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CT Diagnostic Features of Alzheimer Disease: Importance of the Choroidal/Hippocampal Fissure Complex

Ajax E. George^{1,2}
 Mony J. de Leon^{2,3}
 Leonidas A. Stylopoulos^{1,2}
 Jeffrey Miller¹⁻³
 Alan Kluger^{2,3}
 Gwenn Smith^{2,3}
 Douglas C. Miller⁴

Neuropathologic changes in the temporal lobe, including focal atrophy of the subiculum and entorhinal cortex, have been described in association with Alzheimer disease. We studied the usefulness of detecting temporal-lobe structural changes on CT in making the diagnosis of Alzheimer disease. The dementia imaging protocol we use includes thin-section (5 mm) cuts of the temporal lobe oriented 20° negative (caudal) to the plane of the canthomeatal line. Thirty-four patients with suspected Alzheimer disease and 20 normal elderly control subjects, all between 65 and 80 years olds, were studied with a standard protocol that also included neurologic and medical examinations and detailed psychometric testing. All the temporal-lobe evaluations of the five variables measured were significantly associated with the presence or absence of Alzheimer disease. Almost all Alzheimer patients showed evidence of mild or greater severity of overall temporal-lobe atrophy. The absence of temporal-lobe atrophy, seen in approximately one half the normal cases, identified normal individuals with a high degree of specificity (95%). The presence of characteristic hippocampal lucency, apparently due to enlargement of the choroid and hippocampal fissures, showed the highest sensitivity and classification accuracy of all the variables tested (82 and 80% respectively; $p < .001$), correctly identifying 82% of Alzheimer patients and 80% of Alzheimer patients and control subjects.

These results indicate that CT detection of structural changes in the temporal lobe and hippocampus strongly support the diagnosis of Alzheimer disease. A temporal-lobe imaging protocol for CT, and by extension for MR, is suggested for the evaluation of patients with the clinical diagnosis of a dementing disorder.

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¹ Department of Radiology (Neuroradiology), New York University School of Medicine, 560 First Ave., New York, NY 10016. Address reprint requests to A. E. George.

² Department of Psychiatry, The Brain Imaging Laboratory, New York University School of Medicine, New York, NY 10016.

³ Department of Psychiatry (Geriatric Study and Treatment Program), New York University School of Medicine, New York, NY 10016.

⁴ Department of Pathology (Neuropathology), New York University School of Medicine, New York, NY 10016.

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Previous reports from several laboratories including our own have shown that generalized ventricular and sulcal enlargement correlate with the presence and severity of Alzheimer disease [1-6]. However, these correlations have been relatively weak. The structural changes seen in normal aging—that is, ventricular and sulcal dilatation—overlap considerably with the changes seen in Alzheimer disease [7-9]. Consequently, in the evaluation of a dementing disorder, CT has been used primarily to exclude other causes of dementia such as hydrocephalus, metastatic disease, or subdural hematoma, but not to establish a diagnosis of Alzheimer disease. Preliminary neuroimaging data from our laboratory have shown that quantitated measures of ventricular volume derived from slices below the pineal level show stronger correlation with measures of Alzheimer disease than ventricular measures above the pineal level [10]. These data suggest that CT information regarding Alzheimer changes may be most relevant in the basal temporal lobe.

Recent neuropathologic evidence [11-14] has suggested a focal pattern of disease that involves the hippocampal formation in Alzheimer disease. In 1983 we implemented a CT protocol whose purpose was to optimally visualize any atrophic or parenchymal changes that may occur in the temporal lobes. With the use of this protocol, we examined the diagnostic utility of structural changes in the temporal

lobe by comparing the CT scans from a group of patients with presumed Alzheimer disease with those from a group of age-matched control subjects.

Materials and Methods

We reviewed the CT studies of 34 patients with the diagnosis of presumed Alzheimer's disease and 20 aged-matched normal control subjects. The Alzheimer patients were 56–87 years old; 53% were female. The normal subjects were 60–85 years old; 50% were female. All 54 subjects were evaluated at the New York University Aging and Dementia Research Program. These evaluations included neurologic and medical examination, psychometric testing, and a CT scan. The subjects were outpatients from diverse ethnic and socioeconomic backgrounds; they were primarily white and residing in the New York City metropolitan area. The normal elderly subjects usually were the spouses of the impaired patients with presumed Alzheimer disease. The elderly control group therefore was well matched for socioeconomic, educational, and nutritional factors.

Subjects were excluded who had a history of brain damage, seizures, mental retardation or a serious neurologic disorder, alcoholism or drug abuse, schizophrenia or other psychiatric disorder, a score of 4 or greater on the modified Hachinski scale [15], or a score of 16 or more on the Hamilton depression scale [16]. Subjects with clinically relevant cardiac, pulmonary, vascular, metabolic, or hematologic disorders were also excluded. Diabetic patients requiring insulin and hypertensive subjects requiring medication other than diuretics were excluded also.

The CT scans were obtained on a General Electric 9800 CT scanner. The CT protocol (Fig. 1) consisted of a series of 10-mm parallel cuts obtained from the base of the skull to the vertex oriented parallel to the canthomeatal line. Scan parameters were 110 kV, 200 mA, 2-sec scan time, and 512 matrix. In addition, 5-mm cuts of the temporal lobes were obtained with the scanning plane oriented 20°

negative to the plane of the canthomeatal line; that is, caudal to the canthomeatal line with the meatus as the fulcrum. Sections parallel to the long axis of the temporal lobes were thereby obtained. In this way the temporal horns, the medial temporal cortex, and the lateral temporal cortex were visualized simultaneously on at least one and frequently two or three slices (Figs. 2–7).

The cognitive status of the patients was evaluated with the Global Deterioration Scale (GDS) [17]. This evaluation uses a seven-point scale that is based on several functions of day-to-day living, including personal hygiene, dressing, and management of the household. The GDS has been used in our laboratory for several years; a high interobserver reliability has been demonstrated ($r = .92$, $n = 38$, $p < .01$) and it has shown excellent correlation with other commonly used dementia rating scales, such as the Mini Mental State ($r = .89$, $n = 170$, $p < .001$). On the GDS score, 1 is normal, 2 is normal with minor complaints of memory loss, 3 is questionably impaired, 4 is mild dementia, 5 is moderate dementia, and 6 and 7 are severe dementia. The mean GDS score of Alzheimer patients was 4.47; that is, they showed mild to moderate dementia.

The scans were evaluated without knowledge of the patients' clinical status. Evaluations were made of five variables: temporal-horn enlargement, medial cortical atrophy, lateral cortical atrophy, the presence and severity of a "hippocampal lucency," and overall temporal-lobe atrophy. A separate evaluation was generated for each of these variables for the overall right and left temporal lobes. Subjective assessments were made by two observers using a five-point scale (1 = normal, 2 = minimal, 3 = mild, 4 = moderate, and 5 = severe).

The temporal horn was rated as normal if it was slitlike and the side-to-side diameter was no more than 3–5 mm at the level of the origin of the choroid fissure (Fig. 2). It was rated severely enlarged when its side-to-side diameter exceeded approximately 1 cm (Figs. 3B, 4D, and 5).

Assessment of medial atrophy is an evaluation of the sylvian fissure and the size of the perimesencephalic cisterns. In Figures 4A and 4B, the perimesencephalic cisterns are small but the sylvian fissures are

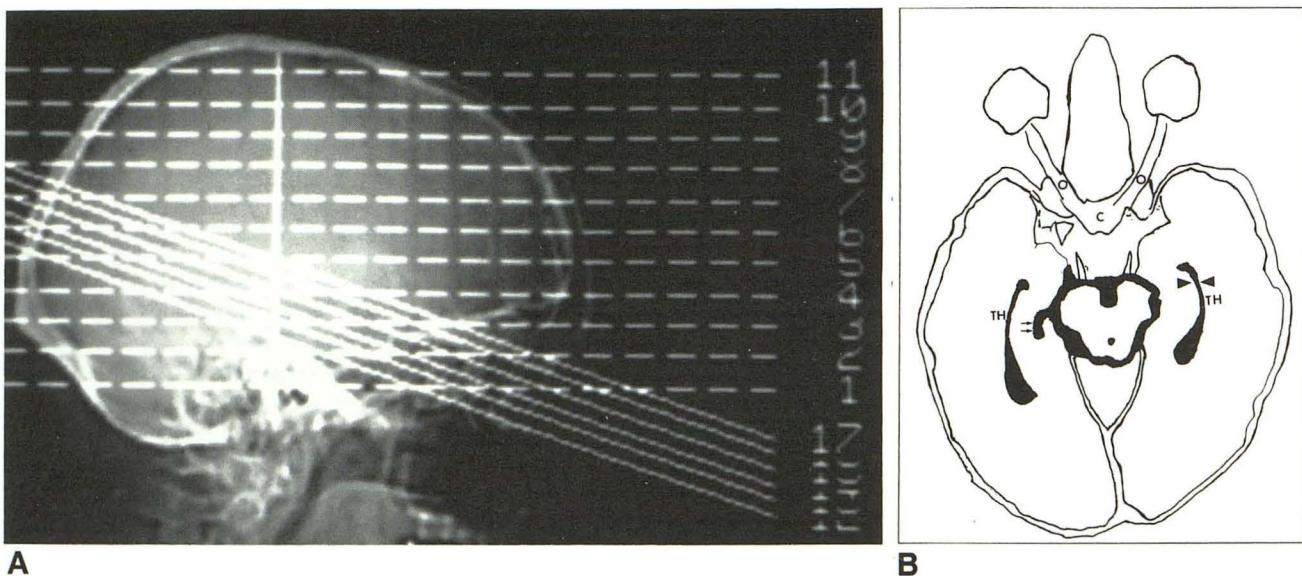


Fig. 1.—New York University imaging protocol for dementia and aging studies.

A, Lateral scanogram with superimposed lines showing location and angulation of individual CT slices. Cuts 1–11: 10-mm scans parallel to canthomeatal line; cuts 12–17: 5-mm scans inclined 20° negative to canthomeatal line.

B, Schematic of negative-angle temporal-lobe cut. Temporal horns (TH), medial and lateral cortex, optic nerves (O), and optic chiasm (C) lie in the same scanning plane. Right choroid/hippocampal fissure (arrows). Temporal-horn assessments are made at level of arrowheads. On CT, cuts are angled as in A. For MR, the plane of the optic apparatus can be used to designate the scanning plane.

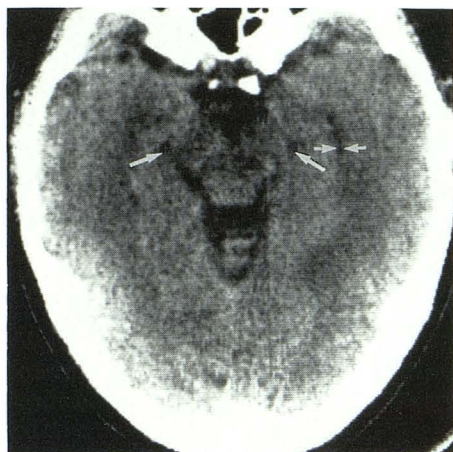


Fig. 2.—CT of normal control subject, 63-year-old man. Negative-angle temporal-lobe cut. Temporal horns (*short arrows*) rated normal bilaterally. Hippocampal lucency (*long arrows*) rated normal bilaterally.

moderately enlarged; medial atrophy was rated moderate. Both right and left sides were rated severe in Figures 4D and 4E.

The rating for lateral atrophy was based on the size of the lateral sulci. For example, Figures 4A and 4B were rated mild and Figure 5 severe.

The hippocampal lucency is a focal area of decreased attenuation that involves the medial temporal-lobe parenchyma and is located medial to the temporal horn (Figs. 1B, 2, 3A, 3B, 4A, 4D, 5, and 6A). This lucency results from partial-volume averaging of the choroid or hippocampal fissures (Figs. 6B and 7C) (choroid/hippocampal fissure complex). In the presence of a very large choroid fissure or choroid/hippocampal fissure complex, the subarachnoid space may be present through the full thickness of the slice without partial-volume averaging (Figs. 5 and 6A). The medial temporal-lobe cortex demonstrates a small indentation or notch that corresponds to the origin of

the choroid fissure at approximately the level at which the quadrigeminal cistern meets the perimesencephalic cistern (Figs. 1B, 2, 7A and 7B). The choroid fissure merges with the hippocampal fissure at this point (Figs. 6B and 7C). A hippocampal lucency was rated normal (Fig. 2) when only the choroidal notch was visible. A moderate lucency (Fig. 3B) was a definite lucency with attenuation intermediate between that of brain and CSF. A severe lucency (Fig. 5) implied that the choroid/hippocampal fissure complex was so enlarged that it filled the entire slice thickness; its density then was virtually equal to that of CSF.

The hippocampal formation and the parahippocampal gyrus together constitute the inferomedial aspect of the temporal lobe [18]. The hippocampal formation consists of the hippocampus, the dentate gyrus, and the subiculum. The hippocampal fissure is bounded inferiorly by the subiculum and superiorly by the dentate gyrus. The hippocampal fissure runs the entire anteroposterior length of the temporal lobe. The hippocampus is the crescent of gray matter that caps the lateral edge of the hippocampal fissure. It bulges into the medial wall and floor of the temporal horn and continues medially above the dentate gyrus [18]. These anatomic structures and especially the subiculum and dentate gyrus have been implicated specifically in the pathogenesis of Alzheimer disease [13, 14] (see Discussion).

The score for overall temporal lobe atrophy was derived by combining all the rating scores. This combined score was determined by the more severe changes regardless of location. Thus, in Figure 3B, even though lateral and medial cortical atrophy is mild, because of severe temporal-horn enlargement overall atrophy was rated severe. Therefore, the final rating was determined by the most pathologically appearing structures evaluated.

To compare the efficacy of the temporal-lobe findings with that of more traditional ventricular measures, we also derived a combined linear measurement of the ventricular system and compared the relative accuracy of this linear measure with the subjective temporal-lobe measures.

The composite linear measure was derived by summing the linear measurements of the bicaudate diameter, the transverse diameter of

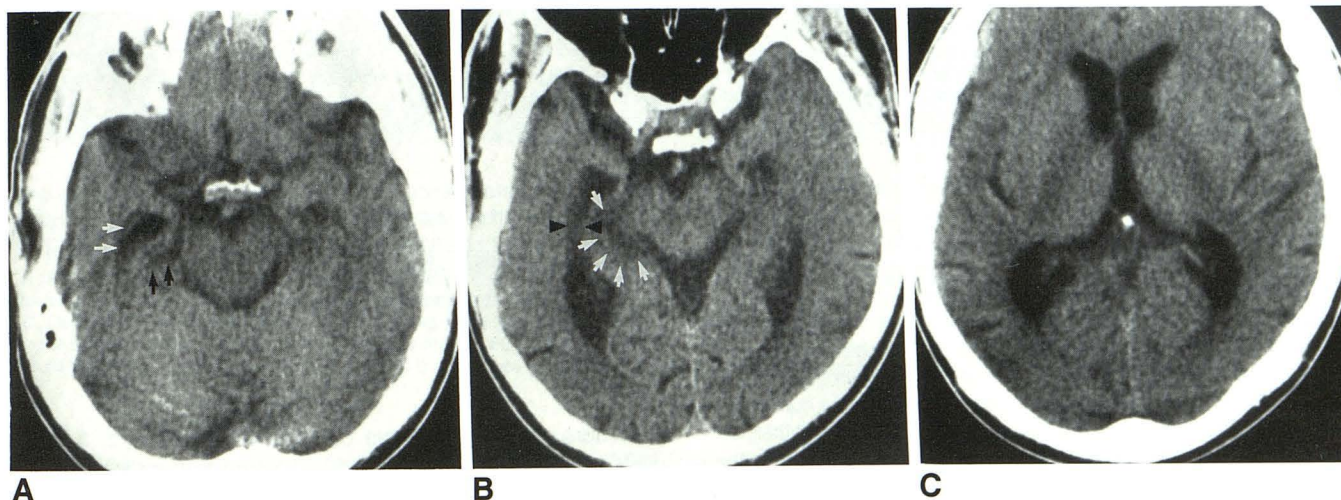


Fig. 3.—CT of 63-year-old man with moderate to severe temporal-lobe atrophy, right more than left. Mild clinical dementia, presumed Alzheimer disease (Global Deterioration Scale, 3).

A, Routine 10-mm cut parallel to canthom. atal line at temporal-lobe level. Enlarged temporal horns (*white arrows*) and choroid/hippocampal fissure (*black arrows*) are partially visualized.

B, Negative-angle CT scan. Characteristic temporal-lobe changes including hippocampal lucency are better demonstrated. Moderate hippocampal lucency is present on right (*arrows*). Right temporal horn (*arrowheads*) enlargement was rated 5 (severe).

C, Ventricular bodies are moderately enlarged.

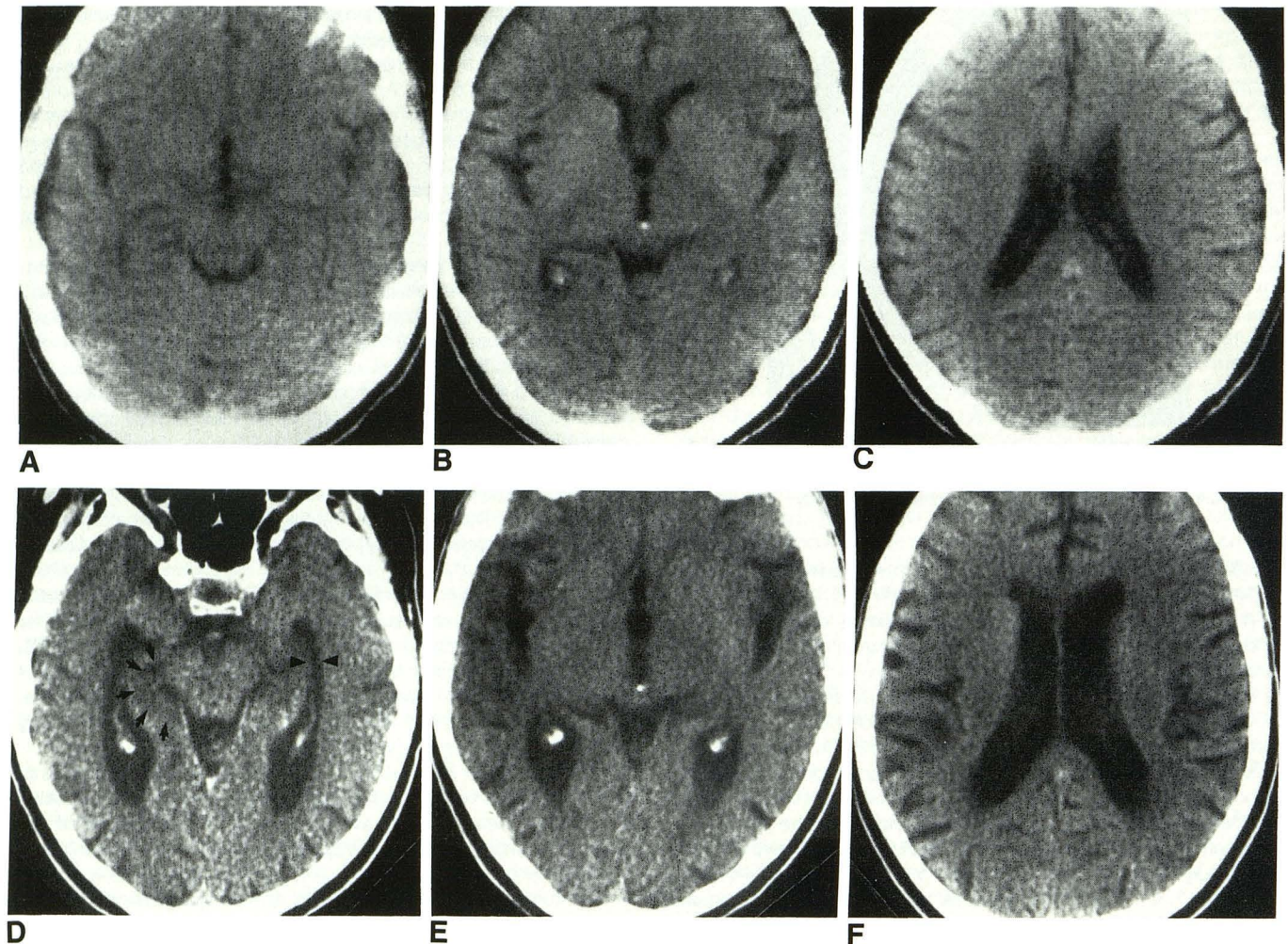


Fig. 4.—Longitudinal CT study of progressive Alzheimer disease in 59-year-old woman with clinical evidence of definite dementia (Global Deterioration Scale, 4).

A–C, CT is normal, suggesting that structural atrophy lags behind clinical deficit.

D–F, 3 years later. The patient is now 61 years old and has clinically progressed to severe dementia (Global Deterioration Scale, 6). CT shows advanced temporal-lobe as well as diffuse atrophy. Negative-angle temporal-lobe cut (D) shows bilateral hippocampal lucencies, moderate on the right (arrows) and mild on the left, and temporal-horn changes, severe on the right and moderate on the left (arrowheads).

the right frontal horn, the transverse diameter of the left frontal horn, and the width of the third ventricle measured 1 cm anterior to the pineal gland. This sum was divided by the maximal width of the brain as measured from inner table to inner table at the level of each ventricular measurement. We have found in previous studies that this measure is highly correlated with ventricular volume when ventricular volume is calculated by using either a density range or a visually determined planimetric method, and has excellent interobserver reliability [5, 9]. Results for the five temporal-lobe and the composite linear measurements were analyzed first to determine whether the prevalence of the pathologic changes was more frequent in the Alzheimer group. This was established by computing the chi-square statistic for the distribution of each measure. The ability of the measure to correctly identify patients (sensitivity) and correctly identify controls (specificity) was assessed by a discriminant function analysis (SPSS-X).

The following neuropathology method was used in this study: after formalin fixation, brains from autopsied patients were sectioned coronally according to a standard protocol for Alzheimer research studies. The hippocampal samples were taken at a coronal plane that

included the lateral geniculate nucleus. After standard processing with paraffin, sections were examined with H and E, Luxol fast blue/PAS, a Luxol fast blue/H and E combination, Congo red, and Naoumenko-Feigin silver stains. (The Luxol fast blue/PAS technique is illustrated in Figures 6 and 7.)

Results

A representative example of choroid/hippocampal fissure dilatation is shown in Figure 6, the postmortem radiologic and pathologic studies of a 90-year-old woman with clinical and pathologic evidence of Alzheimer disease. The postmortem CT scan (Fig. 6A) shows a large hippocampal lucency that is clearly in communication with the adjacent perimesencephalic cistern. A coronal-plane histologic cross section from the autopsy (Fig. 6B) shows severe dilatation of the choroid/hippocampal fissure complex and severe atrophy of the parahippocampal gyrus with loss of both gray and white matter.

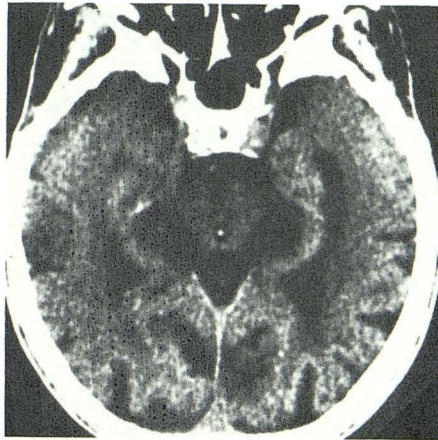
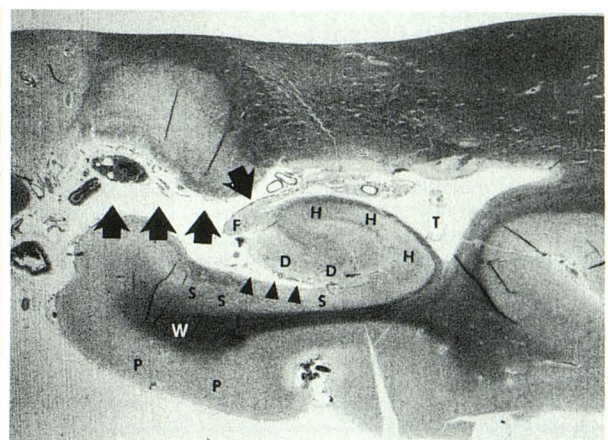


Fig. 5.—Severe hippocampal lucencies in an 88-year-old woman with mild dementia (Global Deterioration Scale, 3). Temporal-lobe negative-angle cut. Hippocampal lucencies are direct extensions of perimesencephalic cisterns.



A

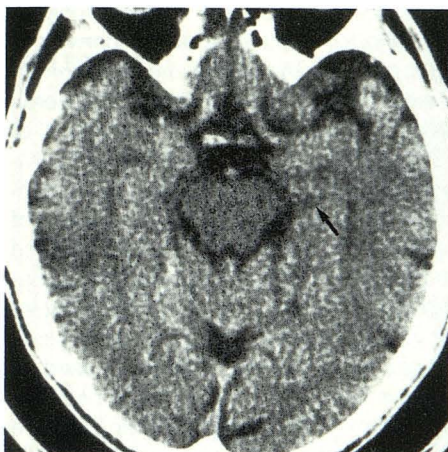


B

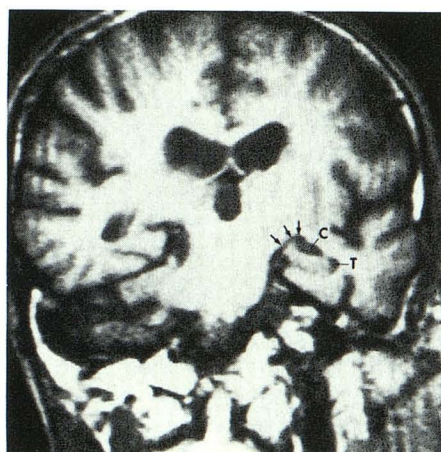
Fig. 6.—Severe hippocampal lucency. Radiologic-pathologic correlation in a 90-year-old severely demented woman with advanced Alzheimer disease both clinically and at autopsy.

A, Postmortem negative-angle CT scan shows large left hippocampal lucency (open arrows) as well as severe enlargement of temporal horn (solid arrows).

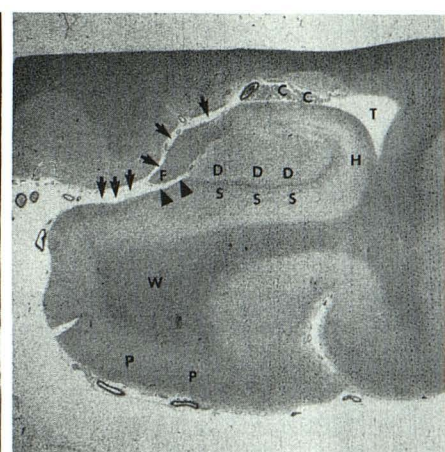
B, Coronal, 4-mm neuropathologic specimen of hippocampus at level of lateral geniculate nucleus. Note severe dilatation of both choroid (arrows) and hippocampal (arrowheads) fissures. Parahippocampal gyrus (P) is severely atrophic with loss of both gray and white matter (W). H = hippocampus; D = dentate gyrus; S = subiculum; F = fimbria; T = temporal horn. (Luxol fast blue/PAS, $\times 25$)



A



B



C

Fig. 7.—Normal choroid/hippocampal fissures (compare with Fig. 6). Radiologic-pathologic correlation in 80-year-old man with no pathologic evidence of Alzheimer disease.

A, Premortem temporal-lobe CT scan at age 75. Hippocampal lucency (arrow) is rated normal.

B, Premortem MR image at age 80. Coronal 6-mm 1.5-T image (TR = 450, TE = 30) at level of subsequent postmortem pathologic section shows mild prominence of left choroid fissure (arrows). C = choroid plexus; T = temporal horn.

C, Coronal 4-mm histopathologic section of hippocampus at level of lateral geniculate nucleus (to match B). Note small size of choroid (arrows) and hippocampal (arrowheads) fissures (compare with Fig. 6B). Note normal configuration of gray and white (W) matter of parahippocampal gyrus (P). C = choroid plexus; T = temporal horn; F = fimbria; D = dentate gyrus; S = subiculum; H = hippocampus. (Luxol fast blue/PAS, $\times 25$)

By comparison, the postmortem imaging studies of an 80-year-old man with the diagnosis of Parkinson disease and no clinical or pathologic evidence of Alzheimer disease (Fig. 7) show normal choroid and hippocampal fissures. A CT scan 5 years prior to death (Fig. 7A) shows normal to minimal evidence of a hippocampal lucency. An MR image less than 1 month before death (Fig. 7B) shows a focal, faintly visualized low-signal lesion corresponding to the choroid/hippocampal fissure complex. The coronal T1-weighted MR image shows

normal to mild dilatation of the choroid/hippocampal fissures bilaterally. A histologic section at autopsy (Fig. 7C) shows similar findings.

For all the measures, the sensitivity (percent of Alzheimer patients correctly identified or 1 – percent false negatives), specificity (percent of normal control subjects correctly identified or 1 – percent false positives), and overall accuracies (percent of Alzheimer and normal control subjects correctly identified) are found in Table 1. The hippocampal lucency

TABLE 1: Classification of Normal ($n = 20$) vs Alzheimer ($n = 34$) Subjects on the Basis of Temporal-Lobe Changes and Ventricular Volume Measurements on CT Scans

Measure	Sensitivity	Specificity	Overall Accuracy	χ^2
Hippocampal lucency	82	75	80	14.2
Temporal horn	79	70	76	19.7
Medial atrophy	56	80	65	12.3
Lateral atrophy	71	70	70	11.0
Overall temporal atrophy	59	80	76	16.7
Ventricular volume (composite linear ventricular measure)	68	85	74	14.0

Note.—sensitivity = percent of Alzheimer patients correctly identified; specificity = percent of normal control subjects correctly identified; overall accuracy = total percent of Alzheimer patients and normal control subjects correctly identified. χ^2 was used to test the significance of the distribution ($p < .001$).

showed the greatest sensitivity (82%), that is, it correctly identified 82% of Alzheimer patients and was also the most accurate of the measures tested (overall accuracy, 80%). The highest specificity (85%) was shown by ventricular volume as measured by the composite linear ventricular measurement, that is, small lateral ventricles correctly identified 85% of normal control subjects.

A regression analysis using combinations of the variables tested, either user- or computer-selected, failed to improve on the accuracy obtained by the individual measures. The hippocampal lucency and the temporal-horn measures were the most significant contributors to diagnostic accuracy.

Discussion

Several mounting bodies of evidence, including in vivo metabolic [19, 20] and structural [21–23] imaging studies and neuropathologic data [11–14, 24], have implicated the temporal lobes and especially the hippocampus in the pathogenesis of Alzheimer disease. In the neuropathologic literature, senile plaques, neurofibrillary tangles, and granulovacuolar degeneration have been described as the histologic features of Alzheimer disease. These are found in addition to the presence of increased cerebral atrophy [25, 26]. These histologic features also may be seen in normal aging, but they are much more common in the brains of patients with Alzheimer disease. Plaques and tangles are numerous in the cortex of Alzheimer brains, especially in the temporal, parietal, and frontal lobes. Plaque counts are correlated with severity of dementia; furthermore, subjects with the highest plaque counts show marked temporal-lobe atrophy [27]. More recent studies have specifically implicated the hippocampus in the pathogenesis of Alzheimer disease. Ball et al. [11, 12] reported that neuronal loss was more severe in the hippocampus of Alzheimer brains when compared with those of normal control subjects and that tangles and granulovacuoles are more common in the posterior half of the hippocampus in Alzheimer brains. Sheffer [24] reported that neurons in several

brain regions including the subiculum were 20% depleted in normal aging, as compared with a 50% loss in Alzheimer disease. The subiculum and entorhinal cortex were recently implicated as the site of early Alzheimer pathology by Hyman et al. [13, 14], who found marked cell loss as well as larger numbers of neurofibrillary tangles in the subiculum and hippocampus than in the cerebral cortex of Alzheimer brains. Hyman et al. postulated that since these affected structures normally interconnect the hippocampus with the cortex and the thalamus, that, in effect, the hippocampus becomes isolated in Alzheimer disease.

In a recent report, LeMay et al. [22] found that perceptual rating of temporal-lobe atrophy on CT produced an average accuracy of 88.6% in identifying Alzheimer patients vs normal control subjects. We found comparable accuracies in our current report and stress the importance of the size of the choroid/hippocampal fissure complex in the assessment of hippocampal atrophy. Furthermore, the assessment of ventricular volume using the composite ventricular measure in combination with the temporal-lobe ratings did not significantly improve the diagnostic accuracy of the temporal-lobe assessment. Preliminary neuropathologic evidence from our laboratory showed dilatation, which can be severe, of the hippocampal and choroid fissures in patients with either in vivo or postmortem CT or MR evidence of a hippocampal lucency. Metabolic, neuroendocrine, and neuropathologic studies, which will be reported separately, are underway to characterize and better evaluate the significance of choroid/hippocampal fissure enlargement. It is known that temporal-lobe glucose utilization and blood flow deficits are typical of Alzheimer disease [19]. We also recently reported [20] evidence from IV glucose tolerance tests that the hypercortisolemia seen in Alzheimer disease is linked to the presence of the hippocampal lucency, cognitive impairment, and glucose utilization deficits, as measured by positron emission tomography. We have found that thin (5 or 3 mm) “negative-angle” cuts of the temporal lobes obtained with a scanning plane inclined along the long axis of the temporal lobes tend to show hippocampal and temporal horn changes to best advantage. For example, compare the zero-angle scan in Figure 3A, obtained parallel to the canthomeatal line, with Figure 3B, the negative-angle cut of the same patient obtained with the scanning plane inclined 20° caudal to the canthomeatal line. The use of a similar scanning angle was proposed by El Gammal et al. [28] for the evaluation of temporal-lobe epilepsy. In their study the scan plane was defined from the scanogram using the top of the dorsum and a point 3 mm inferior to the planum sphenoidale.

In the absence of temporal-lobe atrophy, a specificity measure of more than 95% is obtained, that is, true normals are identified in more than 95% of cases. However, more than one half (55%) of normals do show mild or greater temporal-lobe atrophy. We found that the size of the temporal horns assessed subjectively was only modestly accurate (76%) in distinguishing between Alzheimer and normal control subjects; that is, 76% of normal and Alzheimer subjects were classified correctly but 24% were classified incorrectly. The control subjects with temporal-horn changes were signifi-

cantly older than the subjects with no changes. Kido et al. [29] found temporal-horn enlargement in only one of 29 normal control subjects.

In view of our current findings, it is now of interest to longitudinally follow these subjects, especially the misclassified members of the normal group (that is, those normal subjects who show temporal-lobe atrophy) in order to determine whether they are at risk for the development of clinical Alzheimer disease. MR imaging, with its increased contrast resolution, multiplanar capabilities, and ability to provide improved visualization of the temporal lobes, offers great promise for the continued study of structural temporal-lobe changes in Alzheimer disease as well as in normal aging. In a preliminary MR imaging study of Alzheimer patients and control subjects, we recently reported that there is selective loss of cerebral gray matter in Alzheimer disease associated with preservation of the white-matter volume [23].

In conclusion, this study suggests that structural changes in the temporal lobe and hippocampus strongly support the diagnosis of Alzheimer disease. A highly sensitive sign of focal atrophy seen in Alzheimer disease, dilatation of the hippocampal/choroid fissure complex, or hippocampal lucency, is described. It is suggested that neuroimaging protocols for the workup of dementia using CT as well as MR should include negative-angle thin-section cuts of the temporal lobes.

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