Title

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Journal

Alzheimer's & Dementia Diagnosis Assessment & Disease Monitoring, 5(1)

ISSN

2352-8729

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Publication Date

2016

DOI

10.1016/j.dadm.2016.12.001

Peer reviewed

Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 5 (2016) 15-22

Alzheimer's & Dementia

Neuroimaging

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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http://dx.doi.org/10.1016/j.dadm.2016.12.001

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

non-AD to AD diagnosis). They also reported a 44% increase in diagnostic confidence. Altered management occurred in 71.4% of cases.

Boccardi et al. [21] recently presented data from a large cohort recruited from outpatient clinics for an amyloid PET research study. The final cohort consisted of 126 patients meeting AUC and 21 who did not. Diagnostic changes occurred in 25% of AUC-consistent patients and 29% of AUC-inconsistent patients ($P = .79$). Therapeutic changes occurred in 33% versus 29% of the AUC-consistent versus inconsistent patients ($P = .81$).

While these studies seem to indicate that the amyloid PET scanning improves diagnostic accuracy, increases diagnostic certainty, and results in therapeutic changes, all but one [18] used convenience research cohorts who were recruited for other research studies. The study by Zwan et al. [18] focused solely on early-onset cases, though with a higher than conventional age cutoff. The present analysis is the first to examine an actual clinical population with patients from broad age range, as they were consecutively evaluated in a tertiary medical center. The purpose of our work was to examine the utility of the AUC for amyloid imaging using a case series approach.

2. Methods

2.1. Patient sample

Our data set consisted of all patients who received amyloid PET imaging with F^{18}-florbetapir for diagnostic purposes at University of California Los Angeles (UCLA) before December 2014 (N = 53). Twenty-eight of the cases were documented to have experienced cognitive decline after the age of 65 years (late onset) while 24 started declining before 65 years of age (early onset). Age of symptom onset was not documented in the chart for one case presenting at age 67 years with dementia syndrome and Mini-Mental State Examination (MMSE) score of 24. Forty-eight patients were evaluated by dementia experts. Of these, 35 met AUC. The 23 AUC-consistent early-onset cases, (AUC-consistent by definition - third criterion outlined above in Introduction), had the following pre-PET diagnoses: 11 AD, 6 primary progressive aphasia (PPA), 3 posterior cortical atrophy, 2 MCI, and 1 behavioral variant frontotemporal dementia (FTD) versus frontal-variant AD. Among the 25 late-onset cases, 12 were AUC-consistent and had pre-PET diagnoses of atypical AD (N = 6), MCI (N = 2), PPA (N = 3), and mixed dementia (N = 1). Of the 13 late-onset AUC-inconsistent cases, seven were thought to have dementia due to AD (two with logopenic progressive aphasia variant) and six with MCI due to AD.

The amyloid PET scans for the remaining five patients were ordered by UCLA stroke neurologists who did not meet criteria as dementia experts as proposed by the AUC. Three of these cases presented with lobar hemorrhages thought to be due to underlying cerebral amyloid angiopathy (CAA). One was diagnosed with dementia of undetermined etiology and one with MCI thought to be due to AD-type pathology. Of the same five patients, one experienced early onset of cognitive decline at the age of 47 years while the remainder had late onset (age of onset range 74–93 years). All five cases met the rest of the AUC and were grouped in the AUC-consistent group. As the ordering neurologists were not dementia experts, we also reran all analyses excluding these cases.

For the purposes of this study, post-PET therapeutic changes were defined as follows: (1) medications discontinued after amyloid-negative scan (N = 6) and (2) AD drugs such as cholinesterase inhibitors, memantine, or both started after the results of the PET scan (N = 27). The following were coded as no therapeutic changes as a result of the PET scan: (1) no medications were started (N = 5), (2) medications were not changed (N = 12), (3) medications were only titrated up but not initiated (N = 2). One case was lost to follow-up because of insurance coverage changes, and the medical chart did not indicate whether medications were instituted. This patient was excluded from the analyses of therapeutic changes.

2.2. F^{18}-florbetapir PET acquisition and interpretation

All patients were referred for F^{18}-florbetapir PET evaluation by the Nuclear Medicine Department of UCLA. All scans followed the FDA-approved F^{18}-florbetapir administration protocol and were clinically read by amyloid imaging–trained board-certified nuclear medicine physicians.

We analyzed all F^{18}-florbetapir scans with NeuroQ, an FDA-cleared software for PET image visualization and interpretation, to evaluate how quantitative interpretation of data compares with clinical reads. After correction for tissue-based attenuation, NeuroQ automatically measures the number of radioactive events emitted from each pixel and normalizes these measurements using whole cerebellum as a reference. The program then computes the mean standard uptake volume ratios (SUVRs) based on the Clark method [6] and derives a final mean SUVR value for each subject. Mean SUVR $\geq$1.17 was used as the quantitative cutoff for amyloid positivity [22].

2.3. Statistical methods

We assigned patients to groups based on age of symptom onset and consistency with the AUC. We used Student *t* test and chi-square statistics to compare demographic variables between groups and chi-square statistics to compare the rate of diagnostic and treatment change between groups.

3. Results

3.1. Early-onset versus late-onset comparisons

Subjects were classified based on age of onset (cutoff set at 65 years) as early onset (N = 24, age of onset

Table 1
Early-onset versus late-onset group characteristics

Variable	Early onset, N = 24	Late onset, N = 28	*P*-value
Age at disease onset, y	54.5 (5.7)	75.1 (5.6)	**<.0001**
Age at scan, y	58.9 (4.9)	79.4 (5.7)	**<.0001**
Disease duration	3.8 (2.9)	4.1 (2.4)	.7
Education, y	16.2 (2.2)	16.0 (2.7)	.8
Sex, M/F	9/15	14/14	.4
Positive family history, %	46	29	.2
New patient, %	50	53	.8
Positive amyloid PET read, %	80	57	**.016**
Mean SUVR	1.42 (0.28)	1.35 (0.31)	.4
SUVR > 1.17, %	88	61	**.03**
Change in diagnosis, %	17	43	**.041**
Change in therapy, %	79	59	.13

Abbreviations: PET, positron emission tomography; SUVR, standard uptake volume ratio.
NOTE. Bold text indicates significant *P* value.

< 65 years) and late onset (N = 28; age of onset ≥ 65 years). Age of symptom onset was not documented in the chart for one case presenting at age 67 years with dementia syndrome and MMSE score of 24. Within the late-onset group, 15 cases were AUC-consistent and 13 AUC-inconsistent. Quantitative F^{18}-florbetapir analyses revealed one positive clinical read with mean SUVR of 0.94 and five negative clinical reads with mean SUVRs ranging between 1.30 and 1.44. All scans with disagreement between clinical and quantitative-based assignments occurred in late-onset cases.

There were no differences in sex, education, disease duration, and family history of dementia or proportion of new vs. established patients between early- and late-onset cases. As expected, early-onset cases were significantly younger at the time of symptom onset and at the time of scan ($P < .0001$ for both). A significantly greater proportion of early-onset compared with late-onset cases was amyloid positive (visual read 88% vs. 57%, $P = .016$, quantitative analyses 88% vs. 61%, $P = .03$; Table 1).

We observed significantly greater frequency of diagnostic change in late-onset compared with early-onset cases

Table 2
Diagnostic changes in the early-onset group

Case no.	Pre-PET diagnosis	Post-PET diagnosis (if different)	SUVR	Visual read
Cases with change in diagnosis				
EO1	PPA due to AD	PPA due to FTD	0.815	neg
EO2	PPA due to FTD	PPA due to AD	1.624	pos
EO3	FTD	Frontal variant AD	1.445	pos
EO4	MCI due to AD	Hippocampal sclerosis	0.616	neg
Cases without change in diagnosis				
EO5	AD dementia		1.315	pos
EO6	AD dementia		1.310	pos
EO7	AD dementia		1.531	pos
EO8	AD dementia		1.305	pos
EO9	AD dementia		1.358	pos
EO10	AD dementia		1.423	pos
EO11	AD dementia		1.470	pos
EO12	AD dementia		1.312	pos
EO13	AD dementia		1.696	pos
EO14	AD dementia		1.598	pos
EO15	AD dementia		1.655	pos
EO16	MCI due to AD		1.504	pos
EO17	PCA due to AD (MCI stage)		1.476	pos
EO18	PCA due to AD		1.526	pos
EO19	PCA due to AD		1.591	pos
EO20	PPA due to AD		1.639	pos
EO21	PPA due to AD		1.773	pos
EO22	PPA due to AD		1.772	pos
EO23	PPA due to FTD		1.054	neg
EO24	CAA due to AD		1.338	pos

Abbreviations: PET, positron emission tomography; SUVR, standard uptake volume ratio; PPA, primary progressive aphasia; AD, Alzheimer disease; neg, negative; pos, positive; MCI, mild cognitive impairment; PCA, posterior cortical atrophy; FTD, frontotemporal dementia; CAA, cerebral amyloid angiopathy.

Table 3
AUC-consistent versus AUC-inconsistent late-onset group characteristics

Variable	AUC-consistent, N = 15	AUC-inconsistent, N = 13	*P*-value
Age of disease onset, y	77.0 (5.8)	72.8 (4.6)	**.049**
Age at scan, y	81.6 (6.2)	76.8 (4.0)	**.025**
Disease duration	4.4 (2.8)	3.8 (2.0)	.5
Education, y	16.3 (2.4)	15.7 (3.1)	.6
Sex, M/F	7/8	7/6	.7
Positive family history, %	20	39	.3
New patient, %	47	62	.4
Positive amyloid PET read, %	47	69	.2
Mean SUVR	1.35 (0.36)	1.35 (0.26)	.98
SUVR > 1.17, %	60	77	.3
Change in diagnosis, %	53	23	.1
Change in therapy, %	43	77	*.072*

Abbreviations: AUC, Appropriate Use Criteria; PET, positron emission tomography; SUVR, standard uptake volume ratio.
NOTE. Bold text indicates significant *P* value. Italicized text indicates trending *P* value.

(43% vs. 17%, $P = .041$) but significantly greater rate of therapeutic changes in the early-onset cases (48% vs. 79%, $P = .022$). The results remained largely unchanged when we excluded the non–dementia experts' cases (diagnostic changes 48% vs. 17%, $P = .069$; treatment changes 52% vs. 83%, $P = .028$). There were a total of four diagnostic changes in the early-onset group after amyloid PET results were available (Table 2). Two cases were amyloid positive and two were amyloid negative.

Among the 21 amyloid-positive early-onset cases, both acetylcholinesterase inhibitors (AChEIs) and memantine were initiated in five cases, only AChEIs were initiated in four cases, and AChEIs were titrated up to therapeutic doses in another two cases (actual management). Memantine was added in eight cases and increased in one (actual management). Two patients who were already prescribed therapeutic doses of both AChEIs and memantine required no additional therapeutic intervention. In one case of amyloid angiopathy with a positive amyloid PET scan, the physician (a non–dementia expert) did not recommend any therapy.

Dementia experts discontinued memantine in two of the three amyloid-negative early-onset cases. The third amyloid-negative case was already on donepezil when first evaluated but could not follow up with a dementia expert at UCLA due to change in insurance. Whether his/her outside physician discontinued donepezil in response to the results from the scan was not documented. This case was excluded from our treatment change analyses.

3.2. AUC-based comparisons within the late-onset group

The AUC-inconsistent patients were significantly younger at disease onset and at the time of PET compared with the AUC-consistent group (Table 3). There were no

Table 4
Diagnostic changes in the late-onset AUC-consistent group

Case	Pre-PET diagnosis	Post-PET diagnosis (if different)	SUVR	Visual read
Cases with change in diagnosis				
LO1	Atypical MCI	MCI secondary to SNAP/anxiety	1.061	neg
LO2	PPA (presumed non-AD)*	PPA due to AD	1.368	pos
LO3	PPA (presumed non-AD)*	PPA due to AD	1.637	pos
LO4	AD with CAA	No AD pathology	1.144	neg
LO5	Atypical MCI (presumed non-AD)*	MCI due to AD	2.002	pos
LO6	Mixed dementia	Vascular dementia	0.874	neg
LO7	Vascular cognitive impairment (VCI)	Mixed VCI and AD	1.291	pos
LO8	Possible AD	Dementia due to drug abuse	0.916	neg
Cases without change in diagnosis				
LO9	Atypical MCI (presumed non-AD - depression)*		1.429	neg
LO10	PPA (presumed non-AD)*		1.120	neg
LO11	Atypical MCI (presumed SNAP)		0.998	neg
LO12	Atypical AD		1.431	pos
LO13	Atypical AD		2.050	pos
LO14	CAA due to AD		1.508	pos
LO15	DLB		1.444	neg

Abbreviations: AUC, Appropriate Use Criteria; PET, positron emission tomography; SUVR, standard uptake volume ratio; MCI, mild cognitive impairment; pos, positive; neg, negative; SNAP, suspected non-AD pathophysiology; PPA, primary progressive aphasia; AD, Alzheimer disease; DLB, dementia with Lewy bodies; CAA, cerebral amyloid angiopathy.
*Physician-suspected non-AD pathology (with AD in the differential diagnosis).

differences in sex, education, disease duration, family history of dementia, proportion of new versus established patients, mean SUVR, and proportion of amyloid positive by visual read or quantitative determination between late-onset AUC-consistent and AUC-inconsistent cases (Table 3).

There were a total of eight diagnostic changes (53%) in the AUC-consistent group and three diagnostic changes (23%) in the AUC-inconsistent group ($P = .1$, Tables 4 and 5).

Interestingly, despite the trend for greater rate of diagnostic changes in the AUC-consistent group, treatment changes tended to be more frequent in the AUC-inconsistent group (62% vs. 36%, $P = .18$). The AUC-inconsistent cases were more likely to be new patients relative to AUC-consistent patients, but this difference failed to reach statistical significance (62% vs. 47%, $P = .43$; Table 4). The findings remained unchanged after excluding cases evaluated by non–dementia experts (AUC-inconsistent 67% vs. AUC-consistent 36%, $P = .15$).

3.3. Discrepant visual versus quantitative amyloid PET results

One of the positive clinical reads with normal SUVR (SUVR = 0.94) was in a patient who was already on donepezil. No changes were made after the scan as the visual interpretation supported the treatment. The SUVR was estimated later in the context of this publication at a time when the patient was no longer under the care of the dementia specialist.

There were five negative clinical reads with SUVR in the positive range (1.30–1.44). In three of these cases, the dementia expert strongly suspected false-negative reads and increased donepezil to therapeutic dose in one and added memantine in two. In the remaining two cases, the dementia expert discontinued donepezil. The physician initially discontinued donepezil in the fourth case. After the quantitative analyses showed high SUVR indicative of moderate-to-severe amyloid plaque pathology, the physician restarted donepezil and added memantine later on. The final clinically interpreted as negative but SUVR-positive case was in follow-up diagnosed with dementia with Lewy bodies (DLB), and rivastigmine and later memantine were prescribed.

After careful review of the false-negative and false-positive scans by two of the senior authors (L.G.A. and D.H.S.), the misinterpretation of the scans was attributed to poor scan quality, possible late acquisition, and brain atrophy.

4. Discussion

The AUC were developed to help define a clinical cohort of patients most likely to benefit from amyloid PET scans during their diagnostic workup for cognitive decline. The premises for developing these criteria were both scientific and economic. Our study is, to our knowledge, the first outpatient consecutive clinical case series within the United States that serves to evaluate the utility of the AUC in both early- and late-onset cases.

The late-onset AUC-consistent cases had high rates of both diagnostic and treatment changes, strongly arguing for the value of amyloid imaging for diagnostic refinement in this cohort. Our early-onset cases showed very high rate of amyloid positivity and significantly higher rate of therapeutic changes compared with the late-onset cases. The high rate of amyloid positivity could have, at least in part, been the result of selective referral of cases with high likelihood of AD for amyloid PET imaging. One plausible explanation for the high rate of therapeutic changes could be that these difficult-to-diagnose cases are often referred drug-naïve by their private practice physicians. Thus we can conclude that amyloid imaging for these two groups of

Table 5
Diagnostic changes in the late-onset AUC-inconsistent group

Case no.	Pre-PET diagnosis	Post-PET diagnosis (if different)	SUVR	Visual read
Cases with change in diagnosis				
LO16	Probable AD	SNAP	0.941	pos
LO17	Probable AD	SNAP	1.415	neg
LO18	MCI due to AD	MCI secondary to SNAP	0.795	neg
Cases without change in diagnosis				
LO19	MCI due to AD		1.335	pos
LO20	MCI due to AD		1.663	pos
LO21	MCI due to AD		1.593	pos
LO22	MCI due to AD		1.577	pos
LO23	MCI due to AD		1.357	neg
LO24	Probable AD		1.134	pos
LO25	Probable AD		1.504	pos
LO26	Probable AD		1.582	pos
LO27	Probable AD		1.304	neg
LO28	Probable AD vs. DLB		1.401	pos

Abbreviations: AUC, Appropriate Use Criteria; PET, positron emission tomography; SUVR, standard uptake volume ratio; AD, Alzheimer disease; SNAP, suspected non-AD pathophysiology; pos, positive; neg, negative; MCI, mild cognitive impairment; DLB, dementia with Lewy bodies

patients is both meaningful in terms of establishing the underlying etiology and for implementing appropriate therapeutic changes.

Patients with cognitive decline in whom the etiology of AD is deemed to be highly likely are not recommended by the AIT for amyloid PET scanning as it is thought that such patients will likely have amyloid pathology. Yet our data show that amyloid-negative scans are fairly common in the AUC-inconsistent group, with as many as 23% demonstrating SUVRs <1.17. Proportionately, this rate corresponds well to the documented range of diagnostic sensitivity of 71% to 87% reported in a recent comprehensive analysis of a large data set with postmortem validation [2]. Given that in all such cases our physicians changed their diagnostic considerations and treatment plans, one might conclude that amyloid PET would also be of value in imaging these subjects.

As we compare our results with those of others, we notice several agreements and disagreements. We found significantly greater amyloid-positive rates among early-onset cases as opposed to late-onset cases, in agreement with the work of others [23]. Similar to Dell'Agnello et al. [19], we observed a greater proportion of amyloid-positive cases among the AUC-inconsistent group as opposed to the AUC-consistent group (69% vs. 47% visual read, 77% vs. 60% quantitative read).

One European study [21] reported no difference in change in diagnosis between the AUC-consistent and AUC-inconsistent groups and concluded that the AUC do not have a convincing impact on change in diagnosis. This is consistent with our results.

The two studies that reported treatment changes were both done in cohorts recruited for research studies that involve amyloid PET. The European study [21] reported low rates of treatment changes that were not significantly different between the groups (AUC-consistent 33% vs. AUC-inconsistent 29%, $P = .81$). Similarly, the US study [16] reported high rates of treatment changes that were not significantly different between the groups (AUC-consistent 88% vs. AUC-inconsistent 86%, $P = .9$). This twice observed lack of significance is in agreement with our findings (62% vs. 36%, $P = .18$).

Taken together, our findings and those of others suggest that more studies with larger patient cohorts are needed to definitively determine whether amyloid PET information can result in therapeutic benefits. One such study—the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS)—is now actively recruiting in the United States. The study proposes to enroll more than 18,000 Medicare beneficiaries with the goal to ascertain whether the scan changes management and improves patient-oriented outcomes.

Several strengths and limitations of our work are worth noting. This is to our knowledge the first outpatient clinical case series that evaluates the utility of the AUC in both early- and late-onset cases. This study examined preexisting medical records. At the time of all patient evaluations, our chart review and analyses were not yet planned; hence, the physicians' pre- and post-PET diagnostic impressions, etiological considerations, and treatment plans were completely unbiased. The major limitation of our study is the relatively small sample size and the lack of follow-up for some of the cases. In addition, some otherwise qualified patients might not have had amyloid PET imaging because of financial reasons. We do not know whether these patients would be qualitatively different than the ones we studied here. The patients seen in our institution cannot be considered representative of the general population as they often have higher mean education and socioeconomic status. Both of these factors have been associated with high rates of referral to subspecialists and academic memory clinics. The impact of amyloid PET on the utilization of additional services such as support groups, counseling, legal and health care benefit planning, utilization of retirement benefits, etc. by patients and families was not available for our analyses. Owing to the retrospective nature of the study, we do not have data on change in physicians' confidence in diagnosis, their stipulation whether the subject suspected to have AD has probable versus possible AD, and any other factors that might affect their decision-making. In addition, we do not have information on their apolipoprotein (*APOE*) genotype, which could have enriched our discussion as the risk variant *APOE* ε4 conveys significant risk for presence of brain amyloidosis.

In conclusion, our case series suggests that amyloid imaging information frequently results in both diagnostic and treatment plan changes. At least in the hands of the dementia experts who took part in this study, it seems that the benefit for the early-onset group lies in confirming the presence of cortical amyloid consistent with a diagnosis of AD, which prompted the referral for the amyloid PET scan in the first place, whereas the benefit for the late-onset group lies in identifying amyloid-negative cases. In both groups, physicians made therapeutic changes in over two-thirds of the cases. Our results also suggest that patients who do not fall within the AUC are perhaps no less likely to benefit from amyloid imaging than patients meeting AUC. In fact, in a typical clinical series of patients, they may have as a group more to gain overall from the information that amyloid imaging provides. Future studies employing large-scale well-designed prospective clinical protocols will be needed to further clarify the impact of amyloid PET on patient and family well-being.

Acknowledgment

Funding: This work was supported by the National Institutes of Health (R01 AG040770, K02 AG048240, NIA P50 AG16570, NIA P30 AG010133, and NIA U01AG024904) and the Easton Consortium for Alzheimer's Drug Discovery and Biomarker Development.

RESEARCH IN CONTEXT

1. Systematic review: The literature on the utility of amyloid PET for patient care has been sparse. The vast majority of published studies report convenience research cohorts (i.e., recruited for other research studies). The single outpatient clinical settings' report focused on early-onset cases. Our study examines an actual consecutively evaluated outpatient clinical population with a broad age range.
2. Interpretation: The role of amyloid imaging in the early-onset group was to confirm the suspected etiology and in the late-onset group to detect amyloid-negative cases. Patients who do not fall within the AUC are as likely to benefit from amyloid imaging as patients who do not. Treatment plan changes occurred in a substantial majority of the AUC-inconsistent cases, but only in a minority of the AUC-consistent cases.
3. Future directions: Large-scale, well-designed prospective clinical studies will be needed to further clarify the impact of amyloid PET on patient and family well-being.

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