Molecular Imaging Biomarkers in Dementia

Amyloid and tau PET imaging aids evaluation of patients suspected of having Alzheimer disease or other dementias.
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The field of neurodegenerative dementias, particularly Alzheimer disease (AD), has been revolutionized by the development of imaging and cerebrospinal fluid (CSF) biomarkers. These biomarkers have affected the diagnostic evaluation of symptomatic patients with cognitive impairment or dementia, particularly in dementia specialty practice. In parallel, the field has evolved conceptually, recognizing that, although there are probabilistic relationships between patients’ cognitive-behavioral syndromic diagnosis (the illness) and their etiologic diagnosis (the disease), we need to consider them separately when developing a diagnostic formulation for a patient. This clinical approach is most mature for AD. A new research framework defining AD using the amyloid, tau, and neurodegeneration (ATN) system proposes separating the definition of the neuropathologic disease from the clinical syndrome of cognitive impairment. The ATN framework defines AD biologically, requiring the presence of amyloid plaques (A+) and neurofibrillary tangles (T+) akin to neuropathologic definitions. Although we expect the field will evolve in a similar direction for other diseases causing dementia—AD-disease–related dementias (ADRD)—many diagnostic criteria still consider these as clinicopathologic entities; to meet diagnostic criteria, a patient is usually required to exhibit a particular clinical dementia syndrome(s) and diagnostic test abnormalities supportive of particular neuropathologic changes (eg, behavioral variant frontotemporal dementia [bvFTD] and dementia with Lewy bodies [DLB]). We review amyloid and tau positron emission tomography (PET) imaging, envisioning a future when molecular imaging and fluid biomarkers for other proteinopathies will enable clinicians to take a precision medicine approach to the molecular diagnosis of neurodegenerative diseases that cause cognitive-behavioral impairments and dementia.

Approach to Diagnostic Evaluation
In a person with mild cognitive impairment (MCI), mild behavioral impairment (MBI), or dementia, the differential diagnosis of potential etiologies includes multiple neurodegenerative diseases (eg, AD, FTD, DLB), stroke and other forms of vascular-ischemic brain injury, tumors, infections, inflammation, paraneoplastic disease, demyelination, trauma, hydrocephalus, toxic/metabolic insults, and other rare diseases. The individual’s specific clinical syndrome narrows the differential diagnosis. For example, a man age 67 with a history of progressive aphasia over 2 years whose exam is otherwise unremarkable has a differential diagnosis distinct from a person with a similar history developing over 6 months and an exam notable not only for aphasia but also inattention, right face and arm weakness, and myoclonic jerks. Regardless of whether there is a level of cognitive-behavioral impairment consistent with MCI or dementia, the particular constellation of symptoms and signs may provide important information about the likely underlying cause(s), and therefore play a critical role to guide diagnostic decision-making. Once neurologists or other clinicians generate a prioritized differential diagnosis of the brain disease(s) or condition(s) likely causing or contributing to a person’s clinical syndrome of cognitive and/or behavioral impairment, they can select assessments and tests that follow a tiered and structured process tailored to the individual.

As the field has evolved with a growing number of sensitive and specific tests and biomarkers of neurodegenerative disease pathologic changes (especially for AD), it has become possible to measure evidence supporting an AD or ADRD pathologic process in a living person, rather than waiting until autopsy, as has been the standard. Clinical diagnosis of MCI/MBI or dementia likely caused by AD, DLB, FTD, vascular-ischemic brain injury, or other diseases has advanced from a diagnosis of exclusion to a diagnosis involving supportive evidence with exclusion of other potential etiologies. MRI has widely accepted clinical utility for evaluation of structural brain lesions, including evidence for cerebrovascular disease and atrophy patterns consistent with, but not specific for, neurodegenerative pathologies. There is strong evidence for fluorodeoxyglucose PET (FDG-PET), with a supporting practice guideline, as a
marker of functional brain abnormalities suggestive of several neurodegenerative pathologies associated with dementia.5

In some with a clinical dementia syndrome potentially arising from AD, a clinician may wish to obtain information about whether there is biomarker evidence of AD pathology (ie, amyloid-β plaques and paired helical filament hyperphosphorylated tau neurofibrillary tangles). Although blood biomarkers are in development (see Neurofilament Light as a Dementia Biomarker and Blood Tests for Alzheimer Disease in this issue), currently only CSF biomarkers have appropriate use criteria available.6 CSF analysis for these biomarkers requires a lumbar puncture, usually performed by a neurologist. The available CSF biomarkers for neorodegenerative diseases are primarily for AD, but may eventually be useful for nonAD tauopathies, TDP43 proteinopathies, and synucleinopathies.

**Amyloid PET**

Amyloid PET imaging was developed nearly 20 years ago,7 and 3 PET tracers are approved by the Food and Drug Administration (FDA) for detecting cerebral amyloid plaques, with high sensitivity (89%-98%) and specificity (88%-100%) compared with criterion standard autopsy.8,9 These are flor-betapir, flutemetamol, and florbetaben. In 2020, amyloid PET scans are not reimbursed by the Centers for Medicare & Medicaid Services (CMS) or private payers. Thus, although these are FDA-approved, they are not frequently obtained clinically because of prohibitive cost. For Veterans Administration beneficiaries, amyloid PET is covered and more accessible.

An Amyloid Imaging Taskforce (AIT) developed appropriate use criteria, recommending that amyloid PET is appropriate in the evaluation of a person with persistent or progressive MCI or dementia. In such an individual, a negative amyloid PET scan would strongly weigh against AD as the etiology, supporting a differential diagnosis of other etiologies.10 NonAD neurodegenerative diseases that may cause an amnestic MCI/dementia syndrome include some forms of frontotemporal lobar degeneration (FTLD),11 Lewy body dementia (LBD),12 hippocampal sclerosis, argyrophilic grain disease,13 primary age-related tauopathy,14 and TDP43 proteinopathy15,16; as well as mixed etiologies from such diseases with or without vascular-ischemic brain injury. A positive amyloid PET scan in a person with MCI or dementia indicates that amyloid plaques are present but does not necessarily indicate that AD is the cause because cerebral amyloid plaques may coexist with other pathologies, and these plaques increase with age and can be found in individuals without cognitive impairment.17-20 The AIT considered the use of amyloid PET appropriate in the evaluation of a person with clinically atypical or young-onset dementia possibly owing to AD, given the diagnostic uncertainty in many such cases. The AIT stated it is inappropriate to use amyloid PET in cases with a typical presentation of the core features of dementia owing to AD in whom diagnostic uncertainty is low, to determine dementia severity, or in those who are asymptomatic. The AIT recommend considering amyloid PET when appropriate use criteria are met after a comprehensive diagnostic evaluation is performed by a dementia expert.

We often find elevated signal on an amyloid PET scan is easiest to interpret in the context of FDG-PET (or tau PET; see below). A positive amyloid PET scan in someone with MCI or dementia who has a pattern of FDG hypometabolism not typical of AD pathology or who has FDG-PET without evidence of hypometabolism raises the question of whether amyloid plaques may be present but that AD may not be the primary cause of symptoms.17-19

The clinical utility of amyloid PET was studied in the real-world dementia specialist setting in a study that assessed utility of amyloid PET in Medicare beneficiaries in whom AD was considered a potential cause of MCI or dementia, but in whom there was still diagnostic uncertainty after a complete workup by a dementia specialist.21 Dementia specialists documented the presumed etiologic diagnosis and level of confidence before and after amyloid PET. Of 11,409 study completers the etiologic diagnosis changed from AD to nonAD in 25% and from nonAD to AD in 10.5%. Clinical management changed for 60% of those with MCI and 63.5% of those with dementia.

In contemporary neurology clinical practice, we believe amyloid PET is less useful than CSF because the latter provides more information. Although lumbar puncture to obtain CSF is invasive, it is a safe and well-tolerated procedure that also provides data regarding tau pathology. As stated above, biomarker-based prediction of AD pathology is stronger when markers of both amyloid and tau are available.

**Tau PET**

Since 2013, the field had been imaging tau pathology in vivo using the PET ligand initially named ¹⁸F-T807 that avidly and selectively binds tau aggregates. In May 2020, this ligand, known also as [¹⁸F]AV-1451 or [¹⁸F]flortaucipir, was approved by the FDA for the indication of estimating the density and distribution of aggregated tau neurofibrillary tangles in adults with cognitive impairment being evaluated for AD. Regulatory approval was based on 2 clinical trials with a terminally ill cohort including people with a spectrum of types of clinically diagnosed dementias and people with normal cognition who were followed to autopsy.22 The primary outcome was whether a visual interpretation of the images could detect advanced AD tau neurofibrillary tangle pathology (Braak stages V or VI tau pathology). In trials, the sensitivity of 5 trained readers ranged from 68% to 86% and specificity ranged from 63% to 100%; inter-rater agreement was 0.87. When interpretation of the majority of readers was used, sensitivity was 92% and specificity was 80%. These findings are congruent with
a small sample of patients studied at the Mayo Clinic with a variety of types of dementia who underwent [18F] flortaucipir scans and were followed to autopsy, with a quantitative threshold of PET signal in the temporal lobe identifying AD pathology with 87% sensitivity and 82% specificity.23

In people with amnestic MCI or dementia clinical syndromes typical of those associated with AD pathologic changes, tau PET images show elevated signal in temporal and parietal cortical regions (Figure).24-26 This topographic distribution is consistent with postmortem Braak staging

![Multimodal Imaging](image)

Figure. Multimodal imaging from 3 people with dementia showing from left to right: MRI, fluorodeoxyglucose positron emission tomography (FDG-PET) (Glucose), amyloid PET (Amyloid), and tau PET (Tau). The first individual (A), with progressive Gerstmann syndrome, has left occipitotemporal atrophy and hypometabolism (red arrows on MRI and FDG-PET) which was suspected to be caused by Alzheimer disease (AD) neuropathologic changes, but amyloid PET and tau PET showed low signal, strongly suggesting a different etiologic diagnosis. The second individual (B), with a progressive visuospatial syndrome, has bilateral occipitoparietal atrophy and hypometabolism (red arrows on MRI and FDG-PET) with elevated amyloid PET and tau PET signal, supporting the etiologic diagnosis of AD. The third individual (C), with a progressive aphasic syndrome, has left anterior and lateral temporal atrophy and hypometabolism (red arrows on MRI and FDG-PET) with elevated amyloid PET and tau PET signal, supporting the etiologic diagnosis of AD. Note that in B and C, tau PET signal but not amyloid PET signal is strongly colocalized with atrophy and hypometabolism.
of neurofibrillary tangle pathology, with more prominent tracer uptake in medial, inferior, and lateral temporal, lateral parietal, posterior cingulate, and precuneus, and less in frontal regions and primary sensorimotor cortices.27,28

People with atypical clinical syndromes associated with AD pathology exhibit different spatial patterns of tau PET signal that are colocalized with atrophy on MRI or hypometabolism on FDG-PET (Figure).29-31 Regardless of the localization, greater tau PET signal is associated with worse neurodegeneration (atrophy or hypometabolism) and worse cognition.24,25,29,30

Use of tau PET in persons with nonAD dementia is complicated by a variety of factors reviewed elsewhere.32,33 Current tau PET methods are not validated as sensitive or specific enough for the evaluation of patients with suspected nonAD tauopathies.34-36 Next-generation PET tracers are being investigated for their potential use in nonAD tauopathies.37 Regardless, studies with large samples of participants with diverse clinical dementia syndromes have shown that [18F]Flortaucipir PET can discriminate reasonably well between those likely to have AD neuropathologic change and those likely to have nonAD neuropathologic change (Figure).38,39

Although tau PET is now FDA approved, some barriers remain to use in clinical practice. It will take time to make tau PET widely available at nuclear medicine imaging facilities with radiologists who are trained to interpret these scans. The field will need expert guidance on how to use tau PET in practice; appropriate use criteria are currently in development. Interpretation of tau PET scans is more complex than interpretation of amyloid PET scans, and clinical interpretation methods will likely evolve to increase sensitivity of these scans beyond the methods in the regulatory label. For example, a negative tau PET scan using the current FDA-approved language does not rule out relatively less advanced stages of AD tau pathology or nonAD tauopathies; whereas a positive tau PET scan does not necessarily indicate that AD pathology is the only contributor to a person’s symptoms. Finally, tau PET scans may not be reimbursed by payers for some period of time.

With those caveats, we are tremendously excited to have a new tool that, based on a substantial and growing body of evidence, will undoubtedly contribute importantly to the diagnostic evaluation of patients with cognitive-behavioral impairment or dementia.

Conclusion

As we enter the third decade of 21st century neurologic practice we recognize that the field has made remarkable progress toward more precise molecular diagnosis of the brain diseases underlying dementia. This progress has been made in part with increasing federal research fund-


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