and Braak proposed a six stages spatiotemporal progression of Tau pathology in AD. Tauopathy is also encountered in other neurodegenerative disorders. Our laboratory showed that depending on the neurological disorder considered, different sets of Tau protein isoforms were aggregated. For instance, the six Tau isoforms aggregate in AD whereas only three isoforms aggregate in Pick bodies of Pick’s Disease. These observations suggest that subsets of Tau isoforms are expressed in sub neuronal populations, or alternatively, a defective splicing of Tau is an early event of neurodegeneration. Propagation of Tau pathology may also be specific to these different Tau isoforms. The use of animal models will be a key asset for understanding Tauopathy. Using the Thy-Tau22 mouse transgenic line developed in our laboratory, the analysis of the kinetics of Tau phosphorylation, aggregation and neuronal death in parallel to electrophysiological and behavioural parameters indicates a dysconnection between cognition deficits and neuronal cell death. This model exhibits progressive neuron-specific AD-like Tau pathology devoid of any motor deficits. A progressive development of Tauopathy is observed in the hippocampus and amygdala, which parallels behavioural impairments as well as electrophysiological alterations. These latter changes are observed despite of any striking loss of neuronal/synaptic markers until 12 months of age in the hippocampus. In addition, in the hippocampus, hyper- and abnormally phosphorylated Tau species accumulate within the somato-dendritic area, supporting a possible influence on hippocampal-dependent plasticity always confirmed by behavioural and electrophysiological evaluations. Conclusions: In conclusion, AD and other Tauopathies have likely different etiologies. They are characterized by different Tau aggregates, which may spread in different ways and explain their different clinical presentations. Animal models of Tau pathology may mimic part of the pathology (phosphorylation and/or aggregation, propagation vs. diffusion) and help for the development of new, innovative therapeutic strategies.

WEDNESDAY, JULY 20, 2011
SYMPOSIA
S4-01
BIOMARKERS

S4-01-01 LESSONS FROM MULTICENTER STUDIES ON CSF BIOMARKERS FOR ALZHEIMER’S DISEASE
Kaj Blennow, Clinical Neurochemistry Lab, University of Gothenburg, Malmö, Sweden.

Background: CSF biomarkers for AD will be important tools for early diagnosis if novel drug candidates, such as b-amylloid immunotherapy and secrete inhibitors, prove to be effective. Numerous studies have shown that the CSF total tau (T-tau), phospho tau (P-tau) and Ab42, have high diagnostic accuracy to identify AD, to differentiate AD from normal aging and several important differential diagnoses. Several studies also show that these CSF biomarkers can identify prodromal AD in patients with mild cognitive impairment (MCI). However, there are large differences both in the diagnostic performance and in absolute CSF levels between studies, which need to be evaluated in multi-center studies. Methods: Evaluation of CSF biomarkers in large multi-center studies as compared with mono-center studies. Evaluation of the potential causes of the between-laboratory variability for CSF biomarkers. Results: Several large multi-centre studies show high diagnostic performance of CSF biomarkers to identify both AD with dementia and prodromal AD, but the diagnostic performance is higher at individual centers. The between-laboratory and between-center variability for CSF biomarkers is likely caused by pre-analytical factors (e.g. differences in CSF tapping and sample handling), analytical factors (differences in how the analyses are performed) and batch-to-batch variation for the immunoenasays. Conclusions: CSF biomarkers show promise as diagnostic tools, both in clinical trials, to enrich the patient sample with AD cases, and in clinical routine. The aim of the Alzheimer’s Association worldwide quality control (QC) program for CSF biomarkers is to standardize CSF biomarker measurements, with the goal to provide the basis for the introduction of CSF biomarkers in clinical routine and to get uniform cut-off levels. Until the goals of the QC program have been accomplished, it is recommended that clinical centers use stringent protocols for LP and CSF handling and shipment and CSF biomarkers assays are performed by specialized Clinical Neurochemistry laboratories, with validated cut-off levels. However, it should be noted that the between-center variability for CSF biomarkers does not hinder the implementation of these diagnostic tools at individual centers.

S4-01-02 USE OF CSF BIOMARKERS IN CLINICAL TRIALS: THE ADNI EXPERIENCE
Leslie Shaw, University of Pennsylvania School of Medicine, Philadelphia, Pa., United States.

Background: The Alzheimer’s Disease Neuroimaging Initiative (ADNI) is an ongoing multicenter (n = 57) longitudinal initiative whose purpose is to develop and standardize clinical, imaging, biochemical and genetic biomarkers for early detection and tracking of Alzheimer’s disease (AD). Methods: For biochemical biomarkers measured in CSF important sources of variability include pre-analytical factors for the lumbar puncture procedure and factors involved in the processing of CSF; analytical performance factors that affect the stability and reproducibility of test performance; and the contribution of population-related and statistical methodology selection to clinical diagnostic performance evaluations. Results: In this presentation the experience to date in each of these areas of performance in ADNI studies will be described including results of studies within the ADNI biomarker core laboratory as well as inter-center collaborative studies. Conclusions: The results from the ADNI study will contribute to the design of optimized pre-analytical and analytical protocols for the investigation of biomarkers in AD treatment trials.

S4-01-03 A SERUM PROTEIN-BASED ALGORITHM FOR THE DETECTION OF ALZHEIMER’S DISEASE
Sidney O’Bryant1, Xiao Guanghua2, Barber Robert3, James Hall3, Rachelle Doody4, Joan Reisch5, Donald Royall6, Perrie Adams7, Kirk Wilhelmsen7, Thomas Fairchild7, Ramon Diaz-Arrastia1, Texas Tech University Health Sciences Center, Lubbock, Texas, United States; 2University of Texas Southwestern Medical Center, Dallas, Texas, United States; 3Texas Tech University Health Sciences Center, Ft. Worth, Texas, United States; 4University of North Texas Health Sciences Center at Fort Worth, Fort Worth, Texas, United States; 5Baylor College of Medicine, Houston, Texas, United States; 6UT-HSCSA Psychiatry, San Antonio, TX, Texas, United States; 7University of North Carolina School of Medicine, Chapel Hill, North Carolina, United States; 8University of North Texas Health Sciences Center, Fort Worth, Texas, United States.

Background: We previously created a serum-based algorithm that yielded excellent diagnostic accuracy in distinguishing AD from normal Controls. The current project was designed to refine that algorithm by reducing the number of serum proteins and inclusion of additional clinical variables. Additionally, we sought to determine if the serum-biomarker algorithm was significantly related to neuropsychological performance. Methods: We analyzed serum-protein multiplex biomarker data from 197 patients diagnosed with AD and 200 cognitively normal controls from the Texas Alzheimer’s Research Consortium (TARC) longitudinal cohort. The biomarker algorithm was restricted to only the top 30 markers from the original publication. Additional clinical variables added to the algorithm included cholesterol, triglycerides, HDL, LDL, LpPLA2, homocysteine and C-peptide. The biomarker risk score utilizing only the top 30 markers was generated from a training set containing one half of the AD cases and controls, which was then applied to the test sample. Results: When the biomarker risk score from the top 30 markers was applied to the test sample, the sensitivity, specificity, and AUC were .69, .90, and .80 reflecting a decline from the risk score derived from the larger panel. However, when the demographic data (age, gender, education) and clinical data (see above in addition to APOE genotype) were combined with the biomarker risk score, the SN, SP, and AUC rose to .85, .87, and .94 which is comparable to the previously published algorithm. In linear regression models, the biomarker risk score was most strongly related to neuropsychological tests of language (COWAT and BNT) and memory (WMS LM I and II; Delayed Recall; WMS VR I and