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Critical review of the Appropriate Use Criteria for amyloid imaging: Effect on diagnosis and patient care

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Abstract

Introduction: The utility of the Appropriate Use Criteria (AUC) for amyloid imaging is not established.
Methods: Fifty-three cognitively impaired patients with clinical F^{18}-florbetapir imaging were classified as early and late onset, as well as AUC-consistent or AUC-inconsistent. Chi-square statistics and *t* test were used to compare demographic characteristics and clinical outcomes as appropriate.
Results: Early-onset patients were more likely to be amyloid positive. Change in diagnosis was more frequent in late-onset cases. Change in therapy was more common in early-onset cases. AUC-consistent and AUC-inconsistent cases had comparable rates of amyloid positivity. We saw no difference in the rate of treatment changes in the AUC-consistent group as opposed to the AUC-inconsistent group.
Discussion: The primary role of amyloid imaging in the early-onset group was to confirm the clinically suspected etiology, and in the late-onset group in detecting amyloid-negative cases. The rate of therapeutic changes was significantly greater in the early-onset cases.

Keywords: Appropriate use criteria (AUC); Positron emission tomography (PET); Amyloid; Alzheimer's disease (AD); Mild cognitive impairment (MCI)

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder and the sixth most common cause of death in the United States [1]. A recent evaluation of the accuracy of clinical diagnosis compared to the gold standard (postmortem observations) demonstrated that dementia experts show only modest accuracy when diagnosing AD, with sensitivity ranging from 71% to 87% and specificity ranging from 44% to 71% [2]. Several dementing disorders—hippocampal sclerosis, frontotemporal, Lewy body, vascular, and tangle-only dementia—were commonly mistaken for AD dementia. Among cases thought to harbor non-AD pathology, 39% showed histopathology meeting or exceeding the AD pathologic threshold [2].

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Recent biomarker developments have reshaped the way clinicians perceive AD in terms of clinical staging and pathology progression. Two significant advances—the positron emission tomography (PET) ligands with high affinity for amyloid plaques [3] and neurofibrillary tangles [4]—enable us to visualize AD pathology in vivo. Three amyloid PET imaging compounds are now Food and Drug Administration (FDA) approved and available for clinical use [5–10]. A recent meta-analysis [11] reviewed the diagnostic performance of F^{18}-florbetapir, and F^{18}-florbetaben. Fourteen of the 16 articles included only cognitively normal (mean Mini-Mental State Examination [MMSE] score = 29.3) or dementia subjects (mean MMSE = 21.3). The two compounds demonstrated 89.6% and 89.3% sensitivity, 87.2% and 87.6% specificity, and odds ratios of 91.7 and 69.9, respectively [11]. Regardless, amyloid PET has not become an integral part of routine clinical care as Medicare and most other insurance carriers do not cover it. The major drawbacks cited by insurance carriers are (1) imperfect specificity [2], (2) ethical concern that cognitively normal individuals might be inappropriately scanned (i.e., there are no disease-modifying therapies available for intervention in this group), and (3) the lack of demonstrated cost-effectiveness [12].

In response to these concerns, the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging convened the Amyloid Imaging Task Force (AIT), a group of imaging and dementia specialists, to establish a set of recommendations for which patients and in which clinical scenarios amyloid PET is most appropriate [13,14]. The experts recognized that widespread diagnostic use of amyloid PET was not yet justified or feasible, but that the scan could result in clinical benefit when ordered by experts in specific clinical scenarios. In these Appropriate Use Criteria (AUC), experts outlined three clinical indications for the diagnostic use of amyloid PET imaging: (1) patients with progressive mild cognitive impairment (MCI) in which clinical uncertainty exists and the patient would benefit from greater certainty; (2) patients with dementia syndrome suggestive of AD, but with an atypical presentation or suspected mixed etiology; and (3) patients with early-onset progressive cognitive decline. These criteria are based on the evidence that approximately 40% to 60% of patients with amnestic MCI and 10% to 20% of clinically diagnosed AD dementia patients fail to show amyloid pathology on PET [15].

Another important guideline of the AUC for amyloid PET imaging is the recommendation that the responsibility for determining patients' eligibility should lie with medical professionals who have significant expertise in evaluating and treating patients with dementia defined as 25% or greater proportion of clinical practice devoted to cognitive disorders of the elderly [13]. This recommendation is based on the fact that for a diagnosis of dementia or MCI of the AD type to be established, the evaluating physician has to interpret and carefully consider the complex information contained in several critical parts of the workup, including the clinical and neuropsychological examinations, the laboratory workup, and structural and amyloid PET imaging. A final deliberation on disease stage (cognitively normal vs. MCI vs. dementia) and the presumed etiology can only be concluded after such thorough workup has been completed. Thus significant expertise and experience are deemed necessary.

Last, the committee recommended that amyloid PET scans be administered only when the scan results are expected to alter clinical management [13,14].

Given the lack of disease-modifying drugs for AD, the rationale for using amyloid PET imaging in diagnostic settings is to help with diagnostic and therapeutic decision-making and to improve health outcomes by counseling patients and families on diagnosis, prognosis, patient safety, and legal and financial issues. To date, only a few studies have investigated the impact of amyloid PET on patient diagnosis and management.

Grundman et al. [16] analyzed a data set consisting of 113 amyloid-positive and 116 amyloid-negative patients (some with objective cognitive decline and others with only cognitive complaints without objective cognitive decline). Subjects were recruited as part of a research study aiming to establish the impact of amyloid imaging in a much broader clinical population. All study physicians had previous experience in AD research and 52% had fellowship training in dementia. The AUC were retrofitted to determine whether the participants met the AIT recommendations (N = 125) or not (N = 104). The study revealed that diagnostic changes occurred in 55% of all cases. There was a 22% increase in physicians' diagnostic confidence after amyloid PET. Physicians made changes to their therapeutic plan in 88% of AUC-consistent and 86% of the AUC-inconsistent patients ($P = .69$). The use of cholinesterase inhibitors and memantine increased by 17% in amyloid-positive patients and decreased by 23% in amyloid-negative patients.

Ossenkoppele et al. [17] scanned a mix of early- and late-onset patients recruited from the outpatient clinics of the VU Medical Center in the Netherlands with Pittsburgh compound B. The authors reported 23% change in diagnosis and increase of diagnostic certainty for 71% to 81% after amyloid PET.

Zwan et al. [18] recently presented data regarding the benefits of amyloid PET in early-onset dementia which they defined as age of onset <70 years. Amyloid PET scans resulted in diagnostic change in 20% of the amyloid-positive cases and physicians' confidence in their clinical diagnosis increased from 76% to 90%.

Dell'Agnello et al. [19] reported that 47% of their AUC-consistent patients were amyloid positive compared with 62% of those who failed to meet the AUC recommendations. After a negative scan, the discontinuation rates of AD-targeting drugs were 20% among those who met the criteria versus 33% among those who did not.

Bensaïdane et al. [20] looked at 28 patients with an atypical dementia syndrome, 14 of which were amyloid positive and 14 amyloid negative. They reported diagnostic changes in 32.1% (17.8% changed from AD to non-AD, 14.3% from