Practical utility of amyloid and FDG-PET in an academic dementia center

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ABSTRACT

Objective: To evaluate the effect of amyloid imaging on clinical decision making.

Methods: We conducted a retrospective analysis of 140 cognitively impaired patients (mean age 65.0 years, 46% primary β-amyloid (Aβ) diagnosis, mean Mini-Mental State Examination 22.3) who underwent amyloid (Pittsburgh compound B [PiB]) PET as part of observational research studies and were evaluated clinically before and after the scan. One hundred thirty-four concurrently underwent fluorodeoxyglucose (FDG)-PET. We assessed for changes between the pre- and post-PET clinical diagnosis (from Aβ to non-Aβ diagnosis or vice versa) and Alzheimer disease treatment plan. The association between PiB/FDG results and changes in management was evaluated using χ^2 and multivariate logistic regression. Postmortem diagnosis was available for 24 patients (17%).

Results: Concordance between scan results and baseline diagnosis was high (PiB 84%, FDG 82%). The primary diagnosis changed after PET in 13/140 patients (9%) overall but in 5/13 (38%) patients considered pre-PET diagnostic dilemmas. When examined independently, discordant PiB and discordant FDG were both associated with diagnostic change (unadjusted $p < 0.0001$). However, when examined together in a multivariate logistic regression, only discordant PiB remained significant (adjusted $p = 0.00013$). Changes in treatment were associated with discordant PiB in patients with non-Aβ diagnoses (adjusted $p = 0.028$), while FDG had no effect on therapy. Both PiB (96%) and FDG (91%) showed high agreement with autopsy diagnosis.

Conclusions: PET had a moderate effect on clinical outcomes. Discordant PiB had a greater effect than discordant FDG, and influence on diagnosis was greater than on treatment. Prospective studies are needed to better characterize the clinical role of amyloid PET. ***Neurology*® 2014;82:230–238**

GLOSSARY

Aβ = β-amyloid; **AD** = Alzheimer disease; **AUC** = appropriate use criteria; **CBS** = corticobasal syndrome; **CDR** = Clinical Dementia Rating; **Che-I** = cholinesterase inhibitor; **CMS** = Centers for Medicare & Medicaid Services; **DLB** = dementia with Lewy bodies; **FDG** = fluorodeoxyglucose; **FTD** = frontotemporal dementia; **MCI** = mild cognitive impairment; **PiB** = Pittsburgh compound B; **UCSF** = University of California, San Francisco.

PET ligands that bind to fibrillar β-amyloid (Aβ) enable the in vivo detection of amyloid plaques, a core feature of Alzheimer disease (AD) pathology.[1] Use of the first Aβ-specific tracer, Pittsburgh compound B (PiB), has been limited to research centers because of the short half-life of the carbon-11 radiolabel (20 minutes). Aβ tracers labeled with fluorine-18 (^{18}F, $t_{1/2}$ = 110 minutes) have subsequently been developed for clinical use, with one recently approved by the US Food and Drug Administration.[2] Few studies have evaluated the effect of amyloid PET on patient diagnosis and treatment.[3–6] In a recent decision, the US Centers for Medicare & Medicaid Services (CMS) concluded that there are insufficient data that amyloid imaging affects clinical outcomes to justify reimbursing scans.[7]

Our center has conducted research studies applying PiB and ^{18}F-fluorodeoxyglucose (FDG)-PET to evaluate the utility of PET in differential diagnosis[8] and to study mechanisms of AD.[9–12]

Supplemental data at www.neurology.org

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Although these studies were not designed to assess clinical decision making, scan results were provided to clinicians and could be taken into account in patient management. Here we report a retrospective analysis of the association between PET results and subsequent changes in diagnosis and AD drug treatment. We hypothesized that PiB-PET would have a greater effect than FDG on diagnosis and treatment, given its biochemical specificity for amyloid neuropathology. While we cannot control for additional variables that may have affected these outcomes (e.g., evolution of symptoms, availability of additional test results), this analysis provides a preliminary view into the influence of PiB and FDG on clinical decision making at an academic dementia center.

METHODS

Subject selection and baseline clinical evaluation. We searched the University of California, San Francisco (UCSF) Memory and Aging Center database and identified 140 patients who had undergone amyloid (PiB) PET and been assessed clinically before and after the scan, out of a total of 174 cognitively impaired patients studied with PiB between 2005 and 2011. Scans were performed under research protocols evaluating the utility of PiB in the differential diagnosis of AD and frontotemporal dementia (FTD) spectrum disorders and studies assessing the relationship between amyloid deposition and clinical phenotype in AD.[8–12] Patients with unstable medical comorbidities, brain mass lesions, and significant cerebrovascular disease were not eligible. The pre-PET clinical evaluation included an assessment by a behavioral neurologist, a caregiver interview, cognitive testing, and structural neuroimaging. CSF AD biomarkers were not available. Clinical diagnosis was made by consensus at a multidisciplinary conference. Up to 3 items could be listed on the "differential diagnosis," ranked in order of likelihood. Diagnosis was made based on best clinical judgment, although 89% of patients met published research criteria for their primary clinical diagnosis.[13–19] A detailed description of the diagnostic process is provided in appendix e-1 on the *Neurology*® Web site at www.neurology.org.

PET interpretation. Patients underwent PiB-PET (100%) and FDG-PET (96%) at Lawrence Berkeley National Laboratory.[8] PET scans were visually interpreted by an experienced rater (W.J.J. or G.D.R.) as positive/negative for cortical tracer uptake (PiB+/PiB−), as previously described and validated compared to quantitative classification.[8] FDG scans were rated as consistent with "AD" or its variants (including dementia with Lewy bodies [DLB]) if hypometabolism primarily involved the temporoparietal cortex, posterior cingulate/precuneus, or occipital cortex. Scans were rated as "non-AD" if hypometabolism primarily involved the frontal or anterior temporal cortex (FTD pattern)[8] or appeared within normal limits. Beyond these guidelines, raters were allowed to exercise clinical judgment in classifying scans. PiB and FDG ratings were performed blinded to clinical data and at separate sessions, with PiB reads blinded to FDG results and vice versa. When both reads were complete, the responsible clinician was provided a report that included the dichotomous classification of each scan and a written description of each tracer's spatial binding pattern.

Post-PET clinical assessment. The post-PET visit included a clinical evaluation and review of PET results. Repeat cognitive testing was performed in 54% of patients and repeat MRI was available in 49%. Diagnosis was made by consensus.

Ascertainment of AD drug treatment. Patient charts were reviewed retrospectively by a research associate (P.M.G.) to determine the use of AD symptomatic medications (donepezil, galantamine, rivastigmine, and memantine) at the pre- and post-PET visits.

Neuropathologic studies. Autopsies followed standard procedures for the evaluation of dementia.[20] Consensus neuropathologic criteria were used for AD[21] and frontotemporal lobar degeneration spectrum disorders.[22] Autopsies were performed at UCSF (n = 22), University of Pennsylvania (n = 1), and University of California, Los Angeles (n = 1).

Standard protocol approvals, registrations, and patient consents. Written informed consent was obtained from all patients or surrogates. The study was approved by the University of California (San Francisco and Berkeley) and Lawrence Berkeley National Laboratory institutional review boards for human research.

Data analysis. Pre-PET clinical diagnoses were divided into "Aβ" or "non-Aβ" categories based on the association of the clinical syndrome with amyloid pathology (table 1). Aβ diagnoses consisted primarily of "typical" (memory-predominant) and atypical presentations of AD.[23,24] The non-Aβ category consisted primarily of clinical variants of FTD. Patients with corticobasal syndrome (CBS) were split into suspected AD (CBS-AD) or non-AD (CBS-non-AD) pathology (see appendix e-1).[20] Amnestic mild cognitive impairment (MCI) was included in the Aβ category, and nonamnestic MCI was considered a non-Aβ diagnosis.[18] In cases with multiple items listed on the differential diagnosis, the first diagnosis listed was considered "primary." Patients in whom both an Aβ and a non-Aβ diagnosis were listed on the differential diagnosis were considered "diagnostic dilemmas."

The primary predictor of interest was concordance between PET reads and clinical diagnosis. PiB+/FDG-AD scans were considered concordant with an Aβ diagnosis, while PiB−/FDG-non-AD scans were considered concordant with a non-Aβ diagnosis. The primary outcomes were defined as changes in 1) primary diagnosis, and 2) AD drug treatment between the pre- and post-PET visits. Change in primary diagnosis was defined as a change in the first-listed diagnosis from Aβ to non-Aβ or vice versa. Change in AD drug treatment was defined as initiating or discontinuing cholinesterase inhibitors (ChE-Is) or memantine.

We first assessed the relationship between PET results and clinical outcomes separately for PiB and FDG using χ^2 or Fisher exact tests. Next, we assessed the impact of discordant PiB and discordant FDG together on each outcome by including both in the same logistic regression model. Finally, we performed logistic regression predicting each outcome when accounting for all of the following predictors: discordant PiB, discordant FDG, diagnostic dilemma pre-PET, sex, age at PET $<$ 65 years, baseline Aβ diagnosis, "new patient" (followed at our center for less than 1 year), and Clinical Dementia Rating (CDR) $<$ 1.

RESULTS

PET concordance with clinical diagnosis. The cohort was relatively young, mildly impaired,

Table 1 Clinical and demographic characteristics of patients

Age at PET, y	65.0 ± 8.2
Sex (female), %	41
New patients (followed <1 year), %	55
MMSE	22.7 ± 9.0
Diagnostic dilemmas, %	19
Months pre- to post-PET visit	9.6 ± 5.8
Primary clinical diagnosis (Aβ/non-Aβ), %	46/54
Baseline AD treatment (ChE-I/memantine), %	47/39
CDR < 1, %	42[a]
Pre-PET clinical diagnosis, n (% total)	
Aβ	
AD	25 (17)
PPA: logopenic variant	11 (8)
AD: frontal variant	6 (4)
Posterior cortical atrophy	14 (10)
Amnestic MCI	1 (1)
CBS-AD	6 (4)
Non-Aβ	
Nonamnestic MCI	9 (6)
bvFTD	27 (19)
PPA: nonfluent variant	10 (7)
PPA: semantic variant	15 (11)
CBS-non-AD	12 (9)
Other[b]	4 (3)

Abbreviations: Aβ = β-amyloid; AD = Alzheimer disease; bvFTD = behavioral variant frontotemporal dementia; CBS-AD = corticobasal syndrome with expected AD pathology; CBS-non-AD = corticobasal syndrome with expected non-AD pathology; CDR = Clinical Dementia Rating; ChE-I = cholinesterase inhibitor; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; PPA = primary progressive aphasia.
Continuous variables displayed as mean ± SD.
[a] Data missing for 5 patients.
[b] Prion disease, paraneoplastic syndrome, traumatic brain injury, psychiatric.

and most were new patients (table 1). Overall concordance between scan results and pre-PET diagnosis was 84% for PiB and 82% for FDG. PiB concordance was higher than FDG concordance in typical AD, and PiB concordance was higher in AD than in CBS (figure, A). PiB concordance was higher in more-impaired patients (figure, B) but was not affected by age at onset (figure, C). Overall, PiB and FDG agreed in classifying 83% of patients. Two PiB scans were considered "borderline" positive based on focal cortical uptake. These scans were rated PiB+, but the focal distribution of tracer binding was described in the report.

Diagnostic changes. The primary diagnosis changed after PET in 13/140 patients (9%). The independent associations between each predictor and change in diagnosis are shown in table 2 (unadjusted p). Tested separately, discordant PiB and discordant FDG results were both strongly associated with diagnostic change. There was a trend for changes to be more common in patients who presented as pre-PET diagnostic dilemmas (table 2).

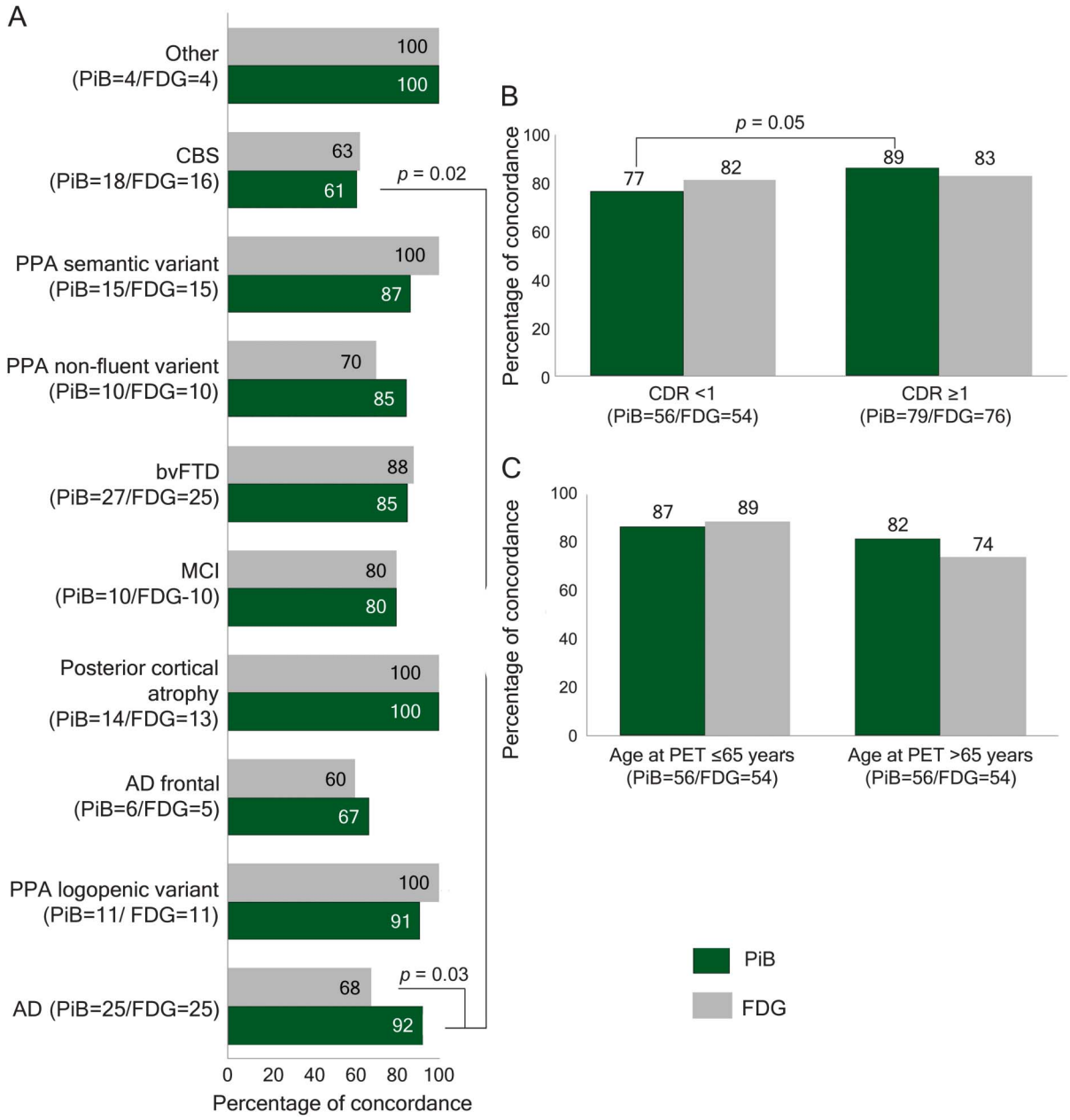
When including both PET scans as predictors in a single logistic regression model, diagnostic changes were associated with discordant PiB ($p < 0.0001$) but not discordant FDG ($p = 0.27$). This is further demonstrated in table 3, which relates diagnostic changes to combinations of PiB and FDG results. Diagnostic changes were most likely when both scans were discordant (8/11), whereas no changes were made when FDG was discordant but PiB agreed with the clinical diagnosis (0/12). Results of the full logistic regression model are presented in table 2 (adjusted p). Changes in diagnosis were associated with discordant PiB and "new patient" status. Discordant FDG was not significant in the full model.

Clinical uncertainty. The number of diagnostic dilemmas decreased from 19% pre-PET to 11% post-PET ($p = 0.09$), with resolution of 14 pre-PET dilemmas but creation of 4 new dilemmas (table e-1).

Treatment changes. Changes in AD drug treatment and their relation to PET results are shown in table e-2. Neither discordant PiB nor discordant FDG was associated with treatment changes when assessed separately (PiB unadjusted $p = 0.33$, FDG unadjusted $p = 0.48$) or in the same model (PiB $p = 0.36$, FDG $p = 0.72$). In the full logistic regression model, there was a trend for an association with discordant PiB (adjusted $p = 0.07$). This finding was significant in the subset of patients with a non-Aβ syndrome (unadjusted $p = 0.054$, adjusted $p = 0.028$). In a post hoc analysis we found that this effect was driven by changes in ChE-Is (unadjusted $p = 0.02$, adjusted $p = 0.015$).

Neuropathology-confirmed cases. Autopsies were available for 24 patients (17%, mean time between PET and death 36.7 ± 4.3 months, table 4). PiB results were consistent with the presence or absence of pathologically confirmed AD (threshold of National Institute on Aging–Reagan intermediate likelihood)[21] in 23/24 of cases, while FDG correctly classified 21/23 patients. In one patient, clinical diagnosis was correctly changed from CBS-AD to CBS-non-AD after PET scans showed PiB−/FDG-non-AD—postmortem diagnosis was corticobasal degeneration. Clinical diagnosis was appropriately left unchanged (from primary progressive aphasia, nonfluent variant) in a patient with a discordant PiB+ scan but FDG-non-AD who was subsequently

Figure Concordance between pre-PET clinical diagnosis and PET results



Numbers refer to number of subjects. (A) Concordance between specific clinical diagnoses and PET. (B) Concordance vs level of impairment, stratified by CDR. (C) Concordance vs age at onset. Significant differences in concordance are indicated with respective *p* values. AD = Alzheimer disease; bvFTD = behavioral variant frontotemporal dementia; CBS = corticobasal syndrome; CDR = Clinical Dementia Rating; FDG = fluorodeoxyglucose; MCI = mild cognitive impairment; PiB = Pittsburgh compound B; PPA = primary progressive aphasia.

found to have primary Pick disease with AD copathology.[25] One patient with low-likelihood AD had a borderline PiB+ scan, possibly due to the presence of frequent diffuse Aβ plaques, which are also known to bind PiB.[26] The PiB result did not lead to a change in the primary non-Aβ diagnosis. Four diagnostic dilemmas were correctly resolved after PET, and ChE-Is were appropriately stopped in 2 patients.

DISCUSSION We report on the relationship between amyloid and FDG-PET results and changes in clinical management in a large and heterogeneous sample of cognitively impaired patients seen at an academic dementia center. Overall, we found a high concordance between the initial clinical diagnosis and both PiB and FDG results, suggesting a confirmatory role for the scans in most patients. Changes in the primary diagnosis occurred in a small percentage of cases (9%). When changes were made they were strongly associated with discordant PiB, whereas the effect of discordant FDG was not significant on multivariate analysis. The influence of PET on AD

Table 2 Factors associated with diagnostic changes

Predictors	No diagnostic change (n = 127), %	Diagnostic change (n = 13), %	Unadjusted[a] p	Adjusted[a] p
Age < 65	54	54	0.98	0.39
Female	41	45	0.72	0.23
Aβ pre-PET clinical diagnosis	46	46	0.97	0.87
Dilemma pre-PET	17	38	0.053	0.62
PiB discordant with pre-PET clinical diagnosis	8	92	<0.0001	0.00013
FDG discordant with pre-PET clinical diagnosis	13	62	<0.0001	0.087
CDR < 1[b]	41	46	0.72	0.26
New patient (followed <1 year)	55	69	0.32	0.04

Abbreviations: Aβ = β-amyloid; CDR = Clinical Dementia Rating; FDG = fluorodeoxyglucose; PiB = Pittsburgh compound B.
[a] Unadjusted *p* values were derived from univariate comparisons. Adjusted *p* values were derived from a logistic regression that includes all predictors in the model.
[b] Data missing for 5 patients.

therapy was more modest, although again PiB had a stronger effect than FDG. Overall, our data support a limited clinical role for amyloid imaging.

The high concordance between amyloid PET and clinical diagnosis in our study (84%) explains the low rate of diagnostic changes. Concordance rates in previous studies have varied between 58% and 82%, depending on the complexity of included patients.[3–6]

Table 3 Combined PiB/FDG results and diagnostic changes

Pre-PET clinical diagnosis	PET results	No. diagnostic changes after PET/total	Specific diagnostic changes
Non-Aβ	PiB−/FDG-non-AD	0/54	
	PiB+/FDG-non-AD	2/6	bvFTD to fvAD/vascular; PPA-SV to fvAD
	PiB−/FDG-AD	0/4	
	PiB+/FDG-AD	5/8	bvFTD to fvAD; naMCI to aMCI; bvFTD to fvAD/vascular; CBS-non-AD to CBS-AD; CBS-non-AD to AD/DLB
	PiB−/FDG n/a	0/4	
Aβ	PiB−/FDG-non-AD	3/4	AD to CBS-non-AD; AD/DLB to naMCI; PPA-LV to CBS-non-AD
	PiB+/FDG-non-AD	0/8	
	PiB−/FDG-AD	2/4	PPA-LV to CBS-non-AD; naMCI to CBS-non-AD
	PiB+/FDG-AD	1/46	fvAD to bvFTD[a]
	PiB+/FDG n/a	0/2	

Abbreviations: Aβ = β-amyloid; AD = Alzheimer disease; aMCI = amnestic MCI; bvFTD = behavioral variant frontotemporal dementia; CBS-AD = corticobasal syndrome with expected AD pathology; CBS-non-AD = corticobasal syndrome with expected non-AD pathology; DLB = dementia with Lewy bodies; FDG = fluorodeoxyglucose; fvAD = frontal variant AD; MCI = mild cognitive impairment; n/a = not available; naMCI = nonamnestic MCI; PiB = Pittsburgh compound B; PPA-LV = primary progressive aphasia-logopenic variant; PPA-SV = primary progressive aphasia-semantic variant.
[a] Pathogenic frontotemporal lobar degeneration mutation found between pre- and post-PET visit.

While our overall rate of post-PET diagnostic changes was lower than previously reported (23%–55%),[4–6] diagnosis changed in 38% of patients who presented as pre-PET diagnostic dilemmas, in line with results from the other studies that included clinically uncertain cases.[4–6] Differences in patient selection, demographic variables, and study design may explain variation in the observed effect of amyloid PET on clinical diagnosis across studies.

An Amyloid Imaging Task Force recently recommended appropriate use criteria (AUC) for clinical amyloid imaging.[27] The AUC state that amyloid PET should be considered only in patients with objective cognitive deficits in whom there is significant diagnostic uncertainty after a comprehensive evaluation by a dementia expert and in whom scan results are expected to increase diagnostic certainty and alter management. Nineteen percent of patients in this study met the "diagnostic dilemma" criterion, and the rate of diagnostic change was higher in these cases, demonstrating that clinicians can identify a subset of patients in whom amyloid PET will be most clinically useful. The AUC further highlight 3 clinical scenarios in which amyloid imaging may have immediate utility: 1) MCI, 2) atypical dementia, and 3) early-onset dementia (<65 years). Our study provides preliminary validation for 2 of these indications. Although only 7% of patients were diagnosed with MCI, 42% had CDR < 1, indicating that a specific degenerative diagnosis was made at a clinically mild stage. Concordance between amyloid PET and clinical diagnosis was lower in these patients, demonstrating the added value of amyloid PET in mildly impaired patients. Similarly, concordance rates were lower in patients with certain atypical syndromes (CBS, frontal variant AD), suggesting that clinical scans are more likely to change management in these patients. While our study included a

Table 4 PET results and clinical effects in patients with neuropathologic confirmation

PET results	Pre-PET clinical diagnosis	Primary pathologic diagnosis	Contributing pathologic diagnoses	AD pathology CERAD (0–3)	AD pathology Braak (0–6)	Clinical effects
PiB−/FDG-non-AD	PPA-NF	FTLD-Tau (PSP)		0	2	
	FTD-ALS	FTLD-TDP-43 (type B)	Hemorrhagic infarct	0	2	
	PPA-SV	FTLD-TDP-43 (type C)	PSP	0	1	Tx (stop memantine)
	CBS-AD	**FTLD-Tau (CBD)**		**0**	**0**	**Dx**
	bvFTD	FTLD-TDP-43 (type NA)		0	3	
	PPA-SV	FTLD-Tau (Pick)		2	1	
	CBS-non-AD	FTLD-TDP-43 (type A)	Unspecified tauopathy	1	0	DL+
	PPA-NF	FTLD-Tau (CBD)	Vascular changes	1	1	
	PPA-SV	FTLD-TDP-43 (type B)	AD	2	4	DL−, tx (start memantine; stop ChE-I)
	FTD-ALS	FTLD-TDP-43 (type B)		0	2	
	FTD-ALS	FTLD-TDP-43 (type B)		3	1	
PiB+/FDG-AD	AD	AD		3	6	
	AD	AD		3	6	
	AD	AD		3	6	
	AD	AD		3	6	
	AD+DLB	AD	DLB, vascular changes	3	6	
	AD+DLB	AD+DLB		3	6	
	AD	AD+DLB		NA	NA	DL−
	CBS-AD	AD	FTLD-Tau (CBD), vascular changes	3	6	DL−
PiB+/FDG-non-AD	**PPA-NF**	**FTLD-Tau (Pick)**	**AD**	**3**	**5**	**Tx (stop memantine)**
	FTD[a]	**Argyrophilic grain disease**		**1**	**2**	**DL−**
PiB−/FDG-AD	**FTD**	**FTLD-Tau (Pick)**		**0**	**0**	**Tx (start memantine)**
	CBS-non-AD	**CBD[b]**		**NA**	**NA**	
PiB−/FDG NA	FTD	TDP-43 type B	Unspecified tauopathy	0	2	Tx (stop ChE-I)

Abbreviations: Aβ = β-amyloid; AD = Alzheimer disease; bvFTD = behavioral variant frontotemporal dementia; CBD = corticobasal degeneration; CBS-AD = corticobasal syndrome with expected AD pathology; CBS-non-AD = corticobasal syndrome with expected non-AD pathology; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; ChE-I = cholinesterase inhibitor; DL− = solved diagnostic dilemma; DL+ = created diagnostic dilemma; DLB = dementia with Lewy bodies; Dx = diagnostic change; FDG = fluorodeoxyglucose; FTD = frontotemporal dementia; FTD-ALS = frontotemporal dementia-amyotrophic lateral sclerosis; FTLD = frontotemporal lobar degeneration; NA = not available; PiB = Pittsburgh compound B; PPA-NF = primary progressive aphasia-nonfluent variant; PPA-SV = primary progressive aphasia-semantic variant; PSP = progressive supranuclear palsy; TDP-43 = TAR DNA-binding protein 43; Tx = treatment change (action).
Cases in which PET results are discordant with pre-PET clinical diagnosis are emphasized in bold.
[a] Focal PiB uptake in parietal and occipital cortex only; frequent diffuse Aβ plaques found at autopsy.
[b] Brain biopsy.

large number of early-onset patients, we did not find an age effect on PET concordance or on clinical outcomes. These results should be interpreted with caution, but they preliminarily suggest a confirmatory role for amyloid imaging in early-onset patients with straightforward clinical phenotypes.

Our data strongly suggest that amyloid imaging has a greater effect on clinical diagnosis than FDG-PET in distinguishing disorders that do and do not have amyloid pathology. Discordant PiB was highly associated with diagnostic change on multivariate analysis, whereas discordant FDG did not affect diagnosis when controlling for amyloid PET results. The reliance of clinicians on PiB over FDG was clear when the 2 scans disagreed in classifying patients (table 3). PiB also had a greater effect on AD therapy and was slightly more accurate when compared to postmortem diagnosis. While the USCMS currently reimburses FDG but not amyloid PET for the differential diagnosis of AD and FTD, this policy is not consistent with data demonstrating that amyloid PET is more biochemically specific, accurate, and reproducible than FDG[8] and has a greater effect on clinical outcomes in this diagnostic scenario.

We found a modest effect of amyloid PET on AD drug therapy, driven largely by the initiation of ChE-Is in patients with a non-Aβ diagnosis who were unexpectedly PiB+. Perhaps this finding represents a "bias to treat" given the current state of AD therapy (symptomatic rather than disease modifying, generally well tolerated, and in practice often used off-label in non-AD dementia[28]). A previous study reported a slightly greater effect on treatment (18% increase in AD drugs in florbetapir PET+ patients and 23% decrease in negative cases).[5] One explanation for this discrepancy may be the true observed clinician behavior in our study vs "intention to treat" in the florbetapir study, in which clinicians were asked not to use scan results to guide patient management. Additionally, the high rate of memantine use in FTD in our study may have decreased the effect of scan results on treatment. The study was conducted at a time when memantine was being evaluated in clinical trials for FTD,[29] possibly encouraging "off-label" use. It now appears that both ChE-Is and memantine are associated with *worse* outcomes in FTD,[29,30] underscoring the importance of accurate diagnosis.

Due to our retrospective design we were not able to assess the effect of PET on diagnostic confidence, whereas previous studies have found that amyloid PET leads to an increase in clinician certainty.[4–6] As a proxy, we assessed diagnostic dilemmas before and after PET and found a trend for a decrease in the number of uncertain cases. Increased diagnostic confidence can provide patients and families with greater clarity about prognosis and limit utilization of medical resources.

Twenty-four patients had neuropathologic studies that confirmed a strong correlation between amyloid PET and Aβ pathology.[31,32] The pathology-proven cases verified the utility of amyloid PET in identifying AD in atypical patients, resolving diagnostic dilemmas, and guiding AD drug therapy. Two patients also highlight the pitfall of overinterpreting a positive amyloid scan: both patients were found to have primary FTD at autopsy, along with AD copathology. The florbetapir clinical impact study reported a substantial decrease in the use of "standard of care" measures such as cognitive testing (33%) and structural imaging (24%) in patients who have undergone amyloid PET.[33] Our data suggest that more caution is required in interpreting the significance of amyloid scans given the prevalence of copathology and the complexity of patients seen at dementia referral centers.

Our study has limitations. The design was retrospective, and we cannot completely separate the influence of PiB and FDG or control for the evolution of clinical symptoms or the availability of additional data at the post-PET visit. The single site design limits the generalizability of our findings, particularly to less-specialized practice settings. Patients were referred for amyloid PET as part of research studies that focused on specific patient populations and were not designed to measure influence on clinical management. Common diagnoses encountered in practice such as DLB, vascular dementia, and amnestic MCI[34] were not represented in large numbers. The added value of amyloid PET in challenging cases may be underestimated, since patients were evaluated by clinicians who are highly experienced in assessing atypical dementia syndromes and diagnosis was made by consensus. Patients with significant comorbidities were excluded, while in practice the presence of confounding clinical issues may be an indication for amyloid PET.[27,35] Amyloid imaging was performed with [^{11}C]PiB rather than the [^{18}F] tracers that will be more prevalent in clinical practice. However, preliminary studies suggest comparable performance between [^{18}F] amyloid ligands and [^{11}C]PiB.[36–39]

Ultimately, studies such as this reflect clinician bias in interpreting the clinical significance of scan results, although the autopsy diagnoses provide a preliminary measure by which to judge clinical decision making. Future prospective studies are needed to better characterize the clinical role of amyloid imaging in different care settings and relative to other biomarkers. Further studies are also needed to estimate effects on critical outcomes that could not be assessed in our retrospective design, including nonpharmacologic patient management, caregiver outcomes, and resource utilization.

AUTHOR CONTRIBUTIONS

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