SUNDAY, JUNE 19, 2005
ORAL SESSION
O1-04
IMAGING AND BIOMARKERS

O1-04-01 IMAGING ALZHEIMER'S DISEASE PATHOLOGY USING T1 RHO MRI

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Purpose: Conventional MRI techniques have proven inadequate in observing the actual senile plaques (SP) and neurofibrillary tangles (NFT) in vivo underlying the pathology of Alzheimer's Disease (AD). An alternate contrast mechanism to conventional T1 and T2 weighted images is T_{1r} or T1 rho, the spin-lattice relaxation time constant in the rotating frame, which determines the decay of the transverse magnetization in the presence of a spin-lock radio-frequency field. T1r relaxation is less prone to effects from diffusion and susceptibility compared to T2 relaxation times and therefore presents a greater dynamic range of values compared to T_2 in biological tissues. T_{1r} MRI has shown promise in delineating tumors.The purpose of our study was to determine T1r relaxation times in vivo in patients with AD and compare these values against age-matched controls. **Material and Methods:** MR Imaging was performed on 6 patients (mean age: 77±7) with AD and 6 controls (mean age: 73±7). An oblique Coronal T_{1r}-weighted image of a slice perpendicular to the AC/PC plane was obtained. This slice was chosen to include the hippocampus head. **MRI Parameters:** T_{1r} pre-encoded Turbo Spin-Echo (TSE) pulse sequence with TE/TR= 12/2000ms, TSL (duration of spin-lock pulse)= 20, 40, 60 and 80ms. Slice thickness- 2mm, FOV=22cm, NEX=1, Matrix= 256 x 128, ETL=4. Total imaging time of 6 minutes. Each image pixel's signal intensity was fitted as a function of TSL by a linear least-squares algorithm to generate T1r maps. A single user manually selected a region of interest in each map in the medial temporal lobe region and recorded average T1r values. Statistical analysis was performed with the JMP software package. A student's t-test was performed to determine any significant difference between the values obtained in patients and controls. **Results:** The average T1r for patients was 95.3±1.4ms (mean ± std. error) and for controls was 87.5±1.7ms and the difference was statistically significant ($p<0.005$). **Discussion:** This is the first demonstration of imaging AD pathology in humans using T1r imaging. Our results indicate that the macromolecular changes underlying AD (including SP, NFT, edema/gliosis) results in the prolongation of the T1r relaxation time of brain tissue.

O1-04-02 CEREBROSPINAL FLUID MARKERS AND CHANGE IN MMSE SCORE OVER AN 8-YEAR FOLLOW-UP PERIOD - THE POPULATION STUDY OF WOMEN IN GOTHENBURG, SWEDEN

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Background: Between 2010 and 2050, Alzheimer's disease (AD) will reach epidemic proportions, highlighting the importance of identifying appropriate preclinical markers for prevention. Biomarkers present in cerebrospinal fluid (CSF) may be useful for predicting progression from preclinical to clinical AD. **Objective:** We investigated the longitudinal relationship between cerebrospinal fluid markers - amyloid beta-42 (Abeta-42), tau, growth-associated protein-43 (GAP-43), and the CSF-to-serum albumin ratio (albumin ratio) - in relationship to dementia occurrence and change in Mini-Mental State Examination (MMSE) score over an 8-year follow-up period in a population-based sample of women. **Methods**: The MMSE and lumbar puncture were performed in 1992 on a representative sample of 84 women without dementia born in 1908, 1914, 1918, and 1922 (aged 70-84 years) as part of the Population Study of Women (PSW) in Göteborg, Sweden. Cerebrospinal fluid was analyzed for Abeta-42, GAP-43, tau protein, and the albumin ratio. Women were followed for 8 years after lumbar puncture for dementia occurrence and a repeat MMSE. Correlation and regression analyses and ANOVA were used to relate CSF markers, dementia, age, and change in MMSE score between 1992 and 2000. **Conclusions:** Women who developed dementia after 1992 (n=6) had a lower Abeta-42 ($p=0.061$) level, and higher tau ($p=0.000$) and GAP-43 ($p=0.023$) levels at baseline compared to women who did not become demented. Women who became demented also experienced a greater decline in MMSE score ($p=0.000$) between 1992 and 2000. Among 51 women who never developed dementia and who participated in the MMSE in 1992 and 2000, decline in MMSE score (range=3 to -8 points) was correlated with decreases in Abeta-42 ($r=0.359$, $p=0.010$). Of those experiencing a decline of at least 2 points in MMSE (n=14), mean Abeta-42 levels were lower compared to those who experienced no decline ($p=0.025$). In a multivariate linear regression model including all CSF markers and predicting change in MMSE, Abeta-42 was the sole predictor ($R^2=0.173$, $p=0.026$). CSF Abeta-42 is a useful marker of cognitive decline as measured using the MMSE among elderly women without dementia, and CSF markers are useful predictors of dementia when measured at least one year prior to dementia onset.

O1-04-03 NOVEL INFECTIOUS BIOMARKERS OF COGNITIVE IMPAIRMENT

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Background: Studies have implicated herpesviruses, such as herpes simplex virus (HSV) and cytomegalovirus (CMV), as potential causal agents or promoters of dementia. Cortisol, a hormone associated with stress, can potentiate the viral action of herpesviruses and has also been shown to affect hippocampal volume. **Objectives:** The overall purpose of this study was to examine whether herpesvirus antibody levels and cortisol are predictive biomarkers of cognitive decline. Specific aims are to: 1) assess whether heightened levels of viral antibodies to herpesviruses influence trajectories of cognitive functioning, and 2) examine whether increased cortisol modifies the effect of viral antibody levels on cognitive decline. **Methods:** Baseline Serum samples from an ongoing cohort of 1,204 Mexican Americans aged 60+ were analyzed for antibody levels reactive to HSV type-1 or CMV and for fasting cortisol values. Over a four-year period participants were annually screened for cognitive functioning using the Modified Mini Mental State Examination (3MSE). The 3MSE scale was squared to improve normality. Hierarchical models were used to obtain specific estimates describing the effect of viral antibody levels at baseline on 3MSE decline and to examine the interaction between increased cortisol and viral antibody levels on decline. All models included control for covariates such as chronic illnesses, age, and education. **Conclusions:** Higher total combined viral antibody levels (CMV + HSV) was associated with greater cognitive decline over four years (slope of annual change in 3MSE-squared: −26.67, $p=0.008$). When examined separately, CMV levels had a stronger effect than HSV on decline in 3MSE scores (CMV slope of annual change in 3MSE-squared: −27.30, $p<0.002$ versus HSV slope: −12.00, $p=0.223$). Serum cortisol did not modify the effect of combined viral antibody levels on cognitive decline. In conclusion, further research is required to assess whether high antibody levels to CMV directly shape cognitive functioning trajectories or whether antibody levels are a marker of subclinical cellular immune dysfunction that is itself a determinant of cognitive decline. The high prevalence of latent infection with CMV and HSV in elderly populations reinforces the need to determine the pathways by which antibody levels influence development of cognitive impairment and dementia.