Enlargement of the Hippocampal Angle: A New Index of Alzheimer Disease

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Background: Imaging diagnosis of Alzheimer disease (AD), the leading cause of dementia, requires evaluation of the extent of hippocampal atrophy. Coronal magnetic resonance (MR) images of patients with AD often demonstrate outward rotation of the hippocampus that is altered from a long horizontal elliptical to a long vertical elliptical shape. Such rotation may be related to the disease process of AD.

Purpose and Methods: To determine whether hippocampal rotation is associated with AD, we investigated MR images from 11 patients with AD and 11 normal controls, measuring the hippocampal angle (HA) and the volume of the left hippocampus on coronal T1-weighted MR images.

The HA is the angle between a horizontal line orthogonal to the falx cerebri and the uncal sulcus line between the deepest point of the uncal sulcus and the point nearest to the side of the ambient cistern in the uncal gyrus facing the uncal sulcus. The HA is measured on the most rostral slice in which the uncal sulcus can be identified and increases with hippocampal rotation.

Results: We found correlation between the HA and standardized hippocampal volume in the AD group, but not in controls.

Conclusion: Hippocampal rotation is a new marker associated with the pathology of AD.

Keywords: Alzheimer disease, atrophy MR imaging, hippocampus

Introduction

The neuropathology of Alzheimer disease (AD) is characterized by atrophy of the medial temporal lobe, including the hippocampus, along with the accumulation of neurofibrillary tangles (NFT) and amyloid plaques.1

Many magnetic resonance (MR) imaging studies have demonstrated hippocampal atrophy to be a sensitive indicator of AD.2–9 On routine coronal MR images, progressive hippocampal atrophy appears to increase adduction of the hippocampus. The angle between the hippocampus and subiculum increases as hippocampal adduction increases. To our knowledge, this hippocampal deformity has not been reported in in vivo MR coronal images. We assume this alternation may be related to the AD disease process.

We defined the hippocampal angle (HA) as above and evaluated its enlargement in patients with AD to elucidate whether it was related to hippocampal atrophy.

Materials and Methods

Subjects were 22 patients (11 patients with AD and 11 normal controls) treated at Shimane University Hospital in Japan from January 2002 to March 2005. All subjects underwent examination by neurologists or psychiatrists.

Eleven patients (2 men, 9 women, aged 63–87 years; mean age 77 years; standard deviation [S.D.] ±7.1) were clinically diagnosed with probable AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association (NINDS-ADRDA).10 Clinical severity was assessed using the Revised Hasegawa Dementia Scale (HDS-R), which is comparable to the Mini-Mental State Examination.11 The mean HDS-R score was 18.7 (range 12 to 24; S.D. ±4.3).

Control subjects were 2 men and 9 women, aged 62 to 81 years (mean 71 years; SD ±5.5) who had
no past neurological or psychiatric history and no abnormal findings on MR images.

MR imaging was performed with a 1.5-tesla MR unit (Signa CVI, General Electric Medical Systems) using a standard head coil with a receive-transmit birdcage design. Thin-slice coronal images were obtained with 3D spoiled gradient recalled acquisition in the steady state (SPGR). The scanning parameters were repetition time (TR), 11 ms; echo time (TE), 2.2 ms; flip angle (FA), 20 degrees; field of view (FOV), 192 × 256 mm; acquisition matrix, 154 × 256; slice thickness, 1.5 mm; and acquisition bandwidth, 11.36 kHz. A total of 124 images were acquired. Voxel size was the volume represented by one pixel on the image and corresponded to the image resolution (0.62 × 1 mm). Voxel size was calculated as the FOV divided by the number of points in the image matrix and multiplied by the slice thickness, which was 0.93 mm³ in this study.

Measurement of the hippocampal angle

First, a coronal plane was defined perpendicular to a line connecting the anterior and posterior commissures, and a horizontal line was drawn orthogonal to the falx cerebri on this plane. Then, the uncal sulcus line was drawn between the deepest point of the uncal sulcus and the point nearest to the side of the ambient cistern in the uncal gyrus facing the uncal sulcus. Finally, the angle between the horizontal line and the uncal sulcus line was measured as the HA (Fig. 1) on the most rostral slice in which the uncal sulcus could be identified (Fig. 2).

One investigator (T.H.), who was blinded to the clinical information, performed all HA measurements.

Volumetric measurement

All volume measurements, including those of the hippocampi, were performed using the automated volumetric method with the IBASPM (Individual Brain Atlases using Statistical Parametric Mapping) software toolbox (http://www.thomaskoenig.ch/Lester/ibaspm.htm)¹² implemented in SPM5 (Statistical Parametric Mapping 2005) (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, London, UK) running on MATLAB 7.0 (Mathworks, Natick, MA, USA). Results were consistent with those obtained by manual volumetry.¹³

Fig. 1. The hippocampal angle (HA) on a thin-slice coronal magnetic resonance (MR) image. The HA lies between the uncal sulcus and a horizontal line. Arrow: uncal sulcus; E: entorhinal cortex; H: hippocampal head; PG: parahippocampal gyrus.

Fig. 2. Measurement of the hippocampal angle (HA; a drawing of the medial aspect of the left hippocampus). The plane for measurement of the HA is located at the anterior part of the uncal sulcus.
**Standardized hippocampal volume**

Total intracranial volume was calculated as the sum of the volume of the brain and that of the cerebrospinal spinal fluid space obtained by IBASPM. Hippocampal volume (HV) was standardized according to the method of Lehéry and colleagues. In brief, HV×1000 was divided by the calculated total intracranial volume in each subject. HA and HV were measured in the left temporal lobe because many previous studies have indicated that verbal memory, which is affected by AD, is predominantly localized to the left hippocampus.

**Statistical analysis**

We performed 2-sample unpaired t-test and Pearson’s chi-square test to assess correspondence of age and sex between patients with AD and controls and 2-sample unpaired t-test to compare the standardized HV and HA between the patients with AD and controls. We employed Pearson’s correlation coefficient analysis and simple regression analysis to assess the relation between the standardized HV and the HA or the HDS-R score. P<0.05 was statistically significant.

We performed analyses using SPSS software (version 11; SPSS, Chicago, IL, USA).

Receiver operating characteristic (ROC) curves were determined using ROCKIT 0.9β and the PlotROC program of Metz’s group (http.bsd.uchicago.edu/kr1). This program calculates the area under a ROC curve (Az), as well as sensitivity, specificity, and accuracy. The combination of these parameters is represented by the point of the curve nearest to the top left corner.

**Results**

We successfully quantified the HA in all 22 subjects. Figure 3B shows a typical enlarged HA and hippocampal atrophy in a patient from the AD group. Age and sex distribution were similar in the AD group and normal controls (P>0.05). HA ranged from 30.07° to 43.22° (mean±SD: 38.24°±4.79) in the AD group and from 15.34° to 35.73° (26.64°±6.22) in controls. HA did not differ significantly in relation to age or sex among the patients with AD.

HV ranged from 1.32 to 4.22 cm³ (2.36 cm³±0.74) in patients with AD and from 1.99 to 3.62 cm³ (3.06 cm³±0.50) in controls. Intracranial volume was 1628 to 2244 cm³ (1853 cm³±188) in the AD group and 1694 to 2326 cm³ (1916 cm³±164) in controls. The standardized HV was 0.68 to 1.88 (1.27±0.32) for the AD group and 1.08 to 1.86 (1.60±0.26) for controls.

The standardized HV was significantly smaller in the AD group than in controls (P=0.014, 2-sample t-test) and the HA significantly larger in the AD

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**Fig. 3.** Enlargement of the hippocampal angle (HA) with atrophy of the hippocampus and the parahippocampal gyrus in Alzheimer disease (AD). A: Coronal magnetic resonance (MR) image shows no atrophy of the medial temporal structures and no HA enlargement in a 62-year-old man in normal controls. The standardized hippocampal volume (HV) is 1.76 and the HA is 15.3°. B: Coronal MR image shows atrophy of medial temporal structures and enlargement of the HA in a 68-year-old man with mid-stage AD (Revised Hasegawa Dementia Scale [HDS-R] = 12). The standardized HV is 0.96 and the HA is 42.7°.
group (P<0.001, 2-sample t-test).

Correlations among the HA, standardized HV, and HDS-R score
In the AD group, we recognized a positive correlation between the standardized HV and the HDS-R score (r = 0.686, P = 0.02) (Fig. 4A) and a negative correlation between the standardized HV and the HA (r = -0.677, P = 0.02), but there were no significant correlations in controls.

Figure 4B shows that the regression line for the HA (y) versus the standardized HV (x) was y = 33.80x + 13.57 in the AD group.

In the AD group, the HDS-R score and the HA also correlated (r = -0.623, P = 0.04) by Pearson’s correlation coefficient analysis (Fig. 4C).

Separation of AD and non-AD groups by the HA
Figure 5 shows ROC curves for the HA and standardized HV. The Az value was 0.93 for the HA and 0.75 for the HV. The HA was 34.4° at the point of the curve nearest to the top left corner. Specificity was 88.7%; sensitivity, 80.8%; and accuracy, 86.4%.

Discussion
Our results indicate that the HA is a new marker of hippocampal atrophy in patients with AD.15

Pathological implications for enlargement of the HA
In patients with AD, the subiculum and CA1 are the most vulnerable brain regions, with little change observed in the CA4 and dentate gyrus.1,15–20

Adachi and associates investigated the internal structure of the hippocampal body using multishot diffusion-weighted images21 and reported decrease in the CA1 subfield as AD progressed and little change in CA3–4.

Csernansky and colleagues investigated variations in hippocampal surface using 3D structural
shape analysis methods\textsuperscript{15} and found the inward deformation of the lateral portion of the left hippocampal surface in a zone corresponding to the CA1 subfield to be an early predictor of the onset of AD. Such atrophy might be explained as a secondary change after degeneration of the superficial medullary lamina.\textsuperscript{16-18,20,21}

Atrophy of the CA1 is believed to lead to enlargement of the HA. In the hippocampal head, the CA1 are the major components, and the inner surface overlying the CA1 subfield approximates the uncal sulcus (the site of measurement in the present study). As the CA1 subfield decreases, the inner surface should deform outward and the lateral surface of the hippocampal head transform inward.

These changes in the CA1 subfield seem to alter the hippocampus from a long horizontal elliptical to a long vertical elliptical shape (Fig. 6), which leads to outward rotation of the hippocampus on routine coronal MR images and, consequently, HA enlargement. Thus, in patients with AD, enlargement of the HA is induced by atrophy of CA1.

Relation between the HA and HV in AD

Our volumetric data for the hippocampus agreed with findings of previous reports,\textsuperscript{2,14-19} and HV has been reported an indicator of the pathology of AD.\textsuperscript{2-9} We found a correlation between HV and results of cognitive function tests and between HA and both HV and cognitive function.

HV measurement is time-consuming, labor-intensive, and unlikely suited to a clinical environment because no fast and robust method for direct hippocampal volumetric quantification is available. On the other hand, HA measurement is fast and easy and suitable to clinical practice as a surrogate marker of volume loss in hippocampal formation. Thus, the HA seems to be an indicator associated with changes in the hippocampus in AD.

Limitations

We showed that the HA is related to the disease process in patients with AD, and we consider HA a suitable marker for routine clinical examination. However, several issues remain to be addressed.

Because atrophy of the medial temporal lobe has been reported to increase linearly with age, further studies are needed to expand the age range of the normative database. In our study, the number of age- and sex-matched control subjects was relatively small.

Evaluation is also needed of the suitability of the HA as a marker to discriminate between stages in AD, especially early-stage AD; the patterns of atrophy associated with other clinical conditions (such as normal pressure hydrocephalus); and whether the measurement of the HA can be available to separate AD and non-AD groups.

Furthermore, anatomical variations, such as depth of the middle temporal fossa, require attention. Though this did not occur in our study population, there may be cases in which the HA is increased without atrophy of the temporal lobe.

The reproducibility of HA measurements also needs examination, and the sensitivity of the HA to longitudinal atrophy should be established and compared with other measurements of atrophy in AD. Most previous measurements of changes in AD were obtained from transverse images, and the partial volume effect could potentially influence linear measurements made along axial images.\textsuperscript{20,21} Adduction of the hippocampus may also influence...
measurements made in the transverse plane as well as the partial volume effect. Previous studies have shown that addition of coronal MR images allows better qualitative assessment of the hippocampal region. We also believe that coronal images are more informative for evaluation of medial temporal lobe atrophy in patients with AD.

**Conclusion**

In patients with AD, the HA is affected by hippocampal atrophy and serves as a new marker of AD that could be useful in the routine clinical setting.

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**References**