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Medial temporal lobe atrophy in memory disorders

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Abstract Medial temporal lobe atrophy determined by temporal lobe oriented computed tomography (CT), 1 year before death, is strongly associated with histopathologically confirmed Alzheimer's disease (AD). The aim of this study was to assess the diagnostic accuracy of medial temporal lobe measurement for the diagnosis of AD in patients referred to a memory disorders clinic, especially those at an early stage of the disease. CT oriented to the temporal lobe was performed in 333 subjects aged 41–93 years consecutively recruited in a Memory Disorders Clinic: 124 had probable AD, Mini Mental State score (MMS) = 17 (8); 50 possible AD [MMS = 21 (5)]; and 119 patients had miscellaneous memory disorders [MMS = 22 (7): frontotemporal lobe dementia, subcortical dementia, cortical Lewy body disease, vascular dementia, Korsakoff syndrome, focal atrophy, etc.]. There were also 19 anxious/depressed patients [MMS = 29 (1)] with normal performance on memory tests, and 21 controls. The minimum width of the medial temporal lobe was measured. The best cut-off to distinguish AD patients from non-AD patients was 11.5 mm, in agreement with data in the literature. At this threshold, 84% of probable AD patients had a positive test and 90% of controls and anxious/depressed patients had a negative test. For the diagnosis of probable AD, sensitivity of the measurement was 0.81, specificity 0.95, predictive positive value 0.99, predictive negative value 0.45, and diagnostic accuracy 0.83. The test was positive in half the possible AD patients, and half those with miscellaneous memory disorders. It was negative in all anxious/depressed patients. Therefore, temporal lobe oriented CT might be a valuable tool for assessment of medial temporal lobe atrophy in AD routine practice.

Key words Computed tomography · Hippocampal atrophy · Alzheimer's disease · Memory disorders · Dementia

Introduction

Computed tomography (CT) of patients with a clinical diagnosis of Alzheimer's disease (AD) shows greater atrophy than in controls [27, 49]. However, there is an overlap of subjective global indices [27] and linear [27] or volumetric [49] indices of ventricles and sulci measured in orbitomeatal or canthomeatal planes between AD patients and controls. Therefore the usual CT indices of cerebral atrophy cannot be used alone as a predictor of AD in individual cases [5]. AD typically involves widespread neuropathology. However, at the very beginning of the disease, neuronal loss, neurofibrillary tangles, and senile plaques are particularly prominent in the hippocampus. The degree of change in the hippocampus is correlated

with hippocampal volume reduction [33]. Therefore there has been an emphasis on in vivo neuroimaging of the hippocampus. de Leon and colleagues [13, 25] used a negative angulation axial scan plane, which enables imaging of the long axis of the hippocampal region. CT detection of cerebrospinal fluid (CSF) accumulation in the fissures of the perihippocampal region is valuable in supporting the clinical diagnosis of AD, as shown by George et al. [13] in a cross-sectional CT study of 175 AD patients and controls. Most importantly, longitudinal results from this study indicated that it predicted the development of dementia among individuals with mild cognitive impairment that was insufficient to warrant a diagnosis of AD. Jobst and colleagues [9, 20] also used negative angulation scan planes to assess medial temporal lobe atrophy (temporal lobe oriented CT). The minimum width of the medial temporal lobe in 44 patients with a histopathological diagnosis of AD was nearly half that in 75 controls of the same age with no clinical evidence of dementia [19]. There was little overlap between the distribution of measurements in cases and controls. However, most CT was performed late in the course of the disease when the detection of AD is less useful; a significant medial temporal lobe atrophy was present in all the 20 patients who had been scanned more than 1 year before death and in 9 of 20 who were scanned more than 2 years before death [19]; in 10 subjects with dementia but with no histological sign of AD, the mean minimum width of the medial temporal lobe was significantly greater than that of cases with AD. Nevertheless, it did not significantly differ from that in controls [19].

The aim of our study was to assess the diagnostic accuracy, the sensitivity and the specificity of medial temporal lobe atrophy for the diagnosis of probable AD in patients referred to a memory disorders clinic, at an early stage of the disease.

Patients and methods

The study was conducted over a 2-year period (January 1993 to December 1994), in 333 consecutive subjects aged 41–93 years recruited in our University Outpatient Memory Disorders Clinic. All patients underwent temporal lobe oriented CT and were followed for over 1 year. The diagnoses were made after several evaluations by a senior staff neurologist, a psychiatrist, a neuropsychologist, and a speech therapist; all patients underwent biological examinations. Magnetic resonance imaging (MRI) and single photon emission computerized tomography (SPECT) were performed in selected cases. Patients were assessed with a comprehensive neuropsychological test battery including the Mini Mental State examination (MMS) [10], the Mattis dementia rating scale (DRS) [29], assessment of short-term and long-term memory [15, 46], aphasia, agnosia, gestural, and constructive apraxia, and a semi-structured interview with the patient and the family conducted by a psychiatrist. AD was diagnosed according to National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorder Association criteria for probable or possible AD [31]. Criteria for possible-AD included a history of AD associated with vascular features, atypical neurological signs, or other pathology preventing the labelling of probable AD, and memory impairment without fulfilling criteria for dementia [1] ("minimally impaired" patients [6]). Patients with memory impairment but no clinical diagnosis of AD were grouped together under the same heading of "miscellaneous memory disorders". The breakdown of clinical diagnoses is shown in Table 1. Dementia of frontotemporal type (DFT) was diagnosed according to the Lund and Manchester groups' criteria [28]. DFT patients had a history of behavioural disturbance predating dementia, with early personality change, loss of social skills, disinhibition, apathy and normal EEG, and showed the characteristic frontal hypoperfusion pattern on SPECT [35, 40]. Vascular dementia was diagnosed according to the NINDS-AIREN international workshop criteria [41]; senile dementia of Lewy body type was diagnosed according to the criteria of McKeith et al. [30]; primary progressive aphasia was diagnosed according to Mesulam's criteria [32, 47]; corticobasal degeneration was diagnosed according to criteria provided by Riley et al. [39]; posterior cortical atrophy was diagnosed according to Benson et al. [2]; and the psychiatric syndromes were diagnosed according to DSM III-R criteria [1]. Patients with anxiety or depressive disorders had attention troubles but performed within the normal ranges in memory tests. Temporal lobe oriented CT was performed in only 21 controls because French law forbids the use of X-rays in healthy subjects. These controls were patients who required CT for otological reasons, free of cognitive complaints. They gave informed consent to participate in the study and to undergo neuropsychological tests. The breakdown of the clinical diagnoses and the characteristics of the populations are described in Table 2.

Table 1 Breakdown of clinical diagnoses in patients with miscellaneous memory disorders (n = 119). For criteria, see text

Frontotemporal dementia	(n = 36)
Parkinson's disease	(n = 28)
Vascular dementia	(n = 16)
Cortical Lewy body disease	(n = 14)
Alcoholic Korsakoff syndrome	(n = 7)
Progressive aphasia	(n = 5)
Corticobasal degeneration	(n = 4)
Psychiatric disorder other than anxiety or depression	(n = 3)
Huntington's disease	(n = 2)
Posterior cortical atrophy	(n = 2)
Progressive supranuclear palsy	(n = 1)
Traumatic head injury	(n = 1)

CT (Siemens, Somatron DR, Erlangen, Germany) was performed according to the procedure of Jobst and colleagues [19]: planes were 20° caudal to the orbitomeatal line in 2-mm contiguous slices through the posterior fossa. Left and right medial temporal lobe width (combined hippocampal formation and parahippocampal gyrus) was measured from the film, about midway through the brain stem, by a neuroradiologist (M.H.) blinded to the clinical diagnosis. The first 50 scans were assessed by two independent neuroradiologists (M.H. and J.P.P.). Inter-rater deviation was less than 1 mm. The raters agreed in 92% of cases.

To choose the best "cut-off" point, i.e. critical value, for medial temporal lobe thickness measurement for diagnosing the presence of atrophy, we used the Likelihood Ratio (LR) [LR = sensitivity/(1-specificity)] [38] and calculated the Figure of Merit (FM) according to the relation: FM = 1–1/LR [44]. The LR is the likelihood that a person with a disease would have a particular test result divided by the likelihood that a person without a disease would have that result. The derivation of the FM allows one to choose the most effective cut-off value corresponding to the highest values for both FM and sensitivity (probability of obtaining a

Table 2 Breakdown of the clinical diagnoses and characteristics of the populations (*AD* Alzheimer's disease, *Miscellaneous* miscellaneous memory disorders, *Anxiety/depression* anxiety and depressive disorders, *SD* standard deviation, *Duration* duration of the disease, *MMS* Mini Mental State, *DRS* Dementia rating scale)

Diagnosis	Probable-AD	Possible-AD	Miscellaneous	Anxiety/ depression	Controls
n	124	50	119	19	21
Age (SD)	71.1 (7.7)	72.7 (7.3)	67.8 (8.9)	60.7 (6.4)	66.7 (8.5)
Men/Women	55/69	18/32	61/58	5/14	11/10
Male/female ratio	0.80	0.56	1.05	0.36	1.1
Duration	4.1 (2.7)	3.8 (2.8)	5.1 (7.0)	4.3 (3.8)	–
MMS	16.9 (7.9)	21.2 (5.5)	22.0 (7.1)	29.0 (1.4)	29.3 (0.9)
Mattis DRS	95.7 (32.8)	114.4 (20.3)	116.6 (21.6)	140.3 (4.7)	136.5 (4.3)

positive test if the disease exists). True positives is the number of probable AD patients with a positive test; false positives is the number of controls with a positive test; false negatives is the number of probable AD patients with a negative test; true negatives is the number of controls with a negative test. The *sensitivity* is the probability that the test is positive when the patient has AD; it is assessed by the ratio True positives/(True positives + False negatives). The *specificity* is the probability that the test is negative when the patient does not have AD; it is assessed by the ratio True negatives/(True negatives + False positives). The *predictive positive value* is the probability of having AD when the test is positive; it is assessed by the ratio: True positives/(True positives + False positives). The *predictive negative value* is the probability of not having AD when the test is negative; it is assessed by the ratio: True negatives/(False negatives + True negatives). The *diagnostic accuracy* of the test is assessed by the formula: (True positives + True negatives)/(True positives + True negatives + Falses positives + False negatives).

Quantitative data were compared with analyses of variances and qualitative variables were compared with the chi square test.

Results

Means and standard deviations of minimum medial temporal lobe thickness for each patient and control groups are shown in Table 3. There was a significant difference between groups for left [$F(4,328) = 24.27$; $P < 0.0001$] and right [$F(4,328) = 27.42$; $P < 0.0001$] medial temporal lobe thickness. Post hoc analysis (Bonferroni test) showed that the medial temporal lobe was significantly smaller ($P < 0.0001$) in probable AD than in anxious/depressed patients, controls, and in patients with miscellaneous memory disorders; it was significantly smaller ($P < 0.0001$) in possible AD than in anxious/depressed patients and controls; it was also significantly smaller ($P < 0.0001$) in patients with miscellaneous memory impairments than in anxious/depressed patients and controls. The difference did not reach the level of significance between probable and possible AD patients ($P = 0.02$ for the right side, $P = 0.03$ for the left side); between possible AD patients and patients with miscellaneous disorders ($P = 0.05$ in both sides); and between anxious/depressed patients and controls ($P = 0.98$ for the right side and $P = 0.70$ for the left side).

The best cut-off value corresponding to the highest values for both FM and sensitivity is obtained for a medial temporal lobe measurement lower than 11.5 mm (Fig. 1). Because there was no difference between anxious/depressed patients and controls for medial temporal lobe thickness measurement, we combined the two groups to calculate the sensitivity, specificity, predictive value, and diagnostic accuracy of the test. Using this threshold value, 104 of the 124 probable AD patients (84%) and 38 of the 40 controls (95%) (anxious/depressed and healthy) were correctly classified. Thus, the sensitivity of the test was 0.84; the specificity was 0.95; the predictive positive value was 0.98; the predictive negative value was 0.66; and the diagnostic accuracy was 0.87.

AD was histologically confirmed in 2 patients with probable AD: both had a 2-year history of memory impairment and spatial and temporal disorientation, followed by language, praxis and gnosis impairments; one patient was a 64-year-old woman with a minimum medial temporal lobe thickness of 6.7 mm and a MMS score of 20/30 a year before death caused by pneumonia; Alzheimer pathology was widespread and severe. The other patient was a 74-year-old man with a MMS score of 18/30 at the time of measurement, 18 months before death; MMS was 10/30 a few weeks before he suddenly died from a heart attack; minimum medial temporal lobe thickness was 16.0 mm. Histological changes were prominent in frontal and parietal lobes and the medial temporal lobes were relatively spared.

The probable AD group of patients with a positive test ($n = 104$) did not differ from the probable AD patients

Table 3 Minimum medial temporal lobe thickness (mm) in the five groups; for statistics see text (*AD* Alzheimer's disease, *Miscellaneous* miscellaneous memory disorders, *Anxiety/depression* anxiety and depressive disorders, *SD* standard deviation)

Diagnosis	Probable-AD	Possible-AD	Miscellaneous	Anxiety/ depression	Controls
Right/left	8.9/ 8.7	10.5/10.4	11.7/11.6	16.4/16.1	16.0/15.6
SD right/left	(3.9/ 4.1)	(4.2/ 3.9)	(4.5/ 4.5)	(2.6/ 2.1)	(2.6/ 3.1)
mini/maxi	1.6/20	3.3/18.3	1.7/23.3	13.3/23.3	10.0/20.0

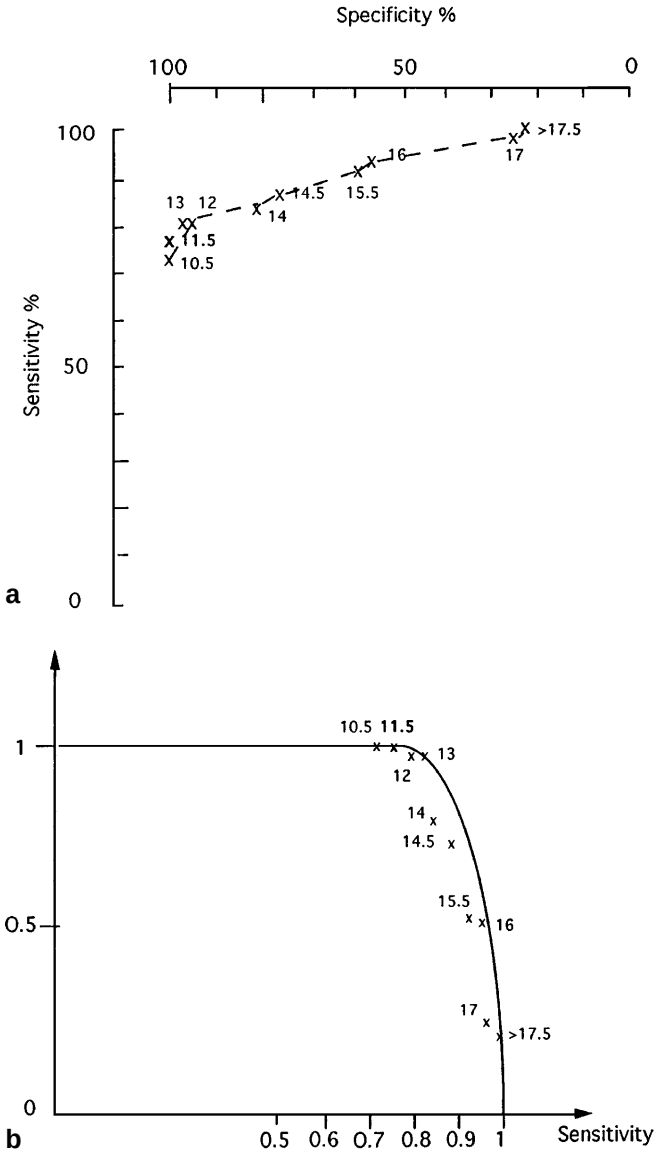

Fig. 1 a, b The Figure of Merit shows that the best cut-off value is 11.5 mm

group with a negative test (n = 20) as regards age [mean (SD) = 71.1 (7.7) vs 71.2 (8.0) years, $F(1,123) = 0.004$; $P = 0.95$], sex [men/women = 48/56 vs 7/13; chi square = 0.56; $P = 0.45$]; level of education [chi square = 1.6; $P = 0.45$]; and duration of the disease [4.2 (2.8) vs 3.7 (2.8) years, $F(1,123) = 0.75$; $P = 0.39$]. Probable AD patients with a positive test had a lower MMS score and a lower Mattis DRS score than those with a negative test [MMS = 16.1 (8.1) vs 19.9 (6.4), $P = 0.02$; DRS = 93.2 (32.0) vs 112.1 (18.6), $P = 0.005$].

The test was positive in half of the patients with possible AD, and in half of the patients with miscellaneous memory disorders (Table 4). It was negative in all anxioux/depressed patients.

Table 4 Breakdown of patients with a positive (medial temporal lobe thickness < 11.5 mm) and a negative (medial temporal lobe thickness >11.5 mm) test according to clinical diagnoses

	Positive	Negative
Medial temporal lobe thickness	<11.5 mm	>11.5 mm
Possible-AD (n = 50)	25	25
Frontotemporal dementia (n = 36)	20	16
Parkinson's disease (n = 28)	11	17
Vascular dementia (n = 16)	8	8
Cortical Lewy body disease (n = 14)	8	6
Alcoholic Korsakoff syndrome (n = 7)	4	3
Progressive aphasia (n = 5)	2	3
Corticobasal degeneration (n = 4)	2	2
Psychiatric disorder other than anxiety or depression (n = 3)	0	3
Huntington's disease (n = 2)	1	1
Posterior cortical atrophy (n = 2)	2	0
Progressive supranuclear palsy (n = 1)	0	1
Traumatic head injury (n = 1)	1	0

The possible AD patient group with a positive test (n = 25) did not differ from the possible AD patient group with a negative test (n = 25) as regards age [74.7 (7.1) vs 72.2 (7.7) years, $F(1,48) = 0.72$; $P = 0.40$], level of education [chi square = 2.43; $P = 0.29$]; and duration of the disease [4.19 (3.29) vs 3.54 (2.46); $F(1,48) = 0.53$; $P = 0.47$] but differed for sex [men/women = 13/12 vs 6/19; chi square = 4.69; P = 0.03]. The two groups also did not differ as regards the MMS score [21.39 (5.41) vs 20.87 (5.75); $F(1,48) = 0.10$; $P = 0.75$] and the DRS score [112.4 (23.66) vs 114.2 (16.3); $F(1,48) = 0.07$; $P = 0.79$].

Possible AD patients with a positive test were patients with a history of AD associated with vascular features preventing them from being labelled probable AD (n = 11) or with atypical neurological signs (pyramidal or extrapyramidal, n = 8); alcoholism (n = 1); hypothyroidism (n = 1); predominant language dysfunction without fulfilling criteria for primary progressive aphasia (n = 1). Three patients were "minimally impaired". Possible AD cases with a negative test were mainly "minimally impaired" patients (n = 13); and patients with extrapyramidal signs (n = 5) suggesting possible senile dementia of Lewy body types but not fulfilling the current criteria for this disease [33]; vascular findings (n = 3); alcoholism (n = 1); hypothyroidism (n = 1); dysarthria (n = 1); and predominant apraxia but not fullfilling criteria for corticobasal degeneration [39] (n = 1).

When DFT patients had a positive test (80%), there was a clear global lobar anterior temporal atrophy, asymmetrical in 3 cases, distinct from the typical medial temporal lobe atrophy and out of proportion with the atrophy of the other part of the temporal lobe seen in AD.

Among patients with miscellaneous memory disorders the group with a positive test did not differ from the group with negative test as regards age [68.6 (9.6) vs 67.2 (8.2)

years, $F(1,117) = 0.70$; $P = 0.40$], sex [chi square = 1.46; $P = 0.22$]; level of education [chi square = 4.06; $P = 0.13$]; duration of the disease [5.4 (3.9) vs 5.7 (4.7) years, $F(1,117) = 0.11$; $P = 0.74$]; and MMS score [21.2 (7.4) vs 23.0 (6.7); $F(1,117) = 1, 39$; $P = 0.24$]. Patients with a positive test had a lower DRS score than those with a negative test [111.5 (21.9) vs 121.1 (20.2), $F(1,117) = 4.28$; $P = 0.04$].

Of 11 patients with Parkinson's disease and a positive test, 9 had severe memory impairment; 3 of these had a mild medial temporal atrophy (10 mm). Ten patients with Parkinson's disease and severe memory impairment had a negative test. Two patients had severe medial temporal lobe atrophy and only slight memory impairment.

Discussion

Our study confirmed that the medial temporal lobe thickness is nearly reduced to half normal in probable AD patients compared with controls [19]. We found that the determination of medial temporal atrophy with temporal oriented CT and a threshold of 11.5 mm fits with 84% of probable AD diagnoses. This cut-off point of 11.5 mm is in agreement with previous studies [19, 20], although this one was conducted in patients at a much earlier stage. The sensitivity of this test is good and its specificity is excellent.

The method we used is very simple. It yielded a diagnostic accuracy close to those of more sophisticated techniques [11, 21, 22, 42, 48], although our patient group was much larger. In a smaller population aged 55–71 years, we did not find overlap between probable AD patients and anxious/depressive controls [37]. Six of the 19 probable AD patients with medial temporal lobe atrophy had MMS scores above 24. These results were in accordance with MRI findings [22].

MRI also shows the association between medial temporal lobe atrophy and AD [6, 9, 11, 21, 22, 26, 42]. Medial temporal lobe atrophy is not significantly related to age, sex, level of education, or presence of infarction [24]. In a recent review of studies that have examined temporal lobe MRI change in AD, O'Brien [36] showed, pooling results from all studies, that temporal lobe MRI has both a sensitivity and a specificity of 85–90% in differentiating AD subjects from controls; and overall 88% (294/333) of subjects examined could be correctly identified by MRI, which is close to our results. Other candidate temporal lobe regions have been examined [6] and only the hippocampal parenchymal volume significantly differentiated the groups [6].

Although magnetic resonance volumetry is probably more sensitive, it also raises difficulties: technical reasons may give errors in measurements [17], and it is not easy to determine accurately the hippocampal boundaries. These difficulties lead to intra- and inter-observer variabilities up to 12% and 14% [3], and even more (30%) on visual assessment [43]; the normal range for one centre cannot be transferred to another centre [3], since normal ranges may vary by 40% [7]. Considerable variations in sensitivity and specificity are found depending on which measurement of which area is chosen in the hippocampal region [9, 36].

In addition, although MRI provides more information about cerebral structure, this examination is more arduous for the patient. It is even not always feasible in demented patients, and less widely available in routine practice. Thus, CT remains the most applicable imaging technique in the clinical practice of a memory disorders unit. The main use of CT was to exclude intracranial mass lesions, cerebral infarction, chronic subdural haematoma, and normal-pressure hydrocephalus. Our study emphasizes that regional atrophy may also be helpful in the differential diagnosis of memory disorders.

Sixteen percent of patients with probable AD, including one histologically proven patient, had no medial temporal lobe atrophy. Some patients with histologically confirmed AD cannot be detected with this technique [19]. Although the hippocampus area is one of the first involved in AD, and usually the most severely affected, it may be relatively spared, as in one of our patients.

We did not use Jobst's method for rating medial temporal lobe atrophy according to age and normal values (multiples of the median) because we did not have enough controls to determine normal ranges. We gave up the idea of using normal values from other groups because we were not sure, for technical reasons, that the measurement would be the same in the two centres. However, we do not think that not taking into account the minimal changes related to age greatly modifies the results. DeCarli et al. [8] showed that in very healthy aging, the volume of the temporal lobe remains constant over the age range of human life, whereas there was a significant age-related decrease (approximately 1% per decade) of posterior frontal lobe volume [8]. Moreover, visual assessment distinguished AD patients from controls as accurately as volumetry [45].

Two-third of patients with a clinical diagnosis of AD but with another cerebral disease (included in the possible AD group) had a medial temporal lobe atrophy. In Jobst's study [19] the group of 10 patients with histologically confirmed AD who had other cerebral diseases did not differ from the "pure" AD group as regards medial temporal lobe thickness measurement. Three of 19 patients with Parkinson's disease and severe memory impairment had medial temporal lobe atrophy. These patients may have had an Alzheimer pathology in addition to the Parkinson pathology [4, 12]. In the same way, the 57% of patients with clinical Lewy body disease may have had both Lewy bodies and Alzheimer pathology [16].

While the majority of patients with probable AD have medial temporal lobe atrophy, a significant number of non-demented individuals do as well [14, 24, 26]. Consequently, the important population for critical longitudinal

research for the identification of an early marker is the non-demented elderly, especially those with minimal cognitive impairments [6]. In clinical practice, these minimally impaired individuals present a difficult challenge as there is clearly something wrong with them, but it is not of sufficient magnitude to classify them as demented or to allow a diagnosis of probable AD. Longitudinal study of this patient group has shown that 50–70% will be diagnosed as AD after 3 years [26]. The next step after the present study is to follow up the minimally impaired "possible AD" patients to see if the presence of medial temporal lobe atrophy precedes the clinical diagnosis of probable AD. Postmortem examinations of individuals dying of non-AD related causes who were not demented but had minimal cognitive impairments show an AD type of neuropathological changes accentuated in the hippocampus [34]. Ninety-one percent of the minimally impaired individuals who were rated as having increased perihippocampal CSF at baseline developed dementia within a 4 year follow-up period [26].

Because of the high prevalence of AD, the simplest and cheapest high-performance tools are welcome. Temporal lobe oriented CT, as well as hippocampal MRI, show considerable promise as positive markers to assist with the diagnosis of AD, although they are unlikely to be definite diagnostic tests, since involvement of the hippocampal area is not always severe at the early stage of the disease. As stressed by Jobst and Smith [18], NINCDS-ADRDA criteria for probable AD [31] give a false positive rate of 35% for a detection rate of 92% [23] so there is a need for an accurate test for AD early in the course of the disease; temporal oriented CT cannot establish a diagnosis of AD but its diagnostic accuracy is good enough to include it in the multidisciplinary arguments that must be put forward to make the diagnosis of AD. This very simple technique should be widely used in so far as CT is indicated for memory disorders.

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