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BIOMARKERS

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LEADS: Sporadic early-onset Alzheimer's disease in the spotlight

Amyloid and tau PET in sporadic early-onset Alzheimer's disease: Preliminary results from LEADS

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Abstract

Background: Previous studies have reported that age modifies the distribution and burden of tau (and, to a lesser extent, amyloid) pathology in sporadic Alzheimer's disease (AD). Here we present preliminary baseline amyloid and tau PET results from the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS), a multi-site longitudinal study of sporadic early-onset AD.

Method: 135 patients meeting clinical criteria for MCI or probable AD and 50 cognitively normal controls (all age<65 at enrollment) were enrolled at 12 US centers between August 2018 and December 2019 (Table 1). ^{18}F-Florbetaben amyloid-PET (FBB) was used to assign patients to EOAD (amyloid-positive) or EOnonAD (amyloid-negative) subgroups based on visual rating and semi-quantification. 130 patients and all controls had ^{18}F-Flortaucipir tau-PET (FTP). Regional Standardized Uptake Value Ratios (SUVR) for FBB (whole cerebellum reference) and FTP (inferior cerebellar gray reference) were extracted using co-registered 3T-MRI.

Result: 98 patients (72.6%) were amyloid PET-positive (EOAD) and 37 (27.4%) were amyloid PET-negative (EOnonAD). Compared to EOAD, EOnonAD patients had higher MMSE, MOCA and CDR sum-of-boxes (CDR-SB) and were more frequently male (Table 1). Patients with EOAD showed elevated FBB and FTP SUVR in temporoparietal and frontal cortex compared to CN and EOnonAD (Figures 1-2). In EOAD, MMSE, MOCA and CDR-SB were significantly correlated with FTP SUVR (Figure 3), while no significant correlations were found with FBB SUVR. EOnonAD patients showed variable FTP binding ranging from negative to mildly elevated binding in anterior temporal and frontal cortex and underlying white matter. Two EOnonAD cases showed intense FTP binding comparable to typical EOAD cases, despite visually and quantitatively negative FBB scans.

Conclusion: Patients with clinically mild, sporadic EOAD typically show an extensive distribution and burden of tau pathology in the setting of positive amyloid PET. Global clinical measures correlate with tau but not amyloid PET. Over 25% of patients meeting clinical criteria for early-onset MCI/probable AD have negative amyloid PET, suggesting alternative etiologies for cognitive decline. These findings will inform future design of drug trials in this important and under-studied population.

Figure 1. FBB-PET and FTP-PET in Early-Onset AD

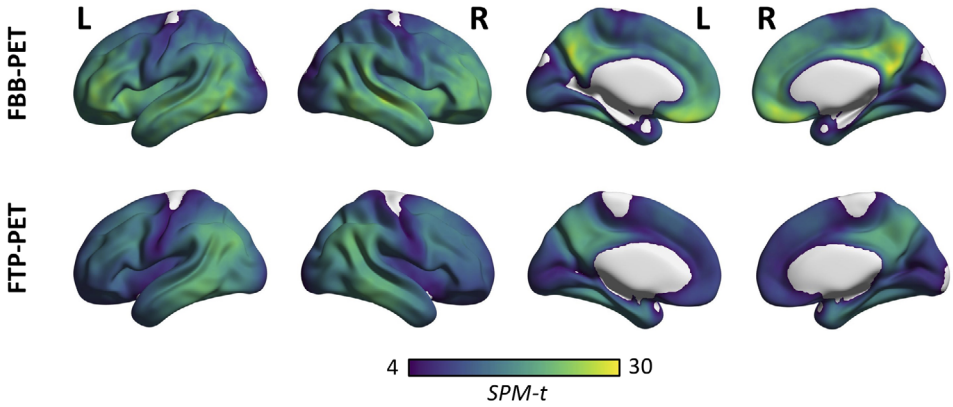
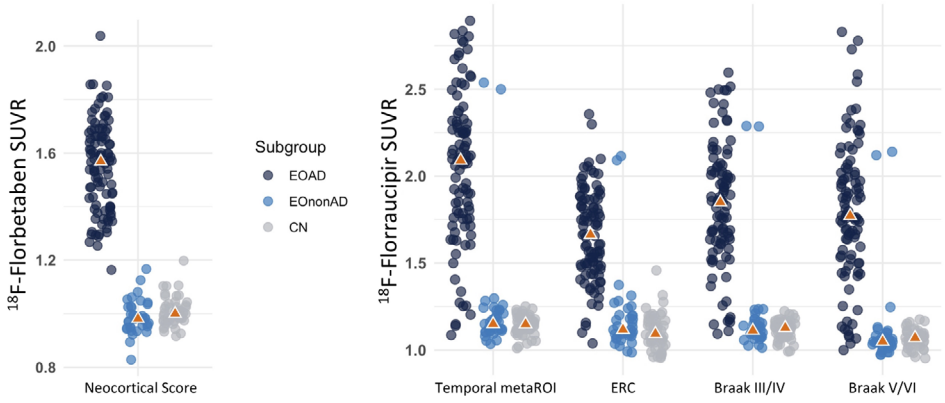


Figure shows Voxelwise analysis comparing Florbetaben-PET (upper panel) and Flortaucipir-PET (lower panel) binding patterns in Early-Onset AD to a set of young cognitively-normal subjects. Statistical thresholds were set at p<0.05 corrected for Family-Wise Error (FWE) with a cluster extent of 100 voxels. 3D rendering was done in MATLAB with BrainNet Viewer (Xia et al., 2013).

Legend: EOAD: Early Onset Alzheimer's Disease; FBB: ^{18}F-Florbetaben; FTP: ^{18}F-Flortaucipir; SPM: Statistical Parametric Mapping

FIGURE 1

Figure 2. FBB-PET and FTP-PET in Early-Onset AD



FTP-PET metaROI (Jack et al., 2017) represents a weighted mean of entorhinal, amygdala, parahippocampal, fusiform, inferior temporal, and middle temporal regions of interest scaled to the inferior cerebellar gray matter.

Legend: SUVR: Standardized Uptake Value Ratio; CN: Cognitively-Normal; EOnonAD: Early-Onset non-Alzheimer's Disease; EOAD: Early Onset Alzheimer's Disease; FBB: ^{18}F-Florbetaben; ROI: region of interest; FTP: ^{18}F-Flortaucipir; ERC: Entorhinal Cortex.

FIGURE 2

Figure 3. Voxelwise correlations between FTP-PET and global cognitive status in Early-Onset AD

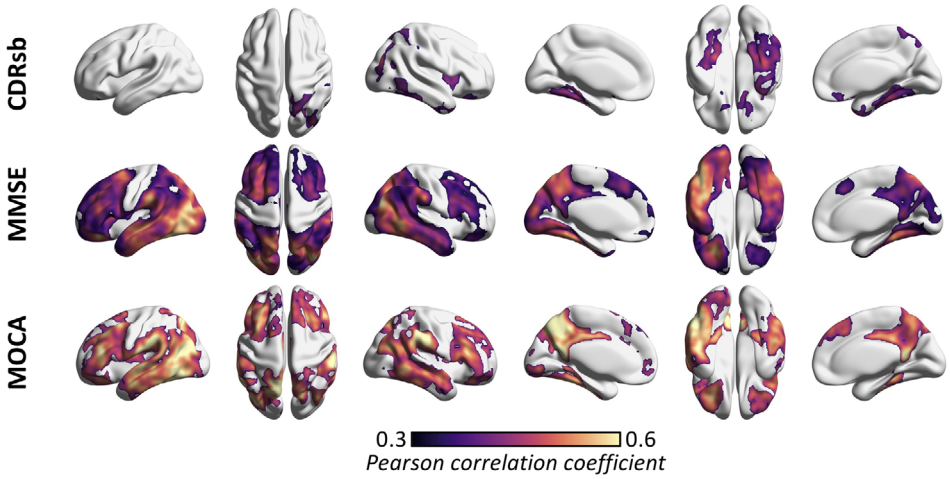


Figure shows Voxelwise correlations between Flortaucipir-PET SUVR and CDR sum of boxes (top), MMSE (middle) and MOCA (bottom) in Early-Onset AD. Statistical thresholds were set at p<0.001 uncorrected for multiple comparisons with a cluster-level PFWE<0.05 correction. 3D rendering was done in MATLAB with BrainNet Viewer (Xia et al., 2013).

Legend: EOAD: Early Onset Alzheimer's Disease; FBB: ^{18}F-Florbetaben; FTP: ^{18}F-Flortaucipir; MMSE: MiniMental State Examination; CDR: Clinical Dementia Rating; MOCA: MOntreal Cognitive Assessment

FIGURE 3

TABLE 1

Table 1. Demographics, clinical and biomarker summary split by group and cognitively-impaired subgroups

	CN	PT*	EOnonAD*	EOAD*	PT vs CN	EOAD vs CN	EOAD vs EOnonAD
Sample Size	50	135	37	98	-	-	-
Age	55(6)	58(5)	57(6)	59(4)	<0.001	<0.001	0.72
Sex F/M	34/16	66/69	11/26	55/43	0.03	0.21	0.007
APOE e4 pos/neg	15/14	17/17	4/6	13/11	1	1	0.71
Education years	17(2)	16(3)	16(3)	16(2)	0.005	0.006	0.87
MMSE	29(1)	23(5)	26(3)	22(5)	<0.001	<0.001	<0.001
CDR sum of boxes	0(0)	4(2)	3(1)	4(2)	<0.001	<0.001	0.03
MOCA	28(2)	18(6)	21(4)	17(6)	<0.001	<0.001	0.01
FBB-PET Composite SUVR	1.01(0.1)	1.40(0.3)	0.99(0.1)	1.55(0.2)	<0.001	<0.001	<0.001
FTP-PET metaROI SUVR	1.14(0.1)	1.83(0.5)	1.23(0.3)	2.05(0.4)	<0.001	<0.001	<0.001

*: Patients were split into EOAD and EOnonAD based on the results of the FBB-PET at screening
P-values indicate Wilcoxon Rank Sum test for continuous variables and Fisher's Exact test for discrete variables.

FTP-PET metaROI represents a weighted mean of entorhinal, amygdala, parahippocampal, fusiform, inferior temporal, and middle temporal regions of interest scaled to the inferior cerebellar gray matter.

Legend: CN: Cognitively-Normal; PT: Patient; EOnonAD: Early-Onset non-Alzheimer's Disease; EOAD: Early Onset Alzheimer's Disease; APOE: Apolipoprotein E; PCA: Posterior Cortical Atrophy; PPA: Primary Progressive Aphasia; MMSE: MiniMental State Examination; CDR: Clinical Dementia Rating; MOCA: MOntreal Cognitive Assessment; RAVLT: Rey Auditory Verbal Learning Test; MRI: Magnetic Resonance Imaging; SUVR: Standardized Uptake Value Ratio;