DOI: 10.1002/alz.081864

ALZHEIMER'S IMAGING CONSORTIUM

POSTER PRESENTATION

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Amyloid-, tau-, and FDG-PET in amyloid-negative patients clinically diagnosed with early-onset Alzheimer's disease in the LEADS study

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Abstract

Background: Negative AD biomarkers are commonly found in patients with a clinical diagnosis of late-onset AD, but little is known about biomarker-negative patients diagnosed with sporadic Early Onset AD (EOAD, <65yo). We explored data from the Longitudinal Early-onset Alzheimer's Disease Study (LEADS) to identify such participants and explored amyloid-, tau-, and FDG-PET.

Method: We identified 380 patients who i) met clinical criteria for MCI or dementia due to AD, and ii) completed baseline amyloid-PET (Florbetaben) and tau-PET (Flortaucipir). Of these patients, 93 (24.5%) were amyloid-PET negative based on a combination of visual read and quantification ("EOnonAD"). A subset of EononAD participants completed FDG-PET (n = 63), 5 had follow-up amyloid-PET and 2 had follow-up tau-PET. 63 age-matched cognitively normal controls were also included. Image acquisition and processing followed ADNI protocols.

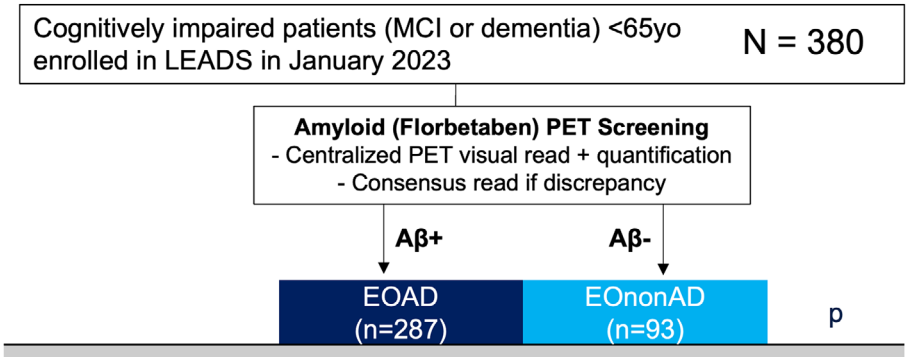
Result: Compared to amyloid-positive patients (EOAD), EononAD patients were less frequently female or APOE4 carriers, and less severely impaired (Figure 1). EononAD patients had a mean Centiloid of 5.6 (Figure 2A). At the group level, temporal Flortaucipir-SUVR was low (1.20.3, not significantly different from controls), although 3 cases had Flortaucipir-SUVR>2 (Figure 2A). Visual inspection showed these cases had asymmetric AD-like Flortaucipir-PET patterns (Figure 2B). Within patients with EononAD, amyloid- and tau-PET were correlated (Spearman's $\rho = 0.29$, $p = 0.005$), even when excluding the 3 high Flortaucipir-SUVR outliers (Figure-2C). 5 patients had follow-up amyloid-PET: 2 showed major amyloid-PET increase (+20 CL over 3 years), exceeding the 25 CL threshold at follow-up, while the other 3 remained amyloid-negative (Figure 2D). Two patients had follow-up Flortaucipir-PET: a low-Flortaucipir case remained low, and one of the three high-tau cases showed increased signal over time (Figure 2D). Group-level FDG-PET analysis showed frontal, temporal, and/or parietal hypometabolism in EOnonAD (Figure 3A). However, individual maps showed high

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heterogeneity: while ~50% showing no clear hypometabolism (normal-looking FDG), the remaining cases showed heterogeneous patterns suggestive of various underlying etiologies (e.g., FTLD-like or AD-like patterns, Figure 3B).

Conclusion: Amyloid-PET negative patients included in LEADS are heterogeneous. While a minority of cases might have underlying AD with subthreshold amyloid- and/or tau-PET values, FDG-PET showed heterogeneous patterns suggesting underlying etiologies include various degenerative and non-degenerative causes. "

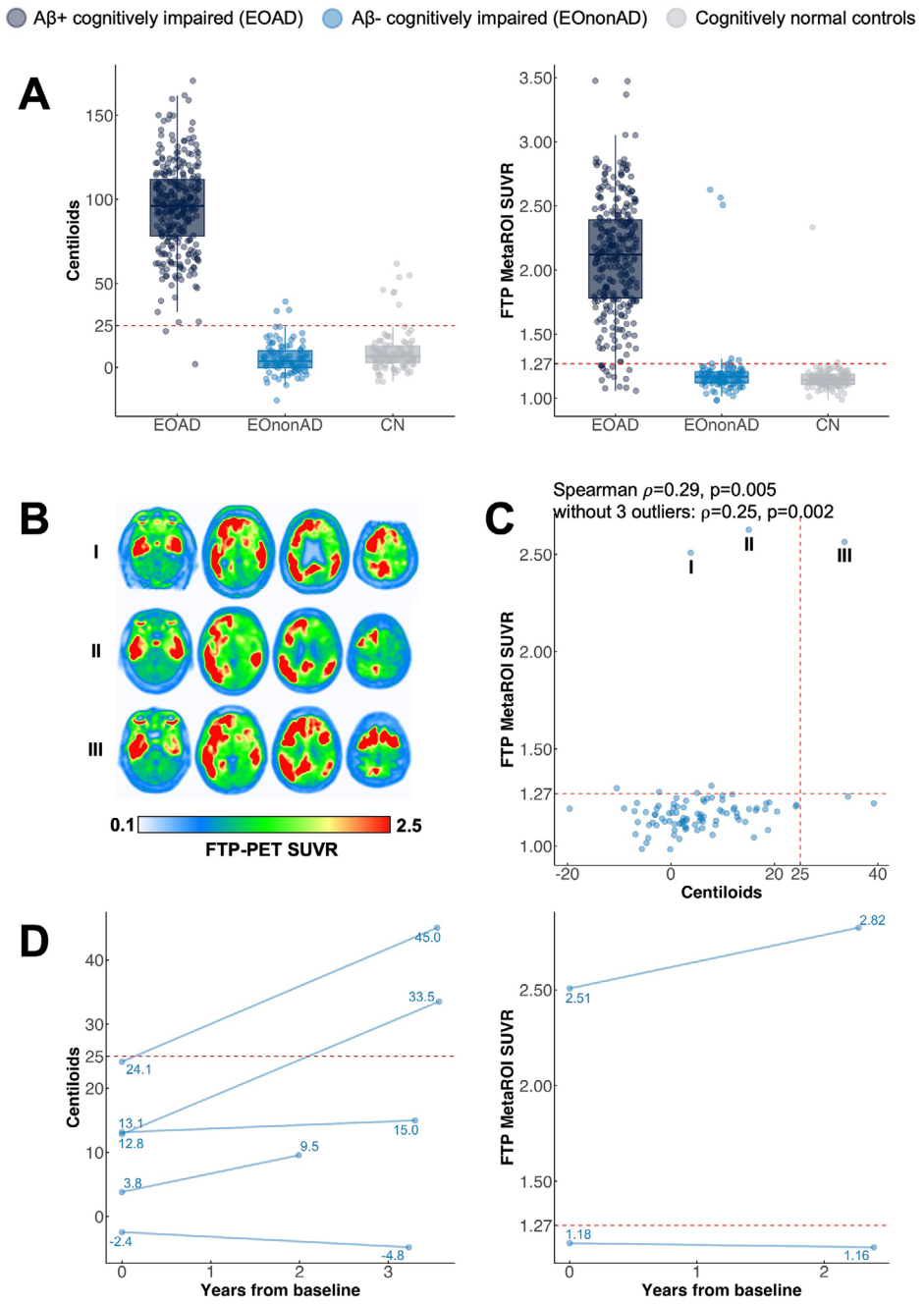
Figure 1: Study design and cohort



	EOAD (n=287)	EOnonAD (n=93)	p
Age at baseline PET	59.1 ± 4.2	58.5 ± 6.0	0.26
Sex (Females)	53%	33%	**0.001**
Education	15.5 ± 2.5	15.5 ± 2.6	0.82
APOE-e4 carriers	55%	41%	**0.04**
MMSE, /30	21.7 ± 5.1	25.6 ± 4.0	**<0.0001**
CDR-SoB, /18	3.7 ± 1.7	2.7 ± 1.8	**0.0025**

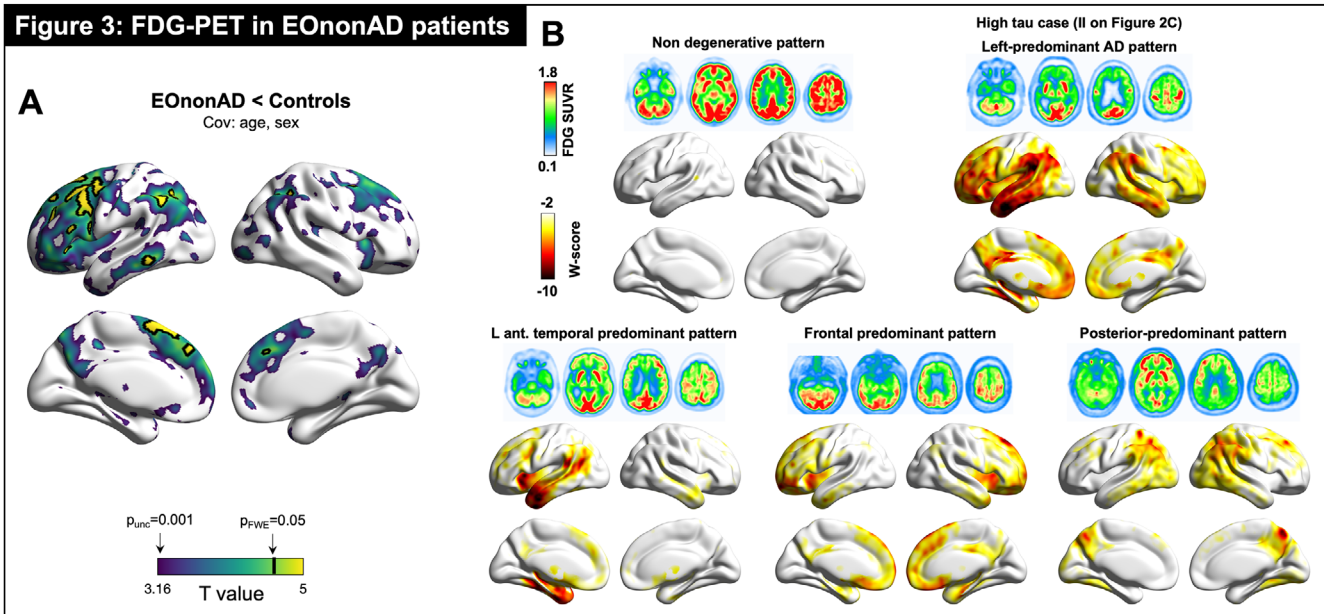
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Figure 2: Amyloid-PET and tau-PET in EOnonAD patients



A. *Distribution of Centiloids and Flortaucipir-metaROI-SUVR across all LEADS groups. Dotted lines indicate pre-determined thresholds (25 CL and 1.27 Flortaucipir SUVR).* ***B.*** *Individual Flortaucipir -SUVR images of 3 high tau EOnonAD outliers.* ***C.*** *Association between FBB-CLs and Flortaucipir-metaROI-SUVR in EOnonAD patients.* ***D.*** *Longitudinal trajectories of amyloid and tau-PET in EOnonAD patients with available follow-up scans.*

Figure 3: FDG-PET in EOnonAD patients



A. *Voxelwise comparison of EOnonAD patients (n=63) and controls (n=61), showing areas of hypometabolism in patients (uncorrected p<0.001; black line indicate areas significant using stringent FWE correction).* ***B.*** *Individual maps for 5 EOnonAD patients, showing slices of the row FDG-SUVR image (top) and a 3d-render of each patient W-map (statistical map comparing the patient scan to age- and sex-matched controls)*