



Rates and Characteristics of Amyloid PET Negativity Among Patients Referred for New Alzheimer's Disease Therapies

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BACKGROUND

Biomarker confirmation of brain amyloidosis is required for eligibility for new Alzheimer's disease (AD) treatments (e.g., lecanemab and donanemab).

A proportion of individuals suspected clinically to have early symptomatic AD may ultimately be biomarker-negative and ineligible for anti-amyloid therapy.

Here, we characterized a cohort of patients referred for consideration of new AD treatments but determined to be amyloid PET negative.

METHODS

Retrospective chart review was completed for patients seen at a tertiary care AD Treatment Clinic.

Typical evaluations included:

- Neurology office visit
- Neuropsychological assessment
- Brain MRI
- Amyloid PET-CT
- Apolipoprotein E (APOE) testing

A subset of patients had complementary plasma ptau217 or CSF ptau181/abeta42 ratio testing.

RESULTS 1

Over an 18-month timeframe, **9% (31/363) of patients evaluated for anti-amyloid treatment eligibility were amyloid negative by PET-CT.**

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RESULTS 2 AND TABLES

Amyloid PET negative individuals (17 male) were similar in age to the overall clinic population (mean 73.0 years) but **displayed higher scores on the Short Test of Mental Status (STMS) (32/38 vs. 28/38) and lower frequency of APOE ε4 positivity (37% vs. 68%). See Table 1.**

Clinical diagnoses included (see Table 1):

- Mild cognitive impairment (24/31)
- Mild dementia (3/31)
- Cognitively unimpaired (4/31; treatment-ineligible on this basis)

Among amyloid PET negative individuals with cognitive impairment, a minority (7/28) had atypical clinical AD syndromes (e.g., non-amnesic-predominant cognitive impairment). See Table 1. See Table 2 for comparison of neuropsychometric testing between subjects with typical and atypical clinical AD syndromes.

Eight cases had a complementary biomarker testing that was discordant from an amyloid negative PET scan, including 5 false positive CSF ratio tests (out of 10 total; false positive rate [FPR] 0.5; true positive rate [TPR] 0.5) and 3 false positive plasma ptau217 tests (out of 7 total; FPR 0.43; TPR 0.57).

Suspected alternative etiologies of cognitive impairment included:

- Non-AD neurodegenerative disease or vascular cognitive impairment (VCI) (17/31)
 - Limbic-associated TDP-43 encephalopathy (LATE) (8/31); frontotemporal dementia (FTD) (5/31); dementia with Lewy bodies (DLB) (1/31); VCI (3/31)
- Multifactorial non-neurologic etiologies (including cognitively normal cases) (6/31)
- Uncertain (8/31)

Comorbid normal pressure hydrocephalus (3/31), obstructive sleep apnea (8/31), and psychiatric disorders (2/31) were also observed in this cohort.

Table 1. Characteristics of amyloid PET negative patients compared to the overall ADTC clinic population.

	Amyloid Negatives	Overall ADTC Clinic Population
Age (y)	73.0 ± 8.0	71.2
Age Range	54 to 84	52 to 85
Sex		
Male	17 (55%)	109 (47%)
Female	14 (45%)	123 (53%)
APOE ε4 status		
Positive	11 (37%)	144 (68%)
Negative	19 (63%)	68 (32%)
Not Tested	1	20
Amyloid PET-CT Centiloid Value	4.7 ± 29.2	
Centiloid Value Range	-61.8 to 55.3*	
STMS Score	31.9 ± 4.8	28
MMSE Equivalent	27	24
CDR-SB Score	1.4 ± 1.6	
CDR-Global Score	0.5 ± 0.3	
FAQ Score	6.0 ± 6.4	
Dementia Syndrome		
Mild Cognitive Impairment	24 (77%)	128 (55%)
Mild Dementia	3 (10%)	72 (31%)
Moderate or Severe Dementia	0 (0%)	27 (12%)
Cognitively Normal	4 (13%)	5 (2%)
Clinical Syndrome Consistent with Typical AD	20 (65%)	187 (81%)

ADTC, Alzheimer disease treatment clinic; APOE, apolipoprotein E; CDR-Global, Clinical Dementia Rating – Global; CDR-SB, Clinical Dementia Rating – Sum of Boxes; STMS, Short Test of Mental Status; FAQ, Functional Activities Questionnaire. Data are presented as mean (SD) or No. (percentage) of patients.

*Outlier centiloid value of 125 excluded after over-read by behavioral neurologists.

Table 2. Performance on selected neuropsychometric tests by cognitive domain.

Cognitive Domain	Neuropsychometric Test	Dementia Syndrome		
		Amnesic Cognitive Impairment	Non-Amnesic Cognitive Impairment	Cognitively Normal
Memory	AVLT Long Delay	6.7 (1.8)	8.2 (1.5)	12.3 (5.5)
	DRS-2 Memory	6.9 (2.9)	7.7 (3.5)	11.7 (2.3)
Executive Function	TMTB	10.9 (2.4)	8.6 (3.5)	10.7 (1.2)
	DRS-2 Attention	10.3 (2.4)	7.4 (2.1)	9.7 (1.5)
	DRS-2 Initiation/Perseveration	9.3 (3.0)	8.0 (2.8)	10.7 (2.3)
	DRS-2 Conceptualization	10.6 (2.0)	9.6 (1.0)	10.3 (3.5)
Language	BNT	10.6 (3.5)	10.5 (5.1)	12.3 (3.3)
Visuospatial	Rey-Copy	9.8 (3.1)	5.9 (2.7)	12.0 (2.0)
	DRS-2 Construction	9.8 (0.9)	10.0 (0)	10.0 (0)
Overall Cognitive Function	DRS-2 Total Score	8.9 (2.9)	7.1 (2.5)	10.7 (3.1)
	DRS-2 Age/Educ Corrected Score	7.5 (2.9)	5.6 (2.8)	9.3 (3.2)

AVLT; Rey Auditory Verbal Learning Test; DRS-2; Dementia Rating Scale-2; TMTB; Trail Making Test Part B; BNT; Boston Naming Test

DISCUSSION

Distinctive features of the amyloid PET negative cohort compared to the general clinic population included:

- Higher score on the STMS (32/38 vs. 28/38)
- Lower rate of APOE ε4 positivity (37% vs. 68%)
- Lower proportion cohort presented with an amnesic cognitive syndrome (65% vs. 81%).

LATE was suspected as the most likely alternative etiology of cognitive impairment in 26% (8/31) of amyloid PET negative cases.

Limitations of this study included its observational nature, referral bias of patients sent to this clinic (who may have had atypical presentations of cognitive impairment), and the absence of complementary biomarker testing in some patients.

Amyloid PET is a valuable tool in AD treatment decision-making, particularly in settings where there is suspicion for non-AD etiologies of cognitive impairment to prevent inappropriate therapeutic targeting.

CONCLUSIONS

A subset of patients referred for consideration of new AD therapies may ultimately be amyloid PET negative, including some individuals with clinical syndromes and fluid biomarker results initially suggesting otherwise.

Clinicians should be aware of factors warranting enhanced suspicion for amyloid PET negativity to optimize screening and referral pathways and prevent inappropriate therapeutic administration.

