cognitive testing showed de?cits in working and reference memory. Dementia comes in different forms like, Creutzfeldt-Jakob Disease (CJD), Dementia with Lewy Bodies Frontotemporal Dementia Huntington's Disease . Normal Pressure Hydrocephalus, Parkinson's Disease Vascular Dementia Wernicke-Korsakoff Syndrome. Alzheimer diseases. One would like to know the role of extracellular and intraneuronal Aß accumulation in initiating neurotoxicity. Is Aß fibrils the principal toxic moiety in Alzheimer diseases or whether small oligomeric assemblies serve as microglia- activating and neuron injuring species. Is the apoptosis of neuron play an important role in the pathogenetic Cascade of VD, that if inhibited will slow or prevent brain dysfunction. **Methods:** Quantitative and qualitative evaluation using Western blotting and immunohistochemistry ,immunofluorescence techniques will be used to evaluate Amyloid beta accumulation in the extracellular and intraneuronal pathways and will give a probable definition of the activities in this cascade. **Results:** Expressions of protein markers present in vascular dementia will enable us to charaterize the extent of Amyloid beta accumulation in the extracellular and intraneuronal pathways. Morphological features expressed after staining will ascertain the extent of damage in the extracellular and intraneuronal morphology. The density of Beta Amyloid will probably indicate an important role of Aß in apoptosis of neurons. **Conclusions:** The outcome of the evaluation of Aß density and immunohistochemical studies will explain if the aggregation of Aß ,Aß fibrils, Apoptosis of neurons will play an important role in Vascular Dementia pathogenetic cascade.

P4-024 HOW DOES DIABETES AFFECT PLAQUE AND TANGLE PATHOLOGY IN ALZHEIMER'S DISEASE?

Aleksandra Obradov[1], Aleksandra Obradov[1], Michael Malek-Ahmadi[1], Thomas Beach[1], Lucia Sue[1], Christine Belden[1], Kathryn Davis[1], Marwan Sabbagh[1], *[1]Banner Sun Health Research Institute, Sun City, Arizona, United States.*

Background: Past studies of AD pathology association with DM2 have provided conflicting results. While several studies indicate that subjects with simultaneous occurrence of AD and DM2 have less AD pathology, others have found no significant differences in AD pathology between the two groups. **Methods:** Data on clinicallyand pathologically diagnosed Alzheimer's disease (NINDS-ADRDA clinically andNIA Reagan intermediate or high pathologically) with DM2 (n = 30) and thosewithout DM2 (n = 464) were included from the Banner Sun Health ResearchInstitute Brain Donation Program by database search. Plaque and tangle scores fromthe frontal, parietal, temporal, entorhinal and hippocampal regions werecompared between the groups. In addition, summary scores from all regions werealso compared. Mann-Whitney U test was used to compare differences between DM2+and DM2- cases. Logistic regression wasthen used to determine the association between total plaque and tangle countswith DM2 status. **Results:** DM2+ cases had lower neurofibrillary tangle (NFT) scores in the frontal lobe (p = 0.04_ and parietal lobe p = 0.07) as well as decreased plaque scores in the CA1 hippocampal area (p = 0.06). There was no significant difference in the summary total plaque and tangle scores, without adjustment for ApoE e 4 status. After accounting for the effect of ApoE e 4 status, no association was found for the sum of plaque [OR 0.89 (0.64, 1.25), p = .52] or sum of tangle [OR 1.09 (0.94, 1.26) p = .28] counts and DM2 status. **Conclusions:** In this clinical-pathological case series, contrary to our hypothesis, we did not find increased plaque and tangle histopathology in AD subjects. Instead, there was a weak trend suggesting that AD subjects with DM2 have decreased NFT pathology in the frontal and parietal lobes, and decreased plaque pathology in the hippocampus. Other data and literature reports indicate that weight loss during the course of dementia may ameliorate many obesity-associated medical conditions, including DM2. Further studies should examine whether DM2 in midlife is associated with increased risk and severity of neuropathologically-confirmed AD and whether DM2 prevalence and severity in AD subjects decreases with disease duration.

P4-025 PATHOLOGICAL CORRELATES OF WHITE MATTER HYPERINTENSITIES ON MAGNETIC RESONANCE IMAGING

YongSoo Shim[1], John Morris[2], Nigel Cairns[3], Tammie Benzinger[2], Chengjie Xiong[4], *[1]The Catholic University of Korea, Bucheon, South Korea; [2]Washington University in St Louis, St Louis, Missouri, United States; [3]Washington University in St Louis, Saint Louis, Missouri, United States; [4]Washington University School of Medicine in St Louis, St. Louis, Missouri, United States.*

Background: White matter hyperintensities (WMHs) are commonly observed on magnetic resonance imaging (MRI) of the brain in elderly persons. We investigated the histopathological correlates of WMHs in Alzheimer's disease (AD) patients, controls and persons with well defined advanced risk factors for cerebrovascular disease. **Methods:** From December 1995 to November 2000 we enrolled a total of 165 participants in the longitudinal study of CCCVD (Cognitive Change in Cerebrovascular Disease). Even after the study ended, participants were followed for clinical evaluations. Of the 60 participants with autopsy, MRIs were available for 57. Brain tissue was classified into white matter (WM), gray matter (GM), cerebrospinal fluid, and WMH. Brain parenchymal fraction, an index of brain atrophy, was calculated as sum of WM and GM volumes divided by the total intracranial cavity volume. Neuropathological examination was performed using the Braak and Braak neurofibrillary tangle stage and the neuropathological criteria of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Large (atherosclerosis) and small vessel disease (arteriolosclerosis and cerebral amyloid angiopathy) were each rated. In addition, we studied areas of tissue corresponding to WMH regions in 14 subjects. Microscopic features were added as follows: demyelination of the deep and periventricular WM, atrophy of the ventricular ependyma, and thickening of the blood vessels in the WM. Correlations between MRI data and pathological findings across the entire sample were performed. **Results:** There was an inverse correlation between WMHs and neurofibrillary tangle scores (r = −0.341, p = 0.014). WMHs were also decreased as neuritic and diffuse plaques (r = 0.344, p = 0.014 and r = 0.280, p = 0.047, respectively) get severe. Periventricular hyperintensities correlated with breakdown of ventricular lining (r = 0.559, p = 0.038) and deep white matter hyperintensities correlated with deep WM demyelination (r = 0.845, p = 0.034). **Conclusions:** WMHs in AD and controls consist of areas of loss of myelinated axons and breakdown of the ventricular lining, which result in a potential increase of water content. These changes are sometimes referred to as the consequences of "small vessel disease." We could not find any direct association of WMHs with the arterial changes. The pathophysiology of these lesions in the context of aging and AD requires further scrutiny.

P4-026 EVALUATION OF RETINOBLASTOMA PROTEIN EXPRESSION IN ASYMPTOMATIC AND SYMPTOMATIC ALZHEIMER'S DISEASE AND NORMAL ELDERLY SUBJECTS

Aderbal Silva[1], Lea Grinberg[2], Jose Farfel[3], Renata Ferretti[4], Rafael Rocha[1], Maria Begnami[1], Helena Brentani[5], *[1]A C Camargo Hospital, São Paulo, Brazil; [2]Memory and Aging Center, University of California, San Francisco, USA, San Francisco, California, United States; [3]University of Sao Paulo, São Paulo, Brazil; [4]University of São Paulo Medical School, São Paulo, Brazil; [5]University of Sao Paulo, Sao Paulo, Brazil.*

Background: The re-expression of many cell cycle-related proteins and inappropriate cell cycle control in specific vulnerable neuronal populations in Alzheimer's disease (AD) is emerging as an important component in the pathogenesis leading to AD. Recent studies strongly support the notion that the dysregulation of cell cycle in neurons ultimately causes cell death. A very important part in the abortive cell cycle re-entry is played by the retinoblastoma protein (Rb) and it might be of particular interest because its activity is involved in neuronal cell death. **Methods:** Using tissue specimens from postmortem human brains

(entorhinal and temporal cortices, and hippocampus) assembled in tissuemicroarray (TMA), immunohistochemistry was performed to examine the expression patterns of Rb in the following groups: 1) *asymptomatic* AD - elderly individuals with AD-related pathology, but no clinical evidence of dementia (Braak IV-VI, CERAD B or C, CDR 0); 2) *symptomatic* AD - elderly individuals with AD-related pathology and dementia (Braak IV-VI, CERAD B or C, CDR = 2); and 3) healthy normal individuals (controls) - (Braak I-III, CERAD 0 or A, CDR 0). **Results:** The nuclear staining was low in all groups, although in the group of normal individuals the number of positive nucleus was higher than in the Alzheimer's groups. However, there also was cytoplasmatic staining with a stronger immunoreactivity in the normal group and a progressive decrease of reactivity in the asymptomatic and symptomatic AD groups, respectively. **Conclusions:** Our results show a progressive lost of Rb expression in AD patient's brain, mainly in the cytoplasm. This shift at the subcellular localization of several makers implicated with cell cycle has been shown in AD, but the real biological significance of this change is still unclear. Considering that Rb function as a cell cycle suppressor, this expression lost could facilitate the cell cycle re-entry and neuronal death. In asymptomatic AD individuals, the Rb expression level higher than in symptomatic AD subjects could be helping, together with other mechanisms, the keeping of their normal cognitive function.

P4-027 GENE EXPRESSION PROFILING OF CHOROID PLEXUS IN ALZHEIMER'S DISEASE REVEALS IMPORTANT IMPLICATIONS OF CSF DYNAMICS

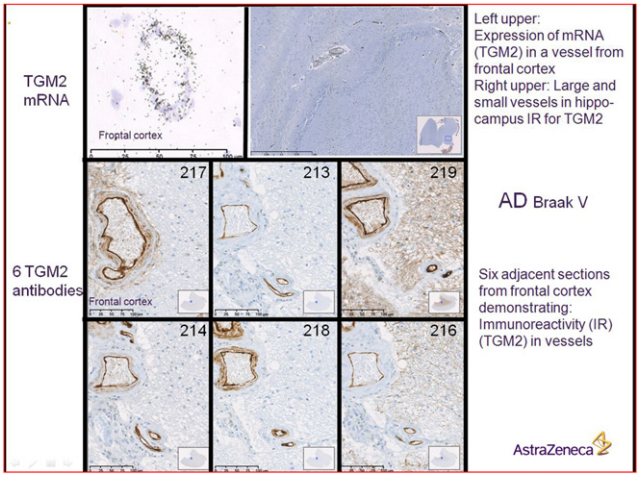
Edward Stopa[1], [1]*Brown University, Providence, Rhode Island, United States.*

Background: In aging, normal pressure hydrocephalus (NPH), and Alzheimer's disease there are striking changes in CSF composition that may be related to altered choroid plexus function. **Methods:** Human Affymetrix 48K gene arrays were used to determine disease-related changes in gene expression within the choroid plexus. Post-mortem tissue samples from healthy controls (mean age/mean PMI: 58 years/22 hours) and patients with advanced (Braak & Braak stage V-VI) Alzheimer's disease (79/18) were snap frozen in liquid nitrogen and stored at -80Â°C. Samples from diseased control patients with frontotemporal dementia (72/NA) and Huntington's disease (71/19) were also collected. RNA from choroid plexus was extracted using Trizol followed by NuGEN Ovation amplification, and cDNA was hybridized to custom chips at Rosetta/Merck. After RMA normalization, analysis of data was performed using one way ANOVA, and most significant gene sets were further analyzed for biological enrichment using individual (Ingenuity) and combined (Target and Gene Information System) pathway tools. **Results:** Clear differences were observed on gene expression level in choroid plexus of advanced AD patients when compared to both the normal and diseased (FTD, HD) control groups. 648 sequences could significantly separate four experimental groups ($p < 0.001$, FDR ~ 8%). About half of those sequences were up regulated in neurodegenerative diseases. The up regulated genes represented overall 15 highly enriched biological functions (multiple correction expectation value < 0.1). Strikingly, cell adhesion and extracellular matrix re-modeling along with post-translational modification (phosphorylation) were highly enriched in AD patients (expectation $<$ 10E04). A significant increase in immune response was evident in AD patients, while oxidative phosphorylation and amyloid processing were both down-regulated. Other observations included decreases in PPARa/RXRa nuclear receptor/retinoic acid, a-adrenergic, glucocorticoid and melatonin signaling, as well as N-glycan, glutathione (antioxidant) and ubiquinone metabolism in AD patients. **Conclusions:** This unique resource may be of interest to numerous investigators working on aging CSF dynamics and hydrocephalus. It can be readily shared with investigators wishing to answer specific questions related to their field of investigation.

P4-028 THE EXPRESSION OF TGM2 IN THE ALZHEIMER BRAIN IS RESTRICTED TO BLOOD VESSELS

Harald Lund[1], Anne Svensson[2], Maria Nilsson[2], Dan Sunnemark[3], [1]*astrazeneca, s151 85, Sweden;* [2]*Astrazeneca, Södertälje, Sweden;* [3]*AstraZeneca, Södertälje, Sweden.*

Background: Transglutaminase 2 (TGM2) is an enzyme that catalyzes cross-linking of proteins between glutamic acid and lysine residues, forming ?-glutamyl-e-lysine isopeptide bonds. This process generates highly resistant protein complexes and has been implicated in Alzheimer's disease. TGM2 has been demonstrated to cross-link both tau and amyloid-ß in vitro, forming higher order species. Additionally, TGM2 activity as well as mRNA and protein levels are upregulated in Alzheimer brains compared to controls. Some groups have also found positive TGM2 immunoreactivity in neuronal layers affected by tau tangles. Based on this, it has been suggested that TGM2 contributes to the generation of pathological aggregates in Alzheimer's disease. **Methods:** We have performed in situ hybridization and immunohistochemistry in order to confirm the localization of TGM2 in brain sections from Alzheimer patients and non-demented elderly. We have studied brain samples from hippocampus and inferior frontal gyrus (cortex), two brain regions severely affected by neurodegeneration in Alzheimer's disease. We have used a very specific ^{35}S-labeled RNA-probe specifically recognizing human TGM2 mRNA for in situ hybridization. For immunohistochemistry, we have used 7 antibodies, epitope-mapping to different regions of the human TGM2 protein. **Results:** We were able to demonstrate evident TGM2 mRNA expression in blood vessels by in situ hybridization. Immunohistochemistry against TGM2 displayed staining in many vessels in sections of both hippocampus and cortex from Alzheimer brains and non-demented control brains. No detection was present in any of the neuronal layers studied. **Conclusions:** We were not able to find any neuronal mRNA or protein expression of TGM2 in any of the Alzheimer or control brains studied. Expression of TGM2 was evident but restricted to endothelium in blood vessels of different sizes. This challenges the view that TGM2 contributes to the accumulation of pathological changes in Alzheimer's disease.



P4-029 INCREASED CORTICAL CAPILLARY DENSITY IN ALZHEIMER'S DISEASE IS MEDIATED BY FRONTAL LOBE NEUROFIBRILLARY DEGENERATION: THE MISSING LINK BETWEEN DEGENERATIVE AND CEREBROVASCULAR BRAIN DISEASE

Haylea Sweat[1], Gregory Jicha[1], [1]*University of Kentucky, Lexington, Kentucky, United States.*