Predicting Lewy Body Pathology in a Community-Based Sample With Clinical Diagnosis of Alzheimer's Disease

Debby Tsuang, MD, MSc, Kate Simpson, MPH, Eric B. Larson, MD, MPH, Elaine Peskind, MD, Walter Kukull, PhD, James B. Bowen, MD, Wayne McCormick, MD, Linda Teri, PhD, Thomas Montine, MD, PhD, Mary Lou Thompson, PhD, and James B. Leverenz, MD

ABSTRACT

Accurate antemortem prediction of Lewy body pathology in patients with dementia is problematic. This study generates a model that better predicts Lewy body pathology in community-based patients with clinical Alzheimer's disease. Lewy body pathology was detected in 80 of 152 participants (52.6%) with an initial diagnosis of probable Alzheimer's disease. In a stepwise logistic regression model, female gender, lower education, being married, bradykinesia, hallucinations, and absence of irritability predicted the greatest likelihood of Lewy body pathology. The predictive model correctly diagnosed Lewy body pathology with an estimated sensitivity of 75%, specificity of 68%, and accuracy of 72%; the area under the receiver operating characteristic curve was 0.75. In a community-based autopsy sample, this predictive model confirmed parkinsonism and hallucinations as important predictors of Lewy body pathology in patients with clinical Alzheimer's disease. The model also identified other demographic and clinical characteristics that might enhance the prediction of Lewy body pathology. (*J Geriatr Psychiatry Neurol* 2006; 19:195-201)

Keywords: clinical-neuropathological; dementia; Alzheimer's disease; Lewy bodies; prediction

Lewy body pathology (LBP), including both "classic" brainstem Lewy bodies (LB) and α-synuclein pathological changes, is a common neuropathological finding in dementia patients. However, accurate antemortem diagnosis of LBP in dementia patients remains difficult.[1] This is particularly true for patients with coexistent Alzheimer's disease (AD) pathology.[2] Because of differences in course of illness and response to treatment between patients with and without LBP, early and accurate clinical identification of LBP patients with dementia consistent with AD is important.

Several studies suggest that patients with both AD and LBP demonstrate more rapid disease progression than AD patients without LBP.[3,4] In addition, patients with LBP are more likely to have severe psychiatric disturbance (specifically visual hallucinations) early in their clinical course.[5] Dementia patients with LBP may also respond more favorably to treatment with cholinesterase inhibitors[6] but are more likely to develop hypersensitivity reactions to antipsychotic medications.[7] Therefore, accurate clinical identification of those AD patients with LBP could lead to different management strategies in these patients.[8]

Despite the value of clinically distinguishing between dementia patients with and without LBP, currently

Received November 3, 2005. Received revised February 3, 2006. Accepted for publication February 8, 2006.

From the University of Washington Departments of Psychiatry and Behavioral Sciences (Dr Tsuang, Ms Peskind, and Drs Leverenz and Simpson), Epidemiology (Dr Kukull), Neurology (Drs Bowen and Leverenz), Internal Medicine (Drs Larson and McCormick), Pathology (Dr Montine), and Biostatistics (Dr Thompson) and the School of Nursing (Dr Teri), Seattle, WA; Mental Illness Research, Education, and Clinical Center, Seattle, WA (Drs Tsuang, Peskind, Leverenz); Parkinson's Disease Research, Education, and Clinical Center, VA Puget Sound Health Care System, Seattle, WA (Dr Leverenz); and Center for Health Studies, Group Health Cooperative (Dr Larson).

Supported by NIA U01AG06781, RO1-AG10845, AG05136, AG06781, and the Department of Veterans Affairs.

Presented as a poster at the annual American Neurological Association meetings, San Diego, CA, September 2005.

Address correspondence to: Debby Tsuang, MD, MSc, VAPSHCS 116, 1660 S. Columbian Way, Seattle, WA 98108; e-mail: dwt1@u.washington.edu.

DOI: 10.1177/0891988706292755

available clinical diagnostic criteria lack consistent validity and applicability in these participants. The most commonly used clinical criteria are those published in 1996 to identify dementia with Lewy bodies (DLB), a distinct clinical syndrome. The consensus criteria for the clinical diagnosis of "probable DLB" proposed by the Consortium on DLB[9] require, in addition to the presence of dementia, 2 of 3 "core" features including fluctuating cognition, recurrent visual hallucinations, and spontaneous motor features of parkinsonism. However, these criteria have demonstrated inconsistent validity across studies. Sensitivity (accurately diagnosing LBP) estimates in particular have ranged from a high of 83%[10] to a low of 30.7% for probable DLB.[1] Specificity (accurately not diagnosing LBP) is typically higher, ranging from 95% to 100%. The low sensitivity is attributable to the observation that many patients with dementia with LBP determined at autopsy never fulfill clinical criteria for DLB. Therefore, improvement in sensitivity would be valuable.

Most diagnostic utility studies have evaluated the sensitivity and specificity of the DLB consensus criteria in autopsied dementia samples. These studies were not designed to generate a set of characteristics that best predict LBP in clinical AD. In fact, only a few studies selected patients with clinical diagnosis of AD.[1,11] In one of the studies, Stern and colleagues[11] did not use α-synuclein immunostaining for the detection of LBP. On the other hand, whereas Lopez and colleagues[1] used α-synuclein immunostaining, they included only cases with cortical LBs as LBP positive. Therefore, LBP-positive cases were likely underdiagnosed in both studies.

In the current study we hypothesized that in patients diagnosed with clinical AD, those with pathologically confirmed LBP would exhibit distinct demographic and clinical characteristics compared with those without LBP. In our study, instead of applying existing clinical DLB criteria, we diverged by exploring the characteristics that predict the presence of LBP in patients with clinical diagnosis of probable AD. The study sample was limited to those with initial clinical diagnosis of AD who subsequently underwent systematic neuropathological assessments with standard histology and α-synuclein immunohistochemical staining for the detection of LBP.

METHODS

Sample

Participants were enrolled by the University of Washington Alzheimer's Disease Patient Registry (ADPR) from the Group Health Cooperative, a well-established consumer-owned health maintenance cooperative (HMO) in the Puget Sound area. The purpose of this registry was to identify and enroll new patients with dementia who required medical attention among persons enrolled in the central Seattle region of the HMO. The eligibility of persons arriving at clinics with symptoms potentially consistent with previously undiagnosed dementia was determined through the review of specialty and primary care clinic logs, hospital records, head computed tomography (CT) scans, and referrals from primary care practitioners and neurologists. The majority of referred patients, 48.8%, were from the participant's primary care physician.[12] In addition, 19.8% of the referrals were based on a participant's CT scan of the brain and 10% were referred from hospital admission records. Other sources for participants included emergency room logs and mental health specialists. Persons with symptoms of memory loss suggestive of dementia were enrolled into the ADPR, where they were given a full work-up for possible dementia followed by differential diagnosis. Those persons who previously had been diagnosed with dementia for more than 1 year (prevalent cases) were excluded from the study. Approximately 20% of persons initially identified as having cognitive impairment declined to participate in the ADPR, and an additional 14% declined to give informed consent.[13]

Participants underwent detailed clinical and neuropsychological assessments. Using all assessments, we applied criteria for dementia from the *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed rev; *DSM-III-R*)[14] and the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).[15] All participants were followed annually with updates on interval medical history and repeat neuropsychological and behavioral assessments. This sample closely resembles the demographics of the general elderly population in the region and has been described in greater detail elsewhere.[12,16-18] Nine hundred and eighty-seven individuals were initially evaluated between 1987 and 1996. Of the 929 participants with necessary clinical information available, 653 met initial *DSM-III-R* criteria for any type of dementia at intake, whereas 276 did not meet criteria for dementia and were excluded. Of 653 initially demented, 431 met *DSM-III-R* diagnosis of probable AD whereas 222 had other types of dementia. Of 431 participants with initial diagnosis of probable AD, 338 have died, 43 are still alive, and 50 have discontinued. Of the 338 deceased participants initially diagnosed with AD, 152 of these have had research neuropathological work-up completed and are included in this analysis.

Assessment of Clinical Features

Research assessments by the ADPR research nurse and psychometrists were conducted prospectively on an annual basis for each participant in the ADPR. These evaluations included physical examination, abbreviated

Table 1. Comparison of Clinical Signs and Symptoms Among LBP-Positive and LBP-Negative Participants

Parkinsonism	*LBP Positive (n = 80) n (%)*	*LBP Negative (n = 72) n (%)*	P *Value*[a]
Tremor	9 (11.3)	7 (9.7)	.76
Rigidity	9 (11.3)	5 (6.9)	.36
Bradykinesia	**15 (18.8)**	**5 (6.9)**	**.03**
Postural/gait	**23 (28.8)**	**13 (18.1)**	**.12**
Masked facies	**8 (10.0)**	**3 (4.2)**	**.17**
Postural instability	**15 (18.8)**	**8 (11.1)**	**.19**
Shuffling gait	**15 (18.8)**	**6 (8.3)**	**.06**
Multiple falls	**22 (27.5)**	**13 (18.1)**	**.17**
Neuropsychiatric symptoms			
Delusions	49 (61.3)	44 (61.1)	.99
Hallucinations	**48 (60.0)**	**24 (33.3)**	**.001**
Agitation	56 (70.0)	50 (69.4)	.94
Depression	51 (63.8)	44 (61.1)	.74
Anxiety	53 (66.3)	51 (70.8)	.54
Apathy	56 (70.0)	45 (62.5)	.33
Disinhibition	**12 (15.0)**	**6 (8.3)**	**.20**
Irritability	**40 (50.0)**	**43 (59.7)**	**.23**
Lability	35 (43.8)	29 (40.3)	.67
Aberrant motor behavior	54 (67.5)	46 (63.9)	.64
Hypersomnia	16 (20.0)	13 (18.1)	.76

Note: Signs and symptoms that differ between the 2 groups with $P < .20$ are in bold.
a. Chi-square statistic with one degree of freedom.

neuropsychological evaluation, and assessment of cognitive and behavioral symptoms. However, no structured interviews or examinations were implemented as part of the initial study.

For the present study, a geriatric psychiatrist (EP) conducted a comprehensive and blinded (to pathological findings) review of the physicians' initial examinations, cognitive and behavior scales, and annual follow-up research evaluations. For assessment of medical and neurological signs and symptoms, the blinded reviewer determined whether specific cardiovascular, neurological, and psychiatric signs and symptoms were absent, present, possible, or unknown during the course of illness. Because the focus of this study was LBP, we targeted behavioral and parkinsonian signs and symptoms in our analyses. For behavioral symptoms, the categories (delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, lability, and aberrant motor behavior) of the Neuropsychiatric Inventory (NPI)[19] were used as guidelines while we reviewed the medical records. Participants with either hallucinations or delusions were considered to be "psychotic." Participants who had a diagnosis of Parkinson's disease (PD) and/or who, based on the neurological examinations, demonstrated motor signs and symptoms that appeared to be parkinsonian in nature (including tremor, rigidity, bradykinesia, postural/gait, masked facies, postural instability, shuffling gait, and/or falls) were considered to have parkinsonian signs/symptoms. Targeted clinical symptom categories were collapsed to indicate "ever present" (present or possible) or "never present" (absent or unknown) during the course of illness.

Neuropathological Evaluation

All autopsy subjects received a standard neuropathological work-up, including gross and microscopic examinations. Histological evaluations include hematoxylin-eosin, modified Bielschowsky, and thioflavine S staining. In addition, α-synuclein immunostaining (antibody LB509, dilution, 1:400; Zymed, San Francisco, CA) was performed to fully characterize LBP in each case. The substantia nigra, hippocampus, parahippocampal gyrus, amygdala, cingulate gyrus, and frontal cortex were reviewed for the presence of LBP.[20,21] Cases were divided into 2 subgroups based on neuropathological findings: (1) LBP negative = no LBP in any region; (2) LBP positive = α-synuclein immunopositive inclusions in the brainstem, limbic system, or neocortex.

Statistical Analysis

Demographic and clinical characteristics were initially evaluated for associations with presence of LBP using *t* tests for continuous variables and chi-square tests for categorical variables.

The model used to estimate the probability of LBP in participants diagnosed with clinical AD included demographics (gender, education, marital status, age at intake) and the NPI categories and specific parkinsonian signs and symptoms shown in Table 1. Predictors of LBP were evaluated using backward stepwise logistic regression, with probability of entry into the model set at 0.15 and probability of removal set at 0.20. It has been shown that optimal rules (ie, those with highest sensitivity for any given specificity) for classifying disease status (here LBP) using multiple predictors are based on thresholds for the probability of disease, given the predictors.[22,23] A priori–specified interactions between presence of hallucinations and the signs and symptoms shuffling, bradykinesia, rigidity, and pacing and between pacing and the signs and symptoms shuffling, bradykinesia, and rigidity were explored using the Mantel-Haenszel test of homogeneity.

The fitted model results in an estimated probability of an individual having LBP, given his or her particular constellation of demographics, signs, and symptoms. Individuals whose predicted probability lay above a certain threshold were than classified as "predicted LBP positive" and individuals below that threshold were classified as "predicted LBP negative." To evaluate the predictive accuracy of the models, we estimated sensitivity, specificity, and overall accuracy for a range of probability thresholds (from 0.4 to 0.6). Because these accuracy estimates were based on the same sample that was used to fit

Table 2. Comparison of Demographic and Clinical Characteristics Lewy Body Pathology (LBP)-Positive and LBP-Negative Participants

Characteristic	*LBP Positive (n = 80) n (%)*	*LBP Negative (n = 72) n (%)*	P *Value*[a]
Female	50 (62.5)	40 (55.6)	.38
Caucasian	78 (97.5)	67 (93.1)	.19
Educated beyond high school	30 (37.5)	36 (50.0)	.12
Married at intake	51 (63.8)	33 (45.8)	0.03
		Mean (SD)	P *Value*[b]
Age at intake	78.6 (6.0)	79.8 (7.6)	.28
Age at death	84.1 (5.3)	84.7 (7.4)	.58
Duration of illness	7.9 (3.0)	7.1 (3.2)	.13
Duration of follow-up	5.0 (2.7)	4.4 (2.8)	.15
Initial MMSE	18.3 (5.4)	20.1 (5.1)	.04
Final MMSE	9.3 (6.8)	13.9 (7.4)	.0001
Years between last MMSE and death	2.8 (2.1)	2.2 (2.2)	.11
Years between last assessment and death	0.6 (0.3)	0.5 (0.3)	.40

Note: MMSE, Mini-Mental State Examination.
a. Chi-square statistic with one degree of freedom.
b. *t* statistic.

Table 3. Stepwise Logistic Regression Estimates for Demographic and Clinical Characteristics as Predictors of the Presence of Lewy Body Pathology

Characteristic	*Odds Ratio*	*95% CI*	P *Value*
Female	3.2	1.2, 8.4	.02
Educated beyond high school	0.45	0.21, 0.94	.04
Married	4.0	1.6, 10.1	.004
Bradykinesia	4.7	1.2, 17.8	.02
Hallucinations	3.4	1.6, 7.2	.001
Irritability	0.44	0.21, 0.93	.03

Note: CI, confidence interval.

the predictive models, we also estimated the "optimism" of the accuracy statistics using 200 bootstrapped samples.[24]

We also explored models based on broad categories of signs and symptoms, but the model including individual behavioral and parkinsonian signs and symptoms had the highest accuracy estimates among the models explored, and these are the results that we report here.

RESULTS

Neuropathological findings of 152 patients with clinical diagnosis of probable AD were available. Of these, 80 patients had LBP, whereas 72 patients did not. Sixty-five of the 80 LBP-positive participants (81.2%) also fulfilled pathologic criteria for AD (Braak stage IV and above and CERAD plaque score B or C[25]). On the other hand, 47 of the 72 LBP-negative participants (65.3%) fulfilled pathologic criteria for AD.

Table 2 displays the demographic characteristics of the sample. LBP-positive participants were more likely than LBP-negative participants to be married at intake (63.8% vs 45.8%, respectively, $P = .03$).

Note that there are discrepancies between "years between last Mini-Mental State Examination (MMSE) and death" and "years between last assessment and death" in that participants were often too impaired to undergo MMSE testing, but caregivers were available to provide information for other assessments (eg, functional status and behavioral complications).

Table 1 compares clinical signs and symptoms between LBP-positive and LBP-negative participants. Nineteen percent of LBP-positive participants had bradykinesia during their course of illness, compared with 7% of LBP-negative participants ($P = .03$). Sixty percent of LBP positive participants had experienced any kind of hallucinations versus 33% of LBP-negative participants ($P = .001$).

In a stepwise logistic regression model evaluating the demographic characteristics from Table 2 (except for race, initial and final MMSE, years between last MMSE and death, and duration between last assessment and death) and the clinical signs and symptoms from Table 1, female gender, lower education, being married at intake, bradykinesia, hallucinations, and the absence of irritability predicted greater odds of the presence of LBP (Table 3). We noted that absence of irritability was particularly associated with LBP when hallucinations were also present. However, estimated interaction (effect modification) of irritability and hallucination was not significant, possibly because of small sample sizes. Because no interactions were significant, none were included in the models.

The estimated prediction model was as follows:

$$\begin{aligned}\text{Logit (Probability[LBP])} = {} & -1.28 + 1.17\ (\text{Female}) \\ & - 0.80\ (\text{Educated beyond high school}) \\ & + 1.38\ (\text{Married at intake}) \\ & + 1.23\ (\text{Hallucinations}) \\ & + 1.54\ (\text{Bradykinesia}) \\ & - 0.82\ (\text{Irritability})\end{aligned}$$

Each variable on the right-hand side of the equation is "1" if the condition is present and "0" otherwise. For example, for a woman with clinical diagnosis of AD, with less than high school education, who was married at intake, and who exhibited hallucinations but no bradykinesia or irritability anytime during the course of illness, the model would predict the likelihood of having LBP at autopsy as follows:

$$\begin{aligned}\text{Logit (Probability[LBP])} = {} & -1.28 + 1.17\ (1) - 0.8\ (0) + \\ & 1.38\ (1) + 1.23\ (1) + 1.54\ (0) \\ & - 0.82\ (0) = 2.5\end{aligned}$$

Table 4. Estimates of Accuracy Characteristics for Stepwise Logistic Regression Model in Predicting the Presence of Lewy Body Pathology

Probability Cutoff [a]	*Accuracy*	*Optimistic Estimate, %*	*95% CI*	*Estimated optimism (%)* [b]	*95% CI*
.4	Sensitivity	83	72, 90	8.6	7.9, 9.3
	Specificity	51	39, 63	8.2	7.4, 9.0
	Overall accuracy[c]	68	60, 75	8.7	8.2, 9.3
.5	Sensitivity	75	64, 84	8.7	8.0, 9.5
	Specificity	68	56, 79	9.4	8.6, 10.2
	Overall accuracy	72	64, 79	9.4	8.8, 9.9
.6	Sensitivity	51	40, 63	8.3	7.6, 9.0
	Specificity	79	68, 88	8.8	8.1, 9.6
	Overall accuracy	64	56, 72	8.9	8.4, 9.5

Note: CI, confidence interval.
a. All individuals with estimated probability of LBP > cutoff, classified as LBP positive.
b. Estimate of expected optimism in same-sample accuracy estimate
c. Fraction of correct classifications overall (LBP positive and negative).

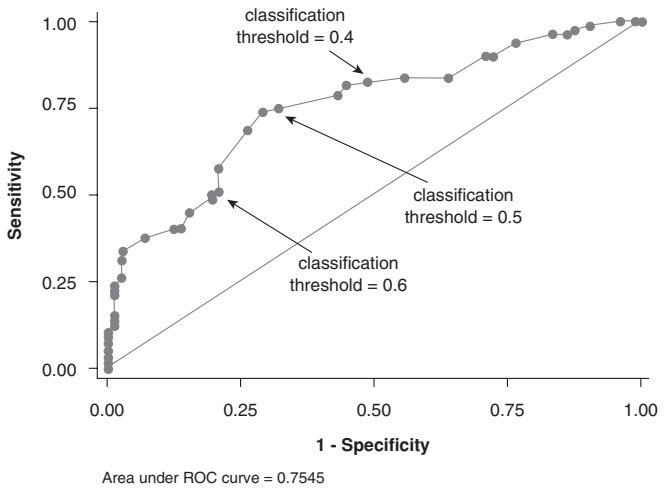

Figure 1. Receiver operating characteristic curve displaying the estimated sensitivity and specificity for predicting LBP based on the model in Table 3.

Hence the estimated Probability(LBP), or probability of having LBP, for this individual would be .92 (probability $[e^{2.5}/(1 + e^{2.5})] = .92$) or 92%, given that the participant was clinically diagnosed with AD. Note that this predictive model is most applicable when signs and symptoms were assessed throughout the course of illness because we have evaluated presence or absence of clinical symptoms over the entire duration of follow-up.

Table 4 explores model accuracy estimates at different probability thresholds for classifying participants as LBP positive. Note that 53% of participants in this study had LBP. Considering all participants with an estimated probability of LBP from the above model of 0.5 or greater to be LBP positive, the predictive model estimated sensitivity of 75% (95% confidence interval [CI] 64% to 84%), specificity of 68% (95% CI 56% to 79%), and overall accuracy of 72% (95% CI 64% to 79%).

Figure 1 shows the receiver operating characteristic (ROC) curve displaying the estimated sensitivity and specificity of predicting LBP over all possible classification thresholds. The area under the ROC curve for this model is 0.75 (Figure 1). Estimates of expected optimism (the extent to which same-sample estimates overestimate accuracy) were about 9% for all accuracy measures. Using the above model and the prevalence of LBP in our sample, positive predictive value (PPV) was 72% and negative predictive value (NPV) was 71% for a classification threshold of 0.5. These estimates were, of course, somewhat lower when adjusted for expected optimism (PPV 64% and NPV 61%).

DISCUSSION

After publication of the clinical consensus criteria for DLB in 1996,[9] multiple investigators have examined the accuracy of these criteria for the prediction of LBP at autopsy.[1,10,11] These studies generally found that, when patients fulfilled the criteria, the autopsy would often confirm the presence of LBP. However, many dementia patients with LBP determined at autopsy had never fulfilled the clinical criteria for DLB. This is particularly true for dementia patients with neuropathological AD.[2]

In the current study we took a different approach to identify demographic and clinical characteristics that would predict LBP at autopsy. Because probable AD is the most common clinical misdiagnosis in patients with LBP, we focused our analysis on these participants. Using a stepwise logistic regression model, we evaluated characteristics that best predicted LBP at autopsy. This method allowed for a relatively unbiased approach to developing a prediction model for LBP in patients who fulfilled clinical criteria for AD.

Our findings support the validity of 2 of the current consensus DLB criteria,[9] because both hallucinations and parkinsonism were found to be important characteristics in the prediction of LBP. However, because the majority of the participants in the study sample were evaluated before the publication of the consensus DLB criteria, we were not able to adequately evaluate the third criterion (fluctuations in cognition). Furthermore, several characteristics that were not used by the consensus DLB criteria were found to be predictive of LBP. These included female gender, lower education, being married, and absence of irritability.

Our study is particularly significant in several ways. First, the study sample consisted of participants from a community-based incident dementia case registry, and therefore findings may be more relevant to the development of a clinical screening for patients in the general medical setting than findings generated from specialty

samples (eg, AD research centers or geropsychiatry consultation services). Second, we did not select our study sample on the basis of any neuropathological finding but rather on the basis of a clinical diagnosis of AD. Third, our neuropathological work-up included α-synuclein immunohistochemical staining for LBP, recognized at the second workshop of the Consortium on DLB as "potentially the most sensitive and specific technique for detecting and quantifying the clinically and pathologically relevant lesions in DLB."[26] Fourth, although others applied the established consensus criteria for DLB in their clinical samples, we did not apply preexisting clinical diagnostic criteria but generated clinical and demographic profiles that best distinguished between cases based on neuropathological findings.

Because of differences in study samples and staining methods, our results are not directly comparable to other studies. Therefore, the following comparisons should be considered cautiously. Although female gender predicted LBP in our sample, previous studies have tended to report either no association with gender[5,10,27-29] or an association between males and LBP.[8,30,31] In a previous study,[18] we demonstrated that gender is not a source of selection bias in undergoing autopsy in this sample. Differences in the frequency of concomitant AD and age of participants in other studies could account for these apparent disparate results.

Four previous studies found no relationship between education and the presence of LBP.[27,28,30] However, only 1 of these studies modeled education dichotomously,[28] and unlike the present study, it included participants who had completed high school in the higher educational category. Few studies have explored the role of marital status in LBP, and the reasons accounting for this observed association remain unclear. Because there is no clear "biological" association between marital status and education status and LBP, the primary analysis (backward selection model) was conducted without these variables. The resulting ("optimistic") accuracy is clearly worse. For example, at the probability cutoff of 0.5 for classifying LBP, the associated estimated sensitivity and specificity are both 65%, compared with 75% and 69% for the model that included marital status and education.

The results of this study would suggest that patients with clinical AD and underlying LBP have a distinct behavioral profile. Consistent with our findings, many studies have found an association between hallucinations in dementia patients and the presence of LBP at autopsy.[5,8,27,30,32,33] However, 2 reports failed to confirm this association.[11,34] Sample sizes were modest in both studies (51 and 39, respectively). Our study results suggested a role for irritability in distinguishing between LBP-positive and -negative patients. In this study, the "absence of irritability" was defined as not having trouble losing one's temper. This result is consistent with 1 study which found that patients with Parkinson's disease dementia were much less likely to have irritability than patients with AD.[35]

Analysis of the relationship between LBP and bradykinesia has produced mixed results. Several studies previously found an association between bradykinesia and LB.[28,33] However, not all studies have reported this association.[11,34] Again, differences in sample composition make direct comparisons across studies difficult.

Despite using more accurate LBP detection methods and a larger sample size than previous studies, the (optimism adjusted) sensitivity and specificity of our predictive model at a probability cutoff of 0.5 were only 66% and 59%, respectively. However, we looked at the most difficult to differentiate group (cases diagnosed with AD). Distinction between clinical AD patients with and without LBP is difficult.[1] Thus, it is perhaps not surprising that sensitivity and specificity were lower compared with previous studies that included all dementia patients or patients who met clinical criteria for DLB.

There are several limitations to this study. Because we only evaluated a select group of uniformly available clinical characteristics, it is also possible that some other symptoms or medical conditions not directly evaluated (such as cognitive fluctuations, hypersomnia, or orthostatic hypotension) would improve the accuracy of screening for DLB. In addition, in some cases, we did not have sufficient information to characterize the specific subtypes of psychiatric symptoms, such as visual versus auditory hallucinations. Indeed several studies that have examined visual hallucinations specifically over the course of illness have reported an association with DLB.[5,8,30] Furthermore, we were unable to evaluate the temporal relationship between symptoms (specifically stage of illness when parkinsonian signs and symptoms and/or visual hallucinations developed) or specifically examine the use of antipsychotic medications and the development of parkinsonian signs and symptoms. All accuracy estimates are subject to selection bias to the extent that autopsied patients differ from nonautopsied patients in characteristics that are likely related to both clinical signs and symptoms as well as neuropathological outcome.[18] Findings from any neuropathological study need to be interpreted in this light.

The findings from this study suggest that specific demographic and clinical characteristics can improve prediction of the presence of LBP in patients with clinical diagnosis of AD. We were able to confirm the importance of hallucinations and parkinsonism in predicting LBP-positive cases, and we found that other symptoms such as absence of irritability may also enhance diagnosis of

LBP in clinical AD patients. However, there is clearly a need for newer approaches to improve diagnostic accuracy of patients with LBP. Thus, functional brain imaging (eg, dopamine transporter) and the identification of other synuclein-related biomarkers (in blood or cerebrospinal fluid), combined with clinical signs and symptoms, may ultimately lead to a more accurate identification of this important subgroup of patients with dementia.

ACKNOWLEDGMENTS

We thank Lynne Greenup and Matthew Kraybill for their technical assistance, Darcy Vavrek for her statistical assistance, and Andrew David and Rebecca Carlson for their editorial assistance.

References

1. Lopez OL, Becker JT, Kaufer DI, et al. Research evaluation and prospective diagnosis of dementia with Lewy bodies. *Arch Neurol* 2002; 59:43-46.
2. Merdes AR, Hansen LA, Jeste DV, et al. Influence of Alzheimer pathology on clinical diagnostic accuracy in dementia with Lewy bodies. *Neurology* 2003; 60:1586-1590.
3. Olichney JM, Galasko D, Salmon DP, et al. Cognitive decline is faster in Lewy body variant than in Alzheimer's disease. *Neurology* 1998; 51:351-357.
4. Kraybill ML, Larson EB, Tsuang DW, et al. Cognitive differences in dementia patients with autopsy-verified AD, Lewy body pathology, or both. *Neurology* 2005; 64:2069-2073.
5. Ballard C, Holmes C, McKeith I, et al. Psychiatric morbidity in dementia with Lewy bodies: a prospective clinical and neuropathological comparative study with Alzheimer's disease. *Am J Psychiatry* 1999; 156:1039-1045.
6. Liberini P, Valerio A, Memo F, Spano P. Lewy-body dementia and responsiveness to cholinesterase inhibitors: a paradigm for heterogeneity of Alzheimer's disease? *Trends Pharmacol Sci* 1996; 1996:155-160.
7. Ballard C, Grace J, McKeith I, Holmes C. Neuroleptic sensitivity in dementia with Lewy bodies and Alzheimer's disease. *Lancet* 1998; 351:1032-1033.
8. Ballard CG, Jacoby R, Del Ser T, et al. Neuropathological substrates of psychiatric symptoms in prospectively studied patients with autopsy-confirmed dementia with Lewy bodies. *Am J Psychiatry* 2004; 161:843-849.
9. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* 1996; 47:1113-1124.
10. McKeith IG, Ballard CG, Perry RH, et al. Prospective validation of consensus criteria for the diagnosis of dementia with Lewy bodies. *Neurology* 2000; 54:1050-1058.
11. Stern Y, Jacobs D, Goldman J, et al. An investigation of clinical correlates of Lewy bodies in autopsy-proven Alzheimer disease. *Arch Neurol* 2001; 58:460-465.
12. Larson E, Kukull W, Teri L, et al. University of Washington Alzheimer's Disease Patient Registry (ADPR): 1987-1988. *Aging (Milano)* 1990; 2:404-408.
13. Kukull WA, Schellenberg GD, Bowen JD, et al. Apolipoprotein E in Alzheimer's disease risk and case detection: a case-control study. *J Clin Epidemiol* 1996; 49:1143-1148.
14. American Psychiatric Association Work Group to Revise DSM-III. *Diagnostic and statistical manual of mental disorders: DSM-III-R*. Washington, DC: American Psychiatric Association, 1987.
15. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984; 34:939-944.
16. Barnhart RL, van Belle G, Edland SD, et al. Geographically overlapping Alzheimer's disease registries: comparisons and implications. *J Geriatr Psychiatry Neurol* 1995; 8:203-208.
17. Lim A, Tsuang D, Kukull W, et al. Clinico-neuropathological correlation of Alzheimer's disease in a community-based case series. *J Am Geriatr Soc* 1999; 47:564-569.
18. Tsuang D, Simpson KL, Li G, et al. Evaluation of selection bias in an incident-based dementia autopsy case series. *Alzheimer Dis Assoc Disord* 2005; 19:67-73.
19. Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology* 1997; 48:S10-S16.
20. Hamilton RL. Lewy bodies in Alzheimer's disease: a neuropathological review of 145 cases using alpha-synuclein immunohistochemistry. *Brain Pathol* 2000; 10:378-384.
21. Tsuang DW, Dalan AM, Eugenio CJ, et al. Familial dementia with Lewy bodies: a clinical and neuropathological study of 2 families. *Arch Neurol* 2002; 59:1622-1630.
22. Green D, Swets J. *Signal detection theory and psychophysics*. New York, NY: Wiley, 1966.
23. McIntosh M, Pepe M. Combining several screening tests: optimality of the risk score. *Biometrics* 2002; 58:657-664.
24. Gong G. Cross-validation, the jackknife and the bootstrap: excess error estimation in forward logistic regression. *JAMA* 1986; 81:108-113.
25. NIA. Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. *Neurobiol Aging* 1997; 18:S1-S2.
26. McKeith IG, Perry EK, Perry RH. Report of the second dementia with Lewy body international workshop: diagnosis and treatment. Consortium on Dementia with Lewy Bodies. *Neurology* 1999; 53:902-905.
27. Luis CA, Barker WW, Gajaraj K, et al. Sensitivity and specificity of three clinical criteria for dementia with Lewy bodies in an autopsy-verified sample. *Int J Geriatr Psychiatry* 1999; 14:526-533.
28. Heyman A, Fillenbaum GG, Gearing M, et al. Comparison of Lewy body variant of Alzheimer's disease with pure Alzheimer's disease: Consortium to Establish a Registry for Alzheimer's Disease, Part XIX. *Neurology* 1999; 52:1839-1844.
29. Gomez-Tortosa E, Newell K, Irizarry MC, et al. Clinical and quantitative pathologic correlates of dementia with Lewy bodies. *Neurology* 1999; 53:1284-1291.
30. Verghese J, Crystal HA, Dickson DW, Lipton RB. Validity of clinical criteria for the diagnosis of dementia with Lewy bodies. *Neurology* 1999; 53:1974-1982.
31. Stern Y, Folstein M, Albert M, et al. Multicenter study of predictors of disease course in Alzheimer disease (the "predictors study"). I. Study design, cohort description, and intersite comparisons. *Alzheimer Dis Assoc Disord* 1993; 7:3-21.
32. Hohl U, Tiraboschi P, Hansen LA, et al. Diagnostic accuracy of dementia with Lewy bodies. *Arch Neurol* 2000; 57:347-351.
33. Mega MS, Masterman DL, Benson DF, et al. Dementia with Lewy bodies: reliability and validity of clinical and pathologic criteria. *Neurology* 1996; 47:1403-1409.
34. Papka M, Rubio A, Schiffer RB, Cox C. Lewy body disease: can we diagnose it? *J Neuropsychiatry Clin Neurosci* 1998; 10:405-412.
35. Aarsland D, Cummings JL, Larsen JP. Neuropsychiatric differences between Parkinson's disease with dementia and Alzheimer's disease. *Int J Geriatr Psychiatry* 2001; 16:184-191.