Magnetic resonance imaging in dementia

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Summary

Scheltens P. Magnetic resonance imaging in dementia. Schweiz Arch Neurol Psychiatr 2004;155: 299–308.

Dementia is a clinical syndrome that has many causes. Structural neuroimaging is needed to refine differential diagnosis and identify comorbidity. Excluding structural lesions remains an important indication for either a CT or MR scan in an individual with cognitive decline, particularly if the presentation is in any way unusual. The ability of CT, if done appropriately with negative angulation and thin slices, and MRI to detect even subtle medial temporal lobe atrophy helps to diagnose Alzheimer's disease and differentiate it from normal aging and non-dementia (i.e. depression) but does not rule out other dementias. Absence may indicate dementia with Lewy bodies if fitting with the clinical suspicion. The sensitivity of MRI to detect vascular pathology aids tremendously to the distinction between Alzheimer's disease and vascular dementia, but has also learnt that overlap syndromes between the two conditions exist.

Definite progress is being made in distinguishing normal aging from neurodegeneration using serial scans. The pattern of atrophy may indicate a focal dementia rather than Alzheimer's disease. Clinically useful measures that distinguish the different neurodegenerative disorders from each other at an early stage are still awaited.

MRI is increasingly being used to predict incipient dementia in subjects with mild cognitive impairment and as such the presence of medial temporal lobe atrophy has more predictive value for Alzheimer's disease than any other measure.

Imaging research is also likely to focus on measuring progression and detecting therapeutic effect. Hence, MRI is already being used in clinical trials in mild cognitive impairment, Alzheimer's disease and vascular dementia.

MRI is increasingly seen as an essential investigation in dementia. Unless and until novel biomarkers are found that can reliably detect and track the underlying pathological processes in the different dementias, MRI will continue to play an important role in the diagnosis of patients with dementia and in research into treatments.

Keywords: dementia; MRI; CT; Alzheimer; diagnosis

Introduction

Dementia, the (progressive) impairment of multiple cognitive domains, may be produced by a large number of pathological processes. Many of these underlying pathologies are difficult to distinguish clinically, particularly in their early stages. Only a few of the causes of dementia can be detected with laboratory tests. Despite the widespread use of screening blood tests such as syphilis serology and measures of thyroid function or vitamin B_{12} the yield from these tests is very low. As a result there has been increasing use of neuroimaging to aid diagnosis in dementia. Traditionally imaging was considered important solely as a means of excluding treatable causes of dementia. These conditions account for a small proportion of all causes of dementia with far more common causes being Alzheimer's disease (AD), vascular dementia, dementia with Lewy bodies and fronto-temporal dementia (FTD) [1]. In the past a nihilistic attitude to the diagnosis of these conditions prevailed with a widely held view that these diseases were difficult to diagnose with any certainty and that in any case there was little point in trying to make a diagnosis for which there was no treatment. Over the last few years this attitude has changed, with the recognition that a more accurate diagnosis and prognosis is important for patients and their families. A specific diagnosis is increasingly influencing

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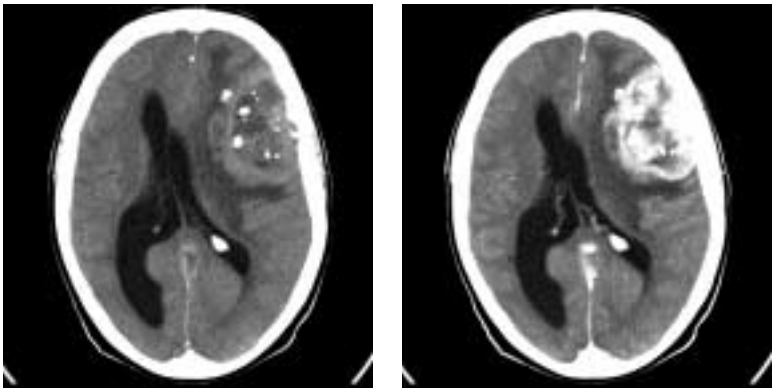
Figure 1 Woman of 71 years with rapidly progressive memory complaints since few months. CT scan before (left) and after (right) intravenous contrast shows massive space-occupying lesion (glioma).



management whether it is in the use of acetylcholinesterase inhibitors in Alzheimer's disease and dementia with Lewy bodies, the modification of vascular risk factors in vascular dementia or caution in the use of neuroleptics in dementia with Lewy bodies or fronto-temporal dementia. The possibility of disease-slowing therapies will further increase the need for an earlier and more accurate diagnosis in dementia. The different pathological processes that produce cerebral dysfunction at a cellular level also produce macroscopic effects which may be detected *in vivo* with imaging. For these reasons neuroimaging in general, and magnetic resonance imaging (MRI) in particular, are increasingly being regarded as a requisite part of the investigation of a patient with dementia.

Practice parameters

Traditionally CT and MRI were used to exclude other illnesses that were potentially amenable to (surgical) treatment, e.g. tumours, haematomata and hydrocephalus. The yield of such a procedure has been debated but probably lies somewhere between 1 and 10% and may even be lower [2]. Farina et al. performed CT in 513 patients referred to a memory clinic of whom 362 were found demented [3]. In 26 of them (7.2%) a potential reversible cause of dementia was detected. However, in none of the cases, CT revealed findings that had not been discovered clinically. Foster et al. carried out a systematic review on the use of CT scanning in dementia [4]. Comparing costs and outcome they concluded that scanning each patient under 65 years and treating only subdural haematomas would be the most cost-effective approach. Treating apparent "normal pressure hydrocephalus" actually reduced quality-adjusted survival. Chui and Zhang also found that imaging did not often reveal reversible disease, but often directed diagnostic revisions that had an impact on patient care [5]. Based on these and other observations, the American Academy Quality Standards Subcommittee concluded in their 2001 practice parameter to the diagnosis of dementia [6] that "structural neuroimaging with either a noncontrast CT or MR scan in the initial evaluation of patients is appropriate (guideline)" (p. 1149). This guideline has important implications for the management and evaluation of patients suspected of dementia because for the first time it no longer considers imaging to be "optional" as in many previous guidelines, and it states the word "initial" which implies that routine scanning should be done at the time of diagnosing. A recent study by Hejl et al. [7] employed this strategy almost to the full, in reporting on 1000 consecutive memory clinic patients of whom 89% underwent CT or MRI scanning. Interestingly, of the 891 patients that had a scan, 42 (almost 5%) had an identifiable lesion (tumour or hydrocephalus) that prompted an alternative diagnosis and management. This percentage changed just marginally when only the demented patients (n = 432) were considered in whom 4% had such a lesion (see fig. 1). Finally, Massoud et al. [8] found clinically unsuspected cerebrovascular disease in 26% of their sample by routine imaging.

Since Gifford et al. [9] have shown that there is considerable uncertainty in the evidence underlying clinical prediction rules to identify which patients with dementia should undergo neuroimaging and application of these rules may miss patients with potentially reversible causes of dementia, it is generally felt that a structural imaging investigation in the evaluation of a patient suspected of dementia should be performed routinely. A probable exception is the very old patient category in which little or no change in management of the patient is expected from the results of such a procedure or when severe contraindications exist.

Aiming for specificity

Imaging is increasingly being used to add positive or negative predictive value in the diagnosis of the more common dementing illnesses. The development of diagnostic clinical criteria has improved diagnostic accuracy, especially sensitivity, but they are still far from perfect. Based on clinico-pathological correlation, the accuracy of criteria for

Alzheimer's disease is limited and depends on the expertise of the clinical centre, with a specificity ranging between 76 and 88% and a sensitivity between 65 and 53% [10]. In population settings, reflecting more the common practice in non-specialised centres, the neuropathological confirmation rate of 'probable' Alzheimer's disease was as low as 65% [11]. Varma et al. found a very low specificity of 23% when using the NINCDS-ADRDA criteria to distinguish patients with Alzheimer's disease from those with fronto-temporal dementia [12]. Diagnostic clinical criteria have also been developed for fronto-temporal dementia, vascular dementia and dementia with Lewy bodies [13–15]. The diagnostic accuracy of these criteria needs to be further defined. Neuroimaging is increasingly being used to add support to a clinical diagnosis, especially by adding specificity to an already quite high sensitivity.

Imaging already forms a mandatory part of some clinical criteria for vascular dementia. Imaging evidence of cerebral atrophy, especially if progressive, has long been cited in criteria for Alzheimer's disease as lending support to this diagnosis. Similarly frontal and temporal atrophy form part of the supporting evidence in consensus criteria for fronto-temporal dementia.

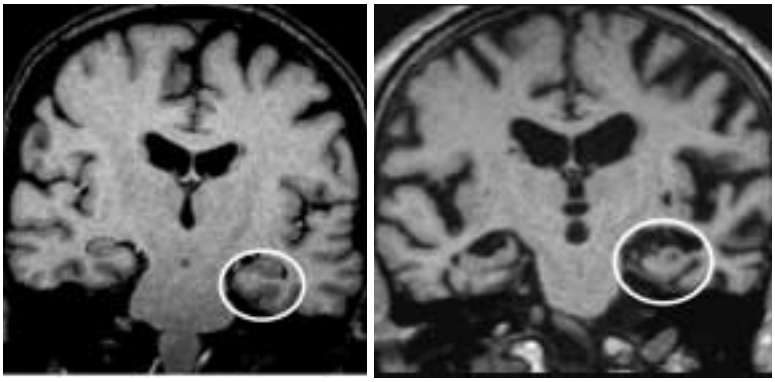
Hippocampal atrophy

The pathology of Alzheimer's disease has a definite topographic distribution [16] that can be well characterised by available neuroimaging methods [17–19]. Hippocampal atrophy is an early and specific marker of the Alzheimer's disease process [17–22]. In addition, Alzheimer's disease is a degenerative process leading to progressive loss of brain volume that is significantly greater in AD patients as compared to age-matched controls [23, 24] and correlates with the rate of cognitive deterioration [25]. Neuropathological studies also show that the pathological features of Alzheimer's disease may be present years before clinical symptoms are evident and pathological evidence of Alzheimer's disease is often present in individuals with memory impairment who are not demented, suggesting that most individuals with mild cognitive impairment (MCI) have early Alzheimer's disease [26]. In addition, careful pathological studies find a close association between hippocampal size as imaged by MRI and the extent of Alzheimer's disease pathology [27].

Although visibility of this region is limited on CT, some CT studies used assessments of medial temporal lobe structures with success [28, 29]. The proposed technique of Jobst et al. required 3 mm or thinner slices oriented parallel to the medial temporal lobe and skilful handling of the caliper. As recently reviewed by Frisoni [30], studies using this technique showed sensitivity values between 70 and 92% in differentiating AD patients from controls with a specificity ranging between 80 and 95%. It should be noted, however, that the patients in these studies were moderately demented. A recent attempt to replicate these results by Frisoni and colleagues resulted in a maximum sensitivity of 74% (with specificity set at 95%) [31]. In addition, they found the reliability of the technique quite low with intraclass correlation coefficients of 0.74 within raters and 0.78 between raters. Interestingly, they experimented with the measurement of the radial width of the temporal horn of the lateral ventricle and found it to have a higher sensitivity (93%), specificity (97%) and reliability (intraclass coefficients between 0.94 and 0.98). More complex analytical tools such as volumetrics of the lateral and third ventricle on CT have never reached those values [32].

Using MRI, it became possible to study specific structures within the medial temporal lobe, such as the hippocampus proper, parahipppocampal gyrus, subiculum, entorhinal cortex and amygdala. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) study group and the work of Bobinski et al. demonstrated the excellent correlations between atrophy on in vivo MR of the temporal lobe with postmortem findings of hippocampal atrophy [27, 33]. These structures have been measured using a variety of tracing techniques and anatomical boundaries. Some studies have employed linear or visual measurements [31, 34–38]. Because of their supposedly (but debatable) greater accuracy and reliability, other studies have used volumetric measures of medial temporal lobe structures. Comparative studies have found good correlations between these assessment techniques [39, 40]. Several studies used a qualitative method that involves a visual rating scale, usually a four- or five-point scale ranging from absent to severe atrophy (see fig. 2) [36, 41]. Frisoni et al. used a compound score of linear measurements that included the temporal horn [42]. Pucci et al. found the best discriminating parameter to be just the height of the left hippocampus [43]. In a novel approach Frisoni and co-workers used the radial width of the temporal horn of the lateral ventricle on axial MR scans as measured with a caliper on paper printouts [31]. Visual assessment is considerably less time consuming than volumetry and easily applicable in clinical practice [44]. The downside may be a larger inter-rater variability [35].

Figure 2 Coronal T_1-weighted MR perpendicular to the long axis of the hippocampus. Hippocampal atrophy absent (left) and present (right).



In an earlier review we calculated the weighted (corrected for number of subjects in the study) sensitivity and specificity figures for detection of mild to moderate Alzheimer's disease vs controls as being 85 and 88% [45]. Thus, it can be concluded that atrophy of the medial temporal lobe is quite sensitive for Alzheimer's disease and the absence is more specific for normal aging [46]. In a real-life practical situation this means that in case of an a priori probability of Alzheimer's disease of 0.60 (which is in line with the sensitivity figures for the NINCDS-ADRDA criteria as mentioned above) a positive result (presence of hippocampal atrophy) adds 31% to a post-test probability of 91% and a negative result (absence of hippocampal atrophy) lowers the post-test probability to 20%.

The prognostic significance of hippocampal atrophy in mild cognitive impairment

Accumulating evidence from quantitative MRI studies suggests that hippocampal atrophy is present before dementia onset [47–51] and progresses with conversion to clinically apparent disease [52]. In a large prospective study of mild cognitive impairment patients, Jack et al. [47] found a fourfold increase in the percentage of individuals converting to dementia within five years when hippocampal size was two standard deviations below age- and sex-defined norms. Similar findings were noted in a second study, although memory scores were also significant predictors [53]. Another study using qualitative estimates of hippocampal size also found similar results [54].

These findings support the utility of anatomical brain imaging in mild cognitive impairment to predict conversion to Alzheimer's disease within the near future [55]. Importantly, future work from population-based studies will be helpful in clarifying the utility of anatomical imaging in the diagnosis of early Alzheimer's disease for populations where clinical definitions of mild cognitive impairment are less predictive [56]. The general use of anatomical imaging, however, requires a simple and convenient method by which clinicians can have reliable and accurate estimates of hippocampal size. Until now, only qualitative scales seem to meet that goal.

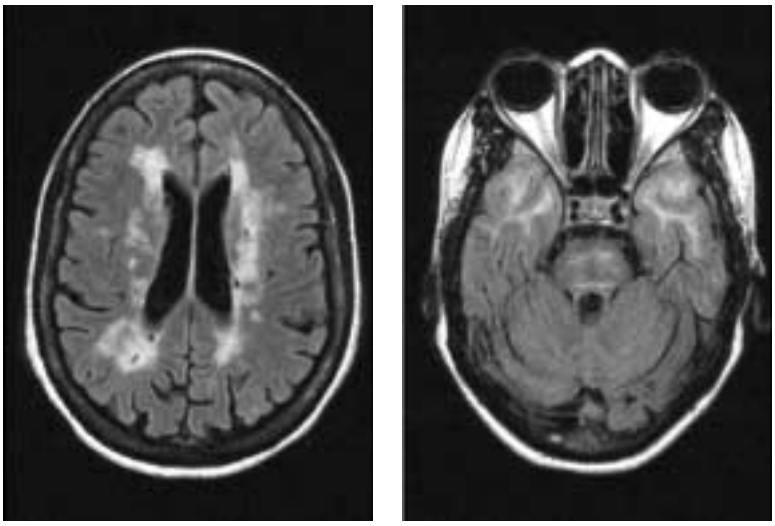
Fronto-temporal lobar degeneration

The well-established clinical criteria by Neary et al. list frontal and temporal atrophy as supportive diagnostic features for fronto-temporal dementia, but the absence does not rule out this diagnosis [13]. Asymmetric, predominantly left-sided perisylvian atrophy characterises progressive nonfluent aphasia and asymmetric anterior temporal lobe atrophy is diagnostic of semantic aphasia. In both conditions, with time, atrophy becomes more widespread but usually remains asymmetric. Galton et al. focused on MRI of fronto-temporal dementia, including patients with semantic dementia and the frontal variant of fronto-temporal dementia (fvFTD) [57]. In a study consisting of 30 patients with Alzheimer's disease, 17 with semantic dementia, 13 with fvFTD and 18 controls, the authors used a new visual scale based on atrophy of the temporal pole, the parahippocampal gyrus and the lateral temporal gyri that could be helpful in distinguishing Alzheimer's disease from semantic dementia as the semantic dementia group has significantly more atrophy in all these regions in both hemispheres. Boccardi et al. [58] performed a discriminant function on a set of AD and FTD patients, showing that including the asymmetry values of frontal and temporal regions could separate fronto-temporal dementia from Alzheimer's disease with 90% sensitivity and 93% specificity. They concluded that a pattern of atrophy is more useful than atrophy of single regions in the differential diagnosis. Chan et al. showed that in addition to asymmetry, a marked anterior to posterior gradient of atrophy within the temporal lobe also suggests a diagnosis of fronto-temporal dementia rather than Alzheimer's disease [59].

Vascular dementia

Criteria for vascular dementia include definitions of (1) dementia, (2) vascular disease and (3) a

Figure 3 Axial FLAIR sequence with severe white-matter lesions in centrum semiovale (left); the involvement of the temporal lobes suggests a diagnosis of CADASIL (right).



relation between the two. Vascular disease can be diagnosed on clinical grounds, on the basis of information from neuroimaging (CT and MRI) or on both. In the DSM-IV criteria for vascular dementia imaging evidence of cerebrovascular disease is exemplified as multiple infarctions involving cortex and underlying white matter that are judged to be aetiologically related to the disturbance. The "State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC)" criteria for ischaemic vascular dementia were the first set of criteria formulated in the format 'possible-probable-definite' vascular dementia [60]. The criteria are restricted to dementia caused by ischaemic vascular disease, but leave room for both 'multi-infarct dementia', dementia after a single stroke and 'Binswanger's syndrome' (widespread microvascular damage to the deep white matter, for which explicit criteria are provided). Vascular disease is defined both clinically and in terms of neuroimaging results. The documentation of a temporal relationship between the dementia and stroke is considered indicative of a causal relationship.

In the NINDS-AIREN international work group criteria for vascular dementia brain imaging is thought to be essential for the diagnosis and without it vascular dementia will be "possible" at best [14]. In addition, the criteria specify which vascular territories are "relevant" for vascular dementia. These include large vessel strokes, such as bilateral infarcts in the arteria cerebri anterior area, infarcts in the arteria cerebri posterior area, association areas or in the watershed regions. The list of radiological criteria has fuelled discussion as to their relevance and validity. In fact, the criteria have low interrater reliability, which is probably caused by the ambiguity in the radiological criteria and the absence of operational guidelines [61, 62]. In a recent attempt to validate operational definitions for these criteria, we tested interobserver reliability of the radiological diagnosis of vascular dementia using the NINDS-AIREN criteria, in a group of experienced and unexperienced raters. We found that by using operational guidelines on how to classify radiological features as fitting into the NINDS-AIREN criteria, interobserver reliability of the diagnosis went up significantly from 40 to 60%, but only in the already experienced raters [63].

MRI is far more sensitive to vascular changes than CT, but CT is more specific, especially with respect to symptomatic cerebrovascular disease [64]. The NINDS-AIREN criteria state that white-matter changes alone may be sufficient to cause dementia when 25% or more of the white matter is involved. Although this percentage is set purely arbitrarily, it agrees with most studies that found that only severe white-matter disease is associated with cognitive dysfunction. From a recent study it was concluded that the majority of the NINDS-AIREN-diagnosed vascular dementia cases has small vessel disease only [65]. This has led a group of investigators to formulate specific criteria for "subcortical vascular dementia" [66]. In practice, to diagnose "subcortical vascular dementia" one has to use a practically feasible and clinically valid rating scale. In a review on existing rating scales in 1998 we concluded that the "ideal rating scale did not exist" [67]. By initiative of the European Task Force on Age-Related White-Matter Changes (ARWMC) a scale was developed that is applicable to both CT and MRI and gives an estimate of the vascular burden in six different regions of the brain (frontal, temporal and parieto-occipital, left and right). The scale has acceptable inter- and intrarater reliability [68]. It seems prudent, however, to use high grades of white-matter changes for a diagnosis of subcortical vascular dementia, as suggested by Erkinjuntti et al. [66]. Using the ARWMC scale for example a score of 3 in at least two regions and a score of 2 in two other regions could be sufficient (see fig. 3).

Identifying vascular disease

Like Alzheimer's disease, the prevalence of cerebrovascular disease, both symptomatic and asymptomatic, increases dramatically with age, and pathological studies often find concomitant

cerebral infarction in patients with definite Alzheimer's disease [69]. Even small, concurrent infarctions significantly increase the likelihood of expressed dementia, suggesting a synergistic effect. Understanding the potential interaction between Alzheimer's disease, cerebrovascular disease and expressed dementia is currently an area of ongoing research [70]. Numerous studies show that silent cerebrovascular brain injury is associated with diminished cognitive performance in older individuals and heralds incipient dementia [71]. More recent studies also suggest that evidence of cerebrovascular disease on brain imaging is associated with an increased risk for mild cognitive impairment and conversion of mild cognitive impairment to dementia [72, 73]. In addition, brain imaging evidence of cerebrovascular disease may influence the clinical presentation and neurobiology of Alzheimer's disease [8, 74–77]. Given that concurrent cerebrovascular disease may be amenable to targeted interventions potentially ameliorating disease progression, brain imaging may prove important to clinical care of the demented patient with coexisting cerebrovascular disease. Preliminary evidence from antihypertensive treatment trials of older individuals supports this notion, although further prospective clinical trials involving brain imaging are necessary.

Miscellaneous

In addition to the above, specific imaging signs may include: bilateral caudate atrophy in Huntington's disease, hyperintense signal in the putamen in sporadic Creutzeldt-Jakob disease and hyperintense signal change in the pulvinar in new variant Creutzeldt-Jakob disease [78]. Diffusion-weighted MRI shows (the earliest) focal changes in Creutzeldt-Jakob disease not yet apparent on FLAIR images and may widely involve the cortex [79]. Corticobasal degeneration shows a typical MRI pattern, with striking, asymmetric parietal (peri-Rolandic) atrophy, sparing frontal and medial temporal regions [80].

Normal pressure hydrocephalus (NPH) is a questionable disease entity and it may be difficult to decide whether such a patient would benefit from a shunting procedure. Vanneste in his recent review concludes that strict adherence to clinical and MRI criteria is important, with additional information from a positive – but not a negative – CSF tap and the occurrence of B-waves [81]. These MRI criteria include widened ventricles with normal sulci and without white-matter pathology. Of more clinical relevance is dementia with Lewy bodies, possibly the third most common degenerative dementia. MRI has been reported to show medial temporal lobe atrophy in a lower frequency than in Alzheimer's disease, leading Barber et al. to state that: "in the differentiation of DLB from AD and VaD the *absence* of MTA is suggestive of a diagnosis of DLB" ([82], p. 1155, italics P. S.).

Serial studies

The majority of imaging studies in dementia have been cross-sectional and this reflects current clinical practice whereby a single CT or MR scan is performed to aid diagnosis. Serial imaging allows an assessment of progression. Subjects serve as their own reference baseline and rates of change (e.g. atrophy) can then be calculated. In cases of diagnostic uncertainty a follow-up scan may support a diagnosis of a degenerative dementia by demonstrating ongoing atrophy. As long ago as the early 1980s, serial imaging studies (mainly CT) showed that when subjects are rescanned after an interval of more than one year, rates of ventricular enlargement were significantly higher in Alzheimer's disease than in normal controls [83]. Rates of atrophy of the medial temporal lobe on CT are also increased in Alzheimer's disease [84]. Using serial MR scans Jack et al. showed hippocampal atrophy rates to be significantly increased in Alzheimer's disease, with a mean rate of 4%/year, compared to age-matched elderly controls (1.6%) [85]. Du et al. showed even 6.8 ± 4.3% annual volume loss of the entorhinal cortex in Alzheimer's disease as opposed to normal aging [86]. Manual measurements such as these, however, are time-consuming and have not yet entered routine clinical practice. Digital subtraction of serial registered (positionally matched) scans allows small amounts of diffuse atrophy to be detected and displayed automatically. Using such methods, rates of whole brain atrophy in Alzheimer's disease (2.5 ± 1.1%/year) have been shown to be several times higher than in normal ageing (0.4 ± 0.4%/year) [24]. Furthermore, rates of cerebral atrophy are already increased in asymptomatic individuals at risk of familial Alzheimer's disease who subsequently become clinically affected [87, 88]. Analysis of the presymptomatic scans suggests atrophy rates increase first in medial temporal lobe and posterior cingulate regions but by the time a clinical diagnosis can usually be made atrophy is already generalised. Serial imaging is likely to be increasingly used in clinical trials in the search for treatments that slow diseases such as Alzheimer's disease. Demonstration of a slowing in rates of

cerebral atrophy would provide a strong suggestion that a therapy is actually slowing degeneration rather than simply providing short-term symptomatic relief. If and when such therapies are found, there will be even greater interest in making an accurate diagnosis earlier in these diseases and MRI will be used to support these diagnoses.

Conclusion

Excluding structural lesions remains an important indication for either a CT or MR scan in an individual with cognitive decline, particularly if the presentation is in any way unusual [6]. The ability of CT, if done appropriately with negative angulation and thin slices, and MRI to detect even subtle medial temporal lobe atrophy helps to diagnose Alzheimer's disease and differentiate it from normal ageing and non-dementia (i.e. depression) but does not rule out other dementias. The sensitivity of MRI to detect vascular pathology has boosted research into and clinical recognition of vascular dementia and aids tremendously to the distinction between Alzheimer's disease and vascular dementia, but has also learnt that overlap syndromes between the two conditions exist, while operational definitions for "mixed" dementia, indicating the presence of both Alzheimer's disease and vascular dementia, are still lacking. Definite progress is being made in distinguishing normal ageing from neurodegeneration using serial scans. The pattern of atrophy may indicate a focal dementia rather than Alzheimer's disease. Clinically useful measures that distinguish the different neurodegenerative disorders from each other at an early stage are still awaited. Differentiation remains most difficult between Alzheimer's disease and dementia with Lewy bodies.

Future perspectives

The most likely future use of imaging will be the identification of patients at risk for Alzheimer's disease or suffering from preclinical Alzheimer's disease or mild cognitive impairment. For MRI this will mean focusing on those areas that are affected earliest in the disease, i.e. entorhinal cortex and hippocampus, using high-resolution structural MRI [89]. Work from the groups of New York University, Mayo and Maastricht/Amsterdam showed that moderate medial temporal lobe atrophy, as measured qualitatively or quantitatively, was a strong predictor (positive predictive value 80% and overall classification accuracy >90%) of development to Alzheimer's disease in mild cognitive impairment subjects [47, 48, 53, 90, 91]. Medial temporal lobe atrophy predicts Alzheimer's disease in MCI patients independently of age, memory function and ApOE genotype [47, 91].

With the ability to rapidly acquire high contrast, high spatial resolution, three-dimensional brain images, a number of laboratories are experimenting with sophisticated brain-mapping algorithms. This process allows an individual MRI to be compared to an 'average' or 'ideal' brain, enabling the detection of anatomical differences at one point in time as well as change in anatomical structure over repeated observations. When this process is applied to brain MRIs from a group of AD patients, volume loss of medial temporal and parietal regions is apparent [92]. A similar result is being achieved through voxel-based morphometry (VBM) [92]. The first VBM pilot study compared 7 AD patients and 7 controls and showed gray-matter volume differences in both medial temporal lobes, left insula and both caudate nuclei and was replicated by another group and ours [93–95]. A recent comparative VBM study in DLB and AD patients has shown preservation of the medial temporal lobe, hippocampus and amygdala in dementia with Lewy bodies compared with Alzheimer's disease [96].

Brain-mapping techniques can also be used to create automatic (or nearly automatic) brain-region identification schemes. This approach has already been applied to estimating hippocampal volume [97]. Further work, however, is necessary to fully understand the sensitivity and specificity of these brain-mapping procedures for the diagnosis of the individual patient. If these methods are validated, these algorithms could be incorporated into regular brain-imaging protocols giving clinicians important additional information when attempting to make an early and accurate diagnosis. Imaging research is also likely to focus on measuring progression and detecting therapeutic effect. As such, MRI is already being used in clinical trials in mild cognitive impairment, Alzheimer's disease and vascular dementia.

MRI is increasingly seen as an essential investigation in dementia. Unless and until novel biomarkers are found that can reliably detect and track the underlying pathological processes in the different dementias, MRI will continue to play an important role in the diagnosis of patients with dementia and in research into treatments.

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