Molecular Imaging of Alzheimer Disease Pathology

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ABSTRACT

Development of molecular imaging agents for fibrillar β-amyloid positron-emission tomography during the past decade has brought molecular imaging of Alzheimer disease pathology into the spotlight. Large cohort studies with longitudinal follow-up in cognitively normal individuals and patients with mild cognitive impairment and Alzheimer disease indicate that β-amyloid deposition can be detected many years before the onset of symptoms with molecular imaging, and its progression can be followed longitudinally. The utility of β-amyloid PET in the differential diagnosis of Alzheimer disease is greatest when there is no pathologic overlap between 2 dementia syndromes, such as in frontotemporal lobar degeneration and Alzheimer disease. However β-amyloid PET alone may be insufficient in distinguishing dementia syndromes that commonly have overlapping β-amyloid pathology, such as dementia with Lewy bodies and vascular dementia, which represent the 2 most common dementia pathologies after Alzheimer disease. The role of molecular imaging in Alzheimer disease clinical trials is growing rapidly, especially in an era when preventive interventions are designed to eradicate the pathology targeted by molecular imaging agents.

ABBREVIATIONS: Aβ = β-amyloid; AD = Alzheimer disease; DLB = dementia with Lewy bodies; MCI = mild cognitive impairment; NIA-AA = National Institutes of Aging and the Alzheimer’s Association; PiB = Pittsburgh compound-B

The pathologic hallmarks of Alzheimer disease (AD) are neurofibrillary tangles of hyperphosphorylated τ and extracellular plaques of β-amyloid (Aβ) proteins, which involve the brain many years before the emergence of symptoms. Molecular imaging with agents that bind to Aβ and τ proteins may detect the presence and progression of Alzheimer disease pathology during the preclinical stage when the disease course may be altered by early intervention. Imaging of the Aβ pathology with PET has been used in clinical research settings for almost a decade and was recently approved by the US Food and Drug Administration for clinical use. Imaging of τ pathology with PET has been investigated less; however, its impact on understanding the pathophysiology of AD and on treatment planning would be significant. Imaging of both Aβ and τ will likely contribute independently to early diagnosis, differential diagnosis, and the tracking of disease progression during the preclinical, prodromal, and clinical stages of AD.

Detecting Preclinical and Prodromal AD Pathology with Molecular Imaging

During the past decade, discovery of Aβ imaging with Pittsburgh compound-B (PiB) PET provided a window into the pathophysiology of AD in living individuals. Although postmortem studies have long suggested a high prevalence of Aβ pathology with moderate-to-frequent plaques reaching 47% in cognitively normal older adults, imaging of Aβ pathology with PET provided an in vivo confirmation of this observation. The prevalence of PiB positivity ranges from 20% to 34% in independent cohorts of cognitively normal individuals. The variability is likely associated with the ascertainment of participants and the cutoff used for PiB positivity as well as the median age of the cohorts. For example, in a population-based study of cognitively normal older adults that included individuals with neurologic, psychiatric, or systemic illnesses, a representative sample of the population, the prevalence of PiB positivity was 31% with a global cortical PiB uptake cutoff of >1.5, but the prevalence increased to 44% with a cutoff of >1.4, which is on par with the postmortem studies in community-based cohorts of cognitively normal elderly.

Although Aβ pathology is common in cognitively normal individuals, the harmful effects of Aβ pathology on cognitive func-
normal carriers of the APOE e4 have higher Aβ loads on PET compared with noncarriers,\textsuperscript{3,5,20} when matched on Aβ load, APOE e4 carriers tend to perform worse on cognitive tests compared with noncarriers (Fig 1).\textsuperscript{7} Thus, APOE e4 not only increases the risk for Aβ deposition but also influences AD pathology by modulating the harmful effects of Aβ on cognitive function through other potentially synergistic mechanisms, such as enhancing hyperphosphorylation of the τ protein\textsuperscript{21} and reducing choline acetyltransferase activity.\textsuperscript{22}

In 2011, the clinical diagnostic criteria for AD were revised under the auspices of the National Institutes of Aging and the Alzheimer’s Association (NIA-AA).\textsuperscript{23} These new guidelines included imaging markers in the diagnostic criteria for AD and proposed research criteria that included imaging evidence of AD for the diagnosis of preclinical AD.\textsuperscript{24} The new criteria require evidence of Aβ pathology of AD for the diagnosis of preclinical AD either through molecular imaging or CSF biomarkers. Any imaging or biomarker evidence of AD-related neurodegeneration measured with an AD pattern of atrophy on MR imaging or an AD pattern of hypometabolism on [18F] fluorodeoxyglucose PET and the presence of subtle cognitive difficulties in addition to the Aβ pathology increase the stage of preclinical AD from 1 to 3.

The preclinical AD research criteria was operationalized in a population-based sample of cognitively normal older adults from the Mayo Clinic Study of Aging.\textsuperscript{25} At fixed cut-points corresponding to 90% sensitivity for diagnosing AD and the 10th percentile of cognitive scores of cognitively normal individuals, 43% of the sample was classified as stage 0; 16%, stage 1 (Aβ PET-positive); 12%, stage 2 (Aβ PET-positive and neurodegeneration-positive on MR imaging or FDG-PET); and 3%, stage 3 (Aβ PET-positive and neurodegeneration-positive on MR imaging or FDG-PET and subtle cognitive difficulties).\textsuperscript{26} Furthermore, the proportion of subjects who progressed to mild cognitive impairment (MCI) or dementia increased with advancing stage (Fig 2).\textsuperscript{27} However, 23% of the population did not fit the preclinical AD stages because they had normal Aβ PET imaging findings but abnormal neurodegeneration biomarker study findings, which we classified as suspected non-AD pathophysiology. The suspected non-AD pathophysiology group is of particular interest because the individuals progress to MCI in the short term (10% in 15 months), albeit at a rate similar to that of subjects with stage 1 preclinical AD (11% in 15 months). The pathologic basis of positive neurodegeneration biomarker findings in the absence of Aβ pathology in this cognitively normal group is under investigation.\textsuperscript{28}

According to the new guidelines by the NIA-AA, the prodromal stage of AD is characterized by mild cognitive impairment, and research criteria further classify patients with MCI as having MCI due to AD on the basis of biomarker evidence of AD pathophysiology. A recent study from the Mayo Clinic Study of Aging
and Alzheimer Disease Neuroimaging Initiative demonstrated that the NIA-AA criteria apply to most subjects with MCI in both the community and clinical trial settings; however, a sizeable proportion of subjects had conflicting biomarkers, which need to be investigated.29 In this population, neurodegeneration on MRI increased the rate of progression to dementia in patients with MCI due to AD and appeared to be a key factor in predicting progression relative to Aβ deposition alone.

Molecular imaging studies with Aβ-binding ligands in preclinical AD indicate that approximately one-third of the population of cognitively normal individuals and 71% of patients with MCI in the community have high cortical Aβ loads. In cognitively normal individuals, high levels of Aβ deposition are associated with subtle cognitive deficits, cognitive decline, and a higher risk of cognitive impairments in the future. However, these relationships appear to be modified by the genetic markers,5,30 lifestyle activities,31 or cognitive reserve.32

Molecular Imaging for the Differential Diagnosis of AD

The high sensitivity and specificity of PiB binding to fibrillar Aβ have been demonstrated in vitro,33 in mouse models,34 and in human tissue.35 The newer [18F] agents for Aβ PET have undergone a similar validation process46-47 and appear to show properties similar to those of PiB.41-45 The specificity of PiB to fibrillar Aβ is preserved even in patients with protein deposits associated with other neurodegenerative dementias such as α-synuclein in dementia with Lewy bodies (DLB) (Fig 3).46-49 However, there may be disagreements between the postmortem report and the PET findings because of the heterogeneity of Aβ deposits. For example, PiB labels both neuritic and diffuse plaques, though labeling of diffuse/amorphous plaques is less prominent than that of compact/cored plaques.35,36 Patients with dementia with Lewy bodies or Parkinson disease dementia, who typically have high loads of diffuse plaques, may have positive Aβ PET scan findings but would not be classified as having AD because of the absence of fibrillar Aβ deposits need further investigation.

One of the key applications of Aβ PET imaging in clinical practice is in the differential diagnosis of AD. The accuracy of Aβ PET in distinguishing AD and frontotemporal lobar degeneration is quite high,55 with an overall classification accuracy of 97% in cases with histopathologic confirmation.56 On the other hand, the 2 most common dementia pathologies after AD are vascular disease and Lewy body pathologies, which commonly are present with additional AD pathology. In these cases, the presence of an intermediate-to-high Aβ load may be insufficient to determine the predominant pathology contributing to the dementia syndrome. In keeping with the postmortem data, 25%–35% of patients with vascular dementia57,58 and 60%–80% of patients with DLB54,59-62 have high Aβ loads on PET. Thus high levels of amyloid load may be insufficient in distinguishing these dementia syndromes from AD, and a multitechnique imaging approach may be useful. We have shown that FDG-PET, Aβ PET, and structural MR imaging are complementary in distinguishing patients with AD and DLB63 and may be useful in predicting the presence of AD pathology in patients with DLB (Fig 4).64 Molecular imaging of the impaired nigrostriatal dopaminergic transmission in DLB with 2β-carboxymethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane with SPECT64 or loss of monoaminergic terminal integrity with vesicular monoamine transporter type 2 radioligands may further detect the Lewy body–related pathologic features in cases with mixed dementia and may be complementary to Aβ PET.55

The added diagnostic value of Aβ PET imaging in the differential diagnosis of dementia across different clinical settings has become a topic of significant interest with the availability of [18F] agents for Aβ imaging.66-70 Although the added value of Aβ PET to clinical decision-making has not been established,66-69 how Aβ load is measured on PET scans (ie, visual evaluation versus various quantitative techniques) appears to make a difference in the value of this diagnostic technique in the clinical setting.69
cates that Aβ presence of Alzheimer disease and dementia with higher rates of Aβ deposition appear to dissipate at very high levels (roughly 2.0 standardized uptake value ratio). After this threshold, the relationship becomes an inverted U, gradually declining and reaching zero at the highest baseline Aβ load levels (2.7 standardized uptake value ratio). The time estimated to start with positive findings on a PiB scan (1.5 standardized uptake value ratio) to the point of plateau is approximately 15 years, corresponding to a large therapeutic window for clinical trials.73

**Molecular Imaging in Clinical Trials for AD**

In autosomal dominant AD, the age of symptom onset can be predicted. It is estimated that increased Aβ deposition precedes clinical symptoms for approximately 15 years, providing a wide window for preventive therapies.82,83 The role of molecular imaging in clinical trials targeting the pathology captured with the molecular imaging agent can be 2-fold: 1) to determine who has the target pathology and enrichment of trials with this information; and 2) to determine whether a treatment is modifying the target pathology. Both of these applications of Aβ imaging are being used in current clinical trials of amyloid-modifying therapies for both treatment and prevention of AD.84,85 Findings from the bapineuzumab phase 2 double-blind placebo-controlled, ascending-dose study indicate that lowering of cortical fibrillar Aβ with bapineuzumab can be detected with PiB PET.86 However, even though there were reductions in the Aβ load, the bapineuzumab trials were halted due to lack of improvement in clinical and functional outcomes in patients with AD dementia. Similarly, it is expected that imaging of the τ pathology of AD87,88 especially with agents specific to the τ pathology that are currently being developed and tested,89 will open avenues for development of new targets for prevention.

**Longitudinal Molecular Imaging for Tracking AD Pathology**

Longitudinal imaging of the Aβ load on PET provides evidence of the progression of Aβ deposition in the preclinical-to-clinical AD spectrum. The hypothetic model proposed by Jack et al.71 indicates that Aβ deposition detected with molecular imaging and CSF biomarkers follows an accelerated course early in the disease process during the preclinical and MCI stages but slows down during the Alzheimer disease stage and reaches a plateau at very high levels. The findings of many longitudinal biomarker studies on Aβ deposition agree with this model.72–81 Cognitively normal individuals who progress to MCI and patients with MCI who progress to AD appear to have the highest rates of Aβ deposition,79 correlating with cognitive decline early in the disease course.76,77 Furthermore, a higher baseline Aβ load78,80 and the presence of APOE ε479 are associated with higher rates of Aβ deposition. However, the association between higher baseline Aβ load measured with the standardized uptake value ratio and a higher rate of Aβ deposition appears to dissipate at very high levels (roughly 2.0 standardized uptake value ratio). After this threshold, the relationship becomes an inverted U, gradually declining and reaching zero at the highest baseline Aβ load levels (2.7 standardized uptake value ratio). The time estimated to start with positive findings on a PiB scan (1.5 standardized uptake value ratio) to the point of plateau is approximately 15 years, corresponding to a large therapeutic window for clinical trials.73

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