Effect of Extrapyramidal Signs and Lewy Bodies on Survival in Patients With Alzheimer Disease

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Background: Patients with Alzheimer disease (AD) who have psychiatric and parkinsonian symptoms experience faster cognitive deterioration and shorter survival vs those without such disease features. Extrapyramidal signs (EPSs) in particular have been associated with the presence of Lewy bodies (LBs) on autopsy and with poorer survival in patients with AD. Lewy bodies found at autopsy are not always correlated with EPSs during late life.

Objective: To determine whether the association between LBs and age at death is modified by the presence of EPSs, hallucinations, or delusions.

Design: An autopsy series of patients with clinically diagnosed AD.

Settings: Three AD clinics (San Diego and Sacramento, Calif, and Portland, Ore).

Patients: Data on 379 patients with a clinical diagnosis of AD who were initially assessed between May 1, 1984, and August 1, 1996, and who were autopsied between January 1, 1990, and April 1, 1998, were pooled from 3 AD centers.

Main Outcome Measures: Presence of LBs on autopsy and differences in age at death in those with EPSs, LBs, or both.

Results: Individuals with EPSs at initial assessment were more than 3 times as likely to have LBs at autopsy than were those without EPSs. Age at death was younger in those with LBs and EPSs than in those with LBs only and those without EPSs or LBs.

Conclusions: The presence of EPSs in patients with AD indicates worse prognosis and may be related to underlying LBs. The presence of EPSs is a strong predictor of LBs.

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It is well recognized that disease progression and survival in patients with Alzheimer disease (AD) vary considerably from patient to patient. Although a host of clinical and demographic factors have been associated with prognosis, some of the most widely reported and replicated factors include the presence of extrapyramidal signs (EPSs) and symptoms of delusions and hallucinations.1,2 Patients with AD who have such symptoms experience faster cognitive deterioration and shorter survival compared with patients without these disease features.3 Such patients may progress more rapidly for several reasons: they may be treated more often with neuroleptic agents, they may have more advanced disease, or they may have a distinct and more fulminant type of AD. A prime candidate for a different form of AD that may progress more rapidly may be dementia with Lewy bodies (DLB) because its diagnostic hallmarks include EPSs and psychotic symptoms,4 which are associated with more rapid progression. We sought to investigate the relationship between EPSs and symptoms of delusions or hallucinations and (1) the presence of Lewy bodies (LBs) and (2) survival in a cohort of 379 autopsied individuals enrolled and followed at 3 AD centers.

Table 1 gives mean values for age at initial assessment, age at death, education, MMSE score, and survival from initial assessment overall and by pathological diagnosis status. Nearly 24% of men and 14% of women had LBs (P=.01). Age at clinical diagnosis, education, and MMSE score did not differ significantly across diagnostic categories. There were significant differences by diagnostic category for age at death and for time from initial assess-
PATIENTS AND METHODS

STUDY POPULATION

Study patients were evaluated, diagnosed, and followed clinically and autopsied as part of 3 ongoing series at dementia research programs at the National Institute on Aging Alzheimer Disease Centers at the University of California, Davis; the University of California, San Diego; and Oregon Health Sciences University. Patients provided written informed consent, and the study was approved by the institutional review boards at the respective institutions. Patients were initially evaluated at 1 of the 3 AD centers between May 1, 1984, and August 1, 1996. Only patients with a clinical diagnosis of AD who were autopsied between January 1, 1990, and April 1, 1998, were included (N = 379). Although these AD centers did not originally collaborate on data collection or attempt to coordinate protocols for this study, each followed comparable and standardized research protocols for clinical and pathological evaluation and made clinical and pathological diagnoses using the same guidelines. Individuals with DLB were excluded because they do not meet CERAD (Consortium to Establish a Registry for Alzheimer’s Disease) criteria for AD. Each contributing site had few such patients, and there was not sufficient power to analyze DLB as a subgroup. Patients with a clinical diagnosis of LBs or DLB also met criteria for possible AD. Because DLB criteria were not published until 1996, they were not available for most patients in this study.

Patients at each AD center underwent a comprehensive initial evaluation that included neurological, psychiatric, and medical histories; a structured neurological examination; psychometric testing; laboratory testing to exclude treatable or reversible causes of dementia; and review of neuroimaging studies. At the initial assessment, patients were asked for autopsy consent. For this analysis, each center provided demographic information, initial Mini-Mental State Examination (MMSE) scores, and information on symptoms of delusions or hallucinations and EPSs from each patient’s initial evaluation. A structured examination of parkinsonian features (EPSs) was carried out by a neurologist (W.J.J., D.G., and J.K.) for each patient included in this analysis. All 3 AD centers have used the Unified Parkinson’s Disease Rating Scale since the early 1990s, and the sample was restricted to patients autopsied from 1990 onward. Before use of the Unified Parkinson’s Disease Rating Scale, a structured neurological examination rating most aspects of parkinsonism that are assessed in the Columbia Rating Scale was used. Extrapyramidal signs were defined as present if at least 2 of the following signs were noted: bradykinesia, rigidity, rest tremor, parkinsonian gait, and masked facies.

Information about the presence or absence of delusions and hallucinations was also collected from informants of patients using semistructured interviews. From 1985 onward, the Diagnostic Inventory Schedule was used as a structured inquiry about psychiatric symptoms and alcohol use. Cases with AD and LBs are equivalent to the LB variant of AD. Patients were selected for inclusion in this analysis based on neuropathological diagnoses. All patients who met CERAD criteria for definite, probable, or possible AD were included. These patients were then categorized as to the presence or absence of LBs in the brain in at least 1 of the following areas: substantia nigra, nucleus basalis of Meynert, temporal lobe, frontal lobe, parietal, cingulate cortex, and hippocampal structures. Counts of the total number of LBs in each brain by region were not available; therefore, LBs were simply categorized as present or absent. Sixty-two percent of patients who died were autopsied during the study (January 1, 1990, to April 1, 1998).

AUTOPSY EVALUATION

All 3 AD centers used a similar set of procedures to examine brains at autopsy. The brain was removed, usually

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within 24 hours of death, and sagittally divided. Coronal slices were cut and examined for infarcts and other gross pathological features. Half of each brain was frozen for neurochemical examination, and the other half was fixed in formalin, stained, and examined microscopically. Sections from standardized brain regions were examined for AD pathological features and other lesions, as specified by the CERAD recommendations for autopsy evaluation. At each AD center, paraffin blocks were obtained from at least the following regions: the neocortex of the frontal, parietal, superotemporal, and occipital lobes; hippocampus; entorhinal cortex; amygdala; substantia innominata; substantia nigra; basal ganglia; pons; and cerebellar vermis. Sections from all blocks were stained with hematoxylin-eosin, and additional staining methods were used to detect plaques and tangles (thioflavin-S at the San Diego center and Bielschowsky silver impregnation at the Davis and Oregon centers). Plaques and tangles were visually counted on 10-µm sections of each neocortical and hippocampal area. After surveying each section to find areas with the most lesions, senile plaques were counted in 5 microscopic fields (original magnification ×125), and neurofibrillary tangles were counted in 3 fields (original magnification ×500). Lewy bodies were initially detected by examining hematoxylin-eosin–stained sections of substantia nigra and other subcortical and neocortical areas and were confirmed by immunostaining with antibodies against ubiquitin. The neuropathological diagnosis of AD was based on semiquantitative assessment of the frequency of neuritic plaques, adjusted for age according to CERAD guidelines.

STATISTICAL METHODS

Extrapyramidal signs, psychiatric symptoms, LBs, and AD diagnosis were coded as binomial variables. Univariate and bivariate descriptive analyses of categorical variables were performed using percentage and frequency distributions. Mean differences by LBs for age at initial assessment and at death, years of education, and MMSE score at initial assessment were compared using analysis of variance (SAS PROC GLM; SAS Institute Inc, Cary, NC). The percentages of EPSs, delusions, and hallucinations were examined overall and were compared with respect to the presence or absence of LBs. Differences at AD centers with respect to the occurrence of LBs, psychiatric symptoms, and EPSs were also compared using a logistic regression model. Center was included as a covariate in all regression models. We first examined differences in survival using a life-table approach (PROC LIFETEST; SAS Institute Inc), with age at death as the time variable. Log-rank tests were used to test survival differences across strata categorized by the presence or absence of LBs and EPSs. We further examined survival differences by the presence or absence of EPSs and LBs, with age at death as the dependent variable in a regression model. The statistical model used was a life-table regression procedure (PROC LIFEREG; SAS Institute Inc), with a Weibull distribution assumption for failure time included. The LIFEREG procedure fits parametric models to failure time data that can be right, left, or interval censored. The models for the response variable consist of a linear effect composed of the covariates and a random disturbance term. The random disturbance term in this study was a Weibull distribution. The PROC LIFEREG estimates the SEs of the variable estimates from the inverse of the observed information matrix. The accelerated failure time model assumes that the effect of independent variables on an event time distribution is multiplicative on the event time. This model included age at death as the dependent variable and EPSs, LBs, or combined EPSs and LBs along with a variable accounting for AD center. Other potentially important confounders (age at initial assessment, sex, educational level, and MMSE score) were examined. These did not affect the statistical significance or the magnitude of the association between EPSs, LBs, or EPSs and LBs and were not included in the final model.

<table>
<thead>
<tr>
<th>Table 2. Characteristics of 379 Autopsied Patients With Alzheimer Disease by Alzheimer Disease Center From an ANOVA Regression Model*</th>
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<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Age at initial evaluation, y†</td>
</tr>
<tr>
<td>Age at death, y</td>
</tr>
<tr>
<td>Education, y†</td>
</tr>
<tr>
<td>Modified Mini-Mental State Examination score‡</td>
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<tr>
<td>Time from initial assessment to death, y‡</td>
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*Data are given as mean (SD). ANOVA indicates analysis of variance.
†Group effect, P < .05.
‡Group effect, P < .001.

AD center. The Sacramento and Oregon centers did not differ on any of these measures.

Table 3 gives percentages and odds ratios with 95% confidence intervals from a logistic regression model for the association between EPSs, hallucinations, or delusions and the presence or absence of LBs. Patients with EPSs had a 3.5-fold increased risk of LBs, and those with hallucinations had a 3.6-fold increased risk of LBs on autopsy. Delusions were not associated with an increased risk of LBs. Most patients with LBs did not have EPSs, hallucinations, or delusions (57%). However, the ability of EPSs to predict the presence of LBs was relatively low. The sensitivity and specificity of EPSs in detecting LBs were 36% and 87%, respectively. The positive predictive value was 39%, and the negative predictive value was 85.3%. The overall prevalence of LBs in patients with
EPSs was 39% (26/67). The absence of EPSs was a strong predictor of a lack of LBs found on autopsy.

Life-table analyses were used to examine unadjusted differences in age at death for patients with LBs, EPSs, and LBs and EPSs combined compared with those with neither diagnosis (Figure). All 3 groups with pathological symptoms from LBs or EPSs differed significantly from those with no pathological symptoms (log-rank test for model, 13.8; \( P = .003 \)). Among patients with at least 1 pathological symptom, those with EPSs only had the longest survival (oldest age at death), followed by patients with LBs only.

Survival differences by LBs, EPSs, and LBs and EPSs combined were further examined using a regression model with a Weibull distribution that included adjustment for AD center and had age at death as the dependent variable (Table 4). The estimates shown are exponentiated regression coefficients. For a 5-year difference in age at death, survival among patients with EPSs and LBs combined was significantly worse compared with those with no pathological diagnosis and those with either pathological diagnosis. Survival rates in those with LBs or EPSs only were worse compared with those with no pathological disease, but the 95% confidence interval included 1.0. Inclusion of AD center also did not affect the significance or magnitude of the association between pathological diagnosis and age at death.

**COMMENT**

We found that patients with AD who have LBs die at a significantly earlier age than those who do not have LBs. Among those with EPSs only, the overall survival rate is substantially worse compared with those with no pathological disease. The survival rate is significantly worse in those with both LBs and EPSs, suggesting a synergistic effect and that EPSs may be associated with more advanced disease. These findings agree with those of many previous studies\(^1\) that the presence of clinical signs of EPSs may be a prognostic indicator for survival in patients with AD. However, our results extend those of these studies by linking the clinical signs to the presence of LBs and by linking the presence of LBs to survival. Although EPSs are not sensitive as indicators of the presence of LBs, the absence of EPSs is a fairly strong indicator that LBs are not present (specificity). The positive and negative

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**Table 3. Association Between Extrapyramidal Signs and Psychiatric Symptoms and LBs From a Logistic Regression Model**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Without LBs, No. (%)</th>
<th>With LBs, No. (%)</th>
<th>Odds Ratio (95% CI) (LBs/No LBs)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrapyramidal signs (n = 67)</td>
<td>41 (61.2)</td>
<td>26 (38.8)</td>
<td>3.52 (1.90-6.60)</td>
</tr>
<tr>
<td>Hallucinations (n = 63)</td>
<td>41 (65.1)</td>
<td>22 (30.6)</td>
<td>3.60 (1.70-7.80)</td>
</tr>
<tr>
<td>Delusions (n = 128)</td>
<td>99 (77.3)</td>
<td>29 (22.6)</td>
<td>1.10 (0.50-2.10)</td>
</tr>
<tr>
<td>No symptoms (n = 199)</td>
<td>175 (57.0)</td>
<td>24 (33.3)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval; LBs, Lewy bodies.
†From a logistic regression model including age, sex, and Mini-Mental State Examination score.
The presence of EPSs may mean different things in different patients. Three hallmark clinical features of DLB have been defined recently: fluctuation, parkinsonism, and visual hallucinations. To our knowledge, ours is the largest study by Lopez and colleagues also did not differ from patients without LBs with respect to survival rate and cognitive and functional decline. Patients with LBs in the study by Lopez and colleagues also did not differ from patients without LBs with respect to survival. These findings are consistent with standard pathological practice at the site. We therefore did not try to evaluate LB density or burden as a variable but used the simplest possible categorization of LBs being present or absent in any location in the brain. This approach would tend to bias our results toward the null hypothesis because presumably patients with more LBs would have a worse prognosis, and we have combined them with those with only 1 LB.

The method of detecting LBs, using hematoxylin-eosin and anti-ubiquitin staining, may be less sensitive for appreciating the full extent of LB pathological effects than immunostaining for α-synuclein. However, the techniques used and the areas of brain tissue examined were consistent with standard pathological practice at the time and were based on examination of representative sections from a broad set of brain regions.

Despite the reasonable similarity of procedures across AD centers, several factors may limit the interpretation of our results. There were center differences in a variety of demographic and clinical variables. We adjusted for AD center in all multivariate analyses to minimize this variability. Because we measured dementia severity (MMSE), EPSs, and psychiatric symptoms at the initial evaluation only, we have no way of knowing whether or when patients may have developed these symptoms during follow-up. This constitutes a form of misclassification that would be likely to attenuate the association found between these symptoms and survival. Differences by AD center in the prevalence of EPSs, hallucinations, and delusions may reflect differences in specific ratings or their predictive values of EPSs for LBs are fairly high as well. However, most patients with EPSs do not have LBs, and there is not a perfect correlation between this symptom and underlying LBs.

Table 4. Association Between Age at Death (1-Year Difference) in Autopsied Patients With a Clinical Diagnosis of AD With LBs, EPSs, or Both From a Regression Model (Weibull Distribution) Including AD Center

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Estimate (Exp)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewy bodies (0,1)</td>
<td>0.97†</td>
<td>0.94-1.00</td>
</tr>
<tr>
<td>EPSs (0,1)</td>
<td>0.97†</td>
<td>0.95-1.00</td>
</tr>
<tr>
<td>Both (0,1)</td>
<td>0.93†</td>
<td>0.90-0.97</td>
</tr>
<tr>
<td>Neither</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

*AD indicates Alzheimer disease; LBs, Lewy bodies; EPSs, extrapyramidal signs; Exp, exponentiated; CI, confidence interval; and ellipses, not applicable.
†Compared with no EPSs or Lewy bodies.
interpretation or differences in referral patterns among centers. We also excluded patients in whom Parkinson disease may have preceded dementia, which has not always been done in autopsy series of AD with LBs.

Extrapyramidal signs at initial assessment are associated with the presence of LBs, and EPSs and LBs are independently associated with shorter survival. Furthermore, the presence of EPSs and LBs in the same individual is associated with a still poorer survival rate than either finding alone. These results have consequences for our understanding of the pathogenesis of DLB. They confirm the association between LBs and specific symptom complexes such as EPSs and specific psychiatric symptoms (delusions and hallucinations). However, they suggest that the relationship among EPSs, LBs, and survival rate is not straightforward because EPSs and LBs contribute independently to survival. Finally, these results suggest that the presence or absence of EPSs adds to the prediction of LBs and thus provides additional pathologic prognostic information.

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Author contributions: Study concept and design (Drs Haan, Jagust, and Galasko); acquisition of data (Drs Haan, Jagust, Galasko, and Kaye); analysis and interpretation of data (Drs Haan, Jagust, Galasko, and Kaye); drafting of the manuscript for important intellectual content (Drs Haan, Jagust, Galasko, and Kaye); statistical expertise (Dr Haan); obtained funding (Drs Jagust and Kaye); administrative, technical, and material support (Drs Haan, Jagust, Galasko, and Kaye); study supervision (Dr Jagust).

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