

AD patients from controls compared to using the core AD biomarkers alone. However, AD patients in advanced clinical stage, as determined by low MMSE score ( $\leq 20$ ), had lower BACE1 activity and sAPP  $\pm$ , sAPP $\beta$  and A $\beta$ 40 concentrations than patients with higher MMSE score. **Conclusions:** Our results highlight the strong diagnostic power of the core CSF biomarkers for AD. We also suggest that BACE1 activity and sAPP  $\pm$ , sAPP $\beta$  and A $\beta$ 40 concentrations may be related to the severity of the disease.

**P1-014** **REDUCED PLATELET AMYLOID PRECURSOR PROTEIN RATIO (APP RATIO) PREDICTS CONVERSION FROM MILD COGNITIVE IMPAIRMENT TO ALZHEIMER'S DISEASE**

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**Background:** Studies have shown that platelet APP ratio (representing the percentage of 120-130 kDa to 110 kDa secreted fragments of the amyloid precursor protein) is reduced in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD). In the present study, we sought to determine if baseline APP ratio predicts the conversion from MCI to AD-dementia after 4 years of longitudinal assessment. **Methods:** Twenty-eight older adults diagnosed at baseline as with MCI according to the Mayo Clinic criteria (Petersen et al., 2001) were reassessed after 4 years. All participants were re-classified according to the conversion status upon follow-up: 20 individuals retained the diagnostic status of MCI and were considered as stable cases (MCI-MCI); conversely, in 8 cases the diagnosis of dementia due to AD was ascertained by the NINCDS-ADRDA diagnostic criteria (McKhann et al., 2011). The APP ratio (APPr) was determined by the Western-blot method in samples of platelets collected at baseline. **Results:** We found a significant reduction of APP ratio in MCI patients who converted to dementia upon follow-up. The overall accuracy of APP ratio to identify subjects with MCI who will progress to AD was  $0.74 \pm 0.10$ ,  $P = 0.05$ . The cut-off of 1.12 yielded a sensitivity of 75% and a specificity of 75%. **Conclusions:** Platelet APP ratio may be regarded as a candidate biomarker to support the early diagnosis of AD, with potential implications for the assessment of abnormalities in the APP metabolism in patients with and at risk for dementia.

Table 1  
Baseline variables according to diagnostic outcome in the follow-up

	Baseline diagnosis – Follow-up Diagnosis		P
	MCI-MCI	MCI-AD	
Gender			
M / W	3 / 17	7 / 1	0.001
Age	70.0 [68.0 - 72.0]	79.5 [75.5 - 82.5]	0.001
Years of education	11.0 [8.0 - 14.0]	10.5 [6.5 - 15.0]	0.94
MMSE	27.0 [27.0 - 29.0]	27.5 [24.0 - 28.5]	0.83
CAMCOG	96.5 [88.0 - 100.0]	89.5 [81.5 - 94.0]	0.12
APP ratio	1.2 [1.1 - 1.4]	1.0 [0.9 - 1.1]	0.05

**P1-015** **BRAIN AND HIPPOCAMPAL RATES OF ATROPHY IN FAMILIAL ALZHEIMER'S DISEASE MUTATION CARRIERS: PRELIMINARY FINDINGS FROM THE DIAN STUDY**

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**Background:** The Dominantly Inherited Alzheimer Network (<http://dian-info.org/>) study is an international clinical, biomarker and multi-modality imaging study of individuals at risk for autosomal dominant Alzheimer's disease and those already mildly affected. This prospective study of these individuals provides an opportunity to follow these individuals through different stages of the disease process, starting several years before symptoms are evident. We report here the first longitudinal analyses of cerebral and hippocampal atrophy rates from the DIAN cohort. **Methods:** All DIAN participants have T1-weighted volumetric MRI scanning at baseline. We analysed data from the first 22 participants with a follow-up MRI scan (mean  $\pm$  sd interval  $12.7 \pm 0.9$  months). Seventeen subjects were symptomatic mutation carriers (sMut+) with Clinical Dementia Rating (CDR) scores  $>0$  aged  $46.4 \pm 9.6$  years; three were asymptomatic carriers (aMut+) with CDR = 0; and two were non-carriers (NC). The aMut+ and NC were combined into one group for this initial analysis (age:  $34.5 \pm 5.4$  years). The whole brain and hippocampi were first delineated using an automated procedure. Annualized atrophy rates were measured by volumetric difference as well as the Boundary Shift Integral (BSI). Two sample t-tests assuming unequal variances were performed between the annualized atrophy rates of the sMut+ group and the combined NC/aMut+ group. **Results:** Brain BSI atrophy rates were higher (see Table) in the symptomatic subjects (1.9% vs. 0%/year;  $P = 0.003$ ). However, the difference in hippocampal atrophy rates was not statistically significant (2.5% vs. 0.5%/year;  $P = 0.057$  for volumetric). **Conclusions:** Initial analysis of atrophy rates from this cohort indicates that brain atrophy rates are higher in symptomatic mutation carriers than in asymptomatic carriers or non-carriers. The lack of a detectable difference in hippocampal atrophy rates may reflect the small sample size and that these preliminary analyses included presymptomatic mutation carriers in the control group who may have already had increasing rates of hippocampal atrophy. Over 200 subjects will be followed longitudinally,

Table 1  
Mean (95%CI) brain and hippocampal atrophy rates as a percentage of baseline volume

Group	Age	Annualized Brain BSI % loss/year	Annualized Hippocampal Volume change % loss/year
NC/aMut+ (n = 5)	34.5 $\pm$ 5.4	0.0 $\pm$ 0.8% (-1.0,1.1)	0.5 $\pm$ 1.7% (-1.6,2.6)
sMut+ (n = 17)	46.4 $\pm$ 9.6	1.9 $\pm$ 1.3% (1.2,2.5)	2.5 $\pm$ 1.7% (1.6,3.3)
P-value	0.006	0.003	0.057

so as more data are acquired, we will separately analyze atrophy rates in asymptomatic carriers and non-mutation carriers, estimate sample sizes for trials and assess the relationship between atrophy rates and symptom onset.

P1-016

### CHOLINESTERASE INHIBITORS INCREASE iPLA2 ACTIVITY IN PLATELETS OF PATIENTS WITH ALZHEIMER'S DISEASE

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**Background:** Decreased PLA 2 activity has been consistently found in the brain and peripheral tissues of patients with Alzheimer's disease (AD). This abnormality may have important implications to neuronal homeostasis, and also be related to specific mechanisms that pertain to the pathogenesis of AD. We have recently shown that reduced calcium-independent PLA 2 activity is an early event in the disease process, in addition to being related to memory acquisition and retrieval. It is widely accepted that cholinesterase inhibitors (ChEIs) yield symptomatic benefits to patients with mild and moderate dementia. Yet, it is unclear whether the use of these drugs may also be associated with disease-modifying effects in AD. **Objective:** To determine the effect of long-term treatment with ChEIs on platelet PLA 2 activity in patients with mild and moderate AD. **Methods:** 36 non-medicated AD patients were recruited to this study. The control group comprised 20 age-matched, healthy individuals. Patients and controls were assessed at baseline with clinical and neuropsychological instruments, and reassessed after 3 and 6 months. PLA 2 activity was determined in platelets by a radio-enzymatic assay addressing PLA 2 subtypes, i.e. calcium-dependent cytosolic PLA 2 (cPLA 2), calcium-dependent secretory PLA 2 (sPLA 2) and calcium-independent intra-cellular PLA 2 (iPLA 2). **Results:** Preliminary results based on the first 8 patients to complete 6 months of follow-up: iPLA 2 activity was decreased in patients with AD as compared with controls ( $P = 0.02$ ); no such differences were found to c- and sPLA 2. After 6 months of ChEI treatment, we observed a significant increase in iPLA 2 activity ( $P = 0.035$ ), restoring enzymatic activity similar to that observed among controls. **Conclusions:** In spite of the small sample size, our preliminary results reinforce our previous findings of decreased platelet iPLA 2 activity in AD, and further suggest that ChEIs may have disease-modifying properties in certain biochemical pathways related to membrane phospholipid metabolism.

P1-017

### PREDICTING 12- AND 24-MONTH PROGRESSION IN MILD COGNITIVE IMPAIRMENT: COMPARISON OF NEUROCOGNITIVE, NEUROANATOMICAL AND CSF BIOMARKER DATA

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**Background:** Clinical trials of potential disease-modifying therapeutics in mild cognitive impairment (MCI) have been hampered by the inclusion of large percentages of subjects who remain clinically stable or "revert" to normal cognition. Identification of inclusion criteria that identify subjects with MCI who are likely to exhibit progressive decline over the near future (i.e., subjects who are truly in the prodromal phase of dementia) is critical for efficient screening of potential therapeutics. Data from the ADNI database were used to compare predictors of progression, defined by worsening on co-primary endpoints of the Alzheimer's-Disease Assessment

Scale-cognitive subscale (ADAS-Cog) and Clinical Dementia Rating (CDR) Scale over 12 and 24 months. **Methods:** This was a retrospective analysis using the ADNI database. Only subjects with baseline diagnosis of MCI with baseline markers of left and right hippocampal volumes, CSF measures of pathological A $\beta$ 1-42 and total-tau, and neurocognitive data were included ( $n = 174$ ), thereby permitting an appropriate head-to-head analysis. A single measure was selected for each category; one score representing bilateral hippocampal volume, one representing the ratio of the log-transformed A $\beta$ 1-42/total tau, and one a global z-score derived using 12 neurocognitive variables (not including the ADAS-Cog). Progression was defined by worsening on the ADAS-Cog ( $\geq 2$  points) AND the CDR ( $\geq 1$  point). All three markers were selected based on prior evidence supporting their individual predictive validity. **Results:** A logistic regression analysis identified only the global neurocognitive z-score as a significant predictor of 12-month decline ( $\hat{\beta} = 12.3$ ,  $p = .001$ ). Neither the hippocampal volume ( $P = .283$ ) or A $\beta$ 1-42/total tau ( $P = .714$ ) added significantly to the prediction at 12 months. Likewise, at 24-months, the global neurocognitive z-score was the strongest predictor of decline ( $\hat{\beta} = 14.15$ ,  $P < .001$ ). The structural MRI data also contributed to the overall significance of this model ( $\hat{\beta} = 7.6$ ,  $p = .007$ ), but the A $\beta$ 1-42/total tau did not. **Conclusions:** A global neurocognitive z-score at baseline was a more robust predictor of clinical progression, as typically defined in clinical trials of MCI/AD, than these selected MRI or CSF biomarkers. Future studies are underway to improve the sensitivity of the imaging and biomarker measures. Implications for clinical trial design are discussed.

P1-018

### RELATION BETWEEN RATES OF A $\beta$ DEPOSITION, APOE GENOTYPE AND COGNITION: RESULTS FROM A 3- TO 5-YEAR LONGITUDINAL STUDY

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Health Research Institute, Melbourne, Australia.

**Background:** Longitudinal evaluation of ageing individuals is providing insight into the different factors leading to Alzheimer's disease (AD). We used data from the AIBL cohort to provide a better understanding of the relationship between A $\beta$  deposition and cognition in the development of AD. **Methods:** One hundred and seventy participants -118 elderly healthy controls (HC); 35 Mild Cognitive Impairment (MCI) subjects; and 17 mild AD patients - were evaluated at enrolment, and 18, 36 and 54 months later. On each visit, participants underwent neuropsychological examination, a MRI and a 11 C-PiB PET scan. Rates of change for A $\beta$  deposition and cognitive decline were derived from the slope of the regression plots over 3-5 years and used in the regression analysis. **Results:** A $\beta$  deposition ( $0.05 \pm 0.04$  vs  $0.01 \pm 0.02$  SUVR/yr,  $P < 0.0001$ ) and memory decline ( $-0.20 \pm 0.27$  vs  $-0.02 \pm 0.25$  SD/yr,  $P = 0.0005$ ) were significantly faster in PiB+ vs PiB- HC. A $\beta$  deposition and memory decline were also faster in PiB+ than in PiB- MCI ( $0.05 \pm 0.02$  vs  $0.01 \pm 0.03$  SUVR/yr,  $P = 0.0008$ ; and  $-0.22 \pm 0.21$  vs  $-0.04 \pm 0.18$  SD/yr,  $P = 0.02$ , respectively). Overall, A $\beta$  deposition was slightly slower in AD ( $0.03 \pm 0.03$  SUVR/yr). A $\beta$  deposition in ApoE E4 carriers was significantly faster only in the MCI group ( $P = 0.005$ ). Memory decline was inversely associated with A $\beta$  deposition in all groups: HC ( $R^2 = 0.09$ ,  $P = 0.039$ ), MCI ( $R^2 = 0.17$ ,  $P = 0.047$ ), and AD ( $R^2 = 0.66$ ,  $P = 0.034$ ). **Conclusions:** A $\beta$  deposition is associated with cognitive decline even in asymptomatic healthy controls. This supports the theory that A $\beta$  deposition plays a fundamental role in the development of AD and suggests that, to be effective, anti-A $\beta$  therapy may need to be given early in the course of the disease, perhaps even before symptoms appear.