TOWARDS MOLECULAR DIAGNOSIS: CLINICAL APPLICATIONS OF AMYLOID AND TAU PET

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Background

Despite recent advances in imaging and other biomarkers of Alzheimer's disease (AD), the diagnosis of AD and other causes of dementia is still made primarily on clinical grounds, with laboratory tests and structural neuroimaging used primarily to "rule-out" non-degenerative causes of cognitive impairment. The limitations of this approach are increasingly evident. A recent study that evaluated the accuracy of clinical diagnosis versus the gold standard of autopsy in over 900 cognitively impaired patients evaluated at U.S. Alzheimer's Disease Centers found that the clinical diagnosis of probable AD was only ~70% accurate when compared to post-mortem findings (Beach et al. 2012). Conversely, ~40% of patients diagnosed with non-AD dementias were found to have AD as the primary causative pathology. Similar rates of misdiagnosis have been reported in AD clinical trials, likely impeding drug development and testing (Salloway et al. 2014). Furthermore, there is increasing evidence to support the notion that deposition of brain pathology in the form of amyloid plaques and neurofibrillary tangles begins 15 years or more before the onset of even mild cognitive symptoms, creating a potential window for early intervention and possibly disease prevention (Jack et al. 2013).

In the past decade there has been great progress in developing molecular imaging probes that bind to AD neuropathological lesions and allow detecting and quantification using positron emission tomography (PET). PET tracers for amyloid-beta (Aβ) bind to fibrillar Aβ aggregates, including neuritic > diffuse amyloid plaques, as well as vascular Aβ deposits in cerebral amyloid angiopathy. The U.S. Food and Drug Administration has approved three Aβ tracers for clinical use in cognitively impaired patients:

- F18-florbetapir (approved in 2012)
- F18-florbetaben (approved in 2013)
- F18-flutemetamol (approved in 2014)

The FDA approval of all three agents was based on evidence that blinded visual reads of amyloid PET scans during life (as positive or negative for cortical uptake) accurately predicted the burden of amyloid pathology found post-mortem in the same individuals, discriminating patients with moderate-frequent neuritic plaques from those with absent-sparse neuritic plaques (as measured by the CERAD scale) with ≥ 80% sensitivity and specificity (Clark et al. 2012, Curtis et al. 2015, Sabri et al. 2015).

Utility of amyloid PET in MCI and differential diagnosis of dementia

Amyloid PET can help increase the confidence that mild cognitive impairment (MCI) is due to underlying AD pathophysiology, and is now included in diagnostic criteria for MCI (National Institute on Aging-Alzheimer's Association Criteria (Albert et al. 2011)), also known as prodromal AD (International Working Group-2 Criteria (Dubois et al. 2014)). Patients with MCI due to AD show a distribution and burden of amyloid that is similar to that seen in AD dementia. Conversely, a negative amyloid PET scan decreases the likelihood that MCI is due to AD. Patients with MCI who are positive on amyloid PET decline as a group more rapidly than amyloid-negative patients, and are more likely to convert to dementia in the next 2-5 years compared to MCI patients who are amyloid PET negative. However, individual trajectories are quite variable. Patients who are positive on both an amyloid biomarker and show evidence of neurodegeneration on structural or functional imaging (e.g. hippocampal atrophy on MRI, or classical temporoparietal pattern of hypometabolism on FDG-PET) are at highest risk of imminent decline (Hazard Ratio ~3-5 in most studies) (Caroli et al. 2015).

In patients with dementia, amyloid PET can be useful in discriminating AD from conditions that don't involve Aβ deposition, such as frontotemporal dementia or pure vascular dementia (Ossenkoppele et al. 2015). Amyloid PET

is not useful in discriminating AD from other conditions in which amyloid is deposited in the brain, such as cerebral amyloid angiopathy or dementia with Lewy bodies.

When interpreting the significance of a positive amyloid scan, it is important to keep in mind that ~25%-30% of cognitively normal older individuals harbor amyloid in the brain and have positive amyloid PET (Jansen et al. 2015). The prevalence of amyloid positivity in normal people increases with age, from ~10% at age 60 to >50% at age 90 and above. At any given age, individuals who harbor the Apolipoprotein E ε4 genotype are ~3 times more likely to be amyloid-positive compared to ApoE4 negative individuals. While many of these individuals may be in the "preclinical" stage of AD, for diagnostic purposes the lack of specificity for cognitive state raises the possibility that a positive scan in an impaired patient may be related to age and not necessarily the cause of cognitive decline. Therefore, while a negative amyloid scan is useful for ruling out Alzheimer's disease at any age, the significance of a positive scan in older individuals needs to be interpreted more carefully (negative predictive value high at all ages; positive predictive value decreases with age).

Appropriate and inappropriate clinical uses of amyloid PET

In order to guide clinicians in the appropriate clinical translation of this new technology, the Society for Nuclear Medicine and Molecular Imaging and the Alzheimer's Association convened a panel of experts to set Appropriate Use Criteria (AUC) for amyloid PET based on current literature (Johnson et al. 2013). The premise of the AUC is that, given the high cost and nuanced interpretation, amyloid PET should not be considered a first-line test in the evaluation of cognitive complaints, but rather an ancillary test to be ordered by sub-specialists ("dementia experts") in a subset of patients who meet the following criteria:

- Cognitive complaint with objectively confirmed impairment (i.e. meet criteria for MCI or dementia).
- Uncertain diagnosis (with AD as a possibility) after comprehensive evaluation by a dementia expert.
- Knowledge of Aβ status expected to increase diagnostic certainty and alter management.

The AUC identified three top clinical scenarios in which clinical amyloid imaging may be considered:

- Persistent/progressive unexplained MCI.
- Possible (rather than probable) AD due to:
  - Atypical or mixed course.
  - Significant co-morbidities (e.g. vascular, psychiatric, substance abuse).
- Atypically early age-of-onset (<65 years).

Just as importantly, the AUC highlighted a number of scenarios in which clinical amyloid PET is considered *inappropriate*. These include:

- Initial evaluation of cognitive complaints.
- Screening of cognitively normal individuals (only appropriate in the context of research or clinical trials).
- When requested solely based on a family history of dementia or presence of other risk factors for AD, such as the ApoE4 gene.
- As a substitute for genetic testing for mutations that cause AD.
- For nonmedical reasons, such as insurance and legal or employment decisions.

Finally, there are scenarios where amyloid imaging is not likely to be useful:

- As a means of determining the severity of dementia.
- In straightforward clinical cases.
- To differentiate AD from other Aβ diseases (e.g. dementia with Lewy bodies; cerebral amyloid angiopathy).

Assessing clinical impact

Relatively few studies have assessed the impact of amyloid PET on clinical decision making and patient outcomes. The few published studies have shown that the scan leads to a change in diagnosis in 35%-50% of diagnostically uncertain patients, significantly increases diagnostic confidence in determining the underlying

condition, and impacts use of AD symptomatic medications as well as other aspects of management (e.g. ordering additional diagnostic studies, referrals to other sub-specialists, and counseling about safety and future planning) (Grundman et al. 2013, Sanchez-Juan et al. 2014).

In September 2013 the U.S. Centers for Medicare and Medicaid Services (CMS) issued a National Coverage Decision determining that there was insufficient evidence of clinical utility to justify reimbursement of amyloid PET. CMS further stated that reimbursement would be considered under a mechanism called coverage with evidence development (CED), in which CMS will reimburse the scans for patients who enroll in studies to assess clinical utility. For CMS to reconsider its coverage decision, studies must demonstrate that amyloid PET improves health outcomes (short-term outcomes related to changes in management as well as longer-term dementia outcomes). The Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study (www.IDEAS-study.org) is a U.S.-wide multi-site study to assess the utility of amyloid PET in Medicare beneficiaries meeting AUC for amyloid imaging under CED. CMS is reimbursing amyloid PET scans for patients enrolled in IDEAS. The study will determine whether amyloid PET alters patient management and improves medical outcomes.

Tau PET on the horizon

In recent years a number of PET tracers have been developed that bind selectively to paired-helical filaments of tau in AD (Villemagne et al. 2015). Early studies suggest that PET imaging with these tracers replicates Braak staging of neurofibrillary pathology, correlates with clinical state, and shows robust signal in expected regions in patients with clinical AD (Ossenkoppele et al. 2016, Scholl et al. 2016). Tau PET also has the potential to detect pathology in non-AD tauopathies such as progressive supranuclear palsy, corticobasal degeneration, chronic traumatic encephalopathy and subtypes of frontotemporal dementia, though individual ligands may show variable binding to these diverse pathologies (Sander et al. 2016).

Summary

Molecular imaging has the potential to revolutionize diagnosis and care of cognitively impaired patients by allowing an *in vivo* assessment of brain pathology. At the moment only amyloid PET is approved for clinical use in the U.S. and Europe. As with any diagnostic agent, clinical context is critical for interpreting the significance of positive and negative amyloid scans. Perhaps most importantly, amyloid and tau PET are already having a major impact on drug development, allowing early (and even preclinical) detection and intervention, biological phenotyping of patients in trials, and confirmation of drug-to-target engagement. These major advances in diagnostics are likely to accelerate the development of effective, biologically-specific therapies, and shift the field towards a model where we aim to not only treat affected patients, but ultimately to delay or even prevent the onset of dementia.

References

1. Beach, T. G., S. E. Monsell, L. E. Phillips and W. Kukull (2012). "Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005-2010." J Neuropathol Exp Neurol **71**(4): 266-273.
2. Salloway, S., R. Sperling, N. C. Fox, K. Blennow, W. Klunk, M. Raskind, et al. (2014). "Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease." N Engl J Med **370**(4): 322-333.
3. Jack, C. R., Jr., D. S. Knopman, W. J. Jagust, R. C. Petersen, M. W. Weiner, P. S. Aisen, et al. (2013). "Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers." Lancet Neurol **12**(2): 207-216.
4. Clark, C. M., M. J. Pontecorvo, T. G. Beach, B. J. Bedell, R. E. Coleman, P. M. Doraiswamy, et al. (2012). "Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-beta plaques: a prospective cohort study." Lancet Neurol **11**(8): 669-678.
5. Curtis, C., J. E. Gamez, U. Singh, C. H. Sadowsky, T. Villena, M. N. Sabbagh, et al. (2015). "Phase 3 trial of flutemetamol labeled with radioactive fluorine 18 imaging and neuritic plaque density." JAMA Neurol **72**(3): 287-294.
6. Sabri, O., M. N. Sabbagh, J. Seibyl, H. Barthel, H. Akatsu, Y. Ouchi, et al. (2015). "Florbetaben PET imaging to detect amyloid plaques in Alzheimer disease: Phase 3 study." Alzheimers Dement.
7. Albert, M. S., S. T. DeKosky, D. Dickson, B. Dubois, H. H. Feldman, N. C. Fox, et al. (2011). "The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-

Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease." Alzheimers Dement **7**(3): 270-279.
8. Dubois, B., H. H. Feldman, C. Jacova, H. Hampel, J. L. Molinuevo, K. Blennow, et al. (2014). "Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria." Lancet Neurol **13**(6): 614-629.
9. Caroli, A., A. Prestia, S. Galluzzi, C. Ferrari, W. M. van der Flier, R. Ossenkoppele, et al. (2015). "Mild cognitive impairment with suspected nonamyloid pathology (SNAP): Prediction of progression." Neurology **84**(5): 508-515.
10. Ossenkoppele, R., W. J. Jansen, G. D. Rabinovici, D. L. Knol, W. M. van der Flier, B. N. van Berckel, et al. (2015). "Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis." JAMA **313**(19): 1939-1949.
11. Jansen, W. J., R. Ossenkoppele, D. L. Knol, B. M. Tijms, P. Scheltens, F. R. Verhey, et al. (2015). "Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis." JAMA **313**(19): 1924-1938.
12. Johnson, K. A., S. Minoshima, N. I. Bohnen, K. J. Donohoe, N. L. Foster, P. Herscovitch, et al. (2013). "Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association." Alzheimers Dement **9**(1): e-1-16.
13. Grundman, M., M. J. Pontecorvo, S. P. Salloway, P. M. Doraiswamy, A. S. Fleisher, C. H. Sadowsky, et al. (2013). "Potential impact of amyloid imaging on diagnosis and intended management in patients with progressive cognitive decline." Alzheimer Dis Assoc Disord **27**(1): 4-15.
14. Sanchez-Juan, P., P. M. Ghosh, J. Hagen, B. Gesierich, M. Henry, L. T. Grinberg, et al. (2014). "Practical utility of amyloid and FDG-PET in an academic dementia center." Neurology **82**(3): 230-238.
15. Villemagne, V. L., M. T. Fodero-Tavoletti, C. L. Masters and C. C. Rowe (2015). "Tau imaging: early progress and future directions." Lancet Neurol **14**(1): 114-124.
16. Ossenkoppele, R., D. R. Schonhaut, M. Scholl, S. N. Lockhart, N. Ayakta, S. L. Baker, et al. (2016). "Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease." Brain.
17. Scholl, M., S. N. Lockhart, D. R. Schonhaut, J. P. O'Neil, M. Janabi, R. Ossenkoppele, et al. (2016). "PET Imaging of Tau Deposition in the Aging Human Brain." Neuron **89**(5): 971-982.
18. Sander, K., T. Lashley, P. Gami, T. Gendron, M. F. Lythgoe, J. D. Rohrer, et al. (2016). "Characterization of tau positron emission tomography tracer [F]AV-1451 binding to postmortem tissue in Alzheimer's disease, primary tauopathies, and other dementias." Alzheimers Dement.