Amyloid Imaging in Dementia: Contribution or Confusion?

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There is mounting evidence and enthusiasm for molecular imaging contribution to the diagnosis of neurodegenerative dementia. A key advance in the imaging field has been the development of selective ligands that can reveal the presence of pathologic deposition of Aβ-amyloid in the cerebral cortex, consistent with dementia due to Alzheimer disease (AD) or a related neurodegeneration [1]. Recently, three amyloid-avid radiotracers with potential for clinical use have been developed (see [2] for review), and are approved for use by the US FDA and by European regulators. The Society of Nuclear Medicine and Molecular Imaging, together with the Alzheimer’s Association, convened a panel of content experts to recommend the appropriate use of these new tools [3]. Conservatively, the panel recommended as the first indication, the use of amyloid imaging probes to distinguish patients with frontotemporal dementias (FTD) from patients with amyloid-dependent neurodegenerations such as typical AD and a significant proportion also of patients with dementia with Lewy bodies (DLB). Clinical rationale for this application follows from recognition that diagnosis of FTD can be difficult[4-6], and may be missed in as many as 70% of patients [7]. This circumstance can lead to inappropriate use of symptomatic medications and incorrect prognostication, and even more importantly, may limit the accuracy and power of future therapeutic trials focused on FTD vs. AD pathological pathways. The recommended use of amyloid imaging in dementia includes focus on patients with features atypical of AD, including prominent aphasia or prominent frontal lobe dysfunction or with relatively early age of dementia onset; each of these features increases the likelihood of an FTD variant over AD.

In the present issue of the Journal, Kobylecki et al. [8] report their experience with the use of [18F]florbetapir in the distinction of FTD vs. AD in demented patients recruited from a university-affiliated cognitive disorders clinic. The intent of the research was to assess the ability of the radiofluorinated tracer to reproduce the previously published results of amyloid imaging with [11C]PiB from several laboratories [9-11]. In essence, patients with clinical presentations favoring FTD vs. AD in demented patients recruited from a university-affiliated cognitive disorders clinic. The intent of the research was to assess the ability of the radiofluorinated tracer to reproduce the previously published results of amyloid imaging with [11C]PiB from several laboratories [9-11]. In essence, patients with clinical presentations favoring FTD vs. AD should have “negative” amyloid scans, and patients with AD should have “positive” scans. However, as often encountered in biomedical research, the study results may raise as many questions as they answer. Kobylecki reports that the recommended clinical interpretation approach to [18F]florbetapir scans resulted in identification of “positive” patterns in 25% of FTD and in 10% of normal comparison subjects. They identified “positive” scans in 80% of AD subjects. These findings raise critically important issues: Are the rating recommendations and rules for clinical amyloid reporting sub-optimal? Do the clinical diagnostic amyloid tracers perform differently than predictions based on the research amyloid tracer [11C]PiB?
There are several considerations that may account for apparent discord between clinical diagnoses and \([^{18}F]\)florbetapir interpretations. First, the clinical diagnoses may be inaccurate. It is well established that clinical classification differs from autopsy diagnosis in a significant proportion of dementia cases (see [12] for overview). In the present study, the investigators employed also \([^{18}F]\)FDG-PET brain imaging, confirming that FTD patients had prominent frontal lobe hypometabolism. This feature, however, is also fallible in diagnosis of FTD when compared to autopsy confirmation [13,14]. Thus, the discrepant amyloid vs. clinical classification results of the Kobylecki study add to reports suggest potential diagnostic gain from the imaging [15-18], even beyond contribution of FDG-PET characterizations. The authors offer the possibility of multiple pathologies in some of their subjects as another explanation, noting particularly the potential impact of ApoE \(\varepsilon4\) genotype on promotion of amyloid deposition. While this cannot be not excluded, the co-occurrence of FTD and fibrillary amyloid deposition is only rarely reported, and is notably absent from most series of autopsy dementia evaluation [15]. Only autopsy confirmation of dementia pathology in the currently-reported cases will reveal the truth underlying the apparent disparities in the Kobylecki report.

Of much greater concern, however, is the performance of visual image interpretations by observers, who had undergone the recommended training experience prior to the study. Of 28 subject scans analyzed, there was lack of concordance among the 4 independent raters in 11 cases, and only a modest statistical assessment of inter-rater agreement. This suggests the need for additional analytical approaches to clinical reading and reporting of amyloid images. To be sure, the studies interpreted by Kobylecki et al. are challenging. Most FTD cases have significant neocortical atrophy in frontal and / or temporal lobes, and this may cause interpretative difficulty with tracer in subcortical white matter appearing potentially of cerebrocortical origin. Another potential source of imaging error in cognitively impaired patients is subject motion during scanning that can worsen the influence of adjacent subcortical white matter on assessment of the gray matter tracer uptake. In the present study, potential effect of subject motion was reduced by means of a dynamic series of images over 50-60 min post-injection with motion correction image realignment. Automated MRI-based cerebrocortical tracer uptake values were obtained from PET voxels classified as gray matter on T1-weighted MRI in parallel with the visual analyses, and these quantitative data suggested better overall agreement with clinical diagnostic classifications than the visual reads. Missing from the report are open reconciliations of readers’ visual interpretations with the combined PET / MRI image displays that could inform as to the nature of inconsistent and potentially misleading qualitative analyses.

In conclusion, the report of Kobylecki et al. provides additional evidence that clinical use of amyloid imaging has the potential to contribute to dementia diagnosis, beyond specialist clinical characterizations and FDG-PET imaging. However, more sophisticated training of image interpreters and consideration of multimodality image display and review approaches may be needed to realize accurate diagnostic amyloid scanning performance in patients with suspected FTD.
DISCLOSURE
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REFERENCES


