Neuroanatomical Predictors of Response to Donepezil Therapy in Patients With Dementia

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**Background:** Patients with dementia of the Alzheimer type (DAT) respond variably to treatment with acetylcholinesterase inhibitors.

**Objective:** To determine whether measures of hippocampal volume and shape predict the response to donepezil in patients with DAT.

**Design:** T1-weighted, magnetic resonance images were obtained from patients with DAT, who subsequently underwent treatment with donepezil. Brain-mapping algorithms were used to quantify hippocampal volume and shape, and growth curves were used to estimate clinical outcome.

**Setting:** A referral outpatient center specializing in treatment of dementia.

**Patients:** Thirty-seven patients with very mild or mild DAT received donepezil therapy for up to 4 weeks before magnetic resonance imaging and for 24 to 96 weeks after magnetic resonance imaging.

**Intervention:** Donepezil, 10 mg/d.

**Main Outcome Measure:** Rate of change in the cognitive portion of the Alzheimer’s Disease Assessment Scale total scores.

**Results:** Smaller hippocampal volume and inward variation of the lateral and inferomedial portions of the hippocampal surface were correlated with a poorer response to donepezil therapy.

**Conclusions:** Measures of hippocampal volume and surface variation can be used to predict the response of patients with DAT to the acetylcholinesterase inhibitor donepezil.

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The ameliorative effects of acetylcholinesterase (AChE) inhibitors on the symptoms of dementia of the Alzheimer type (DAT) can be highly variable. In 2 studies, the presence of 1 or 2 apolipoprotein E4 (APOE4) alleles was predictive of a poorer response to AChE inhibitors. Demographic factors, such as sex, have also been reported to have predictive value, particularly when combined with information about APOE allelic status.

Neuromorphometric measures are being increasingly studied as biomarkers of the Alzheimer disease process. Hippocampal volume loss is present in patients with mild DAT, and the progression of volume loss parallels the worsening of clinical symptoms. Recently, computerized methods for magnetic resonance image (MRI) analysis have been used to improve brain structure measurement in patients with DAT. Using large-deformation, high-dimensional brain mapping, we recently found that reduced hippocampal volume and inward deformations of the lateral portion of the hippocampal surface are present in patients with very mild DAT and in persons without dementia in whom DAT subsequently developed.

In this study we used large-deformation, high-dimensional brain mapping to test the hypothesis that measures of hippocampal structure could be used to predict the response to donepezil in patients with DAT. This hypothesis was based on the premise that cholinergic circuits in the hippocampus are an important pharmacological target for AChE inhibitors. Cholinergic fibers project from the nucleus basalis of Meynert to the hippocampus, and muscarinic and nicotinic cholinergic receptors are densely expressed throughout the hippocampus. In addition, Riekkinen et al previously reported a relationship between hippocampal volume and the clinical response to the AChE inhibitor tacrine.

**METHODS**

**SUBJECT SELECTION AND ASSESSMENT**

Written informed consent was obtained from 39 patients with DAT who were community-dwelling and enrolled in longitudinal studies.
of healthy aging at the Alzheimer’s Disease Research Center, Washington University School of Medicine, St Louis, Mo. No patients had genetic mutations related to Alzheimer disease or other disorders that could have confounded the diagnosis of DAT. The patients were prescribed donepezil by their treating neurologist, and received baseline assessments within 4 weeks of treatment initiation and every 3 months thereafter for 2 years. Two patients withdrew from the study, and their data were excluded from any of the analyses. Of the remaining 37 participants, the mean (SD) duration of treatment was 83.0 (21.6) weeks (range, 24–96 weeks).

The diagnosis of DAT was established using semistructured interviews with the patient and a collateral source who was knowledgeable about the patient.12 The diagnosis was based on National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association (NINCDS/ADRDA) criteria.13 The Clinical Dementia Rating (CDR) scale14 was used as the primary baseline measure of dementia severity, and the Alzheimer Disease Assessment Scale–cognitive subscale (ADAS-Cog)15 total score was used as the primary clinical outcome measure. In addition, the CDR total score,14 the Mini-Mental State Examination total score,15 and the Neuropsychiatric Inventory16 total score were used as secondary measures of clinical outcome.

Apolipoprotein E (APOE) allele status was known in 13 of 37 patients. Five of 13 patients had no APOE4 alleles, 7 had a single APOE4 allele, and 1 had 2 APOE4 alleles.

MRI AND IMAGE PREPROCESSING

Magnetic resonance images were obtained at baseline using a 1.5-T VISION system (Siemens Medical Solutions USA, Inc, Malvern, Pa) and a turbo-FLASH (fast low-angle shot) sequence (repetition time, 20 minutes; echo time, 5.4 minutes; flip angle, 30°; number of acquisitions, 1; matrix, 256×256 pixels; and image time, 13.5 minutes).17

HIGH-DIMENSIONAL DIFFEOMORPHIC MAPPING OF HIPPOCAMPUS

An MRI from an elder control subject without dementia not otherwise included in the study was selected to be the neuroanatomical template. On this scan, delineations of the left and right hippocampal surface including a lateral zone (LZ), superior zone (SZ), and inferomedial zone (IMZ) were manually produced as previously described.8,18 The zones were defined by their proximity to the CA1 (LZ), CA2, CA3, and CA4 subfields, the dentate gyrus subfield (SZ), and the subiculum (IMZ).

Mapping of the template MRI on the 37 target MRIs was performed in 2 steps. First, the template image was coarsely aligned to the target images according to landmarks placed at external brain boundaries, at points where the anterior and posterior commissures intersected the midsagittal plane, and along the hippocampus. Second, the template MRI was finely mapped on the target images using large-deformation, high-dimensional brain mapping, as previously described.18-20

MEASUREMENT OF HIPPOCAMPAL VOLUME AND SURFACE VARIATION

An overall mean hippocampal surface for all 37 patients was derived using an elastic-based transformation of the template.10 The degree of inward (negative) or outward (positive) variation in each of the specific regions (LZ, SZ, and IMZ) of the hippocampal surface was calculated for each patient.

DATA ANALYSIS

Rates of change for the clinical outcome variables were estimated using growth curve models, as previously described.21,22 The growth curve model is based on a statistical framework similar to univariate repeated-measures analysis of variance and generates a slope value and intercept for each subject.23 Partial correlations between the outcome variables and the neuroanatomical variables, corrected for baseline measurements of the outcome variables, were also estimated. An α level of .05 was maintained for all analyses.

RESULTS

The mean (SD) age of the patients with DAT was 74.8 (8.2) years. Twenty-six patients were assessed as having very mild dementia (CDR, 0.5) and 11 had mild dementia (CDR, 1). Baseline characteristics and rates of change for all outcome variables are summarized in Table 1.

Partial correlations between the neuroanatomical measures and the rates of change of the clinical outcome variables, corrected for baseline values, are summarized in Table 2. Significant correlations were found between smaller left and right hippocampal volumes and more positive rates of change in ADAS-Cog total scores. Significant correlations were found between inward variation of the right and left IMZ and the right LZ of the hippocampal surface and more positive rates of change in ADAS-Cog total scores. Similar trends (.05<p<.10) were found between inward variation of other zones of the hippocampal surface and rates of change in ADAS-Cog total scores, CDR sum-of-boxes scores, and Mini-Mental State Examination total scores.

Table 1. Clinical Outcome Variables and Neuronanatomical Measurements in 37 Patients With DAT

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Value</th>
<th>Rate of Change</th>
<th>Range for Rate of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-Cog total score</td>
<td>4.92 (3.44)</td>
<td>0.18 (0.30)</td>
<td>−0.29 to 1.40</td>
</tr>
<tr>
<td>CDR sum-of-boxes total score</td>
<td>4.87 (2.76)</td>
<td>0.14 (0.13)</td>
<td>−0.16 to 0.47</td>
</tr>
<tr>
<td>MMSE total score</td>
<td>23.4 (5.40)</td>
<td>−0.10 (0.22)</td>
<td>−0.74 to 0.19</td>
</tr>
<tr>
<td>NPI total score (n = 35)</td>
<td>9.38 (7.97)</td>
<td>0.12 (0.06)</td>
<td>0.033 to 0.31</td>
</tr>
<tr>
<td>Left hippocampal volume, cm³</td>
<td>1.83 (0.32)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Right hippocampal volume, cm³</td>
<td>2.24 (0.43)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Total cerebral volume, cm³</td>
<td>907 (92.6)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Total intracranial volume, cm³</td>
<td>1254 (125)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: ADAS-Cog, Alzheimer’s Disease Assessment Scale–cognitive subscale; CDR, Clinical Dementia Rating; DAT, dementia of the Alzheimer type; MMSE, Mini-Mental State Examination; NA, not applicable; NPI, Neuropsychiatric Inventory.

*Data are given as mean (SD) unless otherwise indicated.
Smaller left hippocampal volumes were strongly correlated with inward variation of the left LZ (p = 0.93; P < .001) and the left IMZ (p = 0.81; P < .001) but not the left SZ (p = -0.22; P = .19). Smaller right hippocampal volumes were strongly correlated with inward variation of the right LZ (p = 0.91; P < .001) and the right IMZ (p = 0.92; P < .001) but not the right SZ (p = -0.03; P = .83).

In 13 patients for whom information about APOE allelic status was known, there was a correlation between the number of APOE4 alleles and the rate of change of the CDR sum-of-boxes scores (r = 0.39; P = .03) but not the rate of change in ADAS-Cog total scores, Mini-Mental State Examination total scores, or Neuropsychiatric Inventory total scores. Adjusting for the number of APOE4 alleles in these patients eliminated all significant correlations between neuroanatomical measures and the rates of change in clinical outcome variables.

Patterns of hippocampal surface variation associated with various rates of change of ADAS-Cog total scores are illustrated in the Figure. Patients with the most positive rates of change (ie, worsening symptoms of dementia) showed inward variation of the surface of the hippocampus, especially within the LZ and IMZ, relative to the entire population of patients. Conversely, patients with the most negative rates of change (ie, improving symptoms of dementia) showed an expanded hippocampal surface within the LZ and IMZ relative to the entire population of subjects.

**Comment**

In this study, we tested the hypothesis that the volume and shape of the hippocampus would predict clinical outcome during donepezil treatment in patients with DAT. Our findings suggest that smaller hippocampal volumes associated with deformation of the lateral and inferomedial portions of the hippocampal surface predicted the rate of change in ADAS-Cog total scores. However, the magnitude of the correlations between neuroanatomical measures and ADAS-Cog total scores was small (p, 0.3-0.4), suggesting that only a small proportion of the variance was explained.

The correlations observed between hippocampal structure and rates of change in ADAS-Cog total scores were found after removing the influence of baseline ADAS-Cog total scores. Because disease in more severely ill patients would be expected to progress more rapidly, we attempted to remove the influence of disease severity at baseline before evaluating the relationships between the neuroanatomical variables and the rates of change in the clinical outcome variables. Unadjusted correlations between hippocampal shape and volume measures and rates of change in ADAS-Cog total scores were smaller than the correlations observed after removing the effects of baseline values (data not shown). Nevertheless, the response of the subjects to donepezil therapy was overlaid on the rate of progression of the underlying disease, and the correlations we found between hippocampal structure and clinical outcome were likely influenced by disease-related variation in the rate of disease progression.

In 13 patients, APOE allelic status was correlated with the rate of change in CDR sum-of-boxes total scores and nullified the correlations observed between neuroanatomical measures and the rates of change in ADAS-Cog total scores. While this is consistent with some previous findings, correlations were not found between APOE allelic status and other clinical outcome measures, including ADAS-Cog total scores. The most likely explanation for these findings is the few patients with data available for the analysis. However, the presence of an APOE4 allele might also be associated with a form of Alzheimer disease characterized by more abnormal hippocampal structure and a poorer response to treatment. In a previous comparison of similar patients with very mild DAT and control subjects without dementia, we found no difference in measures of hippocampal volume and shape and APOE4 allelic status. Further treatment studies in which information about brain structure and APOE genotype is available will be needed to resolve the relation-
ship, if any, between these 2 types of neurobiological markers and the capacity of patients with DAT to respond to AChE inhibitor treatment.

The pattern of inward variation of the hippocampal surface associated with a poorer clinical outcome during donepezil treatment was similar to the pattern of hippocampal surface deformation previously found to differentiate between patients with very mild DAT and subjects without dementia and to predict the subsequent onset of dementia in elderly persons who did not have dementia at the time of MRI scanning. Thus, reduced hippocampal volume associated with inward deformation of the hippocampal surface in proximity to the CA1 subfield and the subiculum may be both an early marker of disease and a predictor of a poor outcome during treatment with AChE inhibitors.

Further research is needed to find other predictors of treatment with AChE inhibitors in patients with DAT, especially predictors that account for a larger proportion of the variance in clinical outcome. Combining information from multiple markers, including neuroanatomical and genetic markers, might also be useful in predicting treatment outcome with greater power. Because there is substantial variation in the capacity of patients with DAT to respond to donepezil treatment and the commitment to treatment is measured in months to years, there would be substantial value in being able to preselect patients in whom treatment would be most beneficial. The results of this study suggest that neuroanatomical measures, especially measurements of hippocampal structure, may become useful in this regard.

**Figure.** Patterns of hippocampal surface variation associated with various rates of change in the Alzheimer Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) total scores. The patients were divided into 3 groups according to their rate of change in ADAS-Cog total scores. A, Patients with the most negative rate of change (improving, n=12). B, Patients with the most positive rate of change (worsening, n=13). C, Patients with an intermediate rate of change (n=12). In each group, the surface of the left (L) and right (R) hippocampus representing the mean of all patients is shown with a dorsal view angled from the right side (top row) and a ventral view angled from the left side (middle row). Boundaries between the lateral zone (LZ), superior zone (SZ), and inferomedial zone (IMZ) of the hippocampal surface are drawn in black. Flame color represents the difference between the mean surface of the subgroup vs the overall mean. Inward variations of the hippocampal surface are represented by cooler colors (blue-purple), and outward variations are represented by warmer colors (orange-red).
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