Neuroimaging in Alzheimer’s disease: current role in clinical practice and potential future applications

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Alzheimer’s disease is the most common cause of dementia in the general population. Clinical diagnosis of AD is based on a history of progressive and characteristic cognitive decline and the presence of objective cognitive deficits. Exclusion of other diagnoses such as depression, hypothyroidism, other dementias and non-AD brain lesions is an integral part of the diagnostic evaluation. Since AD is the most common type of dementia and its burden is expected to grow substantially owing to aging of the population, improving the diagnostic accuracy of AD is critical.

Neuroimaging examinations are an essential part of the diagnostic investigation of dementia. These examinations are important not only to identify non-AD pathological processes that can lead to cognitive decline (e.g. brain tumors or cerebrovascular disease) but also to search for biological markers that provide supportive features for the diagnosis. Neurofunctional techniques such as single photon emission computed tomography and 18F-fluorodeoxyglucose-positron emission tomography can also be used to complement the diagnostic investigation in cases of uncertainty. Amyloid imaging is a non-invasive technique that uses positron emission tomography technology to investigate the accumulation of the β-amyloid peptide in the brain, which is a hallmark of Alzheimer’s disease. This is a promising test but currently its use is restricted to very few specialized research centers in the world. Technological innovations will probably increase its availability and reliability, which are the necessary steps to achieve robust clinical applicability. Thus, in the future it is likely that amyloid imaging techniques will be used in the clinical evaluation of patients with Alzheimer’s disease.

KEYWORDS: Alzheimer’s disease; Neuroimaging; Amyloid imaging; Diagnosis; Classification.

INTRODUCTION

Alzheimer’s disease (AD) is the most common cause of dementia in the general population. Clinical diagnosis of AD is based on a history of progressive and characteristic cognitive decline and the presence of objective cognitive deficits. Exclusion of other diagnoses such as depression, hypothyroidism, other dementias and non-AD brain lesions is an integral part of the diagnostic evaluation. Since AD is the most common type of dementia and its burden is expected to grow substantially owing to aging of the population, improving the diagnostic accuracy of AD is critical.

Neuroimaging examinations are an essential part of the diagnostic investigation of dementia. These examinations are important not only to identify non-AD pathological processes that can lead to cognitive decline (e.g. brain tumors or cerebrovascular disease) but also to search for biological markers that provide supportive features for the diagnosis of AD. These include medial temporal lobe atrophy as assessed with magnetic resonance imaging (MRI) and reduced glucose metabolism in temporoparietal regions on functional neuroimaging with 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET). Though there is no test to diagnose AD accurately in vivo, in the past few years advances in neuroimaging technology have changed our understanding of AD. This review will focus on recent neuroimaging studies of AD that provide relevant information to clinical practice. We will also examine a new neuroimaging modality – amyloid imaging – and discuss whether such technique can be combined with innovative methods of data processing and analysis to improve AD diagnostic accuracy.

NEUROIMAGING AND AD: UNDERSTANDING THE BRAIN CHANGES UNDERLYING THE SYMPTOMS OF THE DISEASE

Over the past decades, many research investigations have applied neuroimaging techniques to gather information about the anatomical and functional brain changes related to AD. Table 1 summarizes the clinical utility of neuroimaging modalities used in patients with suspected AD. Thanks to major improvements in image acquisition, processing and analysis, these studies have conducted detailed assessments of the human brain in vivo comparing groups of patients with dementia and unaffected elderly volunteers. A very brief summary of clinically relevant neuroimaging findings in samples of patients with AD is presented in Table 2.
MRI has become the most used tool for cerebral imaging in vivo for the assessment of dementia, as it provides detailed information about brain structure, thus allowing the characterization of regional brain atrophy and the identification of causes for the cognitive decline, such as white matter lesions, cerebral infarcts and brain tumors. Conversely, computed tomography (CT) investigations are seldom part of the outpatient diagnostic work-up of cognitive complaints owing to its lower spatial resolution. Notwithstanding, CT can be used in cases of contraindications for MRI (e.g. pacemaker). MRI is used to evaluate the anatomical features of the brain because it provides a clear distinction between gray matter, white matter and cerebrospinal fluid. The most consistent findings in MRI studies of patients with AD are atrophy in the medial temporal lobe (hippocampus, amygdala, entorhinal cortex and parahippocampal gyrus), ventricular enlargement and smaller total brain volume. MRI data have also been used to compare AD with other neurodegenerative conditions, such as dementia with Lewy bodies, frontotemporal lobar degeneration and Parkinson’s disease dementia. Despite some heterogeneity in the results of these studies, they provide consistent evidence for the presence of a characteristic pattern of gray matter atrophy in AD involving mainly the medial temporal lobe, insula and temporoparietal cortices.

The dynamics of atrophy in AD has been assessed by cross-sectional and longitudinal MRI studies. Initially, atrophy is most pronounced in the medial temporal lobe, next, the temporal neocortex is involved; then, the atrophic pattern extends to the parietal and frontal lobes. These descriptions are in accordance with the results of previous neuropathological studies that examined postmortem brains of patients with different stages of AD.

Since the pathological processes that lead to AD are known to begin years before the clinical syndrome, longitudinal studies have provided valuable information about the preclinical stages of AD, such as mild cognitive impairment (MCI), a condition characterized by cognitive decline in the absence of clinical dementia. Recent meta-analyses have shown that gray matter atrophy is a consistent finding in elderly subjects with MCI and also that medial temporal lobe atrophy is a neurostructural biomarker of MCI conversion to AD.

Neurofunctional imaging modalities, such as FDG-PET and regional cerebral blood flow imaging with single photon emission computed tomography (SPECT) provide, respectively, information about regional glucose metabolism and brain perfusion. Several research studies have evaluated samples of patients with AD relative to elderly controls using neurofunctional modalities such as FDG-PET and SPECT. The characteristic pattern found in AD is of hypometabolism/hypoperfusion in the temporoparietal cortex. A recent meta-analysis found that hypometabolism/hypoperfusion of the inferior parietal lobules and precuneus is the most consistent neurofunctional finding in AD in comparison with healthy elderly subjects. Moreover, longitudinal neurofunctional imaging studies have demonstrated hypometabolism/hypoperfusion in the parietal lobe of MCI converters in comparison with those who did not convert to AD. These functional imaging techniques can be useful in cases of diagnostic uncertainty despite thorough evaluation and have been shown to be valuable to distinguish AD from frontotemporal dementia. However, they should not be used as the only imaging modality because they do not allow an adequate evaluation of brain structure.

A distinct regional finding resulting from neurostructural and neurofunctional imaging studies – respectively, medial temporal lobe atrophy and parietal hypoperfusion/hypometabolism – has been reported by authors who assessed patients with AD using both MRI and neurofunctional methods (FDG-PET or SPECT). The neurofunctional decline in the parietal lobe is thought to be due to a...
AMYLOID DEPOSITION AS A BIOLOGICAL MARKER OF AD

In clinical practice, a definite diagnosis of AD is usually not possible owing to the requirement for histopathological examination. Moreover, owing to the heterogeneity of clinical manifestations and low specificity of the cognitive deficits, the diagnosis of AD can be challenging. Neuropathological studies that analyzed postmortem brain tissue found that the clinical diagnosis of AD is frequently inaccurate. Accumulation of the β-amyloid peptide in the brain is a hallmark of AD. β-Amyloid is the product of sequential proteolytic cleavage of the amyloid precursor protein by β- and γ-secretases. Senile plaques found in the brain of patients with AD are primarily composed of insoluble deposits of β-amyloid. Until recently, the investigation of amyloid deposition in living humans was limited because it used to rely on brain biopsy or postmortem examinations. Fortunately, in recent years, the development of radiopharmaceutical agents aimed at identifying amyloid deposition has allowed researchers to study in vivo amyloid deposition in humans. Briefly, amyloid imaging consists of an injection of a radiolabeled ligand targeting amyloid aggregates and use of positron emission tomography (PET) technology to acquire images of the brain in order to display foci of abnormal amyloid accumulation.

Despite the recent development of this PET technology, radiolabeled biomarkers for amyloid imaging have already been used in several research studies. The vast majority of such investigations have employed Pittsburgh compound B labeled with carbon-11. These studies have shown that amyloid deposition: 1) occurs years before clinical dementia, 2) is related to cortical atrophy and cognitive decline, 3) is more intense in patients with MCI who convert to AD than in nonconverters, and 4) plateau when clinical dementia is established (while other neurodegenerative processes such as brain atrophy keep progressing). For the next few years, it is expected that the amount of information provided by amyloid imaging studies will sharply increase. For instance, this imaging modality is now used in a sub-study of the Alzheimer’s Disease Neuroimaging Initiative, a large longitudinal (6-year) multicentric project in the USA involving cohorts of elderly controls and subjects with MCI and AD, aimed at validating neuroimaging and cerebrospinal fluid/blood biomarkers for use in clinical trials of AD treatments. In this project, subjects are investigated with MRI and FDG-PET and then followed, thus allowing measurements of change in these biomarkers at different disease stages.

Amyloid deposition is not pathognomonic of AD and, in fact, it is rather unspecific. For instance, it can be found in dementia with Lewy bodies and in cognitively intact elderly subjects. Therefore, a positive amyloid biomarker scan may have limited diagnostic value; on the other hand, a negative result from such a sensitive imaging test can be informative because amyloid deposition is a defining feature of AD. Thus, the immediate clinical usefulness of sensitive imaging biomarkers for brain amyloid deposition would be to rule out the presence of significant levels of β-amyloid in the brain. In other words, a negative result would mean that AD is an unlikely diagnosis. As an example, researchers showed that amyloid biomarkers could be useful to differentiate between AD and frontotemporal dementia.

Amyloid imaging could also be useful as a non-invasive biomarker allowing a more adequate selection of subjects without overt dementia but with a high likelihood of progressing to AD in clinical trials of disease-modifying agents. Perhaps this imaging tool could even become useful to measure the efficacy of new drugs, as suggested by the results of a recent study that used amyloid imaging to quantify the reduction of β-amyloid load in patients treated with anti-amyloid antibody.

One logistic concern is the short physical half-life of carbon-11, which prevents the applicability of Pittsburgh compound B-PET imaging for wide-spread clinical settings. This has raised interest in the development of amyloid imaging agents that can be labeled with fluorine-18. which has a longer physical half-life. Florbetapir (Amyvid) is one of the most promising of such agents, not only owing to the longer radioactive half-life of 18F, but also because of the rapid kinetics and stable plateau of uptake of florbetapir in the brain following intravenous administration. These properties increase its potential availability and allow short post-dose waiting periods and flexibility in timing of image acquisition. Recent investigations have shown that 18F-florbetapir PET imaging performed during life in a sample of elderly patients from hospice, long-term care and community healthcare facilities accurately predicted the presence of β-amyloid in the brain as verified at autopsy of the same subjects.

In spite of the above advances, there are still important difficulties to be overcome before amyloid imaging with PET can be seen as a useful resource in clinical practice for the diagnostic work-up for dementia. Indeed, florbetapir has been rejected by a recent preliminary document of the United States Food and Drugs Administration (FDA), which highlighted the problem of inconsistencies in reader fluorodeoxyglucose image interpretation. This represents a setback that will force the neuroimaging community to improve the reliability of amyloid imaging interpretations.
The FDA document is based on the first phase 3 study focused on the relationship between florbetapir imaging and postmortem β-amyloid pathology. Results based on the binary classification (positive × negative) of the mean rating given by three trained nuclear medicine physicians resulted in an impressive 93% sensitivity. However, the detailed FDA report pointed out that there was too much variation in the individual reader performance; for instance, one reader demonstrated an unacceptably low sensitivity of 55%. Furthermore, “in over one-third of the subjects, at least one reader would have had a different binary interpretation of amyloid status from the other two readers.” Based on the reader inconsistency, this document concluded that “the data did not produce evidence of clinical usefulness.”

So, what would be the next step?

One of the most relevant messages from the FDA document is the following: “The available data suggest that the variability in 18-f-florbetapir PET test results more likely stems from variability in image interpretation rather than image acquisition.” In other words, if this imaging modality is one day to be widely used in clinical practice, then efforts should be focused on how to improve the reliability of imaging interpretation.

One way would be to improve the physicians’ training, with lengthier and/or more sophisticated learning protocols. In real world clinical settings, this would not only be expensive but also limit the availability of this method to a few physicians and patients. An alternative would be to develop automated methods of image analysis that could help physicians make more accurate interpretations. Numerous results from recent years have provided evidence that automated techniques have a great potential to advance the diagnostic accuracy of neuroimaging methods for dementia and other neurological and psychiatric disorders.

CONCLUSION

Neuroimaging techniques have led to an increasingly large body of knowledge about AD by allowing the study of the brain in living subjects. These imaging methods are not only highly important research tools, but they are also commonly used in the evaluation of patients presenting with dementia in order to improve the accuracy of clinical diagnosis and identify brain lesions contributing to the cognitive decline. A recent major advance is the development of amyloid imaging techniques that allow in vivo identification of amyloid deposition in the brain. This imaging modality has already yielded important results and will likely determine an increase in the diagnostic accuracy of AD in the near future.

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