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Dementia with Lewy bodies: choline acetyltransferase parallels nucleus basalis pathology

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Summary. The biological substrate underlying the reduced cortical choline acetyltransferase (ChAT) in dementia with Lewy bodies (DLB) is incompletely understood. We compared cortical ChAT levels with Lewy body densities and neuronal loss in the nucleus basalis of Meynert (nbM) and cerebral cortex in six DLB, seven Alzheimer's disease (AD), and six control cases. We found greater neuronal loss in the nbM in DLB compared to AD ($U = 9.500$, $p = 0.049$). Mean ChAT levels in the cortex were lower in dementia patients than controls ($t = 17.500$, $p = 0.001$), and DLB cases had slightly lower ChAT levels than AD cases, but this difference was not significant ($t = -0.332$, $p = 0.746$). Overall, cortical ChAT levels correlated inversely with neuronal loss in the nbM (Spearman rank correlation coefficient $= -0.53$). The correlation between ChAT level and the combined factor of nbM LBs and neuronal loss was -0.59. A similar correlation between ChAT level and the combined factor of nbM neurofibrillary tangles and neuronal loss was -0.72. The correlation between ChAT and the combined factor of nbM LBs and neuronal loss was -0.81 when AD cases were excluded from the analysis. Local cortical pathology was not related to ChAT level. We conclude that neuronal loss and Lewy body formation in the nbM may contribute to the reduction in cortical ChAT in DLB.

Keywords: Acetylcholine, Alzheimer's disease, ChAT, dementia, Lewy body, nucleus basalis of Meynert.

Introduction

Neuronal and synaptic loss, neurofibrillary tangle (NFT) formation and deposition of senile plaques have been well described as pathologic features that underlie dementia in Alzheimer's disease (AD) (Ball, 1977; Herzog and

Kemper, 1980; Bondareff et al., 1981; Terry et al., 1981, 1991; Whitehouse et al., 1982; Doucette et al., 1986; Hyman et al., 1986). Since the identification of cortical Lewy bodies (LBs) was simplified by ubiquitin immunohistochemistry (Dickson et al., 1991), we recognize that cortical LBs are also common in dementia patients. The presence of widespread cortical LBs distinguishes a group which is the second most common pathologic subtype of dementia after AD (Lennox et al., 1989; Hansen et al., 1990; Perry et al., 1990; Dickson et al., 1991). In these cases the role of the LB in the pathogenesis of dementia is unknown. However, dementia with Lewy bodies (DLB) can occur either as a pure form (diffuse Lewy body disease [DLBD]) in which AD changes are absent, or in a more common form with AD pathology (Kosaka, 1990). Clinical and pathologic criteria for the diagnosis of DLB are now available (McKeith et al., 1996).

Although the neurochemistry and neurobiology of DLB are incompletely understood, brains from patients with DLB have a cholinergic deficit that is even more marked in some neocortical areas than cholinergic losses in cases of AD without LBs[15–17]. Choline acetyltransferase (ChAT) levels are reduced to a greater degree in pure DLBD brains and in AD brains with cortical LBs (AD/LB) relative to losses present in pure AD (Langlais et al., 1993; Perry et al., 1993, 1994).

The nature of the relationship between LBs and cortical ChAT levels in unclear. ChAT is localized to the synaptic regions of cholinergic neurons. Since the nucleus basalis of Meynert (nbM) supplies the cholinergic input to the cerebral cortex (Mesulam, 1983), neuronal degeneration in the nbM could profoundly influence ChAT levels. Although nbM LBs occur in a number of LB forming disorders, it is not known if ChAT levels are reduced as the direct result of loss or dysfunction of nbM cholinergic neurons. Alternatively, reduced ChAT levels in DLB could be the result of reduced intraneuronal ChAT production or accelerated ChAT degradation. Cortical degeneration might also influence ChAT level if local pathology affected incoming afferent cholinergic tracts.

To investigate factors that might contribute to the reduction in cortical ChAT in DLB we determined the density of cortical and nbM LBs, the severity of histologic changes in the nbM and cortical ChAT levels in the brains of patients with AD, DLB and cognitively normal controls.

Materials and methods

Patients

Clinical data for subjects this in investigation is summarized in Table 1.

AD

We examined brain tissue from the middle frontal gyrus (MFG), superior or middle temporal gyrus (STG) and parietal neocortex (PC) from seven patients with advanced dementia who met Reagan/NIA pathologic criteria for AD (NIA/Reagan institute

Table 1. Clinical data for dementia and control cases

Case	Diagnosis	Age/ gender	Duration (years)	Initial symptom	Psychiatric symptoms	Fluctuation	EPS
1	DLB	87/M	8	Confusion	Delusion	Yes	Yes
2	DLB	79/M	7	Disorientation	V halluc	NA	None
3	DLB	88/F	13	Impaired memory	Paranoia V halluc	NA	Yes
4	DLB	74/F	3	Impaired memory	Delusion	None	None
5	DLB	71/M	22	Impaired memory Confusion	None	NA	NA
6	DLB	81/M	9	Impaired memory	None	None	None
7	AD	84/M	4	Impaired memory	Delusion Paranoia	Yes	None
8	AD	90/F	12	Impaired memory	None	None	None
9	AD	81/F	8	Impaired memory	None	None	None
10	AD	95/M	15	Impaired memory	None	NA	Min gait
11	AD	86/F	11	Impaired memory	None	NA	None
12	AD	75/M	10	Impaired memory	Yes	NA	Min gait
13	AD	94/F	13	Impaired memory	NA	NA	NA
14	Control	70/M	0	None	0	None	0
15	Control	86/M	0	None	0	None	0
16	Control	60/M	0	None	0	None	0
17	Control	75/F	0	None	0	None	0
18	Control	85/M	0	None	0	None	0
19	Control	85/F	0	None	0	None	0

DX Diagnosis, *Age* Age at death (in years), *DLB* Dementia with Lewy bodies, *AD* Alzheimer's disease, *CLB* Cortical Lewy bodies, *NA* Information was not available, *V halluc* Visual hallucinations, *Min gait* A minimally parkinsonian gait

Working Group; 1997). All had abundant AD pathology, receiving a Stage V or VI in the Braak staging system (Braak and Braak, 1995). These patients averaged 86.4 years at death. None met neuropathological criteria for possible or probable DLB (McKeith et al., 1996).

DLB

We examined sections from the same areas from six patients with dementia who had numerous intracortical LBs (McKeith et al., 1996). Four also met NIA/Reagan pathologic criteria for AD (mean age = 79.3 years at death). The remaining two subjects (mean age = 83.0 years at death; Cases 1 and 2) did not meet pathological criteria for AD. Differences between dementia groups for duration of disease were not significant (mean duration between AD, and DLB groups was 10.4 and 10.3 years, respectively; $t = 0.033$, $p = 0.974$).

All AD and DLB dementia patients had advanced symptoms of cognitive dysfunction and were in nursing homes requiring full assistance for all activities of daily living at death.

Control cases

We examined brain tissue from six patients with no history of dementia or other significant neurological disorder. Retrospective chart review confirmed that patients were fully oriented and conversant within days prior to death. These brains had no LBs and they did not meet NIA/Reagan criteria for AD (mean age = 76.8 years old at death). Only histologic data was available on control cases 17–19.

ChAT methods

After death, 1 cm slabs of tissue from the right hemisphere were frozen by placement in a −70° freezer. Samples of frozen cortex from the MFG just rostral to the temporal tip, STG at the level of the mammillary body and PC just caudal to the splenium of the corpus callosum were thawed, gray matter dissected out and homogenized in 9 volumes of 0.32 M sucrose containing 0.5% triton-x-100. ChAT was estimated by the radiometric method of Fonnum (1975) and results were expressed as per mg protein (Lowry et al., 1995).

Lewy body counts and quantitative assessment methods

After fixation in 10% buffered formalin, tissue blocks from the identified areas of all cases were embedded in paraffin and sectioned at a thickness of 6 microns. One section was analyzed in each cortical region. Tissue blocks of the nbM were serially sectioned, and every 10th section was analyzed; approximately six sections were sampled per case. The resulting sections were stained with hematoxylin/eosin (HE) stain. The presence or absence of LBs was confirmed using antibodies to α-synuclein (gift of J Trojanowski; LB509: monoclonal, 1 : 500).

We (CFL and TWS) counted LBs in 20 successive, nonoverlapping 40X (0.16 mm^2) fields in the MFG, STG and PC at two different sites for each lobe. Where possible, sampling was obtained at rostrocaudal levels recommended by recent guidelines (McKeith et al., 1996). A total of 120 40X fields were counted for each case. The depth of cortex that was examined at each site was selected by scanning the section from the pial surface to the gray-white junction. LBs were counted in the spot where they were most numerous. This was generally in layers V and VI. The number of LBs/field was then converted to LBs/mm^2.

Nucleus basalis of Meynert data

Measurements of data in the nbM were obtained using a 0–3 point scale where zero indicates no evidence of neuronal loss, one indicates mild neuronal loss, two indicates moderately severe neuronal loss and three indicates severe neuronal loss. Gliosis was graded using a similar scale where zero indicates no gliosis, and three indicates severe gliosis. LBs and NFTs in the nbM were also graded using a comparable 0–3 point scale where zero indicates no LBs or NFTs/nbM section, one indicates 1–10 LBs or NFTs/nbM section, two indicates 10–20 LBs or NFTs/nbM section, and three indicates >20 LBs or NFTs/nbM section. Data from each section were then averaged for each case.

ChAT levels and all of the neuropathologic data were obtained blinded to the patients diagnoses.

Statistical analysis

Group means for quantitative data were compared using a one way analysis of variance (ANOVA). Semiquantitative data using a 0–3 scale (nbM neuronal loss) was analyzed using the Mann-Whitney U test. The Pearson correlation coefficient (PCC) was used to determine the correlation between local LB density and ChAT level. The Spearman rank correlation coefficient (SRCC) was used to determine correlations between nonlinear (semiquantitative) neuronal loss in the nbM and ChAT level.

Results

Nucleus basalis of Meynert data

Data for the nbM is summarized in Table 2. Neuronal loss was slightly greater in the nbM in the DLB group than in the AD group with average neuronal loss Grade 2.03 ± 0.54 [standard deviation] in AD and 2.83 ± 0.31 in DLB ($U = 34.500$, $p = 0.049$). Gliosis was lightly greater in the DLB group compared to the pure AD group, but these differences did not reach significance (Grade 2.58 ± 0.39 and 2.24 ± 0.78 in DLB and AD, respectively; $p > 0.05$).

Table 2. Nucleus basalis of Meynert data

Case	Neuronal loss	Lewy bodies	NFT	Gliosis
1	2.9	1.3	0.0	3
2	3.0	2.0	0.0	2.2
3	2.2	2.3	0.8	2.3
4	2.8	1.1	0.6	2.8
5	2.8	0.3	2.9	3.0
6	3.0	1.0	1.8	2.2
DLB Mean ± SD	2.83 ± 0.314	1.33 ± 0.723	1.02 ± 1.136	2.58 ± 0.392
7	2.2	0.0	2.0	2.0
8	0.5	0.0	2.2	2.2
9	2.8	0.0	3.0	3.0
10	0.9	0.0	2.0	0.8
11	2.9	0.0	2.1	2.8
12	2.1	0.0	1.7	1.9
13	3.0	0.0	1.2	3.0
AD Mean ± SD	2.83 ± 0.314	1.33 ± 0.723	1.02 ± 1.136	2.58 ± 0.392
14	0.0	0.0	0.0	0.0
15	0.0	0.0	0.0	0.5
16	0.0	0.0	0.0	0.0
17	0.6	0.0	0.0	0.6
18	0.2	0.0	0.0	0.0
19	0.0	0.0	0.0	0.0
Control Mean ± SD	0.13 ± 0.242	0.00 ± 0.00	0.00 ± 0.00	0.183 ± 0.286

Neuronal loss Mean grade of neuronal loss, *Lewy bodies* Average number of LBs per section, *NFT* Average grade of neurofibrillary tangles per section, *Gliosis* Mean grade of gliosis, *SD* Standard deviation

NFT intensity was not significantly greater in the AD group (Grade 1.017 ± 1.17 and 2.03 ± 0.54, respectively; $p > 0.05$). Pathology in the control cases was minimal in all groups. LBs were not present in either AD or control groups.

ChAT levels

As expected, we found ChAT levels were lower in the entire group of dementia cases compared to control cases (mean ChAT level = 2.36 ± 0.92 and 5.00 ± 0.46, respectively; $t = -17.500$, $p = 0.001$). Mean ChAT levels were greater in the pure AD group compared to the DLB group, but this difference did not reach significance (mean ChAT level = 2.44 ± 0.91 and 2.27 ± 1.01; $t = -0.332$, $p = 0.746$). Our two pure DLB cases had slightly lower levels than the AD/LB group (2.10 and 2.35 in DLB, and AD/LB; $F = 0.092$, $p = 0.91$).

Cortical Lewy body densities

Mean cortical LB densities were 1.5/mm^2 overall. They were 1.5/mm^2 and 1.4/mm^2 in AD/LB and DLB ($t = 0.101$, $p = 0.924$). In DLB, local cortical LB densities were not associated with lower ChAT levels (see Tables 3 and 4) (PCC = 0.233).

The SRCC between nbM neuronal loss and cortical ChAT level was −0.71 in our DLB population. The overall SRCC between nbM neuronal loss and cortical ChAT level was slightly lower at −0.53. Since LBs and neuronal loss are mutually exclusive (LB disappear when the neurons degenerate) we also calculated a correlation between ChAT levels and the combined factor of nbM LBs and neuronal loss. A similar correlation was calculated between ChAT level and the combined of nbM NFTs and neuronal loss. These correlations were −0.59 and −0.72, respectively, in the combined dementia group. When the AD group was excluded from the analysis the correlation

Table 3. ChAT levels and cortical Lewy body density in DLB cases

Case	ChAT level (nmol/h/mg protein)	CLB density (LB/mm^2)
1	2.2 ± 0.6	1.7 ± 1.4
2	2.0 ± 1.0	1.0 ± 0.4
3	4.2 ± 1.0	4.3 ± 5.5
4	1.2 ± 0.2	0.1 ± 0.0
5	2.0 ± 0.1	0.2 ± 0.1
6	2.0 ± 0.1	1.4 ± 0.2
Mean ± SD	2.27 ± 1.01	1.45 ± 1.54

DLB Dementia with Lewy bodies, *LB* Cortical Lewy bodies, *CHAT* Choline acetyltransferase levels, *SD* Standard deviation

Table 4. ChAT level and cortical Lewy body density in different brain regions

Diagnosis	Frontal ChAT (nmol/h/ mg protein)	Frontal CLB (per mm^2)	Temporal ChAT (nmol/h/ mg protein)	Temporal CLB (per mm^2)	Parietal ChAT (nmol/h/ mg protein)	Parietal CLB (per mm^2)
Control	7.84 ± 1.21	0.00 ± 0.00	3.55 ± 1.44	0.00 ± 0.00	2.93 ± 0.58	0.00 ± 0.00
AD	2.41 ± 0.80	0.00 ± 0.00	2.05 ± 0.19	0.00 ± 0.00	2.09 ± 1.01	0.00 ± 0.00
DLB-AD/LB	2.25 ± 1.64	0.21 ± 0.37	4.82 ± 1.34	1.72 ± 2.80	1.50 ± 1.00	0.63 ± 0.94
DLB-DLBD	2.31 ± 0.90	0.1 ± 0.14	2.55 ± 1.33	0.1 ± 1.76	1.17 ± 0.12	0.1 ± 0.10

ChAT Choline acetyl transferase, *CLB* Cortical Lewy bodies, *DLB* Dementia with Lewy bodies, *AD* Alzheimer's disease, *AD/LB*. The cases with both Lewy bodies and Alzheimer's pathology, *DLBD* Pure diffuse Lewy body disease. No Alzheimer's changes, *SD* Standard deviation

between ChAT and the combined factor of nbM LBs and neuronal loss was −0.810.

Discussion

We determined that estimates of nbM neuronal loss were greater in DLB than AD cases without cortical LBs. Our findings also confirm the results of others (Bowen et al., 1976; Davies and Maloney, 1976; Perry et al., 1977, 1993, 1994; Langlais et al., 1993) who found reduced ChAT levels in the neocortex of patients with AD and DLB compared to levels in control subjects. Our data is also consistent with data demonstrating that patients with DLB have lower ChAT levels than pure AD cases although our sample did not reach significance due to our relatively small sample size.

Since the nbM gives rise to widespread cholinergic input to the cerebral cortex (Gorry, 1963), we hypothesized that ChAT levels may correlate more closely with neuronal loss in the nbM than with local pathology in the cerebral cortex. Our data supports this hypothesis by demonstrating an inverse correlation between nbM neuronal loss and cortical ChAT levels in DLB patients. We also found an inverse correlation between nbM LBs and ChAT level.

Since neuronal loss was marked in many DLB cases with advanced disease nbM LB counts reflect, in part, the paucity of remaining neurons in which LBs could form. For example, our case with the highest ChAT level had only moderate neuronal loss and gliosis in the nbM, and had numerous LBs in remaining neurons. Similarly, cases with the least nbM neurons had few LBs because there were almost no remaining neurons in which LBs could occur. We partially accounted for this effect by calculating a correlation between cortical ChAT level and the combined factor of nbM LBs and neuronal loss. When pure AD cases were excluded from analysis the correlation was strong at −0.81. A similar correlation was calculated between ChAT level and the combined factor of nbM NFTs and neuronal loss. These correlations supported our hypothesis that there is a relationship between nbM pathology and cortical ChAT. However, our correlation data should be interpreted with

caution since both the range of possible rank values and our sample sizes were small.

The intensity of local cortical LB formation was not associated with the degree of ChAT depletion in the cortical sites we examined. Indeed, our DLB case with the lowest ChAT level had severe neuronal depletion and gliosis in the nbM with NFT formation or LBs in the few remaining neurons. Only rare neocortical LBs were seen. From these data we suggest that nbM neuronal losses, rather than local cortical changes account for the low cortical ChAT levels in cases of DLB as they do in AD (Whitehouse et al., 1982).

We can't exclude the possibility that the surviving nbM neurons also show reduced ChAT synthesis or increased ChAT breakdown. Also, since most dementia patients with nbM LBs have mixed pathology (combined AD and LBs) the ChAT losses may also be, in part, a reflection of the AD process in the nbM. It is unclear what further effect, if any, LBs or NFTs in the remaining neurons in the nbM might also have on neocortical ChAT levels. Possibly "intact" LB and/or NFT bearing neurons also produce less ChAT.

Duration of disease did not appear to correlate well with neocortical cholinergic losses. In particular, Case 3, the case with the highest ChAT levels, had a 13 year history of dementia and was in a nursing home with end stage disease for four years prior to her death. Our two DLB cases with the lowest ChAT levels (Cases 4 & 5) died after three and 22 years, respectively. All of our cases had end-stage disease at death so we cannot assess the effect of disease severity on cortical LB formation or ChAT level.

Lewy body formation and the associated neuronal loss in the nbM in diseases other than DLB has previously been associated with reductions in cortical ChAT levels. Neuronal loss within the nbM in Parkinson's disease was first described in Lewy's original description of Parkinson's disease in 1913 (Lewy, 1913). This has been replicated in more recent studies (Nakano and Hirano, 1984; Yosimura, 1988). Additionally, morphometric studies by Jellinger et al. (1996) have shown that the nbM demonstrates neuronal losses in AD and DLB which may be more severe than those in Parkinson's disease. Decreased ChAT has also been found in the cortex of the Parkinson's disease patient (Gaspar and Gray, 1984; Perry et al., 1985). In demented and nondemented Parkinson's disease brains there is a significant correlation between nbM neuronal numbers and temporal cortical ChAT level which is not observed in AD (Perry et al., 1985).

It has been postulated that nbM neuronal loss may contribute to the dementia that occurs in Parkinson's disease patients since this neuronal loss is greater in patients with dementia than in cognitively normal Parkinson's disease patients (Whitehouse et al., 1982; Nakano and Hirano, 1984; Tagliavini et al., 1984; Perry et al., 1985). Since most of these neurochemical studies of Parkinson's disease were completed before the clinicopathological entity of DLB was well-recognized, it is likely that some of the patients with early dementia in these studies might now be classified as DLB. Similarly, some of our DLB cases might have met pathological criteria for Parkinson's disease, even though all of our DLB cases presented with dementia and had dementia as their primary neurological symptom. Future studies are needed

to determine the relationship between Parkinson's disease and DLB. However, our findings support the hypothesis that LB pathology in the nbM may underlie reduced cortical ChAT in both Parkinson's disease and LB disorders where cognitive symptoms including dementia are the leading complaint.

Acetylcholine is not the neurotransmitter most strongly associated with Parkinson's disease. Dopaminergic losses in subcortical regions are more widely recognized in Parkinson's disease and these patients also have reduced cortical dopamine levels (Javoy-Agid and Agid, 1980; Scatton et al., 1982; Jellinger, 1986; Eggerston, 1986; Gaspar et al., 1991). Dopaminergic losses may also contribute to the cognitive dysfunction associated with Parkinson's disease and DLB. However, a number of other factors may including degeneration of other neurotransmitter systems, cortical neuronal and synaptic loss, infarcts and other CNS pathology may contribute to dementia in the patient with parkinsonism (Jellinger, 1997).

We are unable to draw definitive conclusions about overall, large scale correlations between ChAT level and cortical or nigral neuropathology due to our relatively small sample size. Nonetheless, our data support the hypothesis that ChAT level may be related to neuropathology in the nbM, rather than local cortical pathology. Indeed, we found no evidence to support the hypothesis that cortical pathology influences ChAT. However, the relationship between ChAT levels, cortical LB density and nbM degeneration in these patients is complex. It is likely that the reduced cortical ChAT levels in DLB may depend, in part, upon other factors such as concurrent AD histopathology in the neocortex and nbM, cholinergic metabolism in neurons with intact axonal processes, other nbM degenerative changes and clinical variables such as disease severity at death.

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