Amyloid imaging
Robert Jr Laforce

Introduction

Positron emission tomography (PET) with amyloid ligands has gained considerable momentum in the field of neuroimaging of aging and dementia in the last decade mainly because it allows *in vivo* detection of amyloid plaques, a core pathologic feature of Alzheimer's disease (AD) [Klunk et al., 2004]. The first specific tracer for amyloid-beta (Aβ) applied in human studies was ^{11}Carbon-labelled Pittsburgh Compound-B (PIB). PIB is an analog of thioflavin-T that at PET tracer concentrations binds to beta-sheet rich fibrillar deposits of Aβ with high sensitivity and specificity [Ikonomovic et al., 2008]. Although the 20-minute half-life of carbon-11 has limited its use to research centers equipped with a cyclotron, a second generation of amyloid agents labeled with fluorine-18 (^{18}F, 110-minute half-life) has recently been developed, making it feasible to produce and distribute tracers for clinical use [Jagust 2010]. Last month, *florbetapir* (https://investor.lilly.com/releasedetail2.cfm?ReleaseID=662647) became the first FDA-approved ^{18}F tracer. Apart from higher non-specific white matter binding in the ^{18}F amyloid agents (*flutemetamol*, *florbetapir*, and *florbetaben*; see Section 6 below for a more detailed discussion on new PET tracers), all have performed comparably to PIB in clinical populations, and high correlation with post-mortem measures of fibrillar Aβ have been found [Clark et al., 2011].

Amyloid imaging data has been incorporated in the new consensus guidelines for the diagnosis of AD [McKhann et al., 2011] and predementia AD-related conditions [Albert et al., 2011; Sperling et al., 2011a] which now include the measurement of Aβ in cerebrospinal fluid (CSF) or the brain (i.e. amyloid PET) in conjunction with core clinical criteria to assess the likelihood of AD. For example, in a patient with mild cognitive impairment (MCI) with both positive Aβ (e.g. amyloid PET or CSF $A\beta_{1-42}$ levels) and neuronal injury (e.g. CSF tau, hippocampal/medial temporal atrophy on MRI, hypometabolism on FDG-PET) markers, a diagnosis of 'MCI due to AD-high likelihood' can be made. If markers from both categories are negative, MCI is considered 'unlikely due to AD'.

Amyloid PET in various clinical populations

Cognitively normal elderly individuals (NC) show elevated PIB binding in 10-34% of cases, similar to observed rates of amyloid pathology in autopsy studies [Pike et al., 2007]. Increasing age and the presence of the apolipoprotein E ε4 allele (ApoE ε4) are the major predictors of PIB-positivity in NC [Rowe et al., 2010]. Recent findings in persons without dementia or MCI suggest that amyloid deposition is associated with very subtle cognitive deficits especially among ApoE ε4 carriers [Kantarci et al., 2012]. Interestingly, in a gene-based association analysis of amyloid-pathway candidate genes using PIB uptake value on 103 Alzheimer's Disease Neuroimaging Initiative (ADNI) participants, the *DHCR24* gene showed association with a lower average PIB uptake, hence suggesting a neuroprotective role [Swaminathan et al., 2011].

Although the significance of a positive amyloid scan in NC still remains uncertain, cross-sectional studies have shown 'AD-like' brain changes (hippocampal and temporo-parietal atrophy) [Dickerson et al., 2009] while early longitudinal data have strengthened the notion that many (although probably not all) are in a 'preclinical' phase of AD [Sperling et al., 2011b]. This hypothesis will require further longitudinal investigation. From a diagnostic perspective, the significant baseline rate of amyloid-positive NC emphasizes that amyloid-positivity is not synonymous with AD, and that amyloid scans cannot be interpreted *in lieu* of a detailed clinical evaluation. At present, there is no clinical indication for amyloid imaging in cognitively normal individuals, though this will remain an area of active research in coming years, particularly with the advent of amyloid lowering therapies, which might be most effective if initiated in the presymptomatic disease stage [Ostrowitzki et al., 2011; Klunk 2011].

Current data in MCI patients indicate that amyloid imaging provides prognostic information presumably by identifying patients with underlying AD pathology [Pontecorvo & Mintun, 2011]. As a group, 52 to 87% show elevated PIB binding in a similar regional distribution to AD [Pike et al., 2007]. In longitudinal studies, one year conversion rates to AD range from 33-47% in PIB-positive MCI subjects versus virtually no conversions in PIB-negative subjects [Wolk et al., 2009]. In the largest longitudinal effort to date [Okello et al., 2009], authors compared baseline amyloid deposition between MCI converters and non-converters in 31 subjects followed over 3 years. The conversion rate was 82% in those with increased PIB uptake, but only 7% in PIB-negative subjects. Altogether, PIB-positive amnestic MCI patients are likely to have early AD, and amyloid imaging will help in risk stratification and selection of patients who may benefit from disease-specific therapies.

Most studies in AD have found very high (90% or greater) PIB-PET sensitivity, and in a pattern that closely mirrors the distribution of plaques found at autopsy [Rowe et al., 2010]. Tracer binding is diffuse and symmetric, with high uptake consistently found in prefrontal cortex, precuneus and posterior cingulate cortex, followed closely by lateral parietal, lateral temporal cortex, and striatum. Studies in atypical clinical presentations of AD have shown that amyloid deposition is more common in the logopenic variant of primary progressive aphasia (lvPPA) than in nonfluent or semantic variants [Rabinovici et al., 2008], supporting the hypothesis that lvPPA is predictive of underlying AD. Others have detected high PIB binding in patients with posterior cortical atrophy (PCA), a visuospatial/biparietal clinical syndrome often caused by AD [de Souza et al., 2011]. Much like FDG-PET [Laforce et al., 2010], amyloid imaging will probably not add value to the diagnostic work-up of patients with straightforward clinical AD, but is likely to be useful in patients with atypical complex presentations or early age-of-onset dementia.

Other clinical conditions studied with amyloid PET include vascular dementia (VD), cerebral amyloid angiopathy (CAA), Parkinson's disease dementia (PDD), dementia with Lewy bodies (DLB), and the frontotemporal lobar degeneration spectrum of disorders (FTLD). A detailed discussion of these results is beyond the scope of this article (see Drzezga 2010 or Laforce & Rabinovici, 2011 for more detailed reviews), but key findings are summarized below.

In one study on VD, authors found that 69% of patients were PIB-negative [Lee et al., 2011]. High PIB binding rates were found in non demented patients with CAA [Johnson et al., 2007]. Most studies showed higher amyloid plaques in DLB than in PDD or non-demented PD patients, and in some PIB-positivity was associated with more rapid disease progression [Maetzler et al., 2009]. The high frequency of plaques and high rates of positive scans in DLB suggest that amyloid PET is unlikely to be helpful in differentiating DLB from AD. Finally, considering that FTLD and AD are the leading causes of early age-of-onset dementia [Ratnavalli et al., 2002], that distinguishing the two during life can be clinically challenging [Alladi et al., 2007], and that Aβ plaques are not part of the FTLD pathologic spectrum, several authors have argued for a valuable role of amyloid imaging in the differential diagnosis of these conditions. Small case series have reported low rates of PIB (0 to 15%) and florbetaben-positivity (9%) in FTLD [Villemagne et al., 2011]. Recently, results from the largest study on the diagnostic utility of amyloid PET in FTLD showed in 62 AD and 45 FTLD patients that PIB visual reads had a higher sensitivity for AD than FDG-PET, with similar specificity [Rabinovici et al., 2011]. PIB outperformed FDG in classifying patients with known histopathology, and visual reads showed higher inter-rater reliability and agreement than FDG, suggesting it was the more accurate and precise technique.

Amyloid PET in clinical practice: unresolved questions and recommendations

There are many unknowns that could impact the diagnostic utility of amyloid PET including (1) its sensitivity and specificity compared to pathology, (2) technical and patient factors that could lead to false positives and false negatives, (3) the relative contribution of both diffuse and neuritic plaques' binding to the *in vivo* signal, (4) interpretation of the test as a dichotomous result versus assessing binding degree and spatial distribution, (5) inter- and intra-rater reliability of visual interpretations, (6) determining the optimal quantitative threshold for defining a positive scan, (7) adjusting the threshold for PIB-positivity based on demographic factors such as age or genetic variables, and (8) cost effectiveness issues [Jagust 2011].

At present, studies of practical clinical applications of amyloid imaging lag far behind studies with biological objectives. Nonetheless, in clinics where PIB has been available, results have had implications for treatment, particularly on deciding whether to initiate or discontinue AD symptomatic medications (see Laforce & Rabinovici, 2011 for case vignettes). Currently, acetylcholinesterase inhibitors are prescribed to a large number of patients with non-AD dementia, while certain populations that may benefit are currently not treated (e.g. MCI due to AD). This is based on negative clinical trials that may have been confounded by biological heterogeneity. Such decisions would be more rational if amyloid PET were applied in the right circumstances, and this could result in cost saving. The more immediate impact of amyloid imaging, however, will be in improving clinical trial design by enrolling patients based on biological, rather than clinical phenotype. A positive amyloid scan may eventually be the primary inclusion criterion for a study focused on AD prevention.

Conclusion

Amyloid imaging represents a major breakthrough in the evaluation of dementia that will doubtlessly translate into better clinical care, and ultimately help guide the development of molecular-based therapies for these devastating illnesses. This technique should be regarded as an adjunct imaging tool that is part of a comprehensive clinical evaluation when a more accurate clinical diagnosis is needed in the face of a complex case. Fundamentally, amyloid imaging detects a brain pathophysiology, and is not a clinical diagnosis. Used in isolation, it cannot diagnose AD, MCI, or differentiate normal or abnormal aging. Although an impressive body of research has already been generated in the field, more studies of practical clinical applications are needed. Clinical availability of new ^{18}F agents will help better understand diagnostic performance, added clinical value and cost effectiveness of amyloid imaging.

Recommendations

Recommendations for clinicians on behalf of the 4th Canadian Consensus Conference on Diagnosis (CCCD)

1. Amyloid biomarkers have not yet reached regulatory approval in Canada and are not yet funded for use in clinical settings, yet they represent a major breakthrough in the evaluation of dementia in research studies. It is unclear how the approval of ^{18}F tracer *florbetapir* by the FDA will impact our practice but clinicians should be familiar with the key findings of amyloid imaging research;
2. At present, there are many unknowns that could impact the diagnostic utility of amyloid PET (e.g. sensitivity and specificity compared to pathology, technical and patient factors that could lead to false positives and false negatives, relative contribution of both diffuse and neuritic plaques' binding, dichotomous interpretation versus assessing binding degree and spatial distribution, determining the optimal quantitative threshold for defining a positive scan, adjusting the threshold based on demographic factors, cost effectiveness issues) and therefore, clinicians should be cautious when faced with a situation where amyloid data is discussed;
3. Should this technique become available to Canadian clinicians in the future, it should not be available for routine evaluation due to cost and limited access. Moreover, it should be regarded as an adjunct imaging tool that is part of a comprehensive clinical evaluation under provincial medicare systems for specific patients in referral Memory Clinics when a more accurate clinical diagnosis is needed in the face of a complex case (i.e., atypical presentations, early age-of-onset dementia);
4. Used in isolation, amyloid imaging cannot diagnose AD, MCI, or differentiate normal or abnormal aging. Although further research is needed, early findings in this field has demonstrated the potential clinical utility of amyloid imaging in (1) determining if MCI is due to AD, (2) differentiating AD from non-AD dementia (e.g. FTLD) particularly in early age-at-onset patients, (3) determining if AD co-pathology is present in patients with cognitive impairment and other known neurologic disease (e.g. PD, stroke/vascular disease, MS, epilepsy, HIV), (4) differentiating AD from non-degenerative cognitive decline (e.g. depression, substance abuse), (5) determining if AD is present in patients with advanced dementia and no reliable history, (6) identifying if AD is present in focal

cortical syndromes (e.g. PCA, PPA, CBS), and (7) differentiating CAA from ICH due to small vessel vasculopathy;

5. At present, there is no clinical indication for amyloid imaging in cognitively normal individuals, initial investigation of cognitive complaints, differentiating AD from other Aβ-associated dementia (e.g. DLB, CAA), differentiating between AD clinical variants (e.g. classic amnestic AD vs. PCA or lvPPA), and differentiating between non-AD causes of dementia (e.g. molecular subtypes of FTLD).

Recommendations for research and translational development to clinical care on behalf of the 4th Canadian Consensus Conference on Diagnosis (CCCD)

1. In research settings with amyloid imaging capabilities, investigators should be encouraged to develop projects that further validate the clinical and research uses of this technique and evaluate its readiness for translation to clinical care;
2. Trial designers are strongly encouraged to use this technique to (1) decrease the heterogeneity of their MCI population; (2) identify a cohort that is likely to respond to a drug with anti-amyloid properties; and (3) study patients that are likely to convert to AD in a relatively short time frame;
3. Testing and longitudinal follow-up of asymptomatic individuals or patients with subjective cognitive impairments not meeting MCI criteria, or at-risk individuals (e.g. gene mutation carriers, family history of AD, ApoE ε4) should be restricted to research;
4. Future research should explore (1) the natural evolution of amyloid burden and its role in the pathophysiology of AD and other dementias, (2) its use as a potential surrogate marker for anti-amyloid therapies, (3) the value of new ^{18}F amyloid tracers, (4) perform PET-pathology correlations, and (5) compare amyloid imaging with CSF AD biomarkers as well as downstream markers of degeneration.

Abbreviations

Aβ: amyloid-beta
AD: Alzheimer's disease
ApoE ε4: apolipoprotein E ε4 allele
CAA: cerebral amyloid angiopathy
CBS: corticobasal syndrome
CSF: cerebrospinal fluid
DLB: dementia with Lewy bodies
FDG: ^{18}F-Fluorodeoxyglucose
FTLD: frontotemporal lobar degeneration
ICH: intracranial haemorrhage
MCI: mild cognitive impairment
MRI: magnetic resonance imaging
MS: multiple sclerosis
PCA: posterior cortical atrophy
PD: Parkinson's disease
PPA: primary progressive aphasia

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