Pathophysiology (SNAP), a normal or an unclassified group (Table 1). Longitudinal progression to CDR>0 was modeled using survival analyses. **Results:** Controlling for appropriate covariates, correlations between CSF Aβ $_{42}$ and the mean cortical PIB binding potential (MCBP) were significant (r=-.39, p<.0001), while the relationships between adjusted hippocampal volume and CSF (r=.04, p=.52) and ptau (r=.03, p=.62) were not (Figures 1 & 2). Individuals classified as Stage 2 and 3 were at an elevated risk of later dementia relative to those in Stage 0. (Figures 3-5). **Conclusions:** The NIA-AA preclinical stages successfully stratify dementia risk using both CSF and neuroimaging biomarkers. Measures of amyloid were highly congruent, while measures of neurodegeneration were often incongruent. This suggests that such markers cannot be used interchangeably to represent the same pathology.

IC-P-021 LOWER BODY MASS INDEX IS ASSOCIATED WITH GREATER ALZHEIMER PATHOLOGY IN ASYMPTOMATIC INDIVIDUALS

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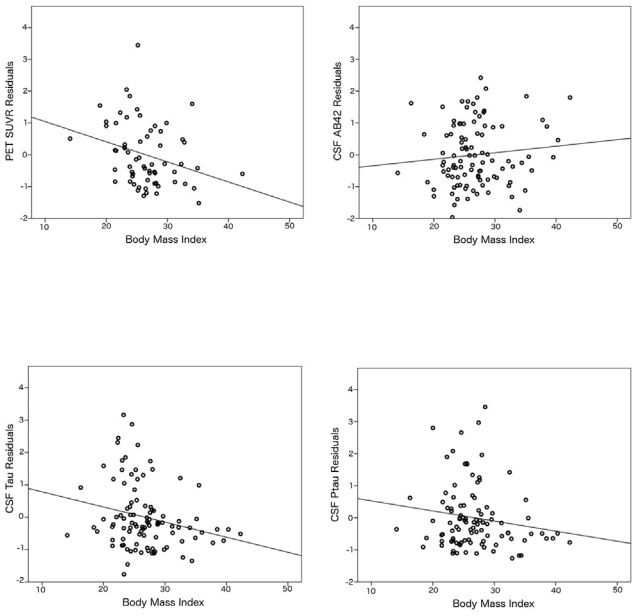
Background: Large-scale cross-sectional and longitudinal epidemiological studies indicate that chronic metabolic dysfunction such as diabetes, insulin resistance, and obesity increases the risk of developing Alzheimer disease (AD) (Akomolafe et al., 2007; Crane et al, 2013). This relationship has led some researchers to characterize AD as a metabolic syndrome. Conversely, a subset of work has demonstrated an almost protective relationship between AD pathology and weight or insulin resistance (Burns et al., 2007; 2012). **Methods:** Participants were 100 cognitively normal individuals (mean age of 72.1, stdev 5.1, 50 females) with a Clinical Dementia Rating (CDR) of 0. All participants had measures of body mass index (BMI), *APOE* genotyping, and a lumbar puncture to measure cerebrospinal fluid (CSF) levels of Aβ_{42}, tau, and ptau$_{181}$. 64 individuals also had positron emission tomography (PET) amyloid imaging using ^{11}[C]Pittsburgh Compound B (PiB). Regression modeling examined the main effects of age, gender, *APOE* genotype(ε4+/-) and BMI. **Results:** In all models advancing age and the presence of the ε4 allele were associated with greater AD pathology, while increasing BMI was associated with less pathology (Figure 1). In the model examining amyloid PET there was a significant effect of age (B=0.06, $F_{1,59}$=11.0, p<0.01), *APOE* genotype (B=0.7, $F_{1,59}$=16.6, p<0.01), and BMI (B=-0.05, $F_{1,59}$=6.4 p<0.01). For ptau$_{181}$ there was a significant effect of age (B=1.3, $F_{1,95}$=4.4, p<0.05) and trends for both *APOE* (B=13.9, $F_{1,95}$=3.6, p=0.06), and BMI (B=-1.2, $F_{1,94}$=3.7, p=0.06). For tau there were significant effects for age (B=10.9, $F_{1,95}$=13.1 p<0.001), *APOE* genotype (B=74.3, $F_{1,95}$=4.1, p<0.05), and BMI (B=-9.4, $F_{1,95}$=6.8, p<0.05). For CSF Aβ_{42} there was a significant effect of age (B=-17.9, $F_{1,95}$=10.7, p<0.01) and *APOE* genotype (B=-211.7, $F_{1,95}$=13.3, p<0.001). **Conclusions:** Lower values of BMI were associated with elevated levels of AD pathology in cognitively normal older adults. The mean BMI for the sample was 26.8 and only three individuals were underweight (BMI<18.5), suggesting individuals with very low weight did not drive this effect. Instead the effects may represent a subtle loss in appetite or behavioral alterations in meal preparation as AD pathology accumulates.



IC-P-022 CEREBRAL GLUCOSE METABOLISM IN A 5XFAD BUTYRYLCHOLINESTERASE-KNOCKOUT MOUSE MODEL OF ALZHEIMER'S DISEASE

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Background: Alzheimer's disease (AD) is a neurodegenerative disorder that causes dementia. Characteristic hallmarks of AD include the deposition of pathological β-amyloid plaques (Aβ) and neurofibrillary tangles (NFT) in the brain. The AD brain also exhibits cholinergic dysfunction; loss of cholinergic neurons contributes to the cognitive and behavioural symptoms of AD. Furthermore, cholinesterases such as butyrylcholinesterase (BuChE) associate with Aβ and NFT pathology. Recent work in our lab involving a novel BuChE knock-out mouse model of AD (5XFAD/BuChE-KO) has revealed that the absence of BuChE expression leads to diminished fibrillar forms of Aβ pathology in the brain. However, the exact role of BuChE on brain function in AD has not been determined. To further elucidate the effects of BuChE on metabolic regulation (thus brain function) in AD, we assessed cerebral glucose metabolism in this 5XFAD/BuChE-KO model using 18FDG-PET. **Methods:** Male 5XFAD/BuChE-KO mice (n=5) and age-matched BuChE-KO wild type controls (n=2) at 5 months underwent PET scanning 30 min after 18FDG administration and subsequently imaged using CT and MRI. Whole brain ROIs were generated from co-registered PET/CT/MRI data. 18FDG standardized uptake values (SUVs) were then compared between 5XFAD/BuChE-KO and BuChE-KO groups. **Results:** At 5 months, significant Aβ deposition was present in the 5XFAD/BuChE-KO mouse brain. 5XFAD/BuChE-KO animals demonstrated a 23% decrease

in whole brain SUVs compared to BuChE-KO controls (p=0.037). This significant decrease had not been observed in our previous investigations of cerebral metabolism in a BuChE expressing 5XFAD model (vs. control counterparts) at 5 months. **Conclusions:** We have previously observed variation in cerebral glucose metabolism with Aβ pathology in 5XFAD mice. Our current investigations suggest that BuChE may also be a modulator of cerebral glucose metabolism in AD, whereby the presence/absence of BuChE could significantly impact not only pathology but also brain function over the course of AD. Comparison of these 5XFAD/BuChE-KO brain metabolism results with those in BuChE expressing 5XFAD counterparts is currently underway. Furthermore, regional assessment of brain metabolism and corroborating neuropathology in these animals may further implicate BuChE in the progression of AD and may highlight the potential role of targeted BuChE imaging approaches for AD diagnostics.

IC-P-023 PILOT STUDY OF ALTERED COPPER METABOLISM AS A BIOMARKER FOR EARLY DIAGNOSIS OF ALZHEIMER'S DISEASE WITH $^{64}CUCL_2$-PET/CT

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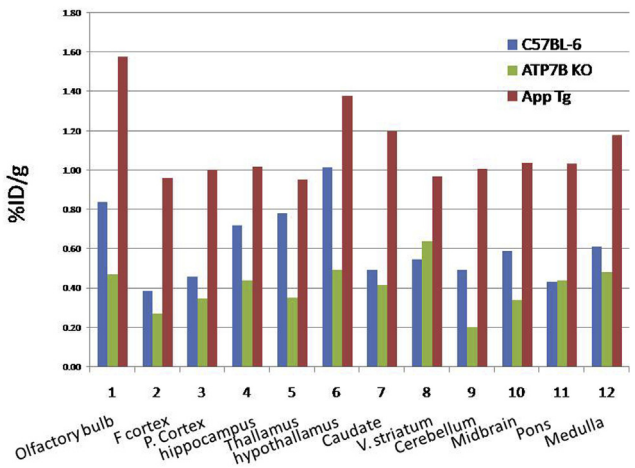
Background: Copper is a trace element required for development and normal function of human brains. Emerging body of evidence suggests the role of copper in pathogenesis of Alzheimer's disease. The aim of this study was to explore the potential of altered copper metabolism as a biomarker for early diagnosis of Alzheimer's disease with positron emission tomography/computed tomography (PET/CT) using copper-64 chloride ($^{64}CuCl_2$) as a radioactive tracer ($^{64}CuCl_2$-PET/CT). **Methods:** APPSWE transgenic mice (N=4, 14 weeks old,), a mouse model of Alzheimer's disease, were subjected to PET/CT after intravenous injection of copper-64 chloride ($^{64}CuCl_2$) as a tracer, using a small animal PET/CT scanner. A group of wild type C57BL/6 mice (N=4, 13 weeks old) and another group of *Atp7b* $^{-/-}$ knockout mice (N=4, 6 to 7 weeks old), a mouse model of Wilson's disease, were used as controls. PET quantitative analysis was performed to compare ^{64}Cu uptake in the brains of the APPSWE transgenic mice with the ^{64}Cu uptake in the brains of C57BL/6 and *Atp7b*$^{-/-}$KO mice, respectively. **Results:** Increased ^{64}Cu uptake was detected in the brains of the APPSWE transgenic mice, compared with the ^{64}Cu uptake in the brains of the C57BL/6 mice and the *Atp7b*$^{-/-}$ KO mice, respectively. In addition to increased ^{64}Cu uptake in the cortex, large increase of ^{64}Cu uptake was also detected in the regions of olfactory bulb and caudate of the APPSWE transgenic mice. Furthermore, cerebral ^{64}Cu uptake in the brains of the *Atp7b*$^{-/-}$ KO mice was found to be lower than the cerebral ^{64}Cu uptake in both the C57BL/6 mice and the APPSWE transgenic mice. Decrease of cerebral ^{64}Cu uptake in the *Atp7b*$^{-/-}$ KO mice was likely secondary to metabolic trapping of ^{64}Cu in the liver of *Atp7b*$^{-/-}$KO mice as visualized on the PET/CT images. **Conclusions:** Increased ^{64}Cu uptake was detected in the brains of APPSWE transgenic mice, compared with the ^{64}Cu uptake in the brains of C57BL/6 mice and *Atp7b*$^{-/-}$ KO mice, respectively. The findings support further investigation of altered copper metabolism as a biomarker for early diagnosis of Alzheimer's disease with PET/CT using $^{64}CuCl2$ as a radioactive tracer ($^{64}CuCl_2$-PET/CT).



IC-P-024 A NOVEL POSITRON EMISSION TOMOGRAPHY CONTRAST AGENT TARGETING CATHEPSIN D SHOWS PREFERENTIAL *IN VIVO* RETENTION IN AN ALZHEIMER'S DISEASE MOUSE MODEL

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Background: Early detection of Alzheimer's disease (AD) pathology remains a serious challenge for both diagnosis and development of treatment. Cathepsin D (CatD), a lysosomal aspartyl protease, is over-expressed in AD and therefore is a potential biomarker. Previously, we introduced a novel Contrast Agent (CA) that was preferentially taken up by CatD over-expressing cells (*in-vitro*) and able to transverse the BBB in mice (*ex-vivo*). We have also found that a Near-Infrared-labeled version of this CA demonstrates prolonged *in-vivo* retention in the brain of a transgenic (Tg) mouse model of AD at 12 months compared to age matched wild type controls. Here, we present the performance of a CA labeled with ^{68}Ga evaluated by micro Positron Emission Tomography (microPET). **Methods:** The CA consists of a Cell Penetrating Peptide (CPP; the Tat peptide from HIV-1), attached to a CatD cleavage sequence followed by a ^{68}Ga labeled DOTA chelator flanked by a fluorescent dye. The CPP allows the agent to cross the blood brain barrier bidirectionally. In the presence of elevated levels of CatD, cleavage of the CatD site removes the CPP resulting in prolonged retention of the imaging moeity. For this study, Tg AD mice (N=8, 5XFAD model) and non-Tg age matched littermates (N=8) at 2 and 4.5 months of age received an intravenous tail vein CA injection of ~12 MBq of CA under isofluorane anesthesia. Mice were scanned for 3 hours using the Inveon preclinical microPET system (Siemens Medical Solutions, Knoxville TN, USA). Regions of interest were identified in reconstructed images and were used to measure the uptake and washout of the CA in the brain, liver, kidneys and bladder. **Results:** The Tg mice demonstrated significantly greater uptake ($p<0.05$) of the CA in the brain in the first two hours following injection at 4.5 months but not 2 months of age compared to controls.