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Clinical Amyloid Imaging

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Amyloid plaques, along with neurofibrillary tangles, are a neuropathologic hallmark of Alzheimer disease (AD). Recently, amyloid PET radiotracers have been developed and approved for clinical use in the evaluation of suspected neurodegenerative disorders. In both research and clinical settings, amyloid PET imaging has provided important diagnostic and prognostic information for the management of patients with possible AD, mild cognitive impairment (MCI), and other challenging diagnostic presentations. Although the overall impact of amyloid imaging is still being evaluated, the Society of Nuclear Medicine and Molecular Imaging and Alzheimer's Association Amyloid Imaging Task Force have created appropriate use criteria for the standard clinical use of amyloid PET imaging. By the appropriate use criteria, amyloid imaging is appropriate for patients with (1) persistent or unexplained MCI, (2) AD as a possible but still uncertain diagnosis after expert evaluation and (3) atypically early-age-onset progressive dementia. To better understand the clinical and economic effect of amyloid imaging, the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) study is an ongoing large multicenter study in the United States, which is evaluating how amyloid imaging affects diagnosis, management, and outcomes for cognitively impaired patients who cannot be completely evaluated by clinical assessment alone. Multiple other large-scale studies are evaluating the prognostic role of amyloid PET imaging for predicting MCI progression to AD in general and high-risk populations. At the same time, amyloid imaging is an important tool for evaluating potential disease-modifying therapies for AD. Overall, the increased use of amyloid PET imaging has led to a better understanding of the strengths and limitations of this imaging modality and how it may best be used with other clinical, molecular, and imaging assessment techniques for the diagnosis and management of neurodegenerative disorders.
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Introduction

Alzheimer disease (AD) is the most common cause of dementia, and is the fifth leading cause of death in individuals older than 65 years in the United States.[1] A recent meta-analysis estimated that 35.6 million people had dementia in 2010 worldwide, with doubling expected every 20 years to 115.4 million in 2050.[2] Clinically, AD is a progressive neurodegenerative disorder characterized by memory loss and cognitive decline, for which there is currently no cure or disease-modifying treatment.[3,4] AD's neuropathologic hallmarks are extracellular amyloid plaques and intracellular neurofibrillary tangles (NFT). These findings, which are superimposed upon characteristic regions of gross brain cortical atrophy, are part of the gold standard histopathologic analysis for diagnosis of AD. Recently, in vivo measurement of AD molecular pathology has become possible with PET molecular imaging techniques, with largest body of imaging targeted toward the molecular constituents of amyloid plaques.[5] Tau imaging is a more recent development, still being evaluated for clinical use, and is discussed elsewhere.[6,7]

Amyloid-β Peptide and Amyloid Plaques

The amyloid-β (Aβ) peptide is formed by the cleavage of a transmembrane protein, amyloid precursor protein (APP), by β- and γ-secretases, yielding Aβ species containing predominantly 39-42 amino acid residues.[8,9] The longer Aβ species, particularly Aβ40 and Aβ42, are released from the cell membrane and aggregate into soluble oligomers in the extracellular space.[10] These oligomers, which are thought to be neurotoxic by an incompletely understood mechanism,[11,12] in turn aggregate into larger insoluble β-sheet fibrils, and ultimately into the dense fibrillary amyloid plaques seen in AD.[13]

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However, not all amyloid plaques are pathologic or closely associated with AD.[14,15] At the broadest level, extracellular amyloid plaques can be diffuse or dense. Diffuse plaques appear less dense or "fleecey on histopathology" and are thought to reflect an earlier stage of amyloid deposition.[16] Dense plaques have denser cores, and are the plaques most associated with AD. Neuritic plaques are a subset of dense plaques that are associated with neuronal inflammation and injury, and are also associated with AD.

Although Aβ plaques are a characteristic pathologic finding in AD, it is important to note that measurable amyloid deposition is also common in asymptomatic patients older than 75 years. In fact, current estimates of amyloid positivity by age are less than 5% for those 50-60-year old, 10% for those 60-70, 25% for those 70-80, and more than 50% in those 80-90.[17,18] Amyloid plaques are also seen with other clinical disorders, including cerebral amyloid angiopathy (predominantly diffuse plaques), dementia with Lewy bodies (DLB), and Parkinson disease.[19-24]

The molecular pathophysiology of how Aβ and NFT pathology are related to neurodegeneration and AD is not completely understood. The "amyloid cascade" hypothesis has for a long time implicated the abnormal accumulation of Aβ plaques (or, more recently, neurotoxic soluble Aβ oligomeric species) as the initiating event in a pathological cascade that ultimately leads to neurodegeneration and the clinical syndrome of AD.[25] The early role for amyloid in the pathogenesis of AD is not strongly disputed, but the cascade hypothesis has been refined over time. Interactions among AD molecular drivers with genetic factors, comorbid disease, and environmental factors, some of which may be protective, are now better identified. For example, although high levels of Aβ deposition in cognitively normal individuals are associated with subtle progressive deficits and a higher risk of cognitive impairment, these relationships appear to be modified by lifestyle activities and cognitive reserve as well as genetic markers.[26-28] From genetics, more than 20 genetic loci have been associated with increased risk for AD, from many mutations that confer a mild increase in risk to less common causative, high-penetrance mutations that result in full disease expression.[29,30] Notably, the three mutations that cause autosomal dominant AD (ADAD) either directly involve APP or its proteolytic cleavage. However, a host of other mutations, including variants of the apolipoprotein E (APOE) molecule, also genetically confer increased risk for AD.[31] Refinements to the amyloid cascade hypothesis are further discussed below.

AD Biomarkers

The AD biomarkers providing clinically useful information can be organized in two groups, those that reflect AD molecular pathophysiology and those that reflect neurodegeneration, including synaptic dysfunction as well as atrophy. Examples of neurodegeneration biomarkers include hippocampal and adjacent cortical atrophy on structural MRI, hypometabolism on FDG-PET scans, and increased cerebrospinal fluid (CSF) total tau concentration. Tau is also seen in other neurodegenerative diseases (NDD) such as frontotemporal dementia (FTD), although the composition of isoforms can be different, and CSF total tau is not specific for AD.[7] Examples of AD-specific pathophysiology biomarkers are CSF Aβ42, CSF phosphorylated tau (p-tau) and, more recently, amyloid PET imaging.[6]

Amyloid PET Tracers

^{11}C-PIB

The ^{11}C-labeled Pittsburgh compound B (PIB) has been the most extensively used radiotracer for research Aβ PET imaging. ^{11}C-PIB was the first amyloid radiotracer with a relatively high specificity for fibrillar Aβ, dense amyloid plaques, and other extracelluar Aβ forms, relative to intracellular Aβ (cf. ^{18}F-FDDNP, the first amyloid radiotracer).[32-34] ^{11}C-PIB also provided the requisite specificity for Aβ relative to other proteins in pathologic aggregates such as tau (NFT) or α-synuclein (Lewy bodies), as well as a low off-target white matter (WM)-binding profile. Demonstrating these features in the first study in humans published in 2004, ^{11}C-PIB was a major breakthrough that provided the first noninvasive in vivo measure of cortical Aβ burden.[35] Nearly all of the research demonstrating the utility of Aβ imaging for more accurate and earlier diagnosis, described in more detail for all amyloid tracers below, was initially conducted with ^{11}C-PIB. However, ^{11}C-PIB is not used clinically because the ^{11}C radionuclide requires specific radiopharmacy expertise and has a short 20-minute half-life, limiting its use to specialized centers.

Clinically Approved Amyloid Tracers and Imaging Protocols

More recently, Aβ imaging agents were developed using fluorine-18, a relatively longer-lived radionuclide with a half-life of 110 minutes, to facilitate regional distribution from a central nuclear pharmacy and in turn make amyloid imaging more clinically viable and widespread.[36] At this time of writing, the following three ^{18}F-labeled Aβ PET imaging agents have been approved by the US Food and Drug Administration (FDA) and the European Medicines Association (EMA): florbetapir, flutemetamol, and florbetaben. The three FDA-approved amyloid imaging agents demonstrate different kinetic behaviors and varying levels of specific Aβ and off-target WM binding, which contribute to different imaging protocols and interpretation methodologies.[37,38] The criteria for a positive scan are also different for the three agents (Table 1).

Even though ^{18}F-labeled amyloid radiotracers generally demonstrate more nonspecific WM binding than ^{11}C-PIB, each of the FDA-approved agents provides nearly identical qualitative evaluation of the presence of cortical Aβ deposition when directly compared with ^{11}C-PIB.[39,38,40] In contrast, quantitative assessments of regional Aβ load with these three tracers have been more variable. While this has raised some concern for their use as quantitative outcome measures, efforts have been made to standardize quantitative Aβ imaging measurements. In particular, the Centiloid project has standardized quantitative Aβ imaging outcomes to a common scaled