Cerebrospinal fluid (CSF) measures

Until recently, the only way to obtain information on tau protein in vivo was to use CSF sampling. A large number of studies have investigated the progression of CSF tau biomarkers in Alzheimer's, showing a relationship between tau levels and the rate of cognitive decline. Longitudinal studies on inherited Alzheimer's reported that elevated CSF tau could be measured decades before the onset of symptoms. Because of discrepancies reported in Aβ measurement between CSF sampling and PET imaging (positron computer tomography), a comparison of CSF tau levels with the newly developed tau tracers is thus of great interest. In a study of CN (Cognitive Normal) subjects only, significant associations were found between both CSF total and phosphorylated tau in the temporal cortex. However another study reported no significant association. Significant positive associations were found when Alheimer's patients were included in the analyses (in combination with CN subjects). This calls for future, larger studies in patients.

One study addressed the relevance of CSF tau and Aβ levels in the differential diagnosis of Alzheimer's by comparing premortem (before death) CSF values with the definitive diagnosis in a well-characterized and diverse group of patients with dementia. It confirmed an association between elevated CSF tau levels premortem and the pathological hallmarks of Alzheimer's, indicating that high CSF tau levels, in the appropriate clinical setting, strongly supports a diagnosis of Alzheimer's. Nevertheless, some patients who meet clinical and pathological criteria for Alzheimer's may have CSF tau levels below the biostatistic (ROC) cutoff value of 234 pg/mL. Therefore, CSF tau and Aβ values *cannot* be used to exclude a diagnosis of Alzheimer's in a patient who meets consensus criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association for that diagnosis.

The source of CSF tau is most likely related to the degeneration of neurofibrillary tangle–laden neurons. The protein has not been well characterized in the CSF and may exist in fragmented forms. There is no information on the steady-state kinetics of CSF tau in normal individuals. Although a recent report indicates that it may require 3 to 5 months for elevated CSF tau levels to return to normal after an acute stroke, the clearance rate of tau (if at all) from the CSF in patients with neurodegenerative dementia remains unknown.

The average tau value for the group with LBVAD (Lewy body variant of Alzheimer's) was lower than the value for patients with Alzheimer's free of Lewy body pathological findings. Patients with Lewy Body pathological findings also have fewer neurofibrillary tangles and more amyloid plaques than patients with Alzheimer's. Several conditions that are clinically distinct from Alzheimer's are associated with marked elevations in CSF tau level, including acute stroke, multiple sclerosis, AIDS dementia, and head trauma.In addition, several of patients with prion diseases had high CSF tau and low Aβ values. The CSF tau level is known to be elevated in many, but not all, patients with Creutzfeldt-Jakob disease.

Reduction of rCBF (regional cerebral blood flow) and various degrees of ventricular enlargement and cortical sulcal widening has been demonstrated in the majority of demented subjects. However, there is no correlation between rCBF values and the severity of ventricular dilatation or cortical atrophy. These findings suggest that loss of brain substance is not an important factor in the reduction of rCBF in dementia. Mean brain rCBF values were generally lower in patients with severe dementia than in those with mild and moderate mental impairment, but the differences were not significant. Higher or lower rCBF values occurs in the demented subjects regardless of the severity of the cerebral atrophy observed in the computerised tomograms. These findings suggest that loss of brain substance does not play an important role in the reduction of rCBF in dementia. It seems, therefore, that not the loss of brain substance but rather the remaining abnormal cerebral tissue is the most important factor producing rCBF reduction in dementia.

Whilst MRI does correlate with change on MMSE scores, changes in CSF tau do not. One study found that baseline CSF tau predicted conversion to dementia and another found a direct correlation between increasing levels of CSF tau and severity of impairment in Alzheimer's. The relationship between CSF tau and stage of the disease may therefore be complex. In contrast, the relationship between clinical disease stage and MRI seems to be a fairly straightforward direct correlation since MRI measures atrophy, which reflects cumulative damage. The literature on MRI is nearly unanimous in indicating close correlation between loss of cognitive function and loss of volume on MRI over time. Brain volume (injury) quantification with MRI has nothing analogous to daily turnover of a soluble protein. Minimal physiologic variation in brain volume may translate into stronger correlations with cognition over many subjects.

In one study of cerebrospinal fluid, mean tau and β-Amyloid levels found were as follows:-

- 627 pg/mL tau ; 67 fmol/mL Aβ for the 74 patients with Alzheimer's
- 272 pg/mL tau; 133 fmol/mL Aβ for 10 patients with frontal dementia
- 282 pg/mL tau; 14 fmol/mL Aβ for 3 patients with dementia with Lewy bodies
- 140 pg/mL tau; 109 fmol/mL Aβ for 73 cognitively normal control subjects
- 784 pg/mL tau;78 fmol/mL Aβ for 4 patients with inherited Alzheimer's
- 2302 pg/mL tau; 60 fmol/mL Aβ for patients with prion disease