Brain Choline Acetyltransferase and Mental Function in Alzheimer Disease

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Objective: To determine whether higher brain levels of choline acetyltransferase (ChAT) are associated with improved neuropsychological function in patients with Alzheimer disease (AD).

Design: Case series with single-blind post hoc analysis of biopsy specimens.

Setting: Urban hospital and medical school.

Patients: A consecutive sample of 8 patients with AD undergoing brain biopsy and surgical implantation of intraventricular pumps for administration of potential chemotherapeutic agents.

Interventions: Brain biopsy, surgical implantation of intraventricular pumps, and, in 1 patient, ventriculoperitoneal shunt placement.

Main Outcome Measures: All patients underwent neuropsychological testing no more than 2 weeks before surgical biopsy. Levels of ChAT were determined in fresh brain tissue from biopsy samples.

Results: Significant positive correlations were found between ChAT levels and 2 neuropsychological test scores, Mini-Mental State Examination and the Logical Memory subtest of the Wechsler Memory Scale.

Conclusion: Degeneration of the cholinergic system in vivo correlates with decreasing cognitive function in patients with AD.

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Since the discovery of Alzheimer disease (AD) in 1897, there has been controversy concerning the cause of the loss of cognitive, intellectual, and social function seen in patients with this disorder. Many have argued that the number of plaques seen in the brain parenchyma of patients with AD correlates directly with loss of function, whereas others have suggested that the degree of cerebral atrophy is a more useful measure. Others have postulated specific systems to be selectively dysfunctional. These have included the hypothalamic-pituitary-adrenal axis, the adrenergic system, and the cholinergic system.

Previous human data have been obtained mainly from autopsy studies, in which there has often been a lapse of a number of hours before tissue could be harvested. This makes determination of specific neurotransmitter levels problematic, as there is often a deterioration of chemical activity seen within minutes of death. Our study was undertaken to more clearly delineate the relationship between neuropsychological function and alteration in the cholinergic system. We used brain biopsy material from patients who underwent complete neuropsychological assessment no more than 2 weeks before surgical brain biopsy. Information from these tests was correlated with neurotransmitter values in fresh brain tissue.

Results

Histopathological analysis confirmed the diagnosis of AD in all 8 patients. Neuropsychological scores are shown in Table 1, and correlations are described in Table 2. Significant positive correlations were found between ChAT levels and 2 neuropsychological test scores (Figure). Patients demonstrating higher Mini-Mental State Examination scores also had higher ChAT levels ($P = .03$). Higher Wechsler Memory Scale Logical Memory scores were also associated with higher ChAT values ($P = .05$).

Comment

The most striking alteration seen in neurotransmitters in AD occurs in the cholinergic system. Clinical trials using cholinergic agents have shown promising reduction of the mental impairment seen in AD. The consistency with which this biochemical disruption is seen in...
AD and its association with mental impairment have led to the general acceptance and refinement of the cholinergic hypothesis of dementia in AD. Indeed, the animal models that have been developed to simulate AD focus on disruption of the cholinergic system.

To date, the human tissue analysis that has verified cholinergic involvement in AD has been performed on postmortem tissue. As neurotransmitter levels can change rapidly following death, it is likely that postmortem tissue levels are different from those in premorbid brain.

Our study analyzed fresh tissue from biopsy samples. In our patients, lower levels of cortical ChAT were negatively associated with neuropsychological performance. Our results indicate that in patients with biopsy-confirmed AD, there is an in vivo loss in ChAT level that correlates with severity of disease measured by loss of neuropsychological function.

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**Table 1.** Neuropsychological Assessment Scores*

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<th>Patient No.</th>
<th>MMSE</th>
<th>GDS</th>
<th>WMS-LM</th>
<th>WMS-LMD</th>
<th>WMS-VRD</th>
<th>BN</th>
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**Table 2.** Correlation of MMSE With Other Neuropsychological Tests†

<table>
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<th>Test</th>
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<td>BN</td>
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<td>.06</td>
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</table>

*MMSE indicates Mini-Mental State Examination; GDS, Global Deterioration Score; WMS-LM, Logical Memory subtest of the Wechsler Memory Scale; WMS-LMD, Logical Memory Delayed subtest of the WMS; WMS-VRD, Visual Reproduction Delayed subtest of the WMS; BN, Boston Naming Test; and ellipses, not done.

Left, Correlation of Mini-Mental State Examination (MMSE) neuropsychological score and choline acetyltransferase (ChAT) activity in the frontal cortex biopsy material. Levels of ChAT had a significant positive correlation (r = 0.77) with the MMSE score (P = .03). Right, Correlation of Wechsler Memory Scale Logical Memory subtest (WMS-LM) neuropsychological score and ChAT activity in the frontal cortex biopsy material. Levels of ChAT had a significant positive correlation (r = 0.80) with the WMS-LM score (P = .05).

**REFERENCES**