CSF Biomarkers of Disease Modification in Alzheimer's Disease

The three major brain hallmarks of Alzheimer's disease (AD) are extracellular amyloid plaques, axonal degeneration and intraneuronal neurofibrillary tangles, which can all be monitored via changes in the cerebrospinal fluid (CSF) biomarkers amyloid beta 42 (Aβ42), total-tau (T-tau), and phosphorylated-tau (P-tau) [1]. Amyloid, the product of amyloid precursor protein, exists in a variety of isoforms of 36 to 43 amino acids in length; however, the focus on CSF amyloid biomarkers has mostly been on the measurement of CSF Aβ42, shown to decrease in AD patients as well as those converting to AD. The underlying assumption is that CSF Aβ42 reflects increased accumulation of Aβ42 in brain forming plaques and brain beta amyloid load [2, 3, 4]. Other CSF biomarkers of interest including total tau (T-tau), a generic measure of cortical axon damage associated with many neurodegenerative disorders, and phosphorylated tau (P-tau), shown to increase threefold in the CSF of confirmed AD patients[4]. There is a consensus from centres around the world suggesting the levels of Aβ42 in the CSF of AD patients are significantly lower than in age-matched, healthy, elderly controls, whereas the levels of total tau (T-tau) and P-tau181P (phosphorylated at threonine 181) in AD CSF are significantly higher than those of age-matched controls. These relatively simple findings have spurred a great deal of research and debate on the role of CSF biomarkers in AD drug development.

Although these CSF biomarkers have shown some degree of utility in diagnostic accuracy as biomarkers in predicting conversion to AD from mild cognitive impairment (MCI), and as a tool to enrich patients for clinical trials to increase statistical power, these biomarkers have not shown similar success in evaluating the effectiveness of therapeutic interventions in AD, especially in the development of disease-modification therapies. This is not surprising considering that confirmation of disease-modifying biomarkers occurs only when they are found useful in predicting the clinical efficacy of a novel disease-modifying agent. However, currently approved drugs in AD and other neurodegenerative disorders only provide symptomatic relief rather than modifying the core pathophysiology of the disease, and do not change disease progression. Thus, current biomarker development for disease modification must advance in the absence of gold standard treatments to validate these biomarkers.

Biomarkers for neurodegenerative disorders can be generally divided into markers of disease state (or diagnostic biomakers) and markers of disease rate or stage that can reliably track disease progression [5]. As the clinical course of AD is very slowly progressive and highly variable, the treatments designed to slow the disease progression require clinical trials with very large subject numbers for much longer durations than symptomatic treatment trials, in order to observe clinical improvement secondary to downstream therapeutic effects on the underlying pathophysiological processes. This circumstance only underscores the necessity for CSF surrogate biomarkers of disease progression.

It is clear that both CSF tau and Aβ42 biomarkers fulfill the requirements for disease state markers of AD as they both exhibit reasonably high specificity and sensitivity in both early and late stages of AD [6]. However, this brief review suggests that at this point in time it can be argued that only CSF tau measures appear to satisfy criteria as a marker of disease rate. Numerous studies have shown that in various groups of AD patients there is no strong correlation between the severity of the disease stage over time with the levels of CSF Aβ42, indicating that the levels of Aβ42 do not significantly and reliably change substantially in mild to severely symptomatic AD patients. However, longitudinal studies of the levels of CSF tau in patients with AD have shown more promising results.

For example, Blennow and colleagues[7] examined exploratory, post-hoc, pooled data from two Phase II international clinical trials in order to determine whether the novel disease-modifying immunotherapy drug bapineuzumab impacted the CSF levels of the downstream biomarkers T-tau, P-tau, and Aβ42. This group reported that immunotherapy reduced CSF T-tau and P-tau biomarker levels in patients with mild to moderate AD. Within the bapineuzumab group, a decrease at end of study compared with baseline was found both for CSF T-tau (-72.3 pg/mL) and P-tau (-9.9 pg/mL). When comparing the treatment and placebo groups, this difference was statistically significant for P-tau (P=.03), while a similar trend for a decrease was found for T-tau (P=.09). Of note, no clear-cut differences were observed for CSF beta amyloid. This supports other studies which have also shown that the amyloid load in the brain of AD patients, as assessed with repeated amyloid positron emission tomography measurements, appears to be stable over time despite cognitive decline. Thus, CSF Aβ42 would not be considered a worthy candidate for a marker of disease stage or rate. Importantly, this was the first study to show that disease-modifying therapy results in decreases in CSF biomarkers, and suggests that CSF T-tau and P-tau, which may reflect downstream effects on the degenerative process, may have some relative utility over Aβ42 as a surrogate biomarker in tracking rate of disease-modifying trials.

Observations such as these are supported by neuropathological studies showing that tau-containing neurofibrillary tangles, but not amyloid plaques, are associated with the cognitive function of AD patients. Furthermore, when using structural imaging measures,

only P-tau has been shown to correlate with neocortical tangle pathology at autopsy. CSF P-tau has also been shown to correlate with the rate of hippocampal atrophy in the brain. Previous postmortem histopathological studies have demonstrated an association between the degree of antemortem MRI hippocampal atrophy and neurofibrillary tangle burden and a strong correlation between both CSF T-tau and P-tau levels with the presence of neocortical neurofibrillary tangles [8]. Additionally, antemortem MRI hippocampal volumes of AD patients correlate with the density of neurofibrillary tangles (but not with senile plaques) at autopsy, suggesting that hippocampal volume may better correlate with CSF T-tau and P-tau levels than CSF beta amyloid levels [9]. Although mean brain volumes correlated with the CSF P-tau level, no correlation was found between any brain measurement and CSF Aβ42 levels. The fact that the CSF T-tau and P-tau levels, but not CSF Aβ42 levels, correlated with hippocampal volumes, suggests that CSF tau biomarkers reflect the neuronal loss associated with the underlying pathophysiological processes of AD and are thus better suited as a marker of disease progression. The lack of Aβ42 correlation with whole brain and hippocampal volumes agree with postmortem studies by demonstrating that the rate of brain volume loss was not determined by the amount of beta amyloid. Collectively, the above suggests a comparative role for CSF tau measures over CSF beta amyloid measures as potential surrogate biomarkers of disease progression that may be "reasonably likely" to predict the clinical benefit and desired clinical outcome in clinical trials assessing disease-modifying drugs for AD, resulting in more efficient clinical trials in terms of subject numbers and study duration.

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