

# Early and Widespread Cholinergic Losses Differentiate Dementia With Lewy Bodies From Alzheimer Disease

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**Background:** Reductions in cholinergic function occur in Alzheimer disease (AD) and dementia with Lewy bodies and correlate with cognitive decline. However, whether such alterations appear in early-stage disease is unclear.

**Objective:** To examine the timing of cholinergic deficits in AD and dementia with Lewy bodies.

**Methods:** Autopsy series of 89 patients with AD and 50 patients with the Lewy body variant of AD (LBV). Stage of disease was stratified according to results of the last Mini-Mental State Examination (MMSE) before death as mild, moderate, severe, or very severe. We analyzed choline acetyltransferase (ChAT) activity in the midfrontal, superior temporal, and inferior parietal cortices.

**Results:** Although compared with a normal control group ChAT activity was decreased in the AD and LBV cohorts, ChAT activity reduction for the LBV cohort was

much greater. Moreover, although the decline in ChAT activity in the AD cohort compared with the normal control group was significant only for patients in later stages of the illness, the decline in the LBV cohort was significant for those who died with mild-stage disease. When less impaired patients in each cohort (MMSE,  $\geq 10$ ) underwent separate analysis, the relationship of ChAT activity with the MMSE score was strong and significant for the LBV cohort alone.

**Conclusions:** Although cholinergic deficits are seen in both AD and LBV, loss of ChAT activity is less severe and occurs later in the clinical course of AD. Conversely, in LBV, loss of ChAT activity is already prominent in the earliest stages of the illness, suggesting that cholinergic replacement therapy may be more effective in LBV than in AD, especially in mild-stage disease.

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**A**LZHEIMER DISEASE (AD) is the most common form of primary degenerative dementia in the elderly, characterized by gradually worsening memory in association with aphasia, apraxia, agnosia, and disturbances of visuospatial perception. Although research in AD has focused on the functional role of multiple neurotransmitter systems, the cholinergic basal forebrain has been the most thoroughly studied. In AD, in which memory impairment is prominent, cholinergic function has been found to be markedly decreased, mainly as a result of neuronal loss in the basal forebrain, especially in the nucleus basalis of Meynert.<sup>1</sup> The activity of choline acetyltransferase (ChAT), the presynaptic synthetic enzyme for acetylcholine, has been shown to be reduced by 50% to 90% in patients with AD compared with age-matched normal control (NC) sub-

jects.<sup>2,3</sup> Changes in other cholinergic markers have also been reported, including a decline in high-affinity nicotinic receptors<sup>4</sup> and a reduction in presynaptic muscarinic receptor activity.<sup>5</sup>

Several studies have correlated decrements in ChAT activity with clinical indices of dementia severity.<sup>2,6,7</sup> However, recent studies have reported that cholinergic enzyme activity is significantly reduced only in brains of severely demented patients with AD, suggesting that cholinergic dysfunction is not present until relatively late in the course of the illness.<sup>8,9</sup>

Dementia with Lewy bodies (DLB) has been recognized as another common cause of cognitive deterioration in the elderly. Much attention has focused on identifying reliable criteria that allow discrimination between DLB and AD.<sup>10-12</sup> In addition to cognitive impairment, the core clinical features of DLB are visual hallucinations, fluctuating attention, and par-

kinsonism.<sup>11,12</sup> Neuropsychologically, patients with DLB may display a different pattern of cognitive decline, with worse performance on tests of visuospatial activity, initiation, and perseveration.<sup>13</sup> Furthermore, the progression of their deterioration on global measures of dementia (eg, the Mini-Mental State Examination [MMSE]<sup>14</sup> and the Mattis Dementia Rating Scale)<sup>15</sup> may be faster than that observed in patients with AD.<sup>16</sup> Neuropathologically, in most brains of patients with DLB, accompanying AD pathologic changes in the form of neocortical diffuse plaques, neuritic plaques, and modest numbers of neurofibrillary tangles are found in the medial temporal lobe (ie, the Lewy body variant of AD [LBV]).<sup>10</sup> A few brains, however, have no more AD pathologic changes than do age-matched controls. Neurochemically, although the decline of ChAT activity has been shown to be much greater in patients with DLB than in those with AD,<sup>17</sup> the strength of its association with cognitive decline has been more controversial.<sup>18-20</sup>

Apart from a small number of autopsy studies that included cases with mild impairment,<sup>8,21,22</sup> descriptions of neurochemical changes in AD and DLB have been generally based on findings in patients with late-stage disease. Moreover, few studies have been performed using biopsy specimens of living patients with mild to moderate dementia.<sup>22,23</sup> Finally, most of these studies considered mixed populations of patients with AD and DLB, since they were performed before DLB had been well defined. Consequently, how early in the course of each of these diseases neurochemical alterations occur remains relatively unclear.

In the present study, we sought to determine whether cholinergic dysfunction was an early event in AD and LBV by examining the activity of ChAT in autopsy specimens of these prospectively observed cohorts who died at different stages of their illness (classified clinically as mild, moderate, severe, and very severe). In addition, we investigated the relationship between the decline in ChAT activity and dementia severity in AD and LBV.

## PATIENTS AND METHODS

### PATIENTS

The patients included in the present study were observed clinically at the University of California–San Diego Alzheimer's Disease Research Center, Seniors Only Care, San Diego, or in the private practices of its senior clinicians. They represent all patients who underwent autopsy between 1985 and the present with a clinical diagnosis of AD or LBV or normal control (NC) for whom ChAT activity was available, and where cognitive testing was administered within 24 months prior to death.

Eighty-nine patients with AD and 50 with LBV met the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* for a clinical diagnosis of dementia<sup>24</sup> or of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association for probable or possible AD.<sup>25</sup> In addition, they met the criteria of the National Institute on Aging for a pathological diagnosis of AD<sup>26</sup> and of the Consortium to Establish a Registry for Alzheimer's Disease for a diagnosis of probable or definite AD.<sup>27</sup> Patients with LBV also met the criteria of the Consortium on DLB for a pathological diagnosis of

DLB.<sup>11,12</sup> All patients with AD and LBV were stratified according to their last MMSE score before death as having mild (MMSE score,  $\geq 20$ ; n=14 for the AD cohort and n=7 for the LBV cohort), moderate (MMSE score, 10-19; n=20 for the AD cohort and n=10 for the LBV cohort), severe (MMSE score, 1-9; n=29 for the AD cohort and n=11 for the LBV cohort), and very severe disease (MMSE score, 0; n=26 for the AD cohort and n=22 for the LBV cohort).

The NC group consisted of 18 patients with no evidence of cognitive impairment or any other neurologic or psychiatric disorder. Twelve of these patients were also considered neuropathologically normal. The remaining 6 patients had only sufficient senile plaques to meet the National Institute on Aging criteria for AD or neuritic plaques to meet the criteria of the Consortium to Establish a Registry for Alzheimer's Disease for possible AD, but did not display any cognitive impairment on results of extensive neuropsychological testing administered in these cases less than 1 year before death.

### NEUROPSYCHOLOGICAL EXAMINATION

Mean scores are reported for the following 3 commonly used measures of global cognitive status: the MMSE, the Blessed Information-Memory-Concentration test,<sup>28</sup> and the Mattis Dementia Rating Scale. Most of the patients had also received the comprehensive neuropsychological battery administered through the Alzheimer's Disease Research Center as part of their annual evaluation.<sup>29</sup>

### NEUROPATHOLOGICAL EXAMINATION

Pathological assessment was performed by one of us (L.A.H.). Autopsy was performed within 12 hours of death using a protocol described by Terry et al.<sup>30</sup> The left half of the brain was fixed by means of immersion in 10% formalin for 5 to 7 days, at which time blocks were taken for paraffin embedding from the midfrontal (MF), rostral superior temporal (ST), and inferior parietal (IP) areas of the neocortex, hippocampus, entorhinal cortex, basal ganglia/substantia innominata, mesencephalon, and pons. The neocortical areas correspond to Brodmann areas 46, 38, and 39. The paraffin blocks of neocortex were cut at 7- $\mu$ m thickness for hematoxylin-eosin and thioflavine S staining. Total plaque, neuritic plaque, and neurofibrillary tangle counts were determined by the same examiner (L.A.H.) using the same criteria consistently. Lewy bodies were detected using hematoxylin-eosin and/or anti-ubiquitin immunostaining, as recommended by the Consortium on Dementia with Lewy Bodies.<sup>11,12</sup> Specifically, to receive a pathological diagnosis of LBV, 1 or more Lewy bodies had to be present in both the neocortex and brainstem in addition to significant AD pathologic changes.

### NEUROCHEMISTRY

Samples were taken from the MF, ST, and IP areas of frozen, unfixed cortex from the right half of the brain and homogenized in 1mM EDTA (pH, 7.0) containing 0.1% Triton X-100 (Sigma-Aldrich Corp, St Louis, Mo). Analysis of ChAT activity was performed by means of the modified Fonnum technique.<sup>31,32</sup> The coefficient of variation was 3%, with an intra-assay variability of 7.9%.

### STATISTICAL ANALYSIS

Mean values among groups (AD vs NC and LBV vs NC) were compared using 1-way analysis of variance (ANOVA). In case of inequality of group variances ( $P < .05$ , Bartlett test), the ANOVA was preceded by logarithmic transformation of raw data.

**Table 1. Demographic, Neuropsychological, and Neurochemical Variables in AD\***

	NC (n = 18)	Mild AD (MMSE = 20) (n = 14)	Moderate AD (MMSE, 10-19) (n = 20)	Severe AD (MMSE, 1-9) (n = 29)	Very Severe AD (MMSE = 0) (n = 26)	P Value†	Entire AD Cohort (N = 89)
Age at death, y	77.4 ± 11.2	80.7 ± 6.3	80.3 ± 6.0	80.1 ± 7.9	80.1 ± 10.2	.83	80.3 ± 7.6
Sex, No. M/F	10/8	7/7	10/10	14/15	13/13	...	44/45
Education, y	15.7 ± 3.1	14.8 ± 3.6	13.9 ± 3.2	13.1 ± 3.9	12.8 ± 3.5	.14	13.5 ± 3.6
Disease duration, y	...	6.1 ± 3.0‡	7.1 ± 3.6§	10.2 ± 3.8	10.6 ± 4.1	<.001	9.0 ± 4.1
Test-death interval, mo	9.5 ± 4.8	5.9 ± 5.2	9.2 ± 3.9	8.7 ± 5.6	8.5 ± 6.0	.43	8.3 ± 5.4
Cognitive tests, final score							
MMSE	28.7 ± 1.6	24.6 ± 3.5	15.4 ± 2.8	4.4 ± 2.6	0	<.001	9.0 ± 9.2
BIMC¶	1.1 ± 1.1 (n = 14)	10.6 ± 7.1 (n = 12)	20.4 ± 3.4 (n = 19)	29.5 ± 2.6 (n = 29)	32.7 ± 0.7 (n = 26)	<.001	25.8 ± 8.4 (n = 86)
DRS	138.3 ± 5.5 (n = 15)	115.8 ± 14.5 (n = 14)	91.6 ± 18.4 (n = 16)	43.8 ± 22.5 (n = 21)	20.1 ± 11.2 (n = 7)	<.001	71.5 ± 39.1 (n = 58)
Results of neurochemistry, nmol per 100 mg/h							
ST ChAT	304.8 ± 113.5 (n = 14)	171.9 ± 105.4 (n = 10)	134.2 ± 99.4# (n = 15)	95.4 ± 68.1# (n = 20)	63.4 ± 40.7# (n = 21)	<.001	103.9 ± 90.3 (n = 66)
IP ChAT	204.4 ± 89.4 (n = 11)	156.0 ± 47.9 (n = 8)	155.8 ± 88.7 (n = 17)	91.8 ± 64.6** (n = 18)	90.2 ± 74.7** (n = 19)	<.001	114.8 ± 79.7 (n = 62)
MF ChAT	214.1 ± 61.2 (n = 18)	205.0 ± 79.4 (n = 14)	162.6 ± 73.7 (n = 20)	142.4 ± 57.7†† (n = 27)	89.5 ± 67.1# (n = 24)	<.001	141.8 ± 77.4 (n = 85)

\*Unless otherwise indicated, data are given as mean ± SD. AD indicates Alzheimer disease; NC, normal control group; MMSE, Mini-Mental State Examination; BIMC, Blessed Information-Memory-Concentration test; DRS, Mattis Dementia Rating Scale; ChAT, choline acetyltransferase activity; ST, superior temporal cortex; IP, inferior parietal cortex; and MF, midfrontal cortex.

†Determined by means of analysis of variance.

‡P < .01, compared with patients with severe or very severe AD.

§P < .05, compared with patients with severe or very severe AD.

||Differences were significant (P < .05 to P = .001) for each of the pairwise comparisons (Tukey-Kramer multiple comparisons test).

¶Score indicates the number of incorrect responses.

#P < .001, compared with the NC group (Tukey-Kramer multiple comparisons test).

\*\*P < .01, compared with the NC group (Tukey-Kramer multiple comparisons test).

††P < .05, compared with the NC group (Tukey-Kramer multiple comparisons test).

When a significant global result (overall P < .05) was obtained, the ANOVA was followed by the Tukey-Kramer multiple comparisons test to compare each pair of means. Correlation analyses were performed by means of Pearson product moment correlations.

## RESULTS

The mean values for the demographics, clinical indices, and biochemical results are summarized in **Table 1** and **Table 2**. As expected, disease duration increased and cognitive performance worsened with disease stage in both cohorts. Compared with the NC group, ChAT activity was significantly decreased in the AD and LBV groups. However, loss of ChAT activity for the LBV cohort was much greater than that for the AD cohort, despite comparable mean ages at death, test-death intervals, and disease severity. Although decline of ChAT activity in AD compared with the NC group was statistically significant only for patients who died in the later stages of the disease, decline of ChAT activity in the LBV cohort was statistically significant in the earliest stages of the illness.

Unlike the LBV group, for whom ChAT activity was significantly reduced (almost maximally) in all brain areas beginning in the mildest stages of the disease (MMSE, ≥20), the AD cohort displayed region-specific differences, with decrements of ChAT activity occurring rela-

tively earlier in the ST cortex (moderate AD) than in the MF and IP cortices (severe AD). Specifically, compared with the NC group, ST ChAT activity was significantly decreased in patients with moderate AD at death (MMSE, 10-19), whereas MF and IP ChAT activities were significantly reduced only in the AD cohort with more severe impairment (MMSE, <10). This pattern of ChAT activity decline in LBV and AD did not change, even when the NC group was limited to the patients with neuropathologically normal findings (n = 12).

The correlations of ChAT activity with the MMSE are shown in **Table 3**. Correlations between the last MMSE score before death and ChAT activity were most robust for AD when the entire AD cohort (including many patients with severe and very severe AD) was considered. However, when only less impaired patients (with mild and/or moderate AD) in each cohort were included in the analyses, the relationship between the last MMSE before death and ChAT activity was considerably stronger for the LBV cohort in all neocortical regions examined.

## COMMENT

The present study investigated the timing and distribution of ChAT activity decline during the course of AD and

**Table 2. Demographic, Neuropsychological, and Neurochemical Variables in LBV\***

	NC (n = 18)	Mild LBV (MMSE = 20) (n = 7)	Moderate LBV (MMSE, 10-19) (n = 10)	Severe LBV (MMSE, 1-9) (n = 11)	Very Severe LBV (MMSE = 0) (n = 22)	P Value†	Entire LBV Cohort (N = 50)
Age at death, y	77.4 ± 11.2	76.3 ± 8.6	73.6 ± 8.0	80.3 ± 6.9	79.6 ± 8.3	.52	78.3 ± 8.2
Sex, No. M/F	10/8	4/3	8/2	5/6	11/11	...	28/22
Education, y	15.7 ± 3.1	15.2 ± 2.2	13.7 ± 3.0	13.2 ± 3.2	13.8 ± 3.0	.14	13.8 ± 2.7
Disease duration, y	...	5.6 ± 3.6	6.0 ± 1.9	6.9 ± 3.8	8.9 ± 3.7	.11	7.5 ± 3.6
Test-death interval, mo	9.5 ± 4.8	11.9 ± 10.3	8.1 ± 5.4	8.2 ± 7.4	8.3 ± 5.4	.73	8.8 ± 6.6
Cognitive test, final score							
MMSE	28.7 ± 1.6	24.4 ± 3.1	14.4 ± 2.9	3.9 ± 2.5	0	<.001‡	7.2 ± 9.3
BIMCS	1.1 ± 1.1 (n = 14)	11.5 ± 4.3 (n = 6)	17.0 ± 4.5 (n = 7)	27.6 ± 3.7 (n = 9)	32.1 ± 1.4 (n = 20)	<.001‡	25.7 ± 8.5 (n = 42)
DRS	138.3 ± 5.5 (n = 15)	91.2 ± 32.4 (n = 5)	79.3 ± 24.0 (n = 6)	33.3 ± 26.2 (n = 7)	13.1 ± 15.3 (n = 7)	<.001‡	50.3 ± 32.3 (n = 25)
Results of neurochemistry, nmol per 100 mg/h							
ST ChAT	304.8 ± 113.5 (n = 14)	164.4 ± 101.8¶	54.6 ± 20.1¶	71.9 ± 47.6¶	59.9 ± 40.5¶	<.001	90.6 ± 97.5 (n = 41)
IP ChAT	204.4 ± 89.4 (n = 11)	55.8 ± 46.2¶	33.0 ± 15.0¶	45.5 ± 30.5¶	41.0 ± 31.1¶	<.001	42.9 ± 30.6 (n = 41)
MF ChAT	214.1 ± 61.2 (n = 18)	74.7 ± 31.6¶	52.5 ± 32.5¶	52.8 ± 39.1¶	53.9 ± 29.4¶	.001	55.5 ± 32.9 (n = 48)

\*Unless otherwise indicated, data are given as mean ± SD. LBV indicates Lewy body variant of AD. Other abbreviations are given in the first footnote to Table 1.

†Determined by means of analysis of variance.

‡Differences were significant ( $P < .05$  to  $P = .001$ ) for each of the pairwise comparisons (Tukey-Kramer multiple comparisons test).

§Score indicates the number of incorrect responses.

¶ $P < .05$ , compared with the NC group (Tukey-Kramer multiple comparisons test).

|| $P < .001$ , compared with the NC group (Tukey-Kramer multiple comparisons test).

**Table 3. Correlations Between MMSE Scores and ChAT Activity in AD and LBV\***

Patients, Impairment	AD Cohort, <i>r</i> and <i>P</i> Values			LBV Cohort, <i>r</i> and <i>P</i> Values		
	ST	IP	MF	ST	IP	MF
Mild (MMSE, ≥20)	0.44; .21	-0.32; .42	0.06; .69	0.64; .12	0.83; .04	0.73; .06
Mild and moderate (MMSE, ≥10)	0.20; .33	-0.04; .83	0.28; .11	0.76; .001	0.67; .004	0.55; .04
Mild, moderate, and severe (MMSE, ≥1)	0.35; .02	0.33; .03	0.32; .01	0.57; .003	0.20; .33	0.30; .14
Entire cohorts	0.47; <.001	0.35; .005	0.46; .001	0.54; .001	0.15; .37	0.28; .07

\*Correlations were performed using Pearson product moment procedure. Normal control subjects were excluded from analyses. Sample sizes and abbreviations are given in the first footnote to Tables 1 and 2.

LBV and the relationship between reduction of ChAT activity and dementia severity in these illnesses. To explore this, we used (1) large and well-characterized cohorts of patients with AD and LBV with the last neuropsychological assessment reasonably close to death, and (2) tissue samples from multiple neocortical areas of the patients.

Although definite conclusions about longitudinal changes occurring in individual patients can hardly be drawn from a cross-sectional study, our data strongly support the view that the integrity of cholinergic neurotransmission is affected at different points in the course of these diseases. Cholinergic dysfunction appears to occur early in LBV, whereas in AD, it is seemingly severely reduced only in the later stages of the illness. Furthermore, although this neurochemical deficit may be fairly generalized beginning with early-stage disease in LBV, there may be region-specific differences, with the tem-

poral cortex more susceptible to the loss of ChAT activity than the frontal and parietal cortices, in AD. In fact, ST ChAT activity was significantly decreased in patients with moderate AD at death, whereas MF and IP ChAT activities were significantly reduced only in the AD cohort with more severe impairment. This is in contrast to a recent study by Davis et al,<sup>8</sup> in which no regional differences in ChAT activity decline were observed, and suggests that the progression of deterioration in AD may depend on the involvement of an increasing number of specific neocortical regions as the disease advances.

In contrast to AD, the pattern of ChAT activity decline in LBV—early and more extensive, involving all neocortical regions—may contribute to its characteristic clinical profile. In particular, the higher prevalence of psychotic symptoms (visual hallucinations and delusions), severe visuospatial dysfunction, and prominent deficits in ex-

ecutive function, attention, and literal fluency reported for patients with mild- to moderate-stage LBV<sup>11-13</sup> may be related to earlier and greater reductions of ChAT activity in the temporal, parietal, and frontal cortices, respectively.

Loss of ChAT activity has been shown to correlate with cognitive decline in patients with AD by several investigators,<sup>2,6-8</sup> who reported correlation coefficients ranging from 0.46<sup>7</sup> to 0.82.<sup>2</sup> Although these discrepancies across studies may have several explanations, such as heterogeneity of populations (demented patients alone vs mixtures of patients with and without cognitive impairment), tissue samples (biopsy vs autopsy specimens), and brain regions considered for biochemical assay (eg, allocortical vs neocortical areas), different disease severity of the cohorts examined was likely the most important reason. In our AD sample, the strength of correlation between ChAT activity decline and cognitive impairment increased with increasing severity of dementia of the patients included in the analyses. When the whole AD cohort and the NC group were considered, our results ( $r=0.52$  [MF and IP cortices];  $r=0.59$  [ST cortex]) were quite consistent with those found by other investigators.<sup>7,8</sup>

The relationship between ChAT activity and cognitive performance has been more controversial in DLB, in which reported correlation coefficients range from 0.25<sup>20</sup> to 0.90.<sup>18</sup> The same reasons raised for discrepancies in studies of AD and, in particular, the different disease severity of the patients examined, might have contributed to this great variability, since the magnitudes of correlation coefficients in previous studies were considerably reduced when more deteriorated patients were included.<sup>20</sup> Moreover, the present study clearly shows that in LBV, unlike AD, the relationship between ChAT activity decline and cognitive impairment weakens as the severity of dementia of the patients included in the analyses increases.

Our findings may have several therapeutic implications. First, our data may provide a rationale for the greater responses reported for patients with more advanced AD in experimental trials of cholinesterase inhibitors, implying that even patients with severe AD retain the capacity to respond to cholinergic treatment. Second, and more important, these results suggest that cholinergic replacement therapy may be particularly effective in LBV, beginning with the earliest stages. Cholinergic replacement therapy has been postulated to play an important role in the treatment of LBV after 3 patients with combined LB-AD pathology and very low neocortical ChAT activity were reported to show a substantial response to tacrine hydrochloride treatment.<sup>33</sup> Evidence has also shown that cholinesterase inhibitors may have neuropsychiatric benefits,<sup>34</sup> including reduction of agitation, delusions, and hallucinations, which are highly prevalent in LBV.<sup>11,12</sup> Although a recent pharmacological trial<sup>35</sup> has only partially supported these findings, the present study strongly suggests that cholinergic replacement therapy may have greater benefits, especially early, for patients with LBV than for those with AD. This observation should be further assessed in well-designed, randomized clinical trials.

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