The Interuncal Distance in Alzheimer Disease and Age-Associated Memory Impairment

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PURPOSE: To examine the value of measurement of the interuncal distance in the diagnosis of mild to moderate Alzheimer disease. **METHODS:** We measured interuncal distance from coronal MR scans acquired on a 1.5-T imager. We estimated interuncal distance from a total of 141 subjects: 54 patients diagnosed according to the National Institute of Neurological and Communicative Disorders and the Alzheimer's Disease and Related Disorders Association criteria of probable Alzheimer disease, 40 subjects fulfilling the National Institute of Mental Health criteria of age-associated memory impairment, 27 healthy cognitively normal older control subjects, and 20 control subjects younger than 50 years of age. For comparison we normalized interuncal distance for a horizontal line drawn through the inner cranium at the level of the uncus (interuncal distance/intracranial width ratio), for the brain area (interuncal distance/brain area) and for the intracranial area (interuncal distance/intracranial area). **RESULTS:** The standard interuncal distance and the interuncal distance/intracranial width differed between the young control subjects and the other groups, but did not differ among the control, age-associated memory impairment, and Alzheimer disease groups. The Alzheimer disease group had significantly greater interuncal distance/intracranial area and interuncal distance/brain area compared with age-matched controls. A considerable overlap was found, however, in the values of patients with Alzheimer disease and control subjects. The cutoff point of 30 mm for interuncal distance yielded 37% sensitivity and 72% specificity to distinguish patients with Alzheimer disease from nondemented elderly subjects. Interuncal distance was not significantly related to the clinical severity of Alzheimer disease as assessed by Clinical Dementia Rating Scale and Mini-Mental Status Examination. Instead, there was a strong correlation between standard and normalized interuncal distance and age in the whole study population and in nondemented subjects. **CONCLUSIONS:** Our results showed that in a series of 54 patients with mild to moderate Alzheimer disease, interuncal distance was not a reliable diagnostic tool. The study also confirmed the strong age dependence for interuncal distance.

Index terms: Age and aging; Dementia; Hippocampus; Brain, measurements; Memory

AJNR Am J Neuroradiol 16:727–734, April 1995

Memory loss is the most common early symptom in Alzheimer disease. The hippocampus, closely associated with memory processing, is known to be particularly damaged in the early stage of Alzheimer disease (1). Previous studies with magnetic resonance (MR) imaging have also documented the volumetric atrophy of the hippocampus to be a sensitive indicator of Alzheimer disease early in the course of the disease (2–5). The measurement of the volume of the hippocampus as a whole is relatively time-consuming, therefore other reliable simple methods that are easily applicable in clinical diagnostics are still needed. The interuncal distance introduced by Dahlbeck et al was presented as a simple method obtainable from a single section on an MR scan in the diagnosis of

Received June 29, 1994; accepted after revision October 25.

This study was supported by the Medical Research Council of the Academy of Finland and the North-Savo Fund of the Finnish Cultural Foundation.

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AJNR 16:727–734, Apr 1995 0195-6108/95/1604–0727

Alzheimer disease. The widening of interuncal distance was considered to reflect hippocampal atrophy. They could separate 10 Alzheimer disease patients from 10 control subjects by interuncal distance (6). It was proposed that the interuncal distance of 30 mm or more suggests presence of Alzheimer disease, or at least the distance is not likely to exceed 30 mm in normal-aging subjects (6, 7). Later, other studies have questioned interuncal distance measurement in the screening of Alzheimer disease because of an overlap in values of Alzheimer disease patients and control subjects (8, 9).

Because previous data are inconclusive, we decided to study the usefulness of interuncal distance to distinguish Alzheimer disease patients from control subjects in a large series of subjects including Alzheimer disease patients at the early phase of the disease, young and elderly cognitively intact subjects, and nondemented subjects with age-associated memory impairment. The age-associated memory impairment group consists of elderly people who have experienced memory impairment and who show deficits on memory tests compared with young controls, but who do not fulfill the criteria of dementia (10–11).

Subjects and Methods

Subjects

We examined 141 subjects: 54 patients fulfilling the National Institute of Neurological and Communicative Disorders and the Alzheimer's Disease and Related Disorders Association criteria of probable Alzheimer disease (12), 40 subjects fulfilling the National Institute of Mental Health criteria of age-associated memory impairment (13), 27 older control subjects, and 20 control subjects younger than 50 years of age. The clinical characteristics of the subjects are presented in Table 1. A local ethics committee approved the study. All subjects gave informed consent for participation in the study after the explanation of the study protocol.

The patients with Alzheimer disease underwent the following examinations: general physical and clinical neurologic examination; assessment of clinical severity using Mini-Mental Status Examination (14) and Clinical Dementia Rating scale (15); extensive battery of laboratory tests to exclude secondary causes of dementia; neuropsychologic tests; electroencephalography; event-related potentials; single-photon emission computed tomography; and MR of the brain. According to clinical dementia rating, 5 patients had questionable dementia (score, 0.5), 33 had mild dementia (score, 1), and 16 had moderate (score, 2) dementia. All patients scored less than four in the modified ischemic scale (16).

The investigation of the age-associated memory impairment subjects and the older controls included clinical neurologic examination, neuropsychological testing, electroencephalogram and event-related evoked potentials, and MR imaging. The younger controls were medical students or staff members volunteering for the study. They were healthy and had no history of central nervous system or other diseases or medication.

MR Imaging

The subjects were scanned with a 1.5-T unit, standard head coil, and a tilted coronal three-dimensional gradient-echo sequence 10/4/1 (repetition time/echo time/excitations); inversion time was 250 milliseconds; flip angle, 120°, field of view, 250 mm; and matrix, 256 × 192. This resulted in 128 T1-weighted partitions with section thickness of 1.5 to 2.0 mm oriented at right angles to the long axis of the hippocampus.

Measurement of Interuncal Distance and Normalization of Values

The radiologist was blinded to the clinical data of the subjects. Determination of the variables was performed with standard work console by measuring the distance

TABLE 1: Clinical characteristics of the younger and older control subjects, subjects with age-associated memory impairment, and patients with Alzheimer disease

	Younger Control Subjects	Older Control Subjects	Subjects with Age-Associated Memory Impairment	Subjects with Alzheimer Disease	Analysis of variance F
N	20	27	40	54	
Women/men	10/10	17/10	29/11	27/27	. . .
Age, y	29 ± 8	71 ± 4	70 ± 6	70 ± 8	209.3*
Age at onset, y	. . .	. . .	. . .	68 ± 8	. . .
Duration, mo	. . .	. . .	. . .	34 ± 21	. . .
Mini-Mental Status Examination	. . .	28.4 ± 1.3	27.5 ± 1.6	21.7 ± 3.7†	79.0*

Note.— Results are expressed as mean ± SD.

* $P < .0001$, Duncan posthoc analysis.

† $P < .05$ differs from older control subjects and age-associated memory impairment subjects.

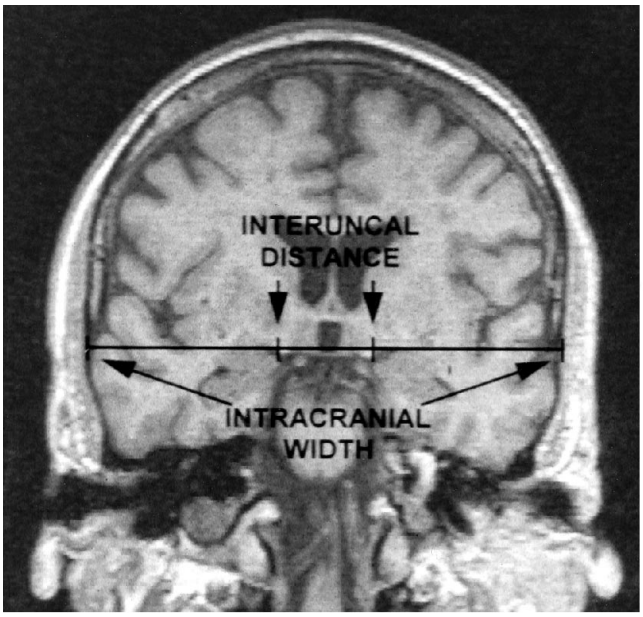

Fig 1. Measurement of interuncal distance and intracranial width.

between the unci on coronal sections (Fig 1). To exclude the effect of individual head and brain sizes, we normalized the values and divided interuncal distance with the intracranial width (interuncal distance/intracranial width), the brain area (interuncal distance/brain area), and the intracranial area (interuncal distance/intracranial area).

Measurements of intracranial width, intracranial area, and brain area were performed at the level where the anterior commissure was first present when proceeding from anterior to posterior (Fig 1). Intracranial width is a line through the inner cranium measured horizontally at the level of the unci. In cases in which the unci were not on the same horizontal level, the intracranial line was tilted horizontally at the midpoint of the interuncal distance. Intracranial area is the intracranial area outlined by the inner table of the skull. Brain area is the brain area from which the lateral and temporal ventricular spaces were excluded. To get reasonable numbers in statistical analysis, the interuncal distance was multiplied by 100 when normalized for the brain area and the intracranial area.

Reproducibility

The interrater reliability for interuncal distance was tested between two raters in 16 subjects. The mean of the measurements was 26.4 for rater 1 (M.L.) and 26.3 for rater 2 (K.P.), the intraclass correlation coefficient was 0.82, analysis of variance (ANOVA) $F(1,15) = .014$, and $P = .907$. Furthermore, we assessed interuncal distance in the same patient so that the measurement is made slightly posterior. For that purpose the same rater measured interuncal distance 1 to 3 sections (4.5 to 6.0 mm) posterior of interuncal distance at the anterior commissure for 16 patients. The correlation coefficient between these two measurements was .64, $P < .01$.

Statistical Analysis

The data were analyzed by using SPSS−PC+ V.4.1 software. ANOVA followed by Duncan posthoc analysis was used to compare the means over the study groups. Correlations were calculated by using Pearson's correlation two-tailed test. Sensitivity, specificity, and positive and negative predictive values for the cutoff point of 30-mm interuncal distance to separate patients with Alzheimer disease from age-matched nondemented subjects were calculated. To test further the accuracy of the measurements to distinguish patients with Alzheimer disease from controls, we used stepwise discriminant function analysis (Wilks's method). The results are expressed as mean ± standard deviation. The level of statistical significance of differences is $P < .05$.

Results

The Alzheimer disease, age-associated memory impairment, and older control groups did not differ significantly in age or sex (Table 1). As expected, Mini-Mental Status Examination scores were significantly lower for patients with Alzheimer disease than for older controls and age-associated memory impairment subjects (ANOVA; $F[2,119] = 79.0$, $P < .0001$).

The MR data are summarized in Table 2. ANOVA over the study groups showed a significant difference in standard interuncal distance ($F[3,137] = 11.4$, $P < .0001$). The younger controls had significantly smaller interuncal distance compared with the three older groups (Duncan, $P < .01$), but older control, age-associated memory impairment, and Alzheimer disease groups did not differ. The scatterplots (Fig 2A) demonstrate the overlap of interuncal distance values across the study groups. Interuncal distance exceeded 30 mm in 21 (37%) of 54 patients with Alzheimer disease, 13 (33%) of 40 age-associated memory impairment subjects, 6 (22%) of 27 older controls, and 1 (5%) of 20 younger controls. The cutoff point of 30 mm resulted in 37% sensitivity and 72% specificity to separate early Alzheimer disease from nondemented elderly subjects (combined age-associated memory impairment and older control groups). The positive predictive value was 53%, and negative predictive value was 59%.

There also was a significant difference in interuncal distance/intracranial width (ANOVA over the study groups, $P < .0001$). The younger

TABLE 2: Standard and normalized interuncal distance for younger and older control subjects, subjects with age-associated memory impairment, and patients with Alzheimer disease

	Younger Control Subjects	Older Control Subjects	Subjects with Age-Associated Memory Impairment	Subjects with Alzheimer Disease	ANOVA F*
N	20	27	40	54	
Interuncal distance, mm	22.8 ± 3.7†	27.4 ± 2.8	27.9 ± 4.7	29.4 ± 4.8	11.2
(range)	(17.4 − 32.4)	(22.6 − 34.4)	(20.6 − 40.2)	(19.6 − 43.1)	
Interuncal distance/intracranial width, ratio	0.17 ± 0.03†	0.21 ± 0.02	0.21 ± 0.04	0.22 ± 0.03	9.4
Interuncal distance/intracranial area, ratio	0.19 ± 0.03†	0.24 ± 0.03	0.24 ± 0.05	0.26 ± 0.05‡	12.1
Interuncal distance/brain area, ratio	0.25 ± 0.05†	0.33 ± 0.04	0.34 ± 0.12	0.41 ± 0.08†	23.6

Note.— Results are expressed as mean ± SD.

* ANOVA over the study groups, $P < .0001$.

† Duncan differs from all other groups, $P < .01$.

‡ Differs from age-associated memory impairment and older control subjects, $P < .05$.

controls differed from all other groups (Duncan, $P < .01$), whereas the values were comparable for age-matched older groups. The interuncal distance/intracranial area and interuncal distance/brain area values also were significantly smaller for younger controls compared with the older control, age-associated memory impairment, and Alzheimer disease groups (Duncan, $P < .01$). In addition, the Alzheimer disease group differed significantly from the older control and the age-associated memory impairment groups in interuncal distance/intracranial area (Duncan, $P < .05$) and interuncal distance/brain area ($P < .01$). Despite the significant differences, the variables overlapped across the age-matched study groups (Fig 2B).

Correlation between Interuncal Distance and Age

In the whole study population, age correlated significantly ($P < .0001$) with interuncal distance ($r = .41$)(Fig 3), interuncal distance/intracranial width ($r = .41$), interuncal distance/intracranial area ($r = .45$), interuncal distance/brain area ($r = .55$), as well as with brain area ($r = -.59$). Similar significant correlations ($P < .0001$) with age were observed when all nondemented subjects (younger and older control subjects and subjects with age-associated memory impairment) were included in the analysis. Within the Alzheimer disease group, standard and adjusted interuncal distance was not related to age, but the brain area was ($r = -.41$, $P < .01$). Brain area correlated significantly with age also within age-associated memory impairment subjects ($-.48$, $P < .01$) and within older controls ($r = -.39$, $P < .05$).

Discriminant Function Analysis

For the further analysis of interuncal distance in the diagnosis of Alzheimer disease, we compared the values of patients with Alzheimer disease with the combined group consisting of elderly controls and age-associated memory impairment subjects. In the first stepwise discriminant function analysis including interuncal distance, interuncal distance/intracranial width, interuncal distance/intracranial area, interuncal distance/brain area, age, and sex, 72% of patients with Alzheimer disease and 79% of age-matched nondemented elderly subjects were correctly classified (Wilks's λ, 0.69; χ^2, 42.5; *df*, 5; and $P < .00001$). This model explained only 31% of variance between the groups. The best distinguishing variable, interuncal distance/brain area, explained 13% of the variance, and further contribution of the other variables was less (interuncal distance/intracranial width, 8%; sex, 4%; age, 3%; and interuncal distance/intracranial area, 2%). In the second discriminant function analysis including interuncal distance/brain area, age, and sex, 63% of patients with Alzheimer disease and 72% of nondemented elderly were classified correctly (Wilks's λ, 0.82; χ^2, 22.8; *df* 3; and $P < .00001$).

Interuncal Distance and Clinical Severity

The mean interuncal distance for patients with Alzheimer disease with Clinical Dementia

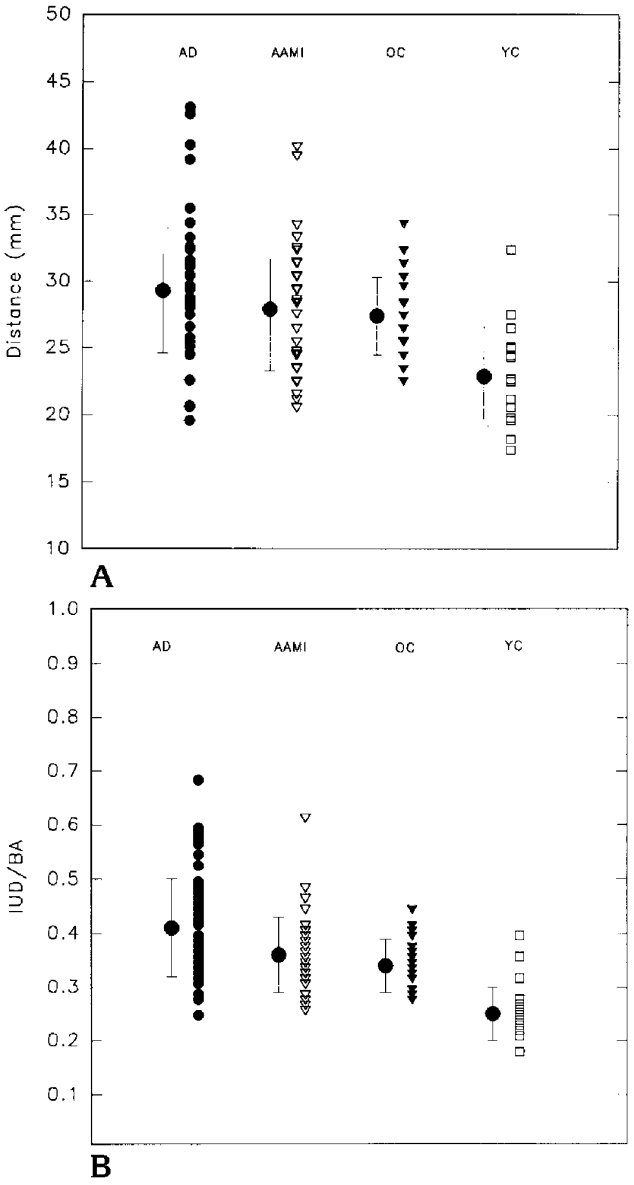

Fig 2. Scatterplots, means, and SD of interuncal distance (mm) (*A*) and ratio of interuncal distance to brain area (*IUD/BA*) (*B*) for patients with Alzheimer disease (*AD*) subjects with age-associated memory impairment (*AAMI*), and older (*OC*) and younger (*YC*) control subjects.

Rating scale indication of questionable, mild, and moderate dementia was 28.9 ± 1.7 mm, 28.7 ± 4.6 mm, and 30.9 ± 5.7 mm, respectively. The difference in standard or normalized interuncal distance was not significant across the Alzheimer disease groups with differing clinical severity. Within the Alzheimer disease group, there was no significant correlation between Mini-Mental Status Examination test scores and interuncal distance either.

Discussion

Despite the effort to find an accurate measurement of a structure, a combination of structures, or even a combination of structural and functional measurements to detect early Alzheimer disease, an effective measurement has not been determined. The Consortium to Establish a Registry for Alzheimer's Disease has tried to develop procedures for standardized imaging and reporting MR findings, but no satisfactory interrater agreement for interpreting MR findings in elderly subjects has been found. Acceptable intraclass correlations in a group of 14 neuroradiologists were obtained only in the ratings of the lateral and third ventricles and the temporal horn. More objective and reproducible procedures for interpretation of neuroimaging findings of Alzheimer disease are needed (17).

A major conclusion of this study with a large number of well-documented subjects is that interuncal distance is not a reliable method in diagnosing early Alzheimer disease. The limit of 30 mm, suggested by previous studies to separate patients with Alzheimer disease from controls (6, 7), was more than the average interuncal distance in our Alzheimer disease group. The 37% sensitivity of the cutoff point of 30 mm for interuncal distance shows that the measurement of interuncal distance is not sensitive enough for clinical use. By contrast, the 72% specificity was modest. As the values of the older controls and age-associated memory impairment subjects did not differ significantly and the subjects in both groups were clinically nondemented, we used the combined group of older controls and age-associated memory impairment subjects in calculations of specificity and positive and negative predictive value. The 30-mm limit was exceeded in 22% of the older control subjects and in 33% of the age-associated memory impairment group, but only in 5% of younger controls. Thus, overlap was considerable among the elderly study subjects, not only for interuncal distance, but also for interuncal distance adjusted for head or brain size. The variable that differed most significantly between the study groups, the interuncal distance adjusted for the brain area, apparently reflects more overall brain atrophy and ventricular space enlargement than hippocampal atrophy, in comparison with intracranial area that remains stable. It is also noteworthy that interun-

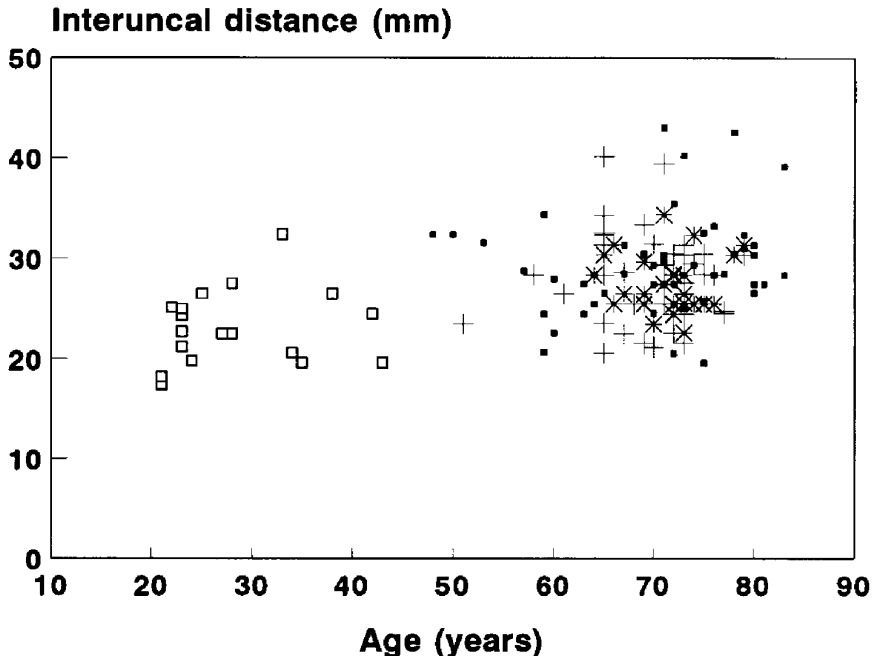

Fig 3. Correlation of interuncal distance and age for patients with Alzheimer disease (*solid squares*), subjects with age-associated memory impairment (*plus signs*), and older (*asterisks*) and younger (*open squares*) control subjects. In the whole study population, interuncal distance correlated with age ($r = .41$; $P < .0001$).

cal distance was not related to the clinical severity of Alzheimer disease. We need, however, to keep in mind that in our patients with Alzheimer disease the range of the severity was narrow.

Doraiswamy et al measured interuncal distance in 75 volunteers from 21 to 82 years of age who were free of neurologic disorders and found a correlation between interuncal distance and age. In their study, interuncal distance never exceeded the limit of 30 mm (7). Discrepancy in findings among our and previous studies (6, 7) may be attributable to a large number of subjects studied and clinical severity in our patients who had mild or moderate degrees of dementia and in whom the diagnosis of Alzheimer disease was recently made. In the study by Dahlbeck et al (6), interuncal distance measurement was done when the patients with Alzheimer disease were discharged from the hospital, but the degree of patients' cognitive impairment was not presented. Moreover, our method differed from the previous studies in which interuncal distance was measured mostly on axial images. In addition, the definition of the term *uncus* has been somewhat unclear. However, in concert with our findings, Howieson et al reported significant group differences among 10 patients with Alzheimer disease and 10 controls, but also found an overlap between the groups and concluded that the measurements of interuncal distance are ineffective in the screening of Alzheimer disease (8). Early et al came to the same conclusion with 17 controls and 12 patients with Alzheimer disease. They also found a significant correlation between interuncal distance and age but no correlation between interuncal distance and the amygdalohippocampal volume (9).

It is obvious that the method of interuncal distance measurement has limitations. The interrater agreement in this study was modest only for a method as simple as interuncal distance. The comparison of the actual interuncal distance and interuncal distance measured 1 to 3 sections more posteriorly yielded a poor correlation, suggesting that the coronal plane selection for measuring interuncal distance should be very exact. The coronal plane was considered to be most accurate and reproducible by Dahlbeck et al (6) and by Howieson et al (8). The best agreement in the study of Howieson et al was achieved in the coronal images at the level where the temporal horn was present. A method of that kind would not be sufficient when it is known that the temporal horn is subject to individual variations (18), and widens during the course of Alzheimer disease (5, 19).

Previous MR studies on Alzheimer disease and hippocampus have suggested that the volume of the hippocampus is a sensitive measure of Alzheimer disease early in the course of the disease (2–5). Still, the hippocampus measured

from a single section did not show significant difference in size between the early Alzheimer disease group and controls (20). Accordingly, Erkinjuntti and coworkers measured hippocampal area at the level of hippocampal head and were able to differentiate only 41% of the early Alzheimer disease group and the controls (19). Linear ratings performed with computed tomography (CT) have earlier produced correct classification of only 65% of patients with Alzheimer disease and controls that resembles our results (21). Low positive and negative predictive values for interuncal distance calculated from our data agree with these studies. It is also worth mentioning that hippocampal atrophy is not specific to Alzheimer disease. The volume of hippocampus has been shown to decrease in epilepsy, schizophrenia, and amnesia (22–24).

The relationship of age-associated memory impairment to normal aging and to Alzheimer disease is debated. On the basis of the current knowledge, it is obvious that age-associated memory impairment category includes a large number of healthy elderly persons as well as a minor proportion of subjects who are at a very high risk to deteriorate to dementia (10, 11). The standard and adjusted interuncal distance for age-associated memory impairment subjects who had slight memory decline not sufficient to allow a diagnosis of dementia did not differ from values of older controls with intact cognitive functions. However, in 33% of age-associated memory impairment subjects, interuncal distance exceeded 30 mm; this percentage is intermediate between 22% of older controls and 37% of patients with Alzheimer disease. Thus, it is possible that among age-associated memory impairment subjects, there are individuals in whom dementia will develop on clinical follow-up.

Taken together, we believe that hippocampal atrophy best predicts Alzheimer disease by MR, but linear measurements like interuncal distance, or measurements of the hippocampal area from a single section, in differentiating patients with Alzheimer disease from control subjects have not been successful compared with volumetric results. Linear or area measurements are more subject to individual variability and more easily affected by artifacts or head position.

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