An Investigation of Clinical Correlates of Lewy Bodies in Autopsy-Proven Alzheimer Disease

Yaakov Stern, PhD; Diane Jacobs, PhD; James Goldman, MD; Estrella Gomez-Tortosa, PhD; Bradley T. Hyman, MD, PhD; Yan Liu, MD; Juan Troncoso, PhD; Karen Marder, MD, MPH; Ming X. Tang, PhD; Jason Brandt, PhD; Marilyn Albert, PhD

Background: Studies of patients meeting clinical and pathologic criteria for Alzheimer disease (AD) have not consistently found associations between the presence of Lewy bodies (LBs) at postmortem examination and a higher frequency during life of the clinical features of dementia with LBs.

Objective: To evaluate the clinical correlates of LBs in patients with AD.

Design and Methods: Fifty-one patients were diagnosed as having probable AD during life and met pathologic criteria for AD. Semiquantitative ratings for LBs were obtained in 4 brain regions: substantia nigra, cingulate, insular cortex, and hippocampus. The patients had been followed up semiannually for up to 9.9 years before death, and clinical features associated with dementia with LBs, including extrapyramidal signs and visual hallucinations, were assessed at each study visit. Logistic regression analyses determined whether patients who had LBs were more likely than those without LBs to express specific clinical signs during follow-up. Cox analyses determined whether patients with LBs developed clinical signs or died earlier. Generalized estimating equations were used to compare rates of cognitive or functional change.

Results: Nineteen of the 51 patients had at least 1 LB in one of the studied regions. In no case was a significant relation noted between LBs and the presence of a measured clinical sign. No LB measure was associated with an increased risk of developing any of the evaluated clinical signs earlier in the disease. There was no association between the presence of LBs and more rapid mortality or more rapid disease progression.

Conclusions: In patients diagnosed as having AD during life, we did not observe a relation of LBs noted during postmortem examination with the presence of any clinical feature that we assessed or with the rapidity of disease progression. The relation between LBs and specific clinical manifestations may be tenuous in these patients.

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As many as one third to half of patients diagnosed as having Alzheimer disease (AD) have concomitant Lewy bodies (LBs) when examined at autopsy. Several studies have asked whether, in patients who meet clinical and pathologic criteria for AD, there are unique or additional clinical features associated with the presence of LBs. The clinical features of interest are those that have been associated with dementia with Lewy bodies (DLB), including extrapyramidal signs (EPS) and psychiatric features (especially visual hallucinations). The findings to date have been inconsistent. The present study was designed to address this issue, using patients from the Predictors Study.

The Predictors Study was designed to study the natural history of patients who meet clinical criteria for probable AD. These patients were followed up prospectively with semiannual visits for up to 9.9 years before their death, and clinical features were recorded at each visit. None of the patients in the Predictors Study could be clinically diagnosed as having DLB to the exclusion of AD. However, many had some of the clinical manifestations associated with DLB, including visual hallucinations and EPS. At autopsy, semiquantitative ratings for LBs were obtained in 4 brain regions. The present analyses determined whether those who had LBs were more likely than those without to exhibit some of the clinical features that have been associated with DLB.

RESULTS

Clinical Severity at Entry and Frequency of LBs

Most patients had mild disease severity at the intake visit; CDR was rated as mild in 84.3% (Table 1) and the mMMSE score averaged 36.9 of 57. Table 2 summa-
SUBJECTS AND METHODS

SUBJECTS

The Predictors Study cohort consists of 236 patients with probable AD recruited at 3 sites: Columbia University College of Physicians and Surgeons, New York, NY; The Johns Hopkins University School of Medicine, Baltimore, Md; and Massachusetts General Hospital, Boston. Inclusion and exclusion criteria, recruitment methods, and the full evaluation methods have been described previously.\(^1\) All patients met National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable AD,\(^2\) except that clinically silent, small subcortical lesions were allowed. To ensure that severity of dementia was mild at study entry, all patients were required to have a modified Mini-Mental State Examination (mMMSE)\(^3\) score of 30 or above (corresponding to approximately 16 on the standard MMSE). To ensure accurate initial assessment of psychotic symptoms, all patients were required to have not been taking neuroleptic medications for at least 1 month before their initial evaluation.

We attempted to follow up all subjects semiannually until they died. At the time of these analyses, 130 patients had died; autopsies were obtained for 61 of them. Final neuropathologic diagnoses are available from 57 autopsies. In 52 (91%) of these 57 cases, the diagnosis of AD was confirmed at autopsy. Two additional cases had senile changes consistent with AD that were not sufficient for the diagnosis of AD (eg, focal tangles). Of the remaining 3 patients, 2 had hippocampal sclerosis and 1 had Creutzfeldt-Jacob disease. Of the 52 patients diagnosed as having AD at postmortem examination, material for this pathologic evaluation study was available for 51.

Thus, 51 patients were members of the Predictors Study cohort who underwent autopsy, who were diagnosed as having AD at postmortem examination, and for whom sufficient postmortem material was available for these pathologic studies.

CLINICAL FEATURES

The following clinical features were assessed at each 6-month visit from the initial study visit until death.

Extrapyramidal Signs

Selected items from the Unified Parkinson’s Disease Rating Scale\(^4\) were used to rate extrapyramidal motor signs. Hypophonia, masked facies, resting tremor, rigidity (neck and each limb), bradykinesia or hypokinesia, and posture and gait abnormalities were rated as absent, slight, mild-moderate, marked, or severe (see Richards et al\(^5\) for complete form). In addition to evaluating individual motor signs, the presence or absence of EPS in general was considered. Patients who had at least 1 sign rated mild-moderate or worse were considered to have EPS, since ratings of this severity are relatively more reliable and are likely to be noted by the average clinician.\(^6\) Our analyses focused on both drug- and non–drug-induced EPS. If, at the visit when they were first detected, the patient was currently taking or had ever taken medications that could induce EPS, then the signs were considered to be drug induced. Otherwise, they were considered non–drug induced, even if at subsequent visits the patient received medications that could induce EPS.

Myoclonus

The presence of myoclonus was also assessed as part of the neurological evaluation and through a structured clinical history.

Psychosis

A semistructured interview, the Columbia University Scale for Psychopathology in Alzheimer’s Disease,\(^6\) was used to elicit information about delusions, hallucinations, and other specific behavioral signs and mental states that occurred the month before assessment. Specific delusions queried included paranoid delusions, delusions of abandonment, and each limb), bradykinesia or hypokinesia, and posture and gait abnormalities were rated as absent, slight, mild-moderate, marked, or severe (see Richards et al\(^5\) for complete form). In addition to evaluating individual motor signs, the presence or absence of EPS in general was considered. Patients who had at least 1 sign rated mild-moderate or worse were considered to have EPS, since ratings of this severity are relatively more reliable and are likely to be noted by the average clinician.\(^6\) Our analyses focused on both drug- and non–drug-induced EPS. If, at the visit when they were first detected, the patient was currently taking or had ever taken medications that could induce EPS, then the signs were considered to be drug induced. Otherwise, they were considered non–drug induced, even if at subsequent visits the patient received medications that could induce EPS.

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RELATION OF LBs TO RISK OF EXPRESSION OF CLINICAL SIGNS AND MORTALITY

Cox proportional hazard analyses were conducted to determine if the presence of LBs at postmortem examination was associated with an increased risk of expressing a clinical sign during the disease or an increased

rizes the frequency of observed LBs in the studied regions of interest. Nineteen of the 51 patients had at least one LB in one of the studied regions. Demographic and clinical features of the patients at the intake visit were compared in patients who did and did not have LBs. At the initial visit, there was no significant difference between the groups in age, mMMSE score, BDRS score, education, or frequency of patients with an APOE \(e4\) allele. Patients with LBs were more likely to be male \((\chi^2=8.1, P<.01)\). There was a trend for the patients with LBs to have a longer duration of illness at the initial study visit than those without LBs \((t=1.8, P<.09)\) and for them to have a CDR of mild vs moderate dementia severity \((\chi^2=2.5, P<.12)\).

**Table 3** summarizes the frequency of the occurrence of specific clinical features in patients with and without LBs. The relation between the presence of LBs and specific clinical features of the disease was explored using cross-tabulation, the \(\chi^2\) statistic, and logistic regression analyses. Clinical features were considered to have been present if they were expressed at any point during patient follow-up. The presence or absence of any LBs, the presence or absence of LBs in each sampled area, and the semiquantitative ratings for LBs in each sampled area were all considered in separate analyses. In each case, separate analyses explored the potential relation between LBs and each of the clinical signs listed in Table 1. Follow-up logistic regression analyses controlled for sex or duration of illness. In no case was a significant relation between LBs and the presence of a clinical sign noted.

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(Continued on next page)
Cognition

Cognitive function was examined using the mMMSE,13,17 which includes the standard MMSE,18 the Wechsler Adult Intelligence Scale digit span subtest,19 and additional attention and calculation, general knowledge, language, and construction items. The maximum score on this test is 57.

Other measures were also obtained at each study visit, including the Blessed Dementia Rating Scale (part 1)30 (BDRS) to assess functional capacity and the Clinical Dementia Rating (CDR) scale31 to rate the overall severity of the dementia.

The apolipoprotein E (APOE) ε genotypes were available for 32 of the patients. The APOE genotype was determined after isolating DNA from white blood cells and digesting the DNA with HhaI. The method for APOE genotyping by Hixson and Vernier22 was modified slightly.23

NEUROPATHOLOGIC EVALUATION

All cases considered herein met neuropathologic criteria for AD using the Consortium to Establish a Registry for Alzheimer's Disease criteria.24 In addition, the presence of LBs was evaluated.

Lewy bodies in the substantia nigra were rated as present or absent. We performed semiquantitative ratings of LBs in 3 other brain regions. Paraffin sections of cingulate, insular cortex, and hippocampus (parahippocampal cortex at the level of the lateral geniculate nucleus) were cut 7-µm thick and stained with an antibody to ubiquitin, using an avidin-biotin peroxidase technique and microwaving (10 minutes at high, 10 minutes at defrost in citrate buffer, pH 6.0, for antigen retrieval). Three randomly selected ×10 microscopic fields from each section were rated for the presence of ubiquitin-reactive inclusions, using the following scale: absent, 1 to 5 per field, 6 to 10 per field, or more than 10 per field. The mean of the 3 ratings was used as a quantitative measure of LB pathologic findings. For some analyses, LBs were also rated as present or absent in each brain region.

STATISTICAL ANALYSES

The intent of the analyses was to determine whether there were differences in the clinical presentation of patients with and without LBs. Both summary variables (such as EPS or psychosis) and specific components of these summary variables (such as rigidity or hallucinations) were included in separate analyses. The following clinical outcomes were evaluated: the presence of non–drug-induced, drug-induced, or both non–drug-induced and drug-induced EPS and specific motor signs, including tremor, rigidity, bradykinesia, gait disorder, or hypophonia; myoclonus; the presence of psychotic features and specific features, including hallucination and delusion, and mortality. The initial approach used cross-tabulation and the χ² statistic to compare the frequency of specific clinical signs at any point during follow-up in patients with and without LBs. Comparisons were conducted for each region using both the semiquantitative ratings and the present vs absent classification. In addition, patients with and without any LBs in any region were compared. Follow-up logistic regression analyses were used to control for disparities in sex and duration of illness.

Cox analyses were used to determine whether the presence of LBs at postmortem examination was associated with clinical signs emerging earlier in the disease. Cox analyses were also used to evaluate potential differences in survival among patients with and without LBs.

To determine whether the rate of decline differed in patients with and without LBs, analysis of prospective change in the mMMSE and BDRS scores was performed by applying generalized estimating equations to regression analyses with repeated measures.25

RAPIDITY OF PROGRESSION

Generalized estimating equation analyses were applied to the prospectively collected mMMSE scores. Separate generalized estimating equation analyses were conducted to assess the effect of the presence or absence of LBs in each brain region. The analyses demonstrated a significant decline in mMMSE scores over time of approximately 3.6 points per 6-month follow-up interval. Across all analyses, there were no differences between patients with and without LBs in mMMSE scores at the initial evaluation (ie, no significant group effect) or in the rate of change of mMMSE scores over time (ie, no significant interaction effect). Similar analysis of the prospectively collected BDRS scores showed no difference between the groups at the initial visit and no group differences in the rate of change over time. Thus, the rate of cognitive and functional progression of the disease did not differ across the 2 groups.

We attempted to determine if there was an association between the presence of LBs in 4 selected brain regions postmortem and clinical features noted in extensive follow-up of the patients during life. We found that the presence of LBs was not related to increased frequency of EPS in general or of any specific extrapyramidal motor sign, psychosis or any specific psychotic feature, or myoclonus. Similarly, we found no relation between LBs and increased risk of developing any of these disease features. Finally, we found no relation between LBs and more rapid disease progression or mortality.

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A major contribution of the present analyses lies in the careful clinical follow-up that patients received. The patients were studied prospectively, with semiannual examinations, for a mean ± SD of 4.6 ± 2.0 years. Clinical signs of interest were ascertained and coded in a standardized fashion at each study visit. This eliminates the potential biases inherent in deriving clinical information from retrospective chart reviews. Long-term follow-up of the patients also minimized the possibility that clinical signs were not detected at a single clinical evaluation or developed after the clinical evaluation.

We also recognize several weaknesses to the analyses presented herein. With regard to the pathologic studies, the semiquantitative analyses of LBs were limited to a small number of brain regions and did not include any regions of association cortex, and some brain samples were unavailable for some of the patients. However, we analyzed the nigra and the paralimbic regions of the brain that are among the most severely affected brain regions in DLB. We also recognize that ubiquitin may not be as sensitive or specific as α-synuclein immunostaining for detecting LBs, and in principle neurofibrillary tangles might be misidentified as LBs. However, quantitative analyses in our laboratories have shown that the number of ubiquitin-positive LBs is virtually identical to the number of α-synuclein–positive LBs, and experienced investigators can differentiate LBs from neurofibrillary tangles.

Some clinical features that have been associated with DLB (eg, falls, syncope, or fluctuations in cognitive functioning) were not formally assessed. It is possible that these might have shown a stronger relation to the presence of LBs.

It is important to stress that the present sample did not include patients encompassing the full clinical spectrum of DLB. Rather, all of the patients in the present study were diagnosed clinically as having AD, had to be mildly impaired clinically, and had to not be taking neuroleptics for 1 month before the initial evaluation. All patients were evaluated initially for cognitive as opposed to motor complaints. These data are most relevant to the issue of whether variability in the clinical spectrum in patients diagnosed clinically as having probable AD is a function of LBs. The data herein do not provide information about clinicopathologic relations in DLB.

Table 1. Demographic and Clinical Variables at the Intake Visit in Patients With and Without Lewy Bodies (LBs)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients</th>
<th>No LBs (N = 32)</th>
<th>LBs (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mMMSE score, mean (SD)</td>
<td>36.9 (6.2)</td>
<td>36.7 (6.3)</td>
<td>37.3 (6.2)</td>
</tr>
<tr>
<td>BDRS score, mean (SD)</td>
<td>9.1 (3.8)</td>
<td>9.6 (4.2)</td>
<td>8.2 (2.9)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>73.2 (8.2)</td>
<td>73.0 (9.0)</td>
<td>73.6 (6.8)</td>
</tr>
<tr>
<td>Sex, No. (%) female</td>
<td>18 (35)</td>
<td>16 (50)</td>
<td>2 (10)†</td>
</tr>
<tr>
<td>Duration of illness, mean (SD), y</td>
<td>4.4 (2.6)</td>
<td>3.9 (2.4)</td>
<td>5.3 (3.3)‡</td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>14.3 (3.1)</td>
<td>14.2 (3.1)</td>
<td>14.5 (3.1)</td>
</tr>
<tr>
<td>CDR at intake, No. (%) Mild (1)</td>
<td>43 (84)</td>
<td>25 (78)</td>
<td>18 (95)</td>
</tr>
<tr>
<td>Moderate (2)</td>
<td>8 (16)</td>
<td>7 (22)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>APOE, No. (%) with e4 allele (n = 32)</td>
<td>14 (44)</td>
<td>11 (50)</td>
<td>3 (30)</td>
</tr>
</tbody>
</table>

* mMMSE indicates modified Mini-Mental State Examination; BDRS, Blessed Dementia Rating Scale; CDR, Clinical Dementia Rating; and APOE, apolipoprotein E.

† P < .01.
‡ P < .05.

Table 2. Number of Lewy Bodies Noted at Postmortem Examination in 51 Patients*

<table>
<thead>
<tr>
<th>Insula</th>
<th>Cingulate</th>
<th>Hippocampus</th>
<th>Brainstem</th>
<th>Any</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>32</td>
<td>32</td>
<td>37</td>
<td>30</td>
</tr>
<tr>
<td>Present</td>
<td>9</td>
<td>15</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>1-5 per ×10 field</td>
<td>6</td>
<td>10</td>
<td>7</td>
<td>...</td>
</tr>
<tr>
<td>6-10 per ×10 field</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>...</td>
</tr>
<tr>
<td>&gt;10 per ×10 field</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>...</td>
</tr>
<tr>
<td>Unavailable</td>
<td>10</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

* Lewy bodies were considered to be present in any region if at least 1 per ×10 field was noted. Semiquantitative counts were not done for the brainstem. For each region, appropriate material was not available in some cases. These are noted as unavailable. For the summary variables, Lewy bodies were considered to be present if at least 1 Lewy body was present in 1 of the included areas.

Table 3. Frequency of the Occurrence of Clinical Signs at Any Time During Follow-up in Patients Without and With Lewy Bodies (LBs) at Postmortem Examination

<table>
<thead>
<tr>
<th>Clinical Sign</th>
<th>No LBs</th>
<th>Any LBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 extrapyramidal sign (mild-severe)</td>
<td>20 (87)</td>
<td>13 (87)</td>
</tr>
<tr>
<td>Rigiidity</td>
<td>23 (88)</td>
<td>16 (94)</td>
</tr>
<tr>
<td>Hypophonia</td>
<td>12 (40)</td>
<td>10 (63)</td>
</tr>
<tr>
<td>Masked facies</td>
<td>14 (61)</td>
<td>12 (75)</td>
</tr>
<tr>
<td>Tremor</td>
<td>9 (35)</td>
<td>8 (47)</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>22 (85)</td>
<td>13 (81)</td>
</tr>
<tr>
<td>Gait</td>
<td>20 (83)</td>
<td>12 (80)</td>
</tr>
<tr>
<td>Any psychotic feature</td>
<td>27 (84)</td>
<td>16 (84)</td>
</tr>
<tr>
<td>Delusion</td>
<td>26 (81)</td>
<td>16 (84)</td>
</tr>
<tr>
<td>Hallucination</td>
<td>16 (50)</td>
<td>9 (47)</td>
</tr>
<tr>
<td>Illusion</td>
<td>9 (28)</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>9 (28)</td>
<td>5 (28)</td>
</tr>
</tbody>
</table>

Table 4 summarizes other studies that have compared clinical features of patients with AD with and without LBs. For many of the clinical features addressed in these studies, the results are inconsistent. Compared with those without LBs, patients with AD with LBs have been reported to have more essential tremor and masked facies; more severe rigidity; increased bradykinesia, masked facies, shuffling gait, and rigidity; and increased frequency of 1 or more of a group of EPS, although the latter found more frequent extrapyramidal side effects of neuroleptics.

It is notable that EPS were present in 32 subjects who lacked LBs at autopsy. Another study evaluated EPS in patients with AD who had no LBs and found that they were associated with the number of neurofibrillary tangles and neuropil threads in the substantia nigra. This suggests that there can be multiple causes of EPS in AD, and their presence does not necessarily indicate the presence of LBs. A recent study of diagnostic accuracy of de-
mentia with LBs in 10 patients also found that of the 5 misdiagnosed patients 4 had AD with EPS. With regard to psychiatric symptoms, 2 studies reported increased frequency of hallucinations, delusions, and depression, and another reported increased visual hallucinations only in AD with LBs. Two other studies besides our own noted no differences in psychiatric features.

Four studies besides our own noted no difference in dementia severity in patients with AD with and without LBs. Another found that patients with AD with LBs performed worse on delayed recall on a list learning task but not on other memory measures or cognitive tests. One reported increased dementia severity. Three studies found different patterns of cognitive changes in the face of equivalent overall dementia severity. One reported that patients with AD with LBs had greater deficits in attention, fluency, and visuospatial processing. A second found that patients with AD plus LBs performed more poorly on tests of arithmetic, verbal fluency, visuospatial processing, and psychomotor speed.

The third found that patients with AD without LBs performed more poorly on the memory subscale on the Dementia Rating Scale, whereas the AD plus LB group performed more poorly on the initiation and perseveration scale.

Six studies besides our own noted no differences in rate of disease progression or survival between patients with AD with and without LBs. One study reported decreased survival time, and another reported both an increased rate of cognitive decline and decreased survival time.

Several considerations affect the interpretation of studies in this area and may account for some of the variability in findings. Since LBs are just one of many pathologic variables that may contribute to the clinical picture, it may be important to evaluate clinical correlates of LBs in the context of other pathologic indices, particularly measures of amyloid burden and cell loss; to date, this has not been done systematically. In addition, many studies, including the present one, examined brain tissue from a limited number of areas. Often,
only the presence or absence of LBs was coded. Finally, the quality of the clinical information about patients during their lifetime and the extent of clinical follow-up are variable.

In patients with AD, we did not observe any relation between the presence or absence of LBs and any clinical feature that we assessed. Despite the quality of our clinical information, one possibility is that more extensive neuropathologic analyses will be required to observe these clinicopathologic relations. The contribution of the LB to the clinical phenotype may not be sufficiently strong enough to be revealed in the presence of concomitant AD. Alternately, the relation between LBs and specific clinical manifestations may be tenuous among patients with pathologically confirmed AD.

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From the Departments of Neurology (Drs Stern, Jacobs, and Marder), Psychiatry (Drs Stern and Marder), Pathology (Drs Goldman and Liu), and Biostatistics (Dr Tang) and the Gertrude H. Sergievsky Center (Drs Stern, Jacobs, Marder, and Tang) and Taub Alzheimer's Disease Research Center (Drs Stern, Goldman, and Marder), Columbia University College of Physicians and Surgeons, New York, NY; Departments of Pathology (Dr Troncoso) and Psychiatry and Behavioral Sciences (Dr Brandt) and Alzheimer's Disease Research Center (Drs Troncoso and Brandt), The Johns Hopkins University School of Medicine, Baltimore, Md; and Departments of Neurology (Drs Gomez-Tortosa and Hyman) and Psychiatry (Dr Albert), Massachusetts General Hospital, Harvard Medical School, Boston.

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Corresponding author and reprints: Yaakov Stern, PhD, Sergievsky Center, 630 W 168th St, New York, NY 10032 (e-mail: ysll@columbia.edu).

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