altered blood thiamine metabolism was associated with reduced activities of thiamine pyrophosphokinase in patients with Alzheiemr's disease as compared with control subjects (1.24 ± 0.06 vs. 1.44 ± 0.07, P<0.05). **Conclusions:** The patients with Alzheimer's disease manifest significant abnormality in blood thiamine metabolism as compared with normal cognitive subjects and patients with vascular dementia. Altered blood thiamine metabolism represents an ideal diagnostic biomarker for Alzheimer's disease with the reliable, non-invasive, simple to perform and inexpensive merits, and is associated with decreased thiamine pyrophosphokinase activities.

O1-02-03 ESTABLISHING APOLIPOPROTEIN J AS A POTENTIAL CANDIDATE FOR ALZHEIMER'S DISEASE BIOMARKER PANEL: AUSTRALIAN IMAGING, BIOMARKER AND LIFESTYLE (AIBL) FLAGSHIP STUDY OF AGING

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Background: Apolipoprotein J (apoJ) is a multifunctional protein, functions as a chaperone of misfolded extracellular proteins. It participates in functions like cell proliferation and apoptosis. Its levels are increased in the CSF of patients with AD. The plasma levels have been correlated to brain atrophy, baseline disease severity and clinical progression in AD. The present study includes longitudinal plasma measurement of apoJ in order to establish it as a potential analyte to be included in AD biomarker panel of AIBL. **Methods:** ApoJ protein levels were measured in the baseline and 18-month follow-up plasma samples from 833 individuals participating in the Australian Imaging, Biomarkers and Lifestyle (AIBL) Longitudinal Study of Ageing. It was assayed by a commercially available ELISA kit (Human Clusterin ELISA, R and D systems). apoJ plasma levels were then compared between healthy controls (HC), mild cognitively impaired (MCI) individuals and Alzheimer's disease (AD) patients. The data was further compared against other collected demographics including but not limited to cerebral amyloid load as measured by positron emission tomography (PET), hippocampal volume, APOE genotype and neuropsychological scores. **Results:** MCI and AD had significantly higher levels of apoJ at b aseline and 18-month data. MCI group had highest percentage change between the two time points viz. 2% (HC), 7% (MCI), 0.5% (AD). Significant correlation was observed with PiB-PET SUVR and hippocampal volumes. Increased levels of plasma apoJ correlate with cognitive decline at both baseline and 18 months. a poJ levels were significantly higher in apoE4 carriers, as compared to the non apoE4 carriers at both the time points. Further analysis will determine the relationship between plasma apoJ and other potential biomarkers such as apoE. **Conclusions:** The results of the present study show that apoJ is a potential candidate to be included in AIBL "AD biomarker panel" for the future development of an AD diagnostic assay. Completed measurements of further time point plasma samples from the same individuals will add great value to this study, by analysing the changes in plasma apoJ over time.

O1-02-04 THE BETA-AMYLOID AGGREGATE COUNT IN CSF IS A BIOMARKER FOR ALZHEIMER'S DISEASE

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Background: Alzheimer's disease (AD) is a fatal neurodegenerative and progressive disorder. Currently, no reliable biomarker for pre-symptomatic diagnosis or therapy monitoring is available. Recent studies support that especially soluble Aβ oligomers are the major toxic species during development and progression of AD. Therefore, we suggest that the number of Aβ oligomers in body fluids can be used as the most direct biomarker for AD. **Methods:** Here, we present an optimized version of the single aggregate sensitive surface-based fluorescence intensity distribution analysis (sFIDA) assay. For the first time, it allowed the determination of the Aβ oligomer count in cerebrospinal fluid (CSF). **Results:** We challenged the assay with CSF samples of 14 AD patients and 12 age-matched control subjects. The Aβ oligomer count allowed a surprisingly clear distinction between both groups. All samples of the control group showed homogenously low numbers of Aβ oligomers. The samples of the AD group had comparably high levels of Aβ oligomers and displayed high variability. The Aβ oligomer levels clearly correlated with the patients' mini-mental state examination (MMSE) scores. **Conclusions:** Our results support the idea that Aβ oligomers play a decisive role in AD pathology and in turn can be used as a diagnostic biomarker. The sFIDA assay is able to reliably quantify the Aβ oligomers in human CSF. The correlation between MMSE and Aβ oligomer count suggests that the quantitity of Aβ oligomers in CSF even reflects the severity of the disease. Further studies will show whether anti-Aβ targeted therapies can affect the Aβ oligomer counts in treated individuals.

O1-02-05 IDENTIFYING MULTI-ANALYTE CSF BIOMARKERS FOR ALZHEIMER'S DISEASE IN A MULTI-COHORT STUDY

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Background: Aβ 42 and tau cerebrospinal fluid (CSF) values measured by ELISA and xMAP technologies are currently used to differentiate between Alzheimer's disease (AD) against cognitively normal (CN) subjects, yet the standardization of these tests are still underway. It seems likely that a combined set of biomarkers will define a patient-specific signature to diagnose AD in the future. The utilization of a discovery-based multi-analyte platform (MAP) by Rules Based Medicine allows for the exploration of a broader set of protein analytes, with the aim of improving the accuracy of AD diagnosis upon current classical CSF biomarkers. Yet special pre-processing steps are required for proper removal of any experimental biases present inside these multiplex data. **Methods:** CSF samples from AD and CN populations were obtained from three independent cohorts: Alzheimer's disease Neuroimaging Initiative, University of Pennsylvania and Washington University. We first performed quality control steps for data from the MAP panel, including 1) removal and imputation of analytes with missing and low values; 2) adjustment of sample outliers by flooring/ceiling their respective protein levels; 3) logarithmic transformation to ensure analytes are of normal distribution; and 4) z-score transformation to account for batch effects across cohorts. 54 common analytes were left across these cohorts.

Next using a random forest based backward elimination method, we identified and compared the sets of CSF protein analytes found in each cohort. Pathway analysis was performed on the commonly selected analytes. **Results:** Fatty acid binding protein, pancreatic polypeptide and vascular endothelial growth factor, in complement with Aβ 42 and t-tau, were consistently identified to be associated with AD diagnosis in all three independent cohorts. Age and gender effects were found to be insignificantly associated with the selected analyses. Canonical pathways related to coagulation system, atherosclerosis signaling and IL-17 signaling were selected by Ingenuity Pathway Analyses ($p<0.001$). **Conclusions:** The quality control steps we standardized contribute to the discovery of three protein analytes in addition to Aβ 42 and tau, with high reproducibility across three independent cohorts, which may serve as important drug targets. Significant pathways identified may provide insights to AD pathology, and hence point out underlying AD mechanisms.

O1-02-06 CSF PKR CAN PREDICT COGNITIVE DECLINE IN ALZHEIMER'S DISEASE

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Background: Neuropathological hallmarks include in Alzheimer's disease (AD), senile plaques composed of Aβ 1-42 peptide, neurofibrillary tangles formed by hyperphosphorylated tau protein and synaptic and neuronal losses. Aβ 1-42 oligomers could induce neurodegeneration. In AD, the Aβ 1-42 cerebrospinal fluid (CSF) levels are reduced and CSF tau and phosphorylated tau (pTau) are augmented. PKR is a pro-apoptotic and pro-autophagic kinase that can block protein translation. Auto-phosphorylation of PKR is produced by virus, cytokines, calcium, and Aβ 1-42. PKR can control inflammation, the levels of BACE 1 and Aβ 1-42 production as well as tau phosphorylation. The genetic knock down of PKR improves memory in experimental mice. In this study we have analyzed CSF levels of PKR and activated PKR (pPKR) in AD patients compared to neurological controls and patients with amnestic Mild Cognitive Impairment (MCI). **Methods:** Forty five AD patients, 11 patients with Mild Cognitive Impairment and 35 neurological controls were enrolled and followed for more than 2 years. All patients had initially, a lumbar puncture to determine CSF levels of Aβ 1-42, Tau, pTau, PKR and pPKR using western blot procedures. Cognitive evaluation was carried out twice a year. All patients or care giver gave their written inform consents. **Results:** The mean CSF pPKR level was augmented by 300% in AD patients compared to neurological disease controls. The sensitivity was 91.1% and the specificity was 94.3%. pPKR concentrations were also increased in the majority of MCI patients. In AD patients PKR and pPKR levels correlate with pTau levels and with the cognitive decline assessed with repeated MMSE over more than 2 years. . **Conclusions:** The evaluation of CSF PKR and pPKR concentrations seems to be appropriate diagnostic and prognostic biomarker and could be proposed in future assessments of AD patients.

ORAL SESSIONS: O1-03 DIAGNOSIS AND PROGNOSIS: CEREBRAL MICROHEMORRHAGES—ROLE OF CEREBRAL NEUROPATHOLOGY

O1-03-01 LINKING DECLINING LEVELS OF PLASMA BETA-AMYLOID 42 TO ALZHEIMER'S DISEASE: THE ROLE OF CEREBRAL MICROBLEEDS

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Background: Older individuals with declining levels of plasma Aβ 42 are at increased risk for the development of Alzheimer's disease (AD), but the mechanism linking the two is unclear. One possibility is that declines in plasma Aβ 42 reflect deposition of circulating Aβ 42 in the walls of cerebral blood vessels, a phenomenon referred to as cerebral amyloid angiopathy (CAA). Small, punctate lesions, or microbleeds, visualized on T2*-weighted magnetic resonance imaging (MRI) are considered markers of CAA, particularly when found in lobar regions of the brain. In the current study, we determined whether individuals with declining levels of Aβ 42 have increased microbleeds. **Methods:** Plasma Aβ 40 and Aβ 42 were measured at two time points (mean interval = 4.6 yrs) in participants in the Washington Heights Inwood Columbia Aging Project, a community-based study of aging and dementia among elders residing in upper Manhattan. T2*-weighted MRI scans were acquired 4.3 (SD=1.3) years following the second Aβ measurement and microbleeds were visually identified and counted separately for lobar and subcortical regions. The sample was divided into beta amyloid change groups based on 0.5 standard deviation of change: increasing, no change, decreasing. The mean number of deep and lobar microbleeds was compared across the three groups with multivariate general linear models with bootstrapping, controlling for age, ethnicity, sex, education and APOE genotype. **Results:** Both plasma Aβ and microbleed data were available for 187 participants (mean age at baseline = 74.9 +/- 5.16 years, 68% women). Twenty-one percent and 9% of the sample had any lobar and deep microbleeds, respectively. Mean number of microbleeds was 1.6 (+/- 0.44) in those with declining Aβ 42, 0.60 (+/- 0.20) in those with no change in Aβ 42 and 0.34 (+/- 0.17) in those with increasing Aβ 42; significant main effect of Group, $F(4,352)=3.05$, $p=0.017$). The three Aβ 42 change groups did not differ in severity of deep microbleeds. Neither Aβ 40 change groups nor Aβ 42/Aβ 40 ratio change groups differed for either lobar or deep microbleed severity. **Conclusions:** The findings suggest that the vascular deposition of circulating beta amyloid may be a pathway through which declining levels of plasma Aβ 42 increases risk for development of AD.

O1-03-02 FOCAL HEMOSIDERIN DEPOSITS AND BETA-AMYLOID LOAD IN THE ADNI COHORT

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Background: Prevalence and incidence of focal hemosiderin deposits are important considerations for inclusion and tracking of adverse events in Alzheimer's disease (AD) therapeutic trials with amyloid-lowering agents. We report the prevalence and regional distribution of focal hemosiderin deposits in the form of microhemorrhages (mH) and superficial siderosis in cognitively normal (CN), early mild cognitive impairment (EMCI), late MCI (LMCI) and AD subjects in the Alzheimer's Disease Neuroimaging Initiative -Grand Opportunity (ADNI-GO) and ADNI-2 studies. We further investigate the number of mH in relation to APOE genotype and Aβ load on PET. **Methods:** Subjects were cognitively normal (n=171), EMCI (n=240), LMCI (n=111) and AD (n=40) ADNI-GO and ADNI-2 participants who underwent 3T MRI studies from June 2010 until March 2012. Microhemorrhages and superficial siderosis were assessed at baseline and on all available T2* gradient recalled echo (GRE) MRIs at 3, 6 and 12 months. β-amyloid load was assessed with 18 F-florbetapir PET. The correlation between mH count and age and 18 F-florbetapir SUVR was tested using Spearman rank-order correlation. Kruskal-Wallis test was used as a one-way nonparametric ANOVA to evaluate the association between mH count and APOE genotype classified as ε2 carriers, ε3/3 homozygotes, and ε4 carriers. **Results:** Prevalence of superficial