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Interuncal Distance: Marker of Aging and Alzheimer Disease

John Howieson,[1,2] Jeffrey A. Kaye,[1] Lynne Holm,[1] and Diane Howieson[1]

PURPOSE: To evaluate the utility of a recently reported simple measure of brain atrophy on MR imaging, the interuncal distance (IUD). **METHODS:** Measurements of the IUD were made over a 12-month interval in 10 patients with probable early Alzheimer disease and in a comparison group of age-matched healthy control subjects. The measurements were made in both the transaxial and coronal planes. **RESULTS:** Significant group differences for the coronal measurement of IUD were found in both the absolute value of the measurement and the IUD corrected for head size. There was overlap in IUD between the disease and the control groups. These differences were not found for the transaxial IUD. Significant positive correlations of the IUD with Mini-Mental State Examination score and Clinical Dementia Rating Scale stage were observed. Over the age range tested, age was not significantly correlated with IUD in the sample. **CONCLUSIONS:** The interuncal distance (IUD) is not a useful screening measurement for Alzheimer disease.

Index terms: Dementia; Brain, measurements; Brain, magnetic resonance; Age and aging; Degenerative brain disease

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Many morphologic measurements have been proposed to differentiate Alzheimer disease (AD) from normal aging (1). Recently Dahlbeck et al (2) suggested that a new measurement on magnetic resonance (MR), the interuncal distance (IUD), the distance measured between the medial borders of the uncus of each temporal lobe, could be used to differentiate patients with AD from a group of patients without historical evidence of dementia. They concluded that a measurement of greater than 30 millimeters could be used as the basis of a diagnosis of hippocampal atrophy associated with AD.

We attempted to replicate this finding using more stringent subject selection criteria. Our control group excluded hypertension, diabetes, past head injury, and many other diseases. Our AD group met NINCDS-ADRA criteria. The control and AD groups were matched with respect to age, gender, and educational level. We also compared the effect of applying different imaging planes and pulse sequences to the measurement. In addition, we looked at the stability of the measurement over a mean of 14 months.

Methods

Subjects

All AD patients with mild dementia, ie, with a Clinical Dementia Rating Scale (3) equal to 1 and two or more consecutive MR scans comprised the patient group (n = 10, seven men and three women). The diagnosis of AD was made according to the NINCDS-ADRDA criteria (4). Patients were excluded if there was a history of major medical illnesses including diabetes, hypertension, angina, cardiac arrhythmia, chronic pulmonary disease, cancer, major affective disorder, transient ischemic attacks, stroke, head injury or other neurologic disease, or a history of drug or alcohol abuse. Subjects took no medications with the following exceptions: vitamins, aspirin, thyroid hormone (subjects must have been euthyroid 1 year before study), and estrogen.

Healthy control subjects were chosen from the Oregon Brain Aging Study, a longitudinal study of the optimally healthy, community-dwelling elderly. Healthy subjects (n = 10) satisfying the same health criteria as the AD patients

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[1] Departments of Radiology and Neurology, Oregon Health Sciences University and the Portland Veterans Affairs Medical Center, Portland, Oregon.

[2] Address reprint requests to John Howieson, MD, Department of Diagnostic Radiology, L340, Oregon Health Sciences University, 3181 Sam Jackson Park Road, Portland, OR 97201.

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were selected to match the age, gender, and education level of the patients. Healthy subjects were required to be functionally independent and to score at least 12 on the instrumental activities of daily living section of the Older Americans Resources and Services multidimensional functional assessment and questionnaire (5), 0 on the Clinical Dementia Rating Scale (3), at least 24 on the Mini-Mental State Examination (6), not greater than 10 on the Cornell Depression Scale (7), and not greater than 11 on the Geriatric Depression Scale (8). Patients and control subjects satisfied these criteria for each year they were evaluated.

Evaluation Procedures

All subjects or their legal guardians gave written informed consent to participate in the project. Within 2 weeks following each MR scan, patients and subjects had a complete medical history and neurologic examination.

Individuals were administered the Mini-Mental State Examination (6) and other cognitive tests. MR was performed on a 1.5-scanner with images obtained in the sagittal, axial, and coronal planes. Standard pulse sequences were used: T1-weighted images, 600/20/1 (TR/TE/excitations), and T2-weighted images, 2800/80, with a section thickness of 5 mm and field of view of 24 cm. The matrix size was 256 × 256. The images were reviewed blinded to the diagnosis, age, or sex of the subject. The IUD was determined directly from the image section through the suprasellar cistern on the transaxial series by measuring the distance between the unci of the temporal lobes with a dial caliper. The coronal measurement was made by selecting the most anterior image that showed the temporal horn and measuring the distance between the unci of the temporal lobes at that level. For both transaxial and coronal measurements, the adjacent images were observed and if a shorter interuncal distance was measured in the adjacent section, the smallest measurement was used. The identical measurements were made on repeat MR scans performed within a subsequent 12-month period. A total of 38 scans were evaluated (two coronal scans were technically inadequate for assessment).

To correct for individual differences in brain size, the width of the intracranial compartment was measured. The largest measurement from the inner table of one side of the skull to that of the other side was used. This was usually at the level of the foramen of Monroe. For certain calculations the IUD was then adjusted for brain size by dividing the IUD by the intracranial width.

Intrarater reliability of the measurements was determined by measuring the IUD on 10 randomly selected scans from the series on two occasions separated by a mean of 3 weeks.

Results

Patient and subject characteristics and IUD measurements are summarized in Table 1. Group differences were analyzed using two-tailed Student *t* tests. There were no significant differences between the AD patients and control subjects in age, sex, or educational level. The IUD measurements are given in Table 2. During year 1, the difference between the AD and healthy control groups was significant for both the absolute value of the IUD and the adjusted IUD measured in the coronal plane, but the difference between the groups was not sufficient to allow a complete separation of those with disease from those in the control group (Fig. 1). There was no significant difference between groups in the IUD measured in the transaxial plane. We further examined the change in the IUD over 1 year. The control group showed slightly but significantly lower values on the second measurement and no change was seen in the AD group.

Correlation of IUD with Mini-Mental State Examination and Clinical Dementia Rating Scale were significant ($P < .005$).

Comparison of the two sets of measurements by the same observer revealed the mean difference between the two transaxial measurements to be 1.4 mm. The mean difference on the coronal measurement was 0.26 mm, indicating the greater reliability of the latter technique.

TABLE 1: Group characteristics expressed in means and standard deviations

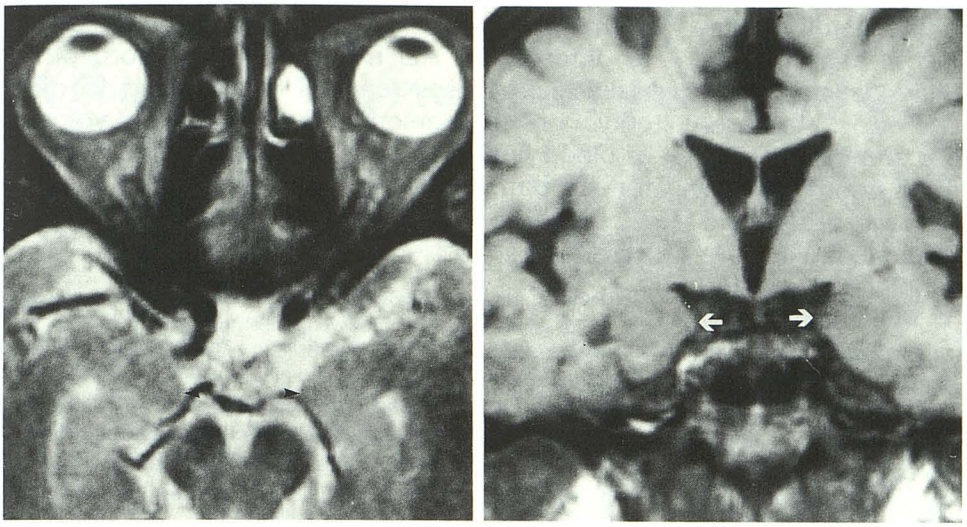
	Controls (n = 10)	Alzheimer Disease Patients (n = 10)
Female/male	3/7	3/7
Age	74.5 (7.5)	73.9 (8.9)
Education	13.8 (2.8)	13.4 (3.7)

TABLE 2: Group comparisons of IUD measurements in the coronal (C) and transaxial (T) planes

	Controls	Alzheimer Disease Patients	Student *t* test
Year 1			
IUDC1	24.1 (3.7)	30.5 (2.8)	$P < .001$
IUDT1	28.4 (5.6)	29.6 (2.7)	NS
IUDC/W[a]	0.18 (0.03)	0.22 (0.03)	$P < .005$
IUDT/W[a]	0.21 (0.05)	0.21 (0.02)	NS
Year 2			
IUDC2	23.9 (2.3)	30.3 (3.2)	$P < .0001$
IUDT2	26.8 (3.1)	30.7 (3.0)	$P < .01$
IUDC/W[a]	0.18 (0.02)	0.22 (0.02)	$P < .0001$
IUDT/W[a]	0.20 (0.02)	0.22 (0.02)	$P < .05$

Note.—Means (in millimeters, corrected for scale); standard deviations in parentheses. IUD = interuncal distance.

[a] Ratios of IUD measures to brain width.



A B

Fig. 1. *A*, T2-weighted (2800/80) transaxial image shows the interuncal measurement.

B, Intraobserver variation of measurements was substantially less on T1-weighted (60/20) coronal images (*arrowheads*).

Discussion

Atrophy of the hippocampus has been documented in studies based on imaging (9) and on pathologic findings (10). This is thought to be the pathologic substrate of the memory deficit which characterizes AD (11). Hippocampal atrophy was thought to be the cause of the increased IUD observed by Dalbeck et al (2).

Any measurement of the distance from the uncus of one side to the other will be subject to error because the uncus is a curved structure. There is no way to be sure that the image used for measurement is optimally placed unless very thin cuts are used. Such a procedure would not be practical for routine clinical imaging. Dahlbeck et al (2) studied 10 AD patients and 10 control subjects. The mean interuncal distance for the AD patients was 37.3 millimeters and the mean of the control subjects 22.2 millimeters. Our results yielded higher value for the controls, but the difference between the two studies was not large. On the other hand, our mean for the AD cases was 30.7, a value much lower than the result of Dahlbeck et al. To account for this difference, we believe it is likely that their AD cases were much more advanced than ours.

We have repeated and expanded the study of Dahlbeck et al (2) with what we regard to be important differences. Our 10 AD patients were compared with 10 control subjects who were matched for age, sex, and education. Our control subjects had to meet very stringent criteria to be included in the study. They had no historical or examination evidence of disease that might influence the results by being associated with brain atrophy itself, such as vascular disease or alcoholism. The AD patients were likely to be accurately diagnosed in that all in this group had documented progression of disease and fulfilled standardized NINCDS-ADRDA diagnostic criteria.

We adjusted the IUD by correcting for a measure of head size, the intracranial width. We made measurements in both the transaxial plane and in the coronal plane. We elected to use the T2-weighted images (2800/80) rather than the spin-density images, because, in our set of images, the interface between the temporal lobe and the adjacent cerebrospinal fluid is much more easily visible on these images. Our coronal images are all T1-weighted. The measurements of Dahlbeck et al were made at the level of the suprasellar cistern on spin-density-weighted axial images (spin-echo 2000/20). They stated that they believed that coronal views would have been more accurate and more reproducible. They did not allude to the possibility that another pulse sequence might provide better delineation of the uncus. Based on the lower mean difference between two sets of measurements by the same observer, we believe that the optimum study to make this measurement is a T1-weighted coronal series.

If one assumes a normal distribution of the measurements, it is clear that the control mean plus or minus two standard deviations (the rule that is used to include 95.4% of a population) would extend to a measurement very close to the mean for the AD group. This result indicates that,

although there is a highly significant difference between the AD group and the control group, the use of the measurement as a diagnostic criterion would, nevertheless, be prone to error. Measurements of greater than 31.3 (two standard deviations above mean for the coronal control group measurement) would provide a valid basis for a diagnosis of AD but would be expected to include approximately 5% of controls and would exclude more than half of the cases of AD. Similarly an upper cutoff point for the exclusion of AD of 24.4 mm would be expected to include 5% of AD cases within the control group and would fail to include approximately half of the true controls. The resulting rule (ie, over 31.3 mm means AD; under 24 mm means normal) may still be useful in some cases but it leaves an excessively wide zone of doubt. It can be expected to be of little use in assisting the early diagnosis of AD.

The lower values for the IUD in the control group on the second measurement are interpreted as a limitation of the method rather than a true decrease over time.

Medical imaging plays an important role in the evaluation of dementia. It is necessary to detect structural diseases such as hydrocephalus, bilateral subdural hematoma, multiple metastases, and other conditions that may produce a progressive mental decline without focal or lateralizing neurologic signs. It would be highly desirable to make on routine MR images a single linear measurement that would establish a diagnosis of AD rather than merely exclude these other causes of dementia. The goal of finding a linear measurement that could be made on routine MR scans to differentiate AD from normal or from other disease processes remains elusive, and to date only more cumbersome measurements of volume or blood flow appear to be sensitive and specific for this purpose.

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