Diagnostic Accuracy of Dementia With Lewy Bodies

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Background: Diagnostic criteria for dementia with Lewy bodies (DLB) are still evolving. No data exist on prospective differentiation of DLB and Alzheimer disease (AD).

Objective: To examine the clinician’s diagnostic accuracy for DLB and analyze factors contributing to false-positive DLB diagnoses.

Methods: A prospective series of 10 patients with clinically diagnosed DLB who came to autopsy was compared with 32 autopsy-confirmed cases of DLB (27 Lewy body variant, 5 diffuse Lewy body disease) and 20 autopsy-confirmed cases of AD (matched on age, sex, education, and initial Mini-Mental State Examination score) with regard to distinguishing and/or confounding clinical features.

Results: The clinical diagnostic accuracy for DLB was 50%, with 5 of the 10 patients clinically presumed to have DLB confirmed at autopsy. Of the 5 misdiagnosed cases, 4 had AD and 1 had progressive supranuclear palsy. The misdiagnosed DLB cases who had pure AD had fewer hallucinations (25%) than those with Lewy body variant (63%) or diffuse Lewy body disease (100%) ($P = .048$); however, an equal amount of spontaneous (in the absence of neuroleptics) extrapyramidal signs was found. There were no differences among groups with regard to daily fluctuations in cognition or falls. Compared with the AD control group, the misdiagnosed DLB cases with pure AD showed significantly more spontaneous extrapyramidal signs ($P \leq .02$).

Conclusions: The clinician’s diagnostic accuracy for DLB was poor. Early spontaneous extrapyramidal signs in AD were associated with false-positive clinical diagnoses of DLB. The distinction between DLB and AD may be improved by greater emphasis on hallucinations.

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Dementia with Lewy bodies (DLB)\(^1\) has been reported to be the second most common neuro-pathological cause of dementia, after Alzheimer disease (AD).\(^2\) Nosologically, this is a very complex area that includes such entities as the Lewy body variant (LBV) of AD,\(^3\) diffuse Lewy body disease (DLBD),\(^4\) and senile dementia of Lewy body type,\(^5\) among others. However, despite variable nomenclatures, most of these patients are found at autopsy to have an admixture of AD and parkinsonian pathologic findings, including senile plaques as well as brainstem and cortical Lewy bodies.

Clinically, extrapyramidal signs (EPSs), including bradykinesia and rigidity, but not resting tremor, are common findings in DLB. Often, EPSs appear early in the course of illness and help to distinguish this entity from “pure” AD. Many patients also have prominent psychiatric features (especially visual hallucinations) and a fluctuating level of consciousness in addition to a history of falls.\(^6\) Although many of these features overlap to some extent with AD, several studies have reported a sufficiently distinctive clinical pattern to distinguish DLB from AD.\(^7,8\) Others\(^9-11\) find that the clinical distinction between AD and DLB is more subtle. However, all of these studies were performed retrospectively by review of clinical records or databases. No study, to our knowledge, has attempted to prospectively evaluate the accuracy of the clinical diagnosis of DLB.

While neuropathological series demonstrate high accuracy for the clinical diagnosis of AD,\(^12\) the accuracy of the clinical diagnosis of DLB remains less clear. One study focusing on differentiating DLB and Parkinson disease from each other and from other parkinsonian disorders reported that DLB was underdiagnosed and mostly misdiagnosed as Parkinson dis...
PATIENTS AND METHODS

PATIENTS

Approximately 120 subjects who were followed up at the Alzheimer’s Disease Research Center at the University of California, San Diego, came to autopsy between 1990 and 1997. Ten patients had received the clinical diagnosis of DLB. Except for 1 patient, all had been examined on an annual basis (mean follow-up, 4 years; range, 2-8 years), with a standardized evaluation including history, psychiatric symptoms (assessed by the Diagnostic Interview Schedule), complete neuropsychological assessment, medical and neurologic examinations, and laboratory testing. Neurologists experienced in the assessment of AD and Parkinson disease had performed the neurologic evaluations and determined the clinical diagnoses. In this series of DLB, we did not include patients with Parkinson disease and dementia to whom the term DLB could potentially apply.

NEUROPATHOLOGICAL EXAMINATION

All autopsies were performed by one of us (L.A.H.) according to a standardized protocol. Tissue blocks from the neocortex, hippocampus, brainstem, cerebellum, and subcortical areas were stained with hematoxylin, eosin, and thioflavin. Senile plaques and lesion counts for senile plaques and neurofibrillary tangles were quantified. When Lewy bodies were identified in the pigmented nuclei of the brainstem, the neocortex was examined for Lewy bodies and their presence was confirmed with antiubiquitin immunocytochemical analysis. The pathological diagnosis of LBV was made when the brain showed Lewy bodies in cortical and subcortical areas and sufficient plaques to meet National Institute on Aging criteria for Lewy body variant of Parkinson disease. The pathological diagnosis of DLBD required cortical and subcortical Lewy bodies without significant AD lesions. All the LBV and DLB cases met the Consortium on Dementia With Lewy Bodies criteria for a pathological diagnosis of DLB.

DIAGNOSTIC ACCURACY

To determine the accuracy of the clinical diagnosis of DLB, we used the last recorded diagnosis for each patient and compared it with the subject’s pathological diagnosis. Except for 1 individual, all patients had died within 1 year of the last clinical diagnosis of DLB. The clinical diagnostic accuracy was defined as (true positive)/(true positive + false positive).

CLINICAL COMPARISON

To examine which factors may have contributed to the clinical misdiagnosis of DLB, we compared the subjects misdiagnosed as having DLB (who had AD pathologic findings only) with clinical features of all patients with autopsy-proved LBV (n = 27) and DLBD (n = 5) who had come to autopsy at our center. Next, we compared the clinical characteristics of these subjects misdiagnosed as having DLB with those of a group of 20 patients with autopsy-proved AD. The latter were carefully matched on the basis of age, sex, education, and initial Mini-Mental State Examination (MMSE) score.

STATISTICAL ANALYSIS

Demographic variables and MMSE scores were compared by means of a Student t test; the frequencies of neurologic signs or symptoms and hallucinations were compared by Fisher exact test. Data are presented as means and SDs.

RESULTS

The clinical diagnostic accuracy for DLB was 50%. In only 5 of the 10 patients clinically presumed to have DLB was the diagnosis confirmed at autopsy. Of the 5 misdiagnosed subjects, 4 were found to have pathologic findings of AD at autopsy and 1 met pathological criteria for progressive supranuclear palsy. Table 1 lists clinical and pathological diagnosis, sex, age at initial examination, interval from first visit to death, and the initial and last MMSE scores of the 10 patients with clinically presumed DLB.

SUMMARY OF CASE HISTORIES

Patient 1 was reported to become delusional at an MMSE score of 18. He developed spontaneous bradykinesia and a shuffling gait at an MMSE score of 15 and subsequently suffered a “collapse.” Patient 2 manifested mild bradykinesia at an MMSE score of 22 and demonstrated rigidity, tremor, and a shuffling gait at an MMSE score of 6 in the absence of neuroleptic medication. Patient 3, receiving a low as-needed dose of haloperidol (0.5 mg), manifested bradykinesia, cogwheeling, and visual hal-
lucinations at an MMSE score of 14. Patient 4 exhibited tremor and an unsteady gait at initial examination, with an MMSE score of 20. One year later, still at a score of 20 on the MMSE, he developed spontaneous rigidity, parkinsonian gait, masked facies, and bradykinesia. Patient 5 had dysarthria at an MMSE score of 23. The following year he showed spontaneous rigidity, hypophonia, masked facies, and bradykinesia with an MMSE score of 13. In patient 6, spontaneous mild bradykinesia was noted at first visit (MMSE score, 18). After 2 years the patient progressed to an MMSE score of 2 and was found to have visual and auditory hallucinations, masked facies, parkinsonian gait, and tremor. Patient 7 had postural instability at an MMSE score of 23. The following year, with an MMSE score of 17, he displayed spontaneous EPSs with masked facies, cogwheeling, bradykinesia, and visual hallucinations. Patient 8 exhibited spontaneous rigidity at his first visit (MMSE score, 20), with subsequent hypophonic speech, bradykinesia, and parkinsonian gait, all in the absence of neuroleptic medication. At an MMSE score of 3, the patient developed visual hallucinations. Patient 9 manifested spontaneous hypophonic speech, masked facies, bradykinesia, cogwheeling, tremor, and visual hallucinations at an MMSE score of 22. Patient 10 was suspected of having visual hallucinations at his first visit, with an MMSE score of 21. Two years later, at an MMSE score of 15, he developed spontaneous EPSs with parkinsonian gait, masked facies, and bradykinesia, in addition to visual hallucinations. Fluctuation in cognition was not described in any of these subjects.

**ADDITIONAL RESULTS**

We further contrasted the patients clinically misdiagnosed as having DLB (who had AD pathologic findings only) with clinical features of all patients with LBV (n = 27) and DLBD (n = 5) who had been examined and came to autopsy through our center. Demographic features and clinical characteristics of these cohorts are shown in **Table 2** and **Table 3**, respectively. In general, patients with DLBD had significantly higher MMSE scores at initial examination but shorter intervals to death than the other cohorts. Hallucinations were more prevalent in the LBV (63%) and especially in the DLBD (100%, P = .048) groups than in the misdiagnosed DLB cases with pure AD. No statistically significant differences were seen with regard to falls, loss of consciousness, or syncope

### Table 1. Characteristics of Patients Clinically Diagnosed as Having Dementia With Lewy Bodies*

<table>
<thead>
<tr>
<th>Patient No./Sex/ Age, y†</th>
<th>MMSE Score</th>
<th>Interval to Death, y</th>
<th>Pathological Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
<td></td>
</tr>
<tr>
<td>1/F/64</td>
<td>20</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>2/F/64</td>
<td>22</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>3/F/B1</td>
<td>14</td>
<td>Unstable</td>
<td>2</td>
</tr>
<tr>
<td>4/M/80</td>
<td>20</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>5/M/76</td>
<td>23</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>6/F/68</td>
<td>18</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>7/M/73</td>
<td>23</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>8/M/74</td>
<td>20</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>9/F/74</td>
<td>22</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>10/M/82</td>
<td>21</td>
<td>15</td>
<td>3</td>
</tr>
</tbody>
</table>

* MMSE indicates Mini-Mental State Examination; AD, Alzheimer disease; PSP, progressive supranuclear palsy; LBV, Lewy body variant; and DLBD, diffuse Lewy body disease.
†Age at initial examination.

### Table 2. Demographics of Patient Groups*

<table>
<thead>
<tr>
<th></th>
<th>DLBD (n = 5)</th>
<th>LBV (n = 27)</th>
<th>Misdiagnosed DLB Having Pure AD (n = 4)</th>
<th>AD (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. F/M</td>
<td>1:4</td>
<td>10:17</td>
<td>3:1</td>
<td>15:5</td>
</tr>
<tr>
<td>Age at first visit, y</td>
<td>73.4 ± 1.5</td>
<td>75.3 ± 6.3</td>
<td>72.3 ± 9.5</td>
<td>72.6 ± 6.4</td>
</tr>
<tr>
<td>Education, y</td>
<td>15.4 ± 2.0</td>
<td>13.6 ± 2.7</td>
<td>13.8 ± 7.2</td>
<td>14.0 ± 3.1</td>
</tr>
<tr>
<td>Interval to death, y</td>
<td>2.4 ± 1.1</td>
<td>3.4 ± 1.8</td>
<td>4.8 ± 3.2</td>
<td>4.7 ± 3.0</td>
</tr>
</tbody>
</table>

* DLBD indicates diffuse Lewy body disease; LBV, Lewy body variant of Alzheimer disease; DLB, dementia with Lewy bodies; AD, Alzheimer disease; and MMSE, Mini-Mental State Examination.
†P = .046, misdiagnosed DLB vs DLBD.

### Table 3. Clinical Characteristics of Patient Groups*

<table>
<thead>
<tr>
<th></th>
<th>DLBD (n = 5)</th>
<th>LBV (n = 27)</th>
<th>Misdiagnosed DLB Having Pure AD (n = 4)</th>
<th>AD (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallucinations</td>
<td>No. (%) of patients</td>
<td>Mean MMSE score</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>5 (100)†</td>
<td>21.4 ± 2.9</td>
<td>14.0</td>
<td>4.0 ± 1.0</td>
</tr>
<tr>
<td>Falls‡</td>
<td>No. (%) of patients</td>
<td>Mean MMSE score</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>1 (20)</td>
<td>19.0 ± 8.6</td>
<td>7.0</td>
<td>12.0 ± 9.7</td>
</tr>
<tr>
<td>Fluctuations</td>
<td>No. (%) of patients</td>
<td>Mean MMSE score</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>0 (0)</td>
<td>10.0 ± 1.0</td>
<td>0</td>
<td>4.0 ± 2.0</td>
</tr>
<tr>
<td>Essential tremor</td>
<td>No. (%) of patients</td>
<td>Mean MMSE score</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>4 (80)</td>
<td>22.5 ± 1.7</td>
<td>21.0 ± 1.4</td>
<td>12.5 ± 8.9</td>
</tr>
<tr>
<td>Bradykinesia§</td>
<td>No. (%) of patients</td>
<td>Mean MMSE score</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>3 (75)</td>
<td>20.7 ± 3.2</td>
<td>19.0 ± 3.6</td>
<td>18.0 ± 8.9</td>
</tr>
<tr>
<td>Rigidities§</td>
<td>No. (%) of patients</td>
<td>Mean MMSE score</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>3 (75)</td>
<td>20.0 ± 2.6</td>
<td>13.0 ± 9.9</td>
<td>5.7 ± 7.4</td>
</tr>
<tr>
<td>Masked facies§</td>
<td>No. (%) of patients</td>
<td>Mean MMSE score</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>3 (75)</td>
<td>20.7 ± 3.2</td>
<td>13.9 ± 9.6</td>
<td>6.5 ± 7.5</td>
</tr>
</tbody>
</table>

* DLBD indicates diffuse Lewy body disease; LBV, Lewy body variant of Alzheimer disease; DLB, dementia with Lewy bodies; AD, Alzheimer disease; and MMSE, Mini-Mental State Examination (mean score at which feature appeared is given); and NA, not applicable.
†P < .05, misdiagnosed DLB having pure AD vs DLBD.
‡Falls include loss of consciousness and syncope.
§Refers to exposure to neuroleptics at any point in the course of the illness.

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among the cohorts. Fluctuations in cognition, although without statistically significant differences across the cohorts, were only reported in patients with LBV. Essential tremor was not a distinguishing feature, as it occurred in 59% of the LBV, 80% of the DLBD, and 50% of the misdiagnosed DLB groups. Comparisons of EPSs were undertaken only with neuroleptic-naive subjects. Although the differences were not statistically significant, the clinically misdiagnosed DLB cases with pure AD pathologic findings had the highest prevalence of bradykinesia and gait disturbances of all 3 groups. Spontaneous parkinsonian gait occurred in 100% of the patients with misdiagnosed DLB who had pure AD pathologic findings, and only 50% of the patients with autopsy-proved LBV and 75% of those with autopsy-proved DLBD. There were also no statistically significant differences with regard to rigidity and masked facies across the cohorts.

Finally, we compared the clinical characteristics of the patients with clinically misdiagnosed DLB who had pure AD pathologic findings with those of a group of 20 patients with autopsy-proved AD, carefully matched on the basis of age at initial examination, sex, education, and initial MMSE score. There were no statistically significant differences with regard to prevalence of hallucinations, falls, cognitive fluctuations, or tremor. However, the clinically misdiagnosed DLB cases with pure AD pathologic findings showed a significantly higher prevalence of bradykinesia ($P = .02$), masked facies ($P = .02$), and gait disorder ($P = .01$).

The results of this study demonstrate that the diagnostic accuracy for DLB is poor. Dementia with Lewy bodies was confirmed at autopsy in only 50% of subjects in our series with a clinical diagnosis of DLB. The majority of the cases of clinically misdiagnosed DLB had pure AD pathologic findings. A comparison of these misdiagnosed cases with clinical features of our autopsy-proved DLBD, LBV, and carefully matched AD cases showed that the patients who were “overcalled” clinically as having DLB generally had spontaneous EPSs, despite an absence of hallucinations, at mild to moderately demented stages of disease. By moderate stages of dementia, EPSs are fairly prevalent even in “pure AD”; thus, in the absence of hallucinations, EPSs at this stage, even in neuroleptic-naive patients, fail to distinguish DLB from AD.

Dementia with Lewy bodies has only recently emerged as a clinical entity. Its criteria are still evolving. The 1996 consensus guidelines for DLB were not operational during most of this study. Retrospectively, only one of the clinically misdiagnosed DLB cases would have met criteria for probable DLB, while the other 4 would have met criteria only for possible DLB. In contrast, all of the patients with correctly diagnosed DLB would have met criteria for probable DLB according to consensus guidelines.

Extrapyramidal signs have been reported to occur earlier and to be more common in patients with DLB than AD. However, other investigators have found no difference with regard to spontaneous EPSs between AD and DLB or have reported that, although EPSs occurred more frequently in DLB, they were not detected in more than 50% of cases of DLB. Clinical case series suggest that spontaneous EPSs occur in patients with AD with mild to moderate dementia with a prevalence of 29% to 40%. Although the erroneous inclusion of cases with DLB in these studies may have accounted for this relatively high prevalence of EPSs, our results suggest that there is a subgroup of patients with AD who display EPSs at a relatively early stage and who may not be distinguishable from patients with DLB on the basis of this criterion.

Hallucinations, especially visual perceptions, have been reported to occur in up to 80% of patients with DLB, while estimated prevalences of hallucinations in AD range from 21% to 49%. Hallucinations have become a core feature in the consensus guidelines for DLB. It has been reported that hallucinations were the best early predictors for the diagnosis of DLB. In our study, hallucinations were present in 63% of the autopsy-proved cases of LBV and 100% of the autopsy-proved DLBD group. In contrast, hallucinations occurred in only 10% of our matched group of 20 patients with autopsy-proved AD. Since only 1 of our patients misdiagnosed as having DLB who had AD pathologic findings manifested hallucinations, this would suggest that the diagnostic accuracy of DLB may be improved by placing more emphasis on hallucinations in the presence of early EPSs.

An additional core feature in the consensus guidelines—fluctuation in cognition—has been reported to occur at any stage in up to 86% of patients with DLB. Interestingly, in our study, fluctuating cognitive impairment was noted to occur only in the LBV group, with a prevalence of approximately 40% in our clinical series. No cognitive fluctuations were reported in any of the autopsy-proved cases of DLBD or in the cases clinically misdiagnosed as DLB that had AD pathologic findings only. Fluctuations, however, were reported in 4 of our 20 autopsy-proved cases of AD. There are several problems with regard to the assessment of fluctuations in cognition in this and probably other studies. For instance, this entity relies heavily on opinion provided by caregivers, is poorly defined, is problematic to identify, and, in patients seen on only an annual basis, is probably difficult to remember.

Repeated falls, loss of consciousness, and syncope belong to the supportive features in the consensus guidelines for the clinical diagnosis of probable or possible DLB. In this study, single or repeated falls and loss of consciousness or syncope were as prevalent in the DLB group as in the AD group and were not helpful in differentiating between cohorts.

In the earlier Newcastle criteria for DLB, neuroleptic sensitivity syndrome had been proposed as a mandatory sign. Later, in the consensus guidelines, this was dropped as a core characteristic but remained as a supporting feature. We did not systematically investigate neuroleptic sensitivity in our cohorts because of obvious difficulties with assessment and quantification. Recent findings indicate that severe neuroleptic sensitivity may occur in up to 30% of patients with confirmed DLB; however, none of our patients with autopsy-proved DLB had a history of neuroleptic malignant syndrome or other dramatic side effects from these compounds.
Early onset of gait impairment and tremor have also been described as prominent features of DLB. In the present study, gait abnormalities or spontaneous parkinsonian gait and tremor, especially essential tremor, were not helpful in distinguishing between our autopsy-proven DLB groups and the misdiagnosed DLB group with pure AD.

Our finding that most of the misdiagnosed DLB cases had, in fact, AD pathologic findings only may be biased because we are a major referral center for AD. However, AD remains the most prevalent cause of dementia in the elderly and the most challenging entity to be differentiated from DLB. It was not the purpose of this study to investigate how often autopsy-proven DLB cases were clinically misdiagnosed as probable or possible AD. Nor did we attempt to determine clinical diagnostic accuracy for DLB at initial examination or early stages of disease. Hence, the challenge of differential diagnosis is particularly illustrative, we think, in that, for the purposes of this study, we compared the pathological diagnosis with the last recorded clinical diagnosis for each patient. Despite our access to extensive longitudinal, clinical, and neuropsychological information regarding these subjects, our diagnostic accuracy for the clinical diagnosis of DLB was poor.

Since all of the patients with correctly diagnosed DLB in the current study would have met criteria for probable DLB according to consensus guidelines, placing more emphasis on hallucinations in the presence of early EPSs (thus requiring subjects to fulfill criteria for probable, not possible, DLB) is probably necessary if one hopes to improve clinical diagnostic accuracy for DLB. Further prospective clinicopathological studies are warranted and essential in this regard. Clinical diagnostic accuracy—because of important neurobiological differences between DLB and AD—will have major implications in terms of improving the homogeneity of subjects enrolled in therapeutic research protocols.

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