Exp Neurol • Volume 67, Number 7, July 2008

© 2008 American Association of Neuropathologists, Inc.
bodies and the severity of Alzheimer-type pathology and not merely Alzheimer pathology, as they suggested. A potential limitation of their study was that some of the cases were diagnosed before 1996, when the First CDLB criteria were published, and before some aspects of the disease, such as RBD, were recognized (30, 31). The present study used more strict inclusion criteria that required antemortem assessment of all the cardinal features in both cases and AD controls, using validated screening instruments as well as information from neurologic history and physical examination.

A minor limitation of the present study was failure to include another supportive clinical feature of DLB, namely, striatal dopamine transporter activity on functional neuroimaging (4). In contrast to the screening instruments used in this study, such imaging is expensive and not widely available. The present study also did not address the validity of the Third CDLB neuropathologic criteria for patients presenting with Parkinson disease with or without dementia, since such cases would by definition not meet strict research criteria for DLB. Nevertheless, a prospective study of Parkinson disease with and without dementia, including use of screening instruments for fluctuation, RBD, and psychiatric features, as well as neuropsychological tests for cognitive function is an important future objective.

**AD With Amygdala Lewy Bodies**

In this series, 2 clinically possible DLB cases had advanced Alzheimer pathology with Lewy bodies confined to amygdala (Fig. 2). Visual hallucinations occurred in these patients at 5 and 7 years after the onset of dementia. In contrast, for clinically probable DBL, the average interval from disease onset to notable visual hallucinations was less than 3 years (2.8 ± 0.4 years, SEM). In previous studies, we and others have noted that approximately 20% of AD cases have Lewy bodies relatively confined to amygdala, suggesting that amygdala Lewy bodies are not uncommon in AD (22, 38). The clinical significance, if any, of amygdala Lewy bodies in the setting of advanced AD is unknown. Clearly, most cases of AD with amygdala Lewy bodies do not present with a DLB clinical syndrome.

In a previous retrospective series, there was no difference in frequencies of neuropsychiatric symptoms or extrapyramidal signs in AD with and without amygdala Lewy bodies (22). This raises the possibility that Lewy bodies confined to the amygdala in advanced AD represents Lewy body pathology affecting an already damaged brain region, which may not add much to the clinical presentation. On the other hand, Lewy body pathology in the amygdala has been reported to correlate with visual hallucinations in Lewy body diseases (39). It is thus of interest that both patients with AD and amygdala Lewy bodies had hallucinations, albeit relatively late in the disease course.

**Possible Changes to CDLB Pathologic Criteria**

In this series, 10 clinically probable DLB cases with diffuse cortical Lewy bodies were considered to be intermediate-likelihood DLB due to the presence of Braak NFT stages V and VI. Only one had Braak NFT stage VI. On the other hand, of 24 clinically probable AD patients, 4 cases with diffuse cortical Lewy bodies were assigned to be intermediate-likelihood DLB due to the presence of Braak NFT stages V and VI, and 3 of the 4 had Braak NFT stage VI. Interestingly, this is consistent with the result of a previous prospective study of DLB because none of their 24 cases clinically diagnosed as probable DLB had a Braak NFT stage VI (34). Merdes et al (5) reported that clinical diagnostic accuracy was 27% in Braak NFT stage VI, whereas it was 40% in Braak NFT stage V. These results may indicate that there are significant differences in clinical presentations between Braak NFT stages V and VI in the setting of diffuse cortical Lewy bodies. Based on the findings from the literature and the results of the present study, a possible modification of the CDLB neuropathologic criteria would be to classify cases with Braak NFT stage VI and diffuse cortical Lewy bodies as

---

### TABLE 5. Possible Changes in the CDLB Criteria With Results From Prospective Cases

<table>
<thead>
<tr>
<th>Alzheimer-Type Pathology</th>
<th>NIA Low (Braak Stage 0–II)</th>
<th>NIA Intermediate (Braak Stage III–IV)</th>
<th>NIA High (Braak Stage V)</th>
<th>NIA High (Braak Stage VI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewy body pathology</td>
<td>CDLB low</td>
<td>CDLB low</td>
<td>CDLB low</td>
<td>CDLB low</td>
</tr>
<tr>
<td>Amygdala only</td>
<td>0/3*</td>
<td>0/9</td>
<td>0/3</td>
<td>1/7</td>
</tr>
<tr>
<td>Brainstem</td>
<td>CDLB low</td>
<td>CDLB low</td>
<td>CDLB low</td>
<td>CDLB low</td>
</tr>
<tr>
<td>Limbic</td>
<td>CDLB high</td>
<td>CDLB intermediate</td>
<td>CDLB low</td>
<td>CDLB low</td>
</tr>
<tr>
<td>Diffuse</td>
<td>2/2</td>
<td>2/2</td>
<td>0/1</td>
<td>2/4</td>
</tr>
</tbody>
</table>

Possible changes in the CDLB criteria with results from prospective cases. Each box shows the ratio of clinically probable dementia with Lewy bodies (DLB) to the total number of cases in that pathologic category for all 76 prospectively diagnosed DLB and Alzheimer disease (AD) cases.

* Includes 2 cases of frontotemporal lobar degeneration with ubiquitin- and TDP-43 inclusions and 1 case of corticobasal degeneration with clinically probable AD.

† Includes 1 mixed progressive supranuclear palsy/AD case that had clinically probable DLB.

CDLB, Consortium on dementia with Lewy bodies; NIA, National Institute on Aging.

© 2008 American Association of Neuropathologists, Inc.
low-likelihood DLB. A future revision might also include categories for cases with no Lewy bodies and cases in which Lewy bodies are relatively confined to the amygdala. Applying this revised scheme to the current prospective clinical series (Table 5), the accuracy of the diagnosis of clinically probable DLB in cases with diffuse cortical Lewy bodies with Braak NFT stage V is 90%, whereas it is only 20% for Braak NFT stage VI.

REFERENCES
tium on Dementia with Lewy Bodies. Neurology 1999;53:902–5

© 2008 American Association of Neuropathologists, Inc.