CT MEASUREMENT OF MEDIAL TEMPORAL LOBE ATROPHY IN ALZHEIMER’S DISEASE, VASCULAR DEMENTIA, DEPRESSION AND PARAPHRENIA

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ABSTRACT

Objective. Measurement of medial temporal lobe atrophy (MTL) by computerised tomography (CT) may be a useful adjunct to the diagnosis of AD. The aim of this study was to assess the sensitivity, specificity, predictive values and diagnostic accuracy of CT measurement of MTL thickness for patients with probable AD, compared with a ‘diseased’ control group, and to correlate the measure with neuropsychological test scores.

Design. Cross-sectional.

Methods. One hundred subjects were prospectively recruited: 60 with probable AD (mean age 73.7 years, mean Mini-Mental State Examination [MMSE] 19.6), 17 with probable vascular dementia (VaD) (mean age 77.9 years, mean MMSE 20.9), 14 with depression (mean age 73.2 years, mean MMSE 25.7) and nine with paraphrenia (mean age 74 years, mean MMSE 25.4). Axial and temporal lobe-oriented CT brain was performed and the minimum MTL thickness was measured electronically.

Results. The mean minimum MTL thickness was significantly smaller in AD subjects compared to VaD (p < 0.0001) and psychiatric subjects (p < 0.0001). For the clinical diagnosis of probable AD, the sensitivity of the measure was 0.75, specificity 0.9, and diagnostic accuracy 0.81. For the mildest cases of AD (CDR 0.5), the sensitivity of the measure was 0.61, specificity 0.91, and diagnostic accuracy 0.81. No significant correlations with neuropsychological test scores were found.

Conclusions. Temporal lobe-oriented CT imaging is a non-invasive test with good discrimination for AD. Potential uses of this technique include as an aid to diagnosis and possibly as a means of monitoring disease progression.

INTRODUCTION

Alzheimer’s disease (AD) is the most common cause of degenerative dementia in individuals over 65 years (McKhann et al., 1984; Katzman, 1986; Kokmen et al., 1993). Dementia affects 1–6% of the population over 65 years, rising to 10–20% of the over 80s (Clark and Goate, 1993). With the projected increase in the older population worldwide, the prevalence of dementia is set to increase into the 21st century (Mann, 1991).

Despite substantial research advances into AD, there is still no biological marker available for the disease in life. The availability of such a marker would be an important advance in assisting earlier detection and improving differential diagnosis.

The diagnosis of AD in life is a clinical one, with the diagnostic accuracy of currently used clinical criteria varying between 63% (Boller et al., 1989) and 90% (Galasko et al., 1994) in
clinicopathological studies. With this undesirable degree of variability in diagnostic precision, there is still a need to continue to seek means of improving the diagnostic approach.

The role of axial computerised tomography (CT) in the diagnosis of AD has principally been one of exclusion of other causes of dementia, e.g. metabolic disease or cerebrovascular accident. Studies have shown a greater degree of cerebral atrophy and ventriculomegaly in AD patients compared with control subjects (Roberts and Caird, 1976; de Leon et al., 1979; Jacoby and Levy, 1980; Gado et al., 1982; Burns et al., 1991), but the overlap between the two groups is too great to be of any clinical use.

Both CT (LeMay et al., 1986; Kido et al., 1989; George et al., 1990; Jobst et al., 1992; de Leon et al., 1993; Pasquier et al., 1997) and MRI (Seab et al., 1988; Jack et al., 1992; Scheltens et al., 1992; Erkinjuntti et al., 1993; O’Brien et al., 1994) studies conducted on atrophy of the medial temporal lobes have suggested the usefulness of this test in supporting the diagnosis of AD. Studies have established the primary role of the hippocampus and related MTL structures in memory formation (Squire, 1992). In addition, the pathology of Alzheimer’s disease occurs early and most severely in medial temporal lobe structures (Hyman et al., 1984; Ball et al., 1985; Braak and Braak, 1991).

The aim of this study was to determine the sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy of medial temporal lobe (MTL) atrophy, as measured by temporal lobe oriented CT views, for the clinical diagnosis of probable AD. We also examined the relationship between MTL atrophy and neuropsychological measures in subjects with probable AD. We hypothesised that increased MTL atrophy would be related to severity of memory dysfunction in AD patients.

METHODS AND MATERIALS

Subjects

One hundred subjects were recruited from our hospital memory clinic, psychiatric unit and the community. Ethics committee approval was obtained from the local authority and informed consent was obtained from the subjects or their relatives where appropriate. Sixty subjects fulfilled criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS–ADRDA) (McKhann et al., 1984) for probable AD. Severity of disease was rated using the Clinical Dementia Rating Scale (CDR) (Hughes et al., 1982), with 0.5 (18 subjects) indicating questionable, 1.0 (19 subjects) mild and 2.0 (23 subjects) moderate disease severity.

Comprehensive diagnostic evaluation included detailed collateral history, medical history, family history, neurological examination, Hachinski Ischaemic Scale (Hachinski et al., 1975), Blessed Dementia Scale (Blessed et al., 1968), BEHAVE-AD (Reisberg et al., 1986, 1987), routine haematological and biochemical investigations, thyroid function tests, vitamin B12 and folate, syphilis serology, chest radiograph and ECG. Neuropsychological assessment included the Cambridge Cognitive Examination (Roth et al., 1986) and the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), the Delayed Word Recall test (DWR) (Knopman and Ryberg, 1989) as a test of memory performance, the FAS letter fluency test (FAS) (Kaplan et al., 1983) and the Boston naming test (Benton, 1986; Williams et al., 1989). Forty ‘diseased’ control subjects were recruited, matched with the AD group for gender and educational level. Seventeen subjects had probable vascular dementia according to criteria of the State of California Alzheimer’s Disease Diagnostic and Treatment Centers (ADDTTC) (Chui et al., 1992). These subjects underwent an identical diagnostic work-up to the AD group. Nine subjects had paraphrenia (ICD 10 criteria) (WHO, 1992) and 14 had depression (major depression n = 9 and dysthymia n = 5) by DSM-IV criteria (American Psychiatric Association, 1994). These subjects underwent brief neuropsychological testing comprising the MMSE, DWR and FAS tests. Table 1 gives a description of the sample.

CT imaging

All subjects underwent standard axial cranial CT and temporal lobe-oriented imaging (Shimadzu 3000X, Japan) according to the technique described by Jobst (Jobst et al., 1992). The temporal lobe-oriented plane was approximately 20° caudad to the orbitomeatal line. Two-millimetre contiguous slices were chosen in order to maximise spatial resolution. The width of the medial temporal lobe at its narrowest point, either right or left, judged by the human eye, was measured level with the brainstem (i.e. between its anterior and posterior limits). In all cases the
measurement was taken midway through the temporal lobes, as in Jobst’s study. The measurement was made in millimetres, directly on the screen using standard designed distance measurement software, by a consultant radiologist with a special interest in neuroradiology, blind to the clinical diagnoses. We do not have our own large normative sample due to ethical concerns regarding the scanning of healthy controls. We therefore used the normative data of Jobst (Jobst et al., 1992) to obtain the predicted mean MTL thickness for age, using the regression equation, \[ \log_{10}(\text{thickness}) = 1.46 - 0.0046 \text{ (age)} \]. The observed value was divided by that predicted for age to give a multiple of median (MoM) value, as described in the literature (Jobst et al., 1992). In this way the confounding effect of age-related tissue loss was controlled for. To assess inter-rater reliability, a second observer, also blind to the clinical diagnoses, reported on the first 40 scans (22 AD, nine VaD, three paraphrenic and six depressed subjects). A correlation coefficient of 0.88 (Pearson’s \( r \)) showed good agreement.

**Statistical analysis**

For analytical purposes, comparisons were made between three groups; probable AD subjects, probable VaD subjects and depressed and paraphrenic subjects. Groups were compared using analyses of variances (ANOVA) with post hoc \( t \)-testing and Bonferroni correction for three group comparisons as appropriate. The validity of each ANOVA was assessed by checking the residuals for normality and constancy of spread. Correlations were calculated with Spearman’s non-parametric rank correlation test. \( p \) values < 0.05 were regarded as statistically significant.

### Table 1. Description of study sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>AD (n = 60)</th>
<th>VaD (n = 17)</th>
<th>Depression (n = 14)</th>
<th>Paraphrenia (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (SD)</td>
<td>73.7 (6.5)</td>
<td>77.9 (5.1)</td>
<td>73.2 (5.6)</td>
<td>74 (4.4)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>36 (60)</td>
<td>10 (60)</td>
<td>9 (64)</td>
<td>6 (66)</td>
</tr>
<tr>
<td>Education years (SD)</td>
<td>11.1 (2.3)</td>
<td>11.3 (1.4)</td>
<td>10.8 (2.4)</td>
<td>10.6 (1.6)</td>
</tr>
<tr>
<td>MMSE (SD)</td>
<td>19.6 (4.5)</td>
<td>20.9 (3.7)</td>
<td>25.7 (4.2)</td>
<td>25.4 (1.3)</td>
</tr>
<tr>
<td>FAS (SD)</td>
<td>21 (9.4)</td>
<td>22.4 (13.1)</td>
<td>23.9 (9.1)</td>
<td>24.1 (6.7)</td>
</tr>
<tr>
<td>DWR (SD)</td>
<td>0.6 (1.02)</td>
<td>2.4 (1.6)</td>
<td>3.8 (1.5)</td>
<td>4.3 (1.4)</td>
</tr>
<tr>
<td>CAMCOG total (SD)</td>
<td>65.1 (1.32)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CAMCOG memory (SD)</td>
<td>11.2 (4.6)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*AD = Alzheimer’s disease, VaD = vascular dementia, MMSE = Mini-Mental State Examination, FAS = FAS letter fluency test, DWR = Delayed World Recall, SD = standard deviation.

### Table 2. Mean MoM values in different diagnostic groups*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Mean MoM (SD)</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>0.73 (0.17)</td>
<td></td>
</tr>
<tr>
<td>VaD</td>
<td>1.02 (0.24)</td>
<td>&lt;0.0001**</td>
</tr>
<tr>
<td>Depressed/paraphrenic</td>
<td>1.04 (0.20)</td>
<td>&lt;0.0001**</td>
</tr>
</tbody>
</table>

*AD = Alzheimer’s disease, VaD = vascular dementia, MoM = multiple of median, SD = standard deviation.

**DIFFERS from AD values, \( p < 0.0001 \).
measure. For the diagnosis of probable AD, the sensitivity was 0.75 and the specificity 0.9. The positive predictive value was 0.92, negative predictive value 0.7 and diagnostic accuracy of 0.81 for our population of subjects.

For the mildest cases of probable AD (CDR 0.5), the sensitivity of the measurement was 0.61, specificity 0.91, positive predictive value 0.73, negative predictive value 0.84 and diagnostic accuracy 0.81 (Table 4). Within the AD group alone (n = 60), the MTL measure did not correlate significantly with any of the neuropsychological tests of memory performance—MMSE, DWR and memory subset of CAMCOG (Table 5).

### DISCUSSION

An important result of this study is the replication of the finding of MTL atrophy on CT imaging in AD subjects described in the literature (Jobst et al., 1992; Pasquier et al., 1994, 1997). We have demonstrated that a simple linear measurement of MTL atrophy on temporal lobe-oriented CT views can provide good discrimination between AD subjects and a ‘diseased’ control group, matched for gender and educational level. Using the same CT technique with a CT scanner of comparable resolution to that in the present study, Jobst et al. reported a detection rate of 74% for probable AD (Jobst et al., 1992). The sex distribution in Jobst’s study is similar to that in ours. Although not rated for disease severity, the AD subjects in Jobst’s study appeared to have well established dementia (mean MMSE 9.3). This is in contrast to the present study which included AD patients of varying dementia severity, while maintaining a detection rate of 75% for probable AD. In addition, Jobst et al. scanned relatively few ‘diseased’ controls, in particular only two cases of vascular dementia were included, which is the most common differential diagnosis in clinical practice.

Pasquier, again using the same CT technique, reported similar sensitivity, specificity, predictive values and diagnostic accuracy as in the present study (Pasquier et al., 1997). MTL thickness of 11.5 mm or less was regarded as indicative of atrophy, irrespective of age. We used the ratio of observed/expected thickness predicted for age as described in the literature (Jobst et al., 1992) and in this way the effects of age-related tissue loss were taken into account (Anderson and Hubbard, 1983; Jernigan et al., 1991). Pasquier et al.’s ‘other dementia’ control group largely comprised cases of frontotemporal dementia (29/48) due to their research bias, while only including five cases of vascular dementia were included, which is the most common differential diagnosis in clinical practice.

Both the above studies measured the minimum width of the MTL from the hard copies with callipers. This is in contrast to the present study

### Table 3. Mean MoM values for AD CDR 0.5, 1 and 2

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Mean MoM (SD)</th>
<th>Mean MMSE (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD CDR 0.5</td>
<td>0.78 (0.14)</td>
<td>23.2 (6.3)</td>
</tr>
<tr>
<td>AD CDR 1</td>
<td>0.72 (0.17)</td>
<td>21.3 (4.5)</td>
</tr>
<tr>
<td>AD CDR 2</td>
<td>0.70 (0.18)</td>
<td>15.3 (7.8)</td>
</tr>
</tbody>
</table>

MoM = multiple of median, AD = Alzheimer’s disease, CDR = Clinical Dementia Rating, MMSE = Mini-Mental State Examination, SD = standard deviation. F-ratio = 1.175, df = 59, p-value = 0.32, (df = degrees of freedom).

### Table 4. Sensitivity, specificity, predictive values and diagnostic accuracy of MTL measures for AD (AD CDR 1.0 and 2.0 eliminated in calculations for AD CDR 0.5)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>AD (total)</th>
<th>AD (CDR 0.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Se</td>
<td>0.75</td>
<td>0.61</td>
</tr>
<tr>
<td>Sp</td>
<td>0.9</td>
<td>0.91</td>
</tr>
<tr>
<td>PPV</td>
<td>0.92</td>
<td>0.73</td>
</tr>
<tr>
<td>NPV</td>
<td>0.7</td>
<td>0.84</td>
</tr>
<tr>
<td>DA</td>
<td>0.81</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Se = sensitivity, Sp = specificity, PPV = positive predictive value, NPV = negative predictive value, DA = diagnostic accuracy, AD = Alzheimer’s disease, CDR = Clinical Dementia Rating.

### Table 5. Correlation of MoM with neuropsychological test scores within the AD group (Spearman’s rank order)

<table>
<thead>
<tr>
<th>Test</th>
<th>r-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>0.29</td>
<td>0.08</td>
</tr>
<tr>
<td>DWR (Recall)</td>
<td>0.05</td>
<td>0.67</td>
</tr>
<tr>
<td>CAMCOG (memory)</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>FAS</td>
<td>0.29</td>
<td>0.09</td>
</tr>
</tbody>
</table>

MMSE = Mini-Mental State Examination, DWR = Delayed Word Recall, FAS = FAS letter fluency test.
where the readings were made directly from the screen using distance measurement software, providing, in our estimation, even more accurate measurements.

Pooling results from temporal lobe MRI studies, O’Brien reported MTL atrophy to have a sensitivity and specificity of 85–90% and diagnostic accuracy of 88% in differentiating AD subjects from controls (O’Brien, 1995). Only one of the ten MRI studies reviewed by O’Brien included a comparison with subjects who were not healthy volunteers (O’Brien et al., 1994). Bearing this in mind, our CT-based study with a sensitivity of 75%, specificity 90% and diagnostic accuracy of 81% compares quite favourably with published MRI studies.

In practice, CT offers many practical advantages over MRI. It is widely available, relatively inexpensive and less technically difficult than MRI. Most importantly, CT scanning is less distressing to the demented patient and the majority of patients tolerate the scan procedure without difficulty. Axial CT brain is part of the routine dementia work-up in most centres and the temporal lobe-oriented view involves only five additional minutes of scanning time. The measurement of the medial temporal lobe may be made directly off the screen, involving little extra time for the radiologist.

Surprisingly, no significant correlations were found between the MTL measure and tests of memory performance (MMSE, DWR and memory subset of CAMCOG) in AD subjects. No previous CT study has addressed this issue to our knowledge, and MRI-based studies have yielded conflicting results. Two MRI studies of MTL atrophy have reported significant correlations with memory performance in AD subjects. Heun reported a significant correlation between amygdala-hippocampal atrophy and the UCLA-auditory verbal learning test (Heun et al., 1997), and Scheltens reported a significant correlation between the MMSE and temporal lobe atrophy (Scheltens et al., 1992). In contrast, the MR studies of Seab (Seab et al., 1988), Pearlson (Pearlson et al., 1992) and O’Brien (O’Brien et al., 1994) failed to detect such findings.

Our failure to show such a correlation may be explained by the inability of CT to quantify the size of individual MTL structures, such as the hippocampus, as is possible with MRI. Another possible explanation is the tendency for tests such as the DWR and the memory subset of CAMCOG to ‘bottom out’ relatively early in the course of AD. Anatomical floor effects must also be borne in mind—the reduction in medial temporal lobe width occurs early in AD and this serves to confound any possible linear correlation with cognitive test scores.

Conclusions and limitations

The usefulness of MTL atrophy as a biological marker for AD will be judged by its ability to help the clinician with more difficult cases (Philpot and Burns, 1993). Our demonstration of acceptable sensitivity, high specificity and diagnostic accuracy in differentiating early AD cases from ‘diseased’ controls is encouraging.

Unlike the NINCDS–ADRDA criteria for AD, the ADDTC (Chui et al., 1992) criteria for VaD have not been subjected to prospective validation. This may add some uncertainty to comparisons between AD and VaD groups.

Although the depressed cohort was recruited from a community sample, the AD subjects and other controls are not necessarily representative of subjects in the community. None of the depressed subjects had pseudodementia (Wells, 1979) which may be difficult to differentiate from dementia in clinical practice.

As all our subjects are still alive to date, no pathological confirmation of the diagnoses is available.

The usefulness of serial measures of MTL atrophy on CT as a marker of the progression of AD over time is uncertain. A longitudinal study is currently underway to determine this.

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REFERENCES


