Use of structural imaging to study the progression of Alzheimer's disease

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Computed tomographic scans in the temporal lobe orientation are a valuable way of studying the medial temporal lobe. In patients with histopathologically-confirmed Alzheimer's disease the size of the medial temporal lobe is almost half that in age-matched controls and the rate of atrophy shown by yearly scans (15% per year) is 10-fold greater. Such a rapid rate of atrophy probably follows a catastrophic event in the brain indicating that Alzheimer's disease is distinct from accelerated normal ageing. The degree of medial temporal lobe atrophy is related to the density of neurofibrillary tangles in the hippocampus; it is a useful guide to diagnosis and has potential as a screening tool in populations. It is proposed that measurement of the rate of atrophy in asymptomatic individuals may be a predictor of Alzheimer's disease and could be used to monitor the effectiveness of therapies designed to retard the rate of neurodegeneration.

The diagnosis and assessment of dementia is still largely based upon clinical and neuropsychological criteria and Alzheimer's disease (AD), in particular, is usually diagnosed by exclusion of other known causes of dementia. The accuracy of clinical diagnostic procedures when assessed by subsequent histopathology is poor, since they either provide a high diagnostic sensitivity but low specificity, or a high specificity but low sensitivity. The need for a biological marker is obvious: firstly, as a guide to diagnosis in life and, secondly, for monitoring the progression of the disease and the effectiveness of any therapy. The discovery of mutations in genes on chromosomes 1, 14 and 21 in the rare familial early-onset forms of AD has identified 'trait' markers that will be of value in counselling (see chapter by Craddock & Owen). However, the search for a biological marker for the common non-familial (sporadic) form of AD is strewn with false trails and with misleading claims. A recent example is the discovery that the epsilon 4 allele for apolipoprotein E is more common in subjects with sporadic AD than in the population as a whole. A dose-dependent effect of this allele upon the age of onset of AD has been shown and it is clearly established as a powerful risk factor for AD (see chapter by Craddock & Owen). However, it is not a biological marker for the disease since about a quarter of those with pathologically-
confirmed AD do not have the epsilon 4 allele and not everyone who carries this allele develops AD\(^2\). While the discovery of genetically determined risk factors is very important for our understanding of AD and for the development of new therapies, such ‘trait’ markers are of no value in the study of the progression of the disease and its response to treatment. Is it possible to identify a ‘state’ marker that is related to the disease process itself? If so, how early can this marker be detected and how is it related to the progression of the disease? In this chapter, we show that neuroimaging methods can provide such markers and that, in particular, a simple application of X-ray computed tomography (CT) has clinical value in the assessment of dementia.

**Early neuroimaging studies in Alzheimer’s disease**

Soon after their introduction to medicine, both functional and structural imaging methods were applied to the study of patients with dementia. Differences were reported between subjects with dementia of Alzheimer’s type (DAT) and age-matched controls, but the field has not been without controversy. One of the main problems is that almost all studies have used clinical criteria rather than histopathological criteria for diagnosis and, furthermore, the majority have been cross-sectional in nature. We shall briefly summarise the salient features of early studies. Throughout we shall use DAT as an abbreviation for clinically diagnosed dementia of Alzheimer’s type and AD for histopathologically confirmed Alzheimer’s disease.

**Functional imaging (see chapter by Goodwin)**

Early studies in Lund, followed by more recent tomographic studies, showed that patients with DAT had focal reductions in blood flow, glucose metabolism and oxygen uptake notably in the lateral temporal and inferior parietal lobes of the neocortex\(^3,4\). However, few functional imaging studies have been longitudinal and fewer still have followed the subjects to necropsy for definitive histopathological diagnoses. Accordingly, the precise diagnostic value of functional imaging remains to be established. OPTIMA’s ongoing studies\(^5-7\) show that single-photon-emission computed tomography (SPECT) evidence of hypoperfusion in the parietotemporal region occurred in 87% of 54 cases with confirmed AD, that it was less common in other dementias and very rare in confirmed controls. Thus, functional imaging has considerable potential as a biological marker for AD.
Structural imaging

Are the functional deficits in the parietotemporal cortex in AD simply the consequence of focal atrophy of this region due to local pathology? Since the 1970s, there have been many CT studies that have searched for evidence of focal atrophy in the brains of subjects with DAT. The search was complicated by the overlap between changes common to AD and normal ageing and because cases were only diagnosed clinically. The overall conclusion from cross-sectional studies on standard axial CT scans is that focal atrophy is not consistently found, although subjects with DAT may show a greater degree of generalised atrophy revealed by sulcal enlargement and ventricular dilatation, leading DeCarli et al. to conclude in 1990: ‘unfortunately, at present there is little definite evidence for clear anatomic brain changes that accurately predict the cognitive dysfunction within a group of patients suffering with DAT...’. In studies where functional and structural imaging have been done in the same subjects there is agreement that parietotemporal atrophy does not fully explain the selective functional deficit in this region. The functional deficit is mainly due to a local reduction in metabolism in intact tissue.

We have suggested that the reduced metabolism in the parietotemporal region might arise as a consequence of decreased synaptic activity following the loss of afferent nerve fibres originating from projection neurons in the medial temporal lobe that are known to degenerate in AD.

The inability of standard axial CT scans reliably to differentiate subjects with AD from elderly controls has had two consequences, one practical and one conceptual. The practical consequence is that physicians and radiologists do not use CT scans to look specifically for AD but only to exclude other causes of dementia, such as cerebral infarcts. The conceptual consequence has been a strengthening of the view that AD and ageing are part of a continuum and that AD is merely the result of an acceleration of normal ageing processes. It is our belief that these views are no longer valid. We shall argue that structural imaging of the medial temporal lobe shows, firstly, that AD can often be detected by a simple CT scan and, secondly, that AD is distinct from accelerated ageing.

Importance of studying the medial temporal lobe

Neuropathological studies have consistently shown that the highest density of neurofibrillary tangles in patients with AD occurs in the hippocampus, subiculum, parahippocampal gyrus and amygdala, struc-
Fig. 1 Lateral topogram showing the standard axial CT angle used internationally (straight arrow: slices 10–26) and the angle used to provide the temporal lobe oriented view (curved arrow: slices 2–9). Note that the temporal lobe oriented protocol provides a series of 2 mm thick contiguous slices that reveal the entire medial temporal lobe in detail. (see Fig. 2).

Tures that comprise the medial temporal lobe. Furthermore, the loss of neurons from the hippocampal formation is very pronounced, which leads to a reduction of up to 60% in the volume of this part of the medial temporal lobe assessed in fixed brain sections. These pathological findings led Ball et al. to suggest that AD is a ‘hippocampal dementia’. Why had such striking changes not been reported in the early CT studies on patients with DAT? The answer is that the standard axial CT used internationally does not show the medial temporal lobe at all well, mainly because of the scan angle used. Changes in the medial temporal lobe itself have to be inferred from dilatation of the temporal horns of the lateral ventricles and enlargement of the suprasellar cisterns; such changes have indeed been observed in DAT. By 1988, an alternative camera angle was in use for evaluating the hippocampus in patients with temporal lobe epilepsy and this angle was applied by de Leon et al. to study patients with DAT. The angle is parallel to the long axis of the temporal lobe and scanning is carried out from below upwards until the inferior margin of the orbit is reached; in this way a complete series of images through the temporal lobe is obtained without exposing the eyes (Fig. 1). Using this ‘temporal-lobe-oriented’ CT procedure, de Leon and his colleagues...
found that 87% of patients with moderate to severe DAT showed dilatation of the hippocampal fissure, compared with 22% of age-matched controls. Hippocampal atrophy was also more common in a group that did not reach the clinical research criteria for DAT but which showed minimal memory impairments, leading these authors to suggest that hippocampal atrophy might be a ‘marker’ for DAT which has been shown both to occur early in the course of the illness and to predict deterioration in early cases before the diagnosis is established.17

This important preliminary report raised two key questions: first, is hippocampal atrophy as detected by neuroimaging in DAT a valid marker for histopathologically-confirmed AD; second, if so, how early in the course of the disease can the atrophy be detected? We are well on the way to answering the first question, but to answer the second requires longitudinal studies lasting many years; such studies are underway in New York and Oxford.

In 1988, the Oxford Project to Investigate Memory and Ageing (OPTIMA) began a longitudinal study in which patients with memory problems and age-matched controls, with no evidence of cognitive deficit, are studied by temporal-lobe-oriented CT scans at yearly intervals until death, when a definitive histopathological diagnosis is obtained. Assessment of the CT scans is done in as simple a way as possible in order to obtain a linear measurement that could be applied in a busy radiological department.18 The measurement chosen was the minimum thickness (as judged by eye, but measured with callipers) of the medial temporal lobe at the level of the brain stem (Fig. 2). A cross-sectional analysis in control subjects revealed a logarithmic age-related decline in this thickness, indicating that the medial temporal lobe normally loses about 1% of its thickness each year. However, in 44 cases with pathologically confirmed AD the median thickness was 56% of that in age-matched controls (Fig. 3). The data for the two populations fitted Gaussian distributions, which allowed us to predict the sensitivity and specificity for the detection of AD in life using this measurement alone. The criterion used was a value below the 5th centile for controls of the same age. Our most recent results, based upon 54 pathologically-confirmed AD cases, 20 cases of other dementias and 108 controls (100 living, 8 dead) gave a sensitivity of 93% and specificity of 81% for AD.8 Thus, this very simple radiological procedure can be used as an aid in the diagnosis of AD. When the result from this structural imaging procedure is combined with the functional imaging criterion of a perfusion deficit in the parietotemporal cortex on SPECT, the accuracy is even greater, with a sensitivity of 83% and a specificity of 91% in the same cohort.8 In practice, of course, the results of these radiological investigations and any other changes revealed by the scans would be combined with detailed clinical findings before arriving at a final diagnosis.
Fig. 2 Temporal-lobe-oriented CT scans of female patient with histopathologically-confirmed Alzheimer's disease. (Note that left of brain is on the right) Top: aged 62 with CAMCOG score of 66. The minimum thickness of the medial temporal lobe at the level of the brain stem was measured at the points marked by arrows: left 7.5 mm; right 14 mm. Bottom: same patient 3 years later, with a CAMCOG score of 29. Measurements were left 2 mm; right 3.5 mm. (OPTIMA, unpublished).
Several cross-sectional studies on subjects with DAT have used structural imaging to reveal atrophy of the medial temporal lobe. Temporal lobe oriented CT scans have been used by de Leon and colleagues in New York\textsuperscript{19,20} and by Pasquier et al.\textsuperscript{21} in Lille; the latter applied the same linear measurement of minimum thickness as OPTIMA uses, with similar results. Studies using volumetric measures from MRI scans have also been reported\textsuperscript{22} which confirm the association between atrophy of structures in the medial temporal lobe and DAT. Although these studies were only on clinically diagnosed cases of DAT, they are consistent with OPTIMA's findings in pathologically confirmed AD\textsuperscript{7,18}. Two practical points should be considered: first, dementia patients tolerate a CT scan much more readily than an MRI scan and, second, the assessment of CT scans by a simple linear measurement of the minimum width of the medial temporal lobe is very rapid compared with volumetric measurements from MRI.

We recommend axial and temporal lobe oriented CT scans as the initial radiological investigation in patients with dementia. The axial scan
Biological psychiatry can be used to look for other possible causes of dementia, such as multiple infarcts, tumours and hydrocephalus, and the temporal lobe-oriented scan (in 1.5–2 mm slices) to reveal atrophy of the medial temporal lobe. MRI volumetric acquisitions are useful in subjects who can tolerate the procedure and these can be reconstructed in 1–2 mm slices along the long axis of the temporal lobe to give the best view of the medial temporal lobe, which can then be measured in exactly the same way as from a temporal-lobe-oriented CT.

Longitudinal structural imaging

A question of considerable clinical importance is: how early in the course of AD can structural imaging reveal a difference between age-related tissue loss and atrophy caused by the disease? If the atrophic process can be detected early enough, before the symptoms are serious, a therapy aimed at arresting the neurodegeneration could then be applied. Longitudinal studies are needed to answer this question, with serial scans on subjects who should ideally be followed to necropsy.

The first detailed longitudinal studies were of the size of the lateral ventricles. These showed a much greater rate of dilatation of the ventricles in subjects with DAT than in age-matched controls. Indeed, it was suggested that the rate of dilatation was a better discriminator of DAT than the absolute size of the ventricle. Clearly, once hydrocephalus is excluded, the dilatation of the ventricles must be due to a loss of brain tissue. Indeed, comparison of longitudinal measurements of the thickness of the medial temporal lobe in controls and in subjects found to have AD reveal a dramatic 10-fold greater rate of atrophy of the medial temporal lobe in AD cases (Fig. 4). The average rate of atrophy in 47 controls was 1.5% per year, while in 20 subjects with AD it was 15.1% per year. An example of the change occurring over 3 years in a patient with AD is shown in Figure 2. Such findings led us to suggest that AD-related atrophy follows a ‘catastrophic event’ in the brain and that it is distinct from an acceleration of normal age-related atrophy. This distinction between AD and normal ageing was also made by West et al. as a result of their finding that the CA1 pyramidal cell group in the hippocampus shows a marked loss of neurons in AD but not in normal ageing. It is noteworthy that the neurofibrillary tangle density in the pyramidal cell layer of the hippocampus correlates both with the extent of atrophy assessed by CT scans in life and with the degree of memory impairment. Thus, there is a direct correlation between a measurement made by imaging in life and one of the principle histopathological markers for AD.
Furthermore, the rapid atrophy of the medial temporal lobe in AD is associated with a rapid rate of cognitive decline\textsuperscript{27}, raising the question whether early detection of atrophy could be used to predict cognitive decline in an individual subject. Cross-sectional studies show a greater degree of hippocampal atrophy in subjects with mild memory impairments than in age-matched normal controls\textsuperscript{29–31}. A follow up of 32 such memory-impaired subjects showed that 23 (72\%) reached the criteria for probable DAT after 4 years\textsuperscript{20}. These findings are consistent with the hypothesis that focal hippocampal atrophy in subjects with mild cognitive impairment is a predictor of DAT\textsuperscript{32}, but they do not tell us whether a rapid rate of atrophy in asymptomatic individuals would be a predictor of DAT. Systematic longitudinal imaging studies in normal subjects over many years are needed to answer this question.
Clinical value of the assessment of medial temporal lobe atrophy

We believe that atrophy of the medial temporal lobe revealed by structural imaging is a 'state' marker for AD and that its quantitative assessment has several potential applications. Such measurements should always be related to values for age-matched controls to avoid the confounding effect of age-related tissue loss\textsuperscript{18,33} and should only be used clinically in the context of the full clinical and radiological picture\textsuperscript{34}.

Screening for AD in populations

Although AD is not the only cause of atrophy of the medial temporal lobe\textsuperscript{18}, it is likely to be by far the commonest cause in the elderly. Thus, screening for such atrophy could be used to estimate the prevalence of AD in different populations. Such screening should use a cut-off value that gives a very low false-positive rate: e.g. for the linear measure of medial temporal lobe thickness from CT, a cut-off value yielding a 1\% false-positive rate will still detect 79\% of cases of AD\textsuperscript{18}. If the prevalence of AD in one population is 5\% and in another it is 10\%, then it would be sufficient to scan approximately 1000 subjects in each population to detect this difference at $p < 0.05$ with a power of 0.85.

Diagnosis of AD

As described above, temporal lobe-oriented CT scans are a valuable aid to diagnosis and in our experience such scans are particularly useful in subjects with early symptoms and in those in whom it is difficult clinically to distinguish DAT from dementia associated with depression or other psychiatric or organic conditions.

Progression of Alzheimer's disease

The rapid rate of atrophy of the medial temporal lobe that is characteristic of AD may be a marker for the progression of the disease and so its measurement by CT or MRI would be a valuable way of monitoring the effectiveness of therapies designed to slow or arrest the neurodegenerative process.
Prediction of AD

We suggest that a rapid rate of atrophy of structures in the medial temporal lobe in asymptomatic individuals might be a marker for the subsequent development of AD. Our suggestion is consistent with OPTIMA’s preliminary findings on asymptomatic subjects (and unpublished) and those of Fox et al. on two subjects with familial DAT. Further work is required to test this hypothesis.

References

3 Frackowiak S. Measurement and imaging of cerebral function in ageing and dementia. Prog Brain Res 1986; 70: 69–85
33 Smith AD. Hippocampal atrophy and cognitive impairment. Lancet 1995; 345: 992