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Contributions and Letters

How Much Is a Picture Worth? Putting Amyloid Imaging to the Test

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Accurate clinical diagnosis of Alzheimer's disease (AD) is vital but has remained challenging because of the dichotomy between clinical diagnosis (made using cognitive tests) and definitive diagnosis (which requires pathological evidence of β-amyloid plaques and tangles in the brain) [1–4]. A recent clinical-autopsy correlative study of more than 900 cases seen at the very best US memory centers found that nearly 40% of patients clinically diagnosed with non-AD dementia had postmortem histopathology consistent with AD [2]. Likewise, studies suggest that up to 30% of patients clinically diagnosed with possible or probable AD may not meet postmortem pathologic criteria for AD [1–4]. It is important to accurately differentiate the early stage of AD from other types of cognitive disorders, which may have different prognosis and different potential for treatment [1–4]. Efforts to bridge the gap between clinical and pathological diagnosis have led to the development of PET tracers with high affinity for β-amyloid neuritic plaques, such as ^{11}C-PiB, ^{18}F-florbetaben and ^{18}F-florbetapir [1] as well as the recent US marketing of florbetapir for clinical use [1, 3–7]. Although these amyloid PET tracers correlate well with postmortem histopathology [1, 3], less is known about their impact on clinical decision-making and patient outcomes.

The need to assess the effectiveness of amyloid imaging in clinical practice is addressed in this issue of *Dementia and Geriatric Cognitive Disorders Extra* by Frederiksen et al. [3]. The study examined the diagnostic value of PiB-PET imaging in 57 memory clinic patients (mean age: 65.7 years) who had cognitive impairment of uncertain etiology despite extensive clinical workup prior to the scan. The PiB-PET scan led to diagnostic reclassification in a total of 13 (23%) patients, most commonly in cases with indeterminate etiology prior to the scan. The number of patients that had to undergo the scan for one change in diagnosis (number needed to test, NNT) was 4.4 for all diagnostic categories. Furthermore, the clinicians' overall confidence increased in 28 (49%) patients and their confidence to confirm or rule out AD increased in the majority of cases, including cases that were not reclassified. As such, this

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is the first study to document the value of a binary PiB-PET scan read (as positive or negative) on clinical diagnostic planning.

While these results clearly show the diagnostic value of amyloid PET imaging, some limitations of the study should be highlighted. The study's implementation in a specialized center and the very extensive workup subjects underwent prior to the scan (e.g. extensive cognitive testing, CSF markers, FDG-PET, SPECT scan) makes it likely that the study may have significantly underestimated the utility of amyloid PET scans. The current workup in general practice mainly consists of simple cognitive screening tests (such as the MMSE) and a structural brain scan (e.g. CT). In such settings, where diagnostic uncertainty is higher, it is likely that amyloid PET imaging may have a greater impact and a smaller NNT. Since there was no control group and since participants were not followed longitudinally, this study cannot determine if amyloid PET information translates into improved outcomes or more optimized patient care.

^{11}C-PiB was the first β-amyloid PET ligand, but its short half-life limits wide use of this agent outside research settings [1]. Efforts to develop agents that would allow wider clinical use have led to the development of ^{18}F-PET ligands, such as ^{18}F-florbetapir and ^{18}F-florbetaben [1, 3–7]. ^{18}F-florbetapir PET imaging was recently approved by the FDA for the detection of neuritic amyloid plaques in the context of evaluating patients with progressive cognitive decline [3]. A negative scan, suggestive of sparse to no plaques, would be inconsistent with a pathologic diagnosis of AD and hence would allow a clinician to focus on other possible causes for the cognitive impairment. A positive scan, indicative of moderate to frequent plaques, is not specific for AD since this can also be seen in other conditions, such as dementia with Lewy bodies or aging [1, 3].

The findings of Frederiksen et al. [3] suggest that clinicians are likely to use both positive and negative scans in their diagnostic planning since the positive scan may provide useful information in the context of other available clinical information and history. The study also shows that, even at top expert centers where patients have undergone extensive workup, the scans are likely to confer additional value. These findings have recently been confirmed in a multicenter study of ^{18}F-florbetapir PET imaging, which showed that amyloid PET significantly improved clinician confidence and also significantly impacted diagnostic and treatment planning in cognitive disorder patients with diagnostic uncertainty [5]. ^{18}F-florbetaben PET has also been shown to increase the confidence of AD diagnosis and influence the management of cognitively impaired patients [6]. Taken together, these studies suggest considerable promise for amyloid PET imaging to enhance diagnostic accuracy and also suggest that clinicians are likely to place heavy emphasis on the scans. These data have important implications since an incorrect diagnosis of AD can have devastating consequences on a patient's work and home life.

As with any technological innovation, it is essential to ensure new costly technology helps rather than hurts patients and society. Therefore, it is important to educate both clinicians and nuclear medicine physicians about the strengths and limits of amyloid PET imaging and its judicious use. The risks of PET scanning, such as radiation and the possibility of incorrect interpretation, must be borne in mind. Although there is accumulating data supporting a possible prognostic utility for amyloid PET [7], it is not currently indicated as a predictive or screening tool and is not diagnostic by itself but an adjunct to clinical examination and history. While existing studies document the potential clinical utility of amyloid PET imaging, the results of randomized controlled trials testing its effects on outcomes and cost of care will more definitively guide the integration of amyloid PET imaging into routine patient care.

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