

Background: Amyloid and FDG-PET have been previously independently tested for their abilities to predict future cognitive and functional decline. A subset of subjects who undergo FDG-PET have scans that are ambiguous for predicting subsequent cognitive course. We recently reported that for most of such subjects, this ambiguity could be resolved by repeating FDG-PET one year later (JNM 2013; 54:142). In the present analyses, we tested an alternate strategy: namely, analyzing amyloid PET data obtained contemporaneously with the initial FDG-PET scan. **Methods:** A total of 108 subjects with mild cognitive impairment (MCI) (98 early MCI, 10 late MCI) from the Alzheimer's Disease Neuroimaging Initiative undergoing amyloid and FDG-PET within one month of each other and who had at least 2yrs of clinical follow-up were assessed. Conversion was defined by clinical dementia rating increasing from 0.5 to ≥ 1 within 2yrs. Using commercially available software FDA-cleared for clinical use, both a metabolic dementia prognosis index (DPI), optimized for FDG predictive value, and an amyloid tracer retention index (TRI), based on recently published literature and optimized for amyloid imaging diagnostic value, were automatically calculated and used to assess accuracies of predicting conversion to dementia. FDG criteria defined in an independent ADNI-1 data set were applied to classify ADNI-2 subjects as having high, low, or statistically indeterminate risk of progression to dementia. **Results:** Of 108 subjects, 6 (6%) converted to dementia, 12 (11%) reverted to normal cognition, and 90 (83%) remained cognitively stable. By baseline metabolic DPI, 11 (10%) were predicted to show imminent cognitive progression, 71 (66%) had low risk for progression, and 26 (24%) were in the indeterminate range. Repeating FDG for ambiguous scans one year later had yielded a prognostic accuracy of 78%. By amyloid TRI, 19/26 (73%) were correctly classified, while applying the DPI to baseline amyloid scans yielded correct classifications in 81% of cases. **Conclusions:** A strategy of following up an indeterminate FDG-PET scan with an amyloid scan obtained within a month had comparable prognostic value for predicting likelihood of conversion of MCI patients to dementia as did repeating FDG-PET scans in such patients one year after the initial FDG-PET.

IC-P-028 ASSOCIATION BETWEEN SERUM LIPIDS AND CEREBRAL AMYLOIDOSIS IN COGNITIVELY NORMAL ELDERLY

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Background: Cerebral amyloid-beta protein (A β) deposition has been considered as a key initiating step in Alzheimer's disease (AD) process. Although many preclinical studies have suggested the possible linkage between dyslipidemia and cerebral amyloidogenesis or amyloid deposition, the association between serum lipids and cerebral A β deposition in human brain is still poorly known. We aimed to investigate such association in cognitively normal (CN) elderly individuals. **Methods:** Sixty two CN elderly individuals were included. All participants received comprehensive clinical and neuropsychological assessment based on the CERAD protocol, 11 C labeled Pittsburgh Compound B (PiB) positron emission tomography volumetric MRI, and quantification for serum lipid components including total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) with apolipoprotein A1 (APOA1) and B (APOB). **Results:** Global cerebral A β deposition was defined as mean cortical PiB retention of the cortical regions including frontal, lateral temporal, lateral parietal and precuneus/posterior cingulate cortices. Univariate analyses showed significant positive association of mean cortical PiB retention with the levels of serum TG and APOB, and negative association with HDL-C and APOA1 levels. Multivariate statistical models that controlled age, education, gender, apolipoprotein E ϵ 4 genotype revealed independent associations between the levels of TG and mean

cortical 11 C-PiB retention. Higher serum TG level was associated with heavier cortical 11 C-PiB retention. No association was found between both total cholesterol and LDL-C, and cortical 11 C-PiB retention. **Conclusions:** Our findings strongly support the association between lipid profiles in serum, especially TG level, and the degree of cerebral amyloidosis in cognitively normal elderly people. The findings also suggest that the mechanisms through which serum lipid or lipoproteins affect cerebral A β could provide novel targets of AD therapeutics. More specifically, various approaches known to reduce blood TG level, such as moderate exercise and omega-3 fatty acid intake, might be helpful for slowing A β deposition and reducing AD occurrence.

IC-P-029 ENHANCED BRAIN UPTAKE OF C11-PIB IN MOUSE MODEL OF ALZHEIMER'S DISEASE VIA A SYNTHETIC PEPTIDE CARRIER

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Background: Uptake of amyloid imaging agents by specifically binding to amyloid protein in the human brain is compromised by a relatively weak target to background ratio in the range of 3 to 1. Blood brain permeability may be a limitation to improved target to background signal. We tested the ability of a novel blood-brain permeability peptide, termed K16ApoE, to enhance uptake of C11 (Pittsburgh Compound B) PiB in animal models of Alzheimer's disease (AD). **Methods:** AD mice (APP/PS1) (n= 12) and wild type (WT) mice (N=13) were imaged with C11 PiB PET dynamically with K16ApoE and without. Quantitation using SUV measurements of PET uptake in brain, liver and heart was performed. Mice were then sacrificed and autoradiography of brain tissue was performed to assess the quantitative uptake measured in digital light units (DLU). Analysis was performed to compare brain-uptake of PiB on PET and on autoradiography with and without K16ApoE. **Results:** Brain uptake of C11 PiB on PET was enhanced 3 fold in AD mice when delivered with K16ApoE at early perfusion phase and 6 fold at 40 minutes (Figure 1; p = 0.01). The degree of enhancement in AD mice on PET was similar to that seen in WT. No enhancement of PiB uptake was seen in heart or liver on PET. Autoradiography confirmed a 20-fold increase in specific brain retention of PiB in amyloid carrying mice when delivered with K16ApoE. **Conclusions:** Enhancement of C11 PiB uptake in AD mice on PET imaging occurs by using blood brain barrier permeability enhancement with a novel blood-brain permeability peptide. This model could allow for more sensitive imaging of human brain amyloid in the future.

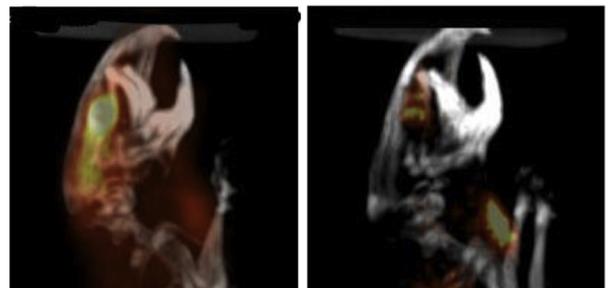


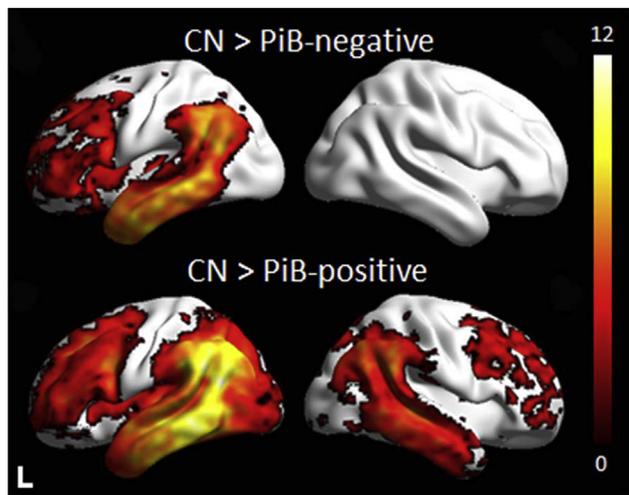
Figure 1. C-11 PiB PET image of an AD mouse performed with (left) and without (right) the blood-brain permeability peptide. Greater brain uptake is seen when the permeability peptide is used.

IC-P-030 CLINICAL AND NEUROIMAGING BIOMARKERS OF ALZHEIMER'S DISEASE PRESENTING WITH PROGRESSIVE APHASIA

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Background: Patients with Alzheimer's disease (AD) can present with early and prominent deficits in language, characterized by anomia, difficulty repeating sentences and phonological errors. Our aims were to determine what proportion of patients presenting with these signs and symptoms have beta-amyloid (A β) deposition, and whether clinical or neuroimaging features differ between those with and without A β deposition. **Methods:** Fifty patients that presented with at least two of the following three language features (anomia, difficulty repeating sentences and phonological errors), underwent speech/language, neurological, and neuropsychological assessments, MRI, diffusion tensor imaging, 18-F-fluorodeoxyglucose and Pittsburgh Compound B (PiB) PET. A β positivity was determined by a cortical-to-cerebellar ratio >1.5. PiB-negative subjects were screened for mutations in progranulin, tau, C9ORF72 and TARDBP. Patterns of atrophy, hypometabolism, and white matter integrity were assessed. **Results:** Forty-four patients (88%) were PiB-positive. Three of the six PiB-negative patients (50%) harbored progranulin gene mutations. PiB-positive patients performed better on action fluency and worse on spatial perception tasks, and showed greater atrophy and hypometabolism in right temporoparietal and frontal lobes than PiB-negative patients (Figure). Strikingly more asymmetric left-sided patterns, with greater involvement of left anteromedial temporal lobe, medial prefrontal cortex, inferior longitudinal fasciculus, uncinate fasciculus and forceps minor, were observed in the PiB-negative group. **Conclusions:** Alzheimer's disease pathology accounts for a high proportion of patients presenting with anomia, difficulty repeating sentences and phonological errors. Highly asymmetric MRI findings and preserved spatial perceptual skills, suggest that AD pathology is absent. In such instances, a progranulin gene mutation should be suspected.



IC-P-031

A COMPARISON OF THE REGIONAL DISTRIBUTION OF MICROBLEEDS IN ATYPICAL AND TYPICAL PRESENTATIONS OF ALZHEIMER'S DISEASE

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Background: Alzheimer's disease (AD) can often be associated with the presence of small hemosiderin deposits, or microbleeds, in the brain. Sub-

jects with AD typically present with episodic memory deficits, although a large proportion present with other cognitive complaints, including difficulty with language or visuospatial/perceptual function. It is unknown whether the proportion of subjects affected by microbleeds, or the regional distribution of microbleeds, differs between subjects with typical and atypical presentations of AD. **Methods:** A cohort of 45 subjects that had amyloid deposition on Pittsburgh compound B (PiB) PET and presented with predominant language (n=31) or visuospatial/perceptual (n=14) deficits were prospectively recruited and underwent a T2* weighted MRI. These subjects were compared to a cohort of 40 subjects with typical dementia of the Alzheimer's type from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Each microbleed was identified by an expert rater and assigned a lobar location. **Results:** Prevalence of microbleeds was 40% in atypical AD and 32% in typical AD. Within the subjects with microbleeds, the mean (SD) number of microbleeds per subject was 14.2 (35.3) in atypical AD and 3.2 (4.6) in typical AD. The topographic density of microbleeds was highest in the frontal and temporal lobes in atypical AD. In contrast, density in typical AD was highest in the temporal and occipital lobes, with lowest density observed in frontal lobes. Subjects with atypical AD had a higher proportion of deep grey and white matter microbleeds than typical AD (13% vs. 0%, p=0.02), with similar proportions of microbleeds observed in infratentorial regions (7% vs. 5%, p=0.74). The total number of microbleeds was associated with age (p=0.07), but not PiB-PET burden, in atypical AD. Within atypical AD, the prevalence of microbleeds was higher in subjects with language (52%) versus visuospatial/perceptual deficits (14%, p=0.02). **Conclusions:** Microbleeds affect a large proportion of subjects with atypical clinical presentations of AD, particularly those with language deficits. The topographic distribution of microbleeds differs from typical AD, with greater burden in the frontal lobes and deep brain regions suggesting possible differences in underlying etiology.

IC-P-032

COMPARATIVE ANALYSIS OF PIB *IN VIVO* WITH 6-CN-PIB AND A β -IMMUNOHISTOCHEMISTRY POSTMORTEM IN FAMILIAL ALZHEIMER DISEASE ASSOCIATED WITH THE PSEN1 I229F MUTATION

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Background: In AD, a correlation of in vivo [C-11]Pittsburgh Compound B (PiB) retention with postmortem measures of fibrillar A β pathology is essential for interpretation of PET imaging results. **Methods:** Structural magnetic resonance imaging (MRI) and Positron emission tomography (PET) with [C-11]PiB images of a familial AD (FAD) patient were acquired 12 months ante-mortem, using a standardized protocol to assess amyloid pathology in vivo. MRI and PET images were visually compared with those obtained postmortem using histopathology. The entire left cerebral hemisphere, sliced into 22 coronal slabs, and left cerebellar hemisphere, sliced into parasagittal sections, were processed postmortem and embedded in paraffin. Serial sections were stained for histology and A β 1-42 immunohistochemistry (IHC). Sections were also incubated in 10 μ M 6-CN-PiB (a highly fluorescent derivative of PiB). High resolution low magnification images of complete coronal (cerebrum) or sagittal (cerebellum) sections were created and analyzed. **Results:** A 39 year old woman developed memory