Imaging and Alzheimer’s Disease: A Review

Neuroimaging in Alzheimer’s disease (AD) has moved beyond the stage where it was used purely to exclude other disease processes. Structural brain magnetic resonance imaging (MRI) is useful to assess hippocampal atrophy on coronal slices; clinicians can use a simple visual rating scale, which can help to confirm the diagnosis of AD. Another useful indication for neuroimaging is to assess the contribution of cerebrovascular disease (CBVD) to the clinical syndrome of dementia. It has become clear in recent years that the most common situation in the general population is the combination of AD and CBVD. A neuroimaging procedure (CT scan or, preferably, MRI) can detect silent CBVD, which would modify management of modifiable risk factors. The recent Canadian Consensus on Dementia recognized this indication.

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Neuroimaging has traditionally been recommended as a way to exclude potentially reversible causes of dementia, even though the prevalence of treatable causes of dementia in typical referral clinics is very low. This traditional view was largely held until the previous Canadian Consensus in 1999, where specific guidelines were stated to restrict the indications of neuroimaging in dementia. However, there has been much development since those guidelines were published. The most recent Practice Parameter from the American Academy of Neurology recommends that at least one neuroimaging procedure should be done in every patient with a dementing disorder. This article reviews structural and functional imaging in the diagnosis of Alzheimer’s disease (AD). Future developments of imaging hold great promise and are briefly overviewed.

Background

The process that leads to AD probably begins decades before we can detect it clinically. At one point, the functional connectivity and molecular changes that occur within cells result in neuronal loss and brain atrophy. This atrophy follows a specific, systematic anatomical pattern for reasons that are still a matter of debate. One hypothesis holds that the AD process follows brain regions in decreasing order of “neuroplasticity potential.” This view states that the hippocampus and its connections in the entorhinal cortex (the part of the medial temporal lobe just adjacent to the hippocampus) remain the most active in terms of plasticity throughout the lifespan. Indeed, the forming of new memories occurs during adult life, and is supported by structural changes in the hippocampal-entorhinal complex: these structural changes are termed neuroplasticity. Neuroplasticity failure would affect the medial temporal lobe first, then its connections within the limbic and para-limbic regions, then the multimodal associative cortex. It is this topographical selectivity that allows early detection of atrophy in the medial temporal regions.
Structural Neuroimaging: Brain Atrophy

Several studies using CT and MRI scans have shown significantly smaller hippocampi in subjects with AD compared with normal controls, with accuracy of classification in the 85% range. There is a whole spectrum of tools with varying degrees of technological intensity, ranging from the simplest visual rating scale to the most sophisticated 3D shape-deformation analysis of the hippocampus, which require advanced hardware, software and statistical knowledge. Visual rating scales (Figure 1) can be performed by clinicians quickly (one to two minutes), with minimal training, and have been validated against volumetric measures.

For reasons of ease-of-use and availability, this simple type of imaging analysis is probably the one with the most potential usefulness in clinical practice for now. Recent developments have brought automated measures closer to clinical practice, but even “simple” techniques require registration to standardized 3D templates, which is not likely to be widely available.

It should be kept in mind that hippocampal atrophy alone may not be sufficient to diagnose AD in cohorts comparing different diagnostic groups: the addition of a Mini Mental State Examination (MMSE) score to a visual rating of medial-temporal-lobe atrophy was found to be necessary to discriminate between AD and non-AD in one study, and other temporal-lobe structures were assessed in another. There are several reports where medial-temporal-lobe atrophy is found in non-AD dementias, such as fronto-temporal dementia. Nevertheless, a group of experts recently recommended that research criteria for AD be revised, and that assessment of medial-temporal atrophy should be a part of the new criteria, which also include cognitive information and other biomarkers.

In conclusion, although medial-temporal atrophy does contribute to diagnostic specificity in expert hands, it has yet to be translated into widespread clinical and radiological practice. According to a recent stringent evidence-based review, there is insufficient data on MRI in general-practice settings to recommend its widespread use.

Structural Neuroimaging: Cerebrovascular Disease

In recent years, CBVD has been reconceptualized as a major factor in cognitive decline and dementia, including AD. Ischemic lesions such as lacunar infarcts greatly influence the clinical syndrome of dementia; this could be an additive or a synergistic effect. It appears that the most common pathological substrate of dementia in population-based autopsy series is combined CBVD and AD pathology; mixed dementia could be more frequent in the general population than “pure” AD. It is also well known from large-scale, population-based imaging studies that the prevalence of...
of silent CBVD should lead to a more pro-active management of modifiable vascular risk factors.27 These considerations have resulted in a statement from the 3rd Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCĐTĐ):28 “There is fair evidence to support use of structural neuroimaging to rule in concomitant CBVD that can affect patient management.”

Ever since neuroimaging was integrated in clinical routine,29 there has been much controversy about the white-matter changes (or leukoaraiosis) that appear ubiquitous in aging.30 Recent years of research have finally crystallized knowledge on this phenomenon, and there is an emerging consensus that confluent lesions (as opposed to punctate lesions) do progress with time,31 and are associated with certain cognitive deficits as well as motor and functional disability.32-34 Moderate-to-severe leukoaraiosis is thus far from benign, and can easily be assessed with simple rating scales (Figure 2).35,36,37

Advanced Structural Neuroimaging Techniques

Until now we have dealt with traditional neuroimaging techniques that are in common clinical use. Recent developments in MRI technology have revealed that structural damage can be detected in areas outside of visibly abnormal regions on the standard images: several techniques are available, but will not be reviewed in detail here. One of the most promising techniques is diffusion tensor imaging (DTI), where integrity of the white-matter tracts can be assessed by analyzing the movement of free water molecules within the tracts.38 More degraded tracts will result in increasingly random movements, which can be detected by DTI; such abnormalities can be correlated with cognitive functions.39 Studies have now shown that AD is associated with degradation of white-matter tracts.40 It is still a technical challenge to obtain such data and thus routine availability of DTI will not happen in the foreseeable future.

Functional Neuroimaging

Nuclear medicine has been used in the study of dementia for many years, with single photon emission computed tomography (SPECT) and positron emission tomography (PET) scans tested as diagnostic tools in AD and other dementias. There are reports on PET imaging that show it is more sensitive and specific compared with clinical assessment in the early diagnosis of dementia. The value of PET in the differential diagnosis of frontotemporal dementia versus AD has recently been demonstrated in a well designed study that looked at added benefit over clinical information alone, notably with a simple visual rating by the (experienced) clinician.41 SPECT is more
widespread availability, but is generally less sensitive and specific than PET. Nevertheless, it has some value in the diagnosis of AD and differential diagnosis of dementias, including frontal and anterior temporal hypoperfusion in fronto-temporal dementias, and occipital hypoperfusion in dementia with Lewy bodies.

**Advanced Functional Neuroimaging Techniques**

Direct imaging of neuropathological hallmarks of AD is becoming possible with the development of specific tracers in PET imaging. This has some potential to help in the early diagnosis of AD, but unfortunately correlations between amyloid on neuropathology and cognition have been far from compelling. Also, there is a substantial proportion of elderly without cognitive impairment who also have high amyloid burden on pathology. The specificity of an amyloid imaging technique remains to be proven in light of these known pathological correlates. Future development in tau imaging might contribute more substantially to this field since tau and neurofibrillary tangles are more robustly associated with cognition in AD.

**Conclusion**

In summary, the diagnosis of dementia will likely remain clinical for most purposes in the next few years. However, there are potential benefits and diagnostic utility of some widely available imaging techniques. In particular, systematic rating of medial-temporal atrophy on MRI has the potential of increasing diagnostic certainty for AD in specialty clinics. Similarly, identification of lacunes and application of a simple rating of leukoaraisosia on CT scans of the brain can provide prognostic information and alter management of patients.

The real challenge facing clinicians will be increasing pressure to diagnose AD earlier and with more accuracy and diagnostic confidence. This pressure will become much more important when efficent disease-modifying therapies are available. Neuroimaging perhaps will have to be used in that early period of the disease, where it is likely to be more useful. New research criteria have been proposed for that purpose, and rightfully include medial-temporal-lobe atrophy as a neuroimaging biomarker. These criteria will certainly give an impetus to the systematic rating of medial-temporal-lobe atrophy by radiologists and clinicians in the next few years. A large-scale, open-access database is currently being developed in the U.S. and Canada and will likely be very useful to further delineate the diagnostic value of neuroimaging in AD.

**References**

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