Brain Imaging in Differential Diagnosis of Dementia

Imaging biomarkers hold the promise of earlier diagnosis that may lead to more effective treatment.

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Introduction

β amyloid and phosphorylated tau proteins are pathologic hallmarks of Alzheimer’s disease (AD) that accumulate and spread predictably through distributed neural networks, causing progressive metabolic abnormalities, neuronal injury, and cellular death. Neuroimaging facilitates a detailed assessment of these pathologic changes in patients undergoing workup for cognitive decline. Previously, a definitive diagnosis of AD was possible only by postmortem observation and neuroanatomic staging of these protein aggregates. Recent advances in molecular imaging, however, allow for the visualization of amyloid and tau deposits in living human brain and have brought us closer to an in vivo definitive diagnosis of AD.

Structural Imaging

The American Academy of Neurology (AAN) guidelines for diagnostic workup of people with cognitive complaints recommend structural brain imaging with noncontrast CT or MRI in any person with a positive clinical history and objective cognitive changes. In this context, the primary role for brain imaging is to rule out nondegenerative structural lesions, 5% of which may not be evident from clinical history or physical examination and are potentially treatable. The AAN also recommends excluding vascular dementia (VaD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD) clinically. Structural imaging can improve diagnostic certainty and changes clinical diagnosis in 19% to 28% as well as management of 15% of clinical cases.

The imaging modalities of choice when assessing structural atrophy are CT and MRI. Disease-specific patterns of atrophy have been thoroughly described and validated using these modalities. Although atrophy is observable on CT, the inherently lower spatial resolution and inferior gray/white matter contrast result in the loss of potentially useful subtle observations regarding neurodegenerative changes. Therefore, clinicians often rely on MRI to assess the pattern and severity of structural changes, to rule out non-neurodegenerative causes of cognitive decline, and to evaluate the severity and extent of white matter changes as discussed in greater detail below.

Vascular damage is an important consideration when
assessing individuals with cognitive impairment. Ischemic change is common in normal aging and is accelerated by common comorbidities (eg, hypertension, diabetes, and hypercholesterolemia). Vascular contributions to cognitive impairment are often inferred when significant white matter hyperintensities (WMH), cortical strokes, or strategically located lacunes are detected on T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequences. Lacunar strokes of the basal ganglia and WMH in the centrum semiovale and corona radiata are indicators of chronic small-vessel ischemic damage (Figure 2). In contrast, periventricular caps are often nonischemic in origin and reflect subependymal gliosis. There are several WMH severity scales (eg, the Fazekas scale) that can be used in clinical settings. Such scoring algorithms all agree that widespread confluent WMH and subcortical lacunar infarcts are, at least in part, likely to be contributing factors to cognitive decline.

Diffusion tensor imaging (DTI) is a new MRI sequence sensitive to the diffusion of water through tissue that assesses white matter integrity because the architecture of axons constrains the flow of water. Mean diffusivity and fractional anisotropy measures are often used to characterize neurodegenerative changes on DTI. The former measures the magnitude of diffusion and the latter measures whether water is flowing preferentially in a single direction as expected in healthy axons. Decreased mean diffusivity and reduced fractional anisotropy have been consistently reported in both MCI and dementia AD populations. Several studies have also identified DTI changes in asymptomatic individuals at risk for developing AD indicating that these changes occur.

Figure 1. Medial temporal atrophy (MTA) scale ratings. MTA 0—no to minimal gapping of the choroid fissure; MTA 1—subtle widening of the choroid fissure; MTA 2—further widening of the choroid fissure which merges with the temporal horn of the lateral ventricle, mild decrease of the height of the hippocampal formation; MTA 3—moderate decrease of the height of the hippocampal formation, prominent enlargement of the temporal horn of the lateral ventricle; MTA 4—severe decrease of the height of the hippocampal formation, prominent enlargement of the temporal horn of the lateral ventricle.
Figure 2. Structural atrophy patterns across Alzheimer’s disease (AD) (A), dementia with Lewy bodies (DLB) (B), frontotemporal dementia (FTD) (C) and vascular dementia (VaD) (D). Coronal T1-weighted MRI demonstrates generalized cortical atrophy but differing degrees of hippocampal atrophy in AD (A) and DLB (B). Axial T1-weighted MRI demonstrates bvFTD atrophy with a focal predilection for the medial and lateral prefrontal cortices (C). Axial T2-weighted MRI demonstrates confluent periventricular cap and halo white matter hypointensities (WMHs) involving the corona radiata and extending into the lateral prefrontal neocortex, mild scattered WMHs and WMHs of the subependymal ventricular lining and septum pellucidum in VaD (D).
early on in the disease course. In addition to assessing white matter integrity, DTI can be used to model gross structural connectivity between cortical regions using tractography algorithms. This has gained traction in the field of AD as evidence suggests that amyloid and tau pathology may propagate via brain connections. Although DTI shows potential as a measure of white matter integrity, its sensitivity to movement and other technical constraints, limit, at least for the time being, its clinical application.

**Functional Imaging**

Brain hypometabolism is readily observed in neurodegenerative disorders and can aid in differential diagnosis. Neuron function is dependent on oxygen and glucose from the blood, delivery of which is facilitated by regional vasodilation. 

The characteristic hypometabolic cortical signature of AD consists of early changes in the posterior cingulate (PCC); precuneus; temporal, parietal, and, in later stages, frontal cortices. This pattern manifests early, even presymptomatically, and is clinically helpful in distinguishing AD from FTD.

The Center for Medicare & Medicaid Services deems FDG-PET “reasonable and necessary” only for those meeting criteria for both AD and FTD, in whom full diagnostic workup as per AAN guidelines has not definitively established an etiology. Functional MRI (fMRI) can also measure brain activity by using sequences that are sensitive to temporal changes in oxygenated/deoxygenated hemoglobin due to brain activity. In this way, fMRI is related to oxygen and glucose delivery, but the changes in hemoglobin are driven by glucose metabolism required for brain activity. Temporal dependencies between regions can be used to infer functional connectivity (ie, which regions are actively communicating). Compared with FDG-PET, fMRI offers improved spatial resolution, allowing more accurate mapping of connectivity. Another advantage of fMRI is that it can be acquired during performance of a task or at rest. The former identifies connectivity patterns driven by specific active states, whereas the latter identifies connectivity patterns present at rest known as the default mode network (DMN). The DMN is defined by functional hubs, the PCC and precuneus, which connect to a dorsal medial subsystem and a medial temporal subsystem. Amyloid deposition is thought to begin in the functional hubs of the DMN. The DMN is known to be affected in AD. In contrast, the DMN is spared in FTD while salience or attention networks are affected. Currently, fMRI technology is limited to research applications, but avenues to develop relevant clinically applicable algorithms are actively being explored.

**Molecular Imaging**

The criterion standard for a definitive diagnosis of AD is postmortem neuropathologic brain examination. Even in the hands of experienced dementia experts, clinical diagnosis of AD reaches only the unsettling sensitivity of 70.9% to 87.3% and specificity of 44.3% to 70.8%. Most pertinent to improved clinical diagnostic accuracy of AD has been the development of radio-labeled PET imaging tracers with specific affinity for AD-related β amyloid and phosphorylated tau aggregates (Figure 3), which allow in vivo demonstration of the underlying neuropathology (Table) once only possible postmortem.

**Amyloid Positron Emission Tomography**

Amyloid, and more recently, tau imaging have revolutionized our ability to visualize AD pathology even in presymptomatic stages. Amyloid PET imaging tracers are valid and reliable for detecting in vivo AD pathology at various stages of disease. These imaging tracers bind specific conformational motifs of the amyloid protein and result in a tracer uptake that is tightly correlated with postmortem amyloid deposition.

Compared with tau, amyloid pathology begins in a more diffusely distributed regional pattern spreading from the basal portions of the frontal, temporal, and occipital lobes to the dorsal neocortical association areas with only late stage involvement of the primary sensory and motor cortices.

Most notable areas of tracer uptake are frontal, parietal, and lateral temporal cortices (Figure 3), with uptake 1.5 to 2 times greater in people with AD vs control groups or those with other dementias.

Amyloid PET images are assessed for cortical tracer uptake in characteristic areas of AD amyloid distribution. Positive scans show loss of gray/white matter distinction as tracer uptake extends into neocortex. Negative scans retain gray/white matter distinction, showing only white matter off-target binding. Amyloid PET imaging patterns can reliably predict cognitive decline in both healthy people and those with MCI.

18F-florbetapir, 18F-florbetaben, and 18F-flutemetamol are approved by the Food and Drug Administration (FDA) for clinical use. Insurance carriers, however, have not embraced the technology, owing to expense and risk of clinical overuse in the absence of disease-modifying therapies and established cost benefit. A meta-analysis reported 95% sensitivity and 57% specificity of a positive amyloid PET scan for predicting conversion from MCI to AD.
Figure 3. Axial amyloid-PET demonstrating amyloid negative (A) and amyloid positive scans (B). In amyloid negative images (A) the radiotracer signal shows low intensity and is limited to nonspecific white matter binding. The gray/white matter junction is preserved. In amyloid positive images (B) the radiotracer signal is of high intensity and extends diffusely into cortical gray matter regions obscuring the gray/white matter junction. Coronal tau-PET demonstrating tau negative (C) and tau positive (D) scans. In tau negative scans there is minimal, nonspecific low intensity radiotracer signal in the medial temporal, basal forebrain, and basal ganglia regions. In tau-positive scans (D) radiotracer signal is of higher intensity and involves the inferior and lateral temporal cortices following the known trajectory of progression of neurofibrillary tangles.
The uncertain relationship among cost, risk, and benefit has led to the development of appropriate-use criteria for amyloid imaging, ascribing the need for amyloid PET evaluation to persons with unexplained MCI, atypical AD presentations, and early onset dementia. Experts have also identified inappropriate indications for amyloid imaging that include stand alone evaluation for cognitive concerns prior to thorough clinical, cognitive, laboratory, and structural neuroimaging workup; in the absence of objective cognitive impairment; in high likelihood of AD (ie, in the absence of a clinical equipoise; and for staging of dementia severity.

The imaging dementia-evidence for amyloid scanning (IDEAS) study—an ongoing Center for Medicare and Medicaid Services study—is presently validating the appropriate-use criteria and evaluating the impact of PET-determined amyloid status on disease management and long-term outcomes for Medicare beneficiaries with MCI or atypical presentations. Interim analysis revealed that integrating amyloid PET in the clinical workup resulted in disease management changes in 60.2% of people with MCI and 63.5% of those with dementia. Long-term outcomes are still being determined.

###Tau Positron Emission Tomography

Tau is the second protein that is deposited in the brains of those with AD. Tau PET imaging tracers are currently under development and already show promise. Similar to amyloid PET, tau PET tracers target particular conformational motifs of phosphorylated tau. The specificity of tau tracers has been validated postmortem, and the observed tau PET signal closely matches the anatomic distribution of neurofibrillary tangles currently used for a neuropathological diagnosis of AD. The earliest stages of tau pathology that can be visualized with tau PET imaging are the neurofibrillary tangle deposits in entorhinal cortex and the hippocampus. Next, tau deposits become detectable in the inferior and lateral temporal (Figure 3), followed by the parietal and occipital, and finally the frontal cortices following the well-established Braak and Braak pathologic staging of tau deposition through the brain. Tau tracers are not without diagnostic limitations and are undergoing further development to better define their clinical role. However, given that tau tracer binding dynamically changes throughout the entire clinical course of AD, this imaging modality will likely play a significant role in staging disease severity in vivo.

###TABLE. THE AMYLOID-TAU-NEURODEGENERATION BIOMARKER RESEARCH FRAMEWORK FOR ALZHEIMER’S

<table>
<thead>
<tr>
<th>Cognitive Status</th>
<th>Amyloid Status</th>
<th>Tau Status</th>
<th>Neurodegeneration Status</th>
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</thead>
<tbody>
<tr>
<td><strong>A⁻ T⁻ N⁻</strong></td>
<td>Normal cognition with negative AD biomarkers</td>
<td>MCI with negative AD biomarkers</td>
<td>Dementia with negative AD biomarkers</td>
</tr>
<tr>
<td><strong>A⁻ T⁺ N⁻</strong></td>
<td>Preclinical nonAD pathology: negative amyloid, must have 1 or more biomarkers of pathological tau or neurodegeneration</td>
<td>MCI with nonAD pathology: negative amyloid, must have 1 or more biomarkers of pathological tau or neurodegeneration</td>
<td>Dementia with nonAD pathology: negative amyloid, must have 1 or more biomarkers of pathological tau or neurodegeneration</td>
</tr>
<tr>
<td><strong>A⁻ T⁺ N⁺</strong></td>
<td>Preclinical amyloid-positive state: normal cognition with positive amyloid biomarkers only</td>
<td>MCI with amyloid-positive state: impaired cognition with positive amyloid biomarkers only</td>
<td>Dementia with amyloid-positive state: impaired cognition with positive amyloid biomarkers only</td>
</tr>
<tr>
<td><strong>A⁺ T⁻ N⁻</strong></td>
<td>Preclinical amyloid-positive state with non-AD neurodegenerative change: normal cognition, positive amyloid and neurodegenerative biomarkers only</td>
<td>MCI with amyloid-positive state and nonAD neurodegenerative change: normal cognition, positive amyloid and neurodegenerative biomarkers only</td>
<td>Dementia with amyloid-positive state and nonAD neurodegenerative change: normal cognition, positive amyloid and neurodegenerative biomarkers only</td>
</tr>
<tr>
<td><strong>A⁺ T⁺ N⁻</strong></td>
<td>Preclinical AD: normal cognition with positive amyloid and tau and variable neurodegenerative biomarkers</td>
<td>MCI due to AD: impaired cognition with positive amyloid and tau and variable neurodegenerative biomarkers</td>
<td>Dementia due to AD: impaired cognition with positive amyloid and pathologic tau and variable neurodegenerative biomarkers</td>
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Amyloid biomarker status (CSF amyloid beta levels or amyloid PET) is represented by A; pathological or hyperphosphorylated tau (tau PET or CSF phosphorylated tau levels) by T; neurodegenerative markers (total tau, brain atrophy, or hypometabolism) is indicated by N. This framework is agnostic to clinical diagnosis and based solely upon neurodegenerative biomarker results and is able to accommodate a wide variety of neurodegenerative biomarkers and etiologies leading to cognitive impairment. Abbreviations: AD, Alzheimer’s disease; A, amyloid; MCI, mild cognitive impairment; N, neurodegeneration; T, tau.
Future Directions

Given that AD pathology can be readily detected up to 20 years before the diagnosis of dementia and follows a predictable staged distribution, research is now focused on early presymptomatic detection and improvement of diagnostic accuracy through the use of biomarkers (Table). A proposed amyloid-tau-neurodegeneration (ATN) research framework focused on detecting 3 biomarker changes in the brain forecasts the clinical relevance of multimodal imaging. The ATN classification system is agnostic of clinical syndromes and captures the full spectrum of neurodegenerative illnesses through an AD biomarker lens. Following further development and refinement, the ATN, through objective in vivo biomarker categorization, is expected to dramatically improve clinical diagnostic accuracy and enhance quality of care.

Conclusion

Neuroimaging offers unique information about the underlying etiology of cognitive impairment and facilitates guidance for patients and families through a fearful and uncertain experience. All neurodegenerative diseases show significant clinical heterogeneity, and before the most recent molecular imaging advances, none could be diagnosed definitively before death. The modern imaging brain technology is able to detect multitude epiphenomena reflecting the underlying neuropathology, some of which is quite proximal to the source of disease. The most confident clinical diagnosis is currently based on an integration of clinical history, physician observations, physical examination, medical workup, neuropsychologic testing and informed interpretation of diagnostic neuroimaging. As the ATN biomarkers are further refined, clinical diagnoses will be made earlier and more definitively in living patients, rely less on symptom classification, and clinical diagnoses will be made earlier and more definitively. The modern imaging brain technology is able to detect multitude epiphenomena reflecting the underlying neuropathology, some of which is quite proximal to the source of disease. The most confident clinical diagnosis is currently based on an integration of clinical history, physician observations, physical examination, medical workup, neuropsychologic testing and informed interpretation of diagnostic neuroimaging. As the ATN biomarkers are further refined, clinical diagnoses will be made earlier and more definitively in living patients, rely less on symptom classification, and provide opportunities for earlier treatment intervention that may alter the trajectory of neurodegenerative illness.