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CSF biomarkers for Alzheimer's disease: Current utility and potential future use

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Abstract

Over the last 15 years, cerebrospinal fluid (CSF) biomarkers have been shown to be useful for both the diagnosis as well as the prognosis in Alzheimer's disease. It has been shown the CSF levels of Aβ42 are a very good marker for the presence of amyloid deposition in the brain regardless of clinical status and that total tau and phosphorylated forms of tau are useful in detection of neurodegeneration. When combined together, these CSF markers are useful not only in differential diagnosis but also in predicting conversion and rate of progression from mild cognitive impairment/very mild dementia to more severe impairment. The markers are also useful in predicting conversion from cognitive normalcy to very mild dementia. This field is briefly reviewed and recommendations for future studies in this area is provided.

With the emergence of disease-modifying strategies for the treatment of Alzheimer's disease (AD), impetus has intensified to diagnose the condition in its early 'preclinical' stages — before significant brain damage has occurred. Since their first description in 1907, amyloid plaques and neurofibrillary tangles (NFTs) have been the hallmark histopathological features of AD. Historically, they have also been associated with the dementia caused by the disease. It is clear, however, that these lesions begin to accrue in significant amounts in many 'cognitively normal' elderly individuals (Crystal, et al., 1988) and likely together with other synaptic and cellular damage, must reach a threshold to enable the clinical manifestations we recognize as dementia. A growing body of evidence now supports the idea that amyloid plaques and NFTs actually define but do not fully represent the disease process, which also involves inflammation as well as neuronal, axonal, and synaptic loss and dysfunction. All of these changes begin to occur years before significant cognitive decline; however, the pathological processes of AD currently come to attention during life only when it manifests clinically. The early clinical signs that are believed to be due to AD (e.g. decline in memory and executive functions relative to prior level of functioning) are referred to in different ways by clinicians. Some report this syndrome as very mild dementia (Morris, 1993). Others prefer the term mild cognitive impairment (Petersen, et al., 1999). Because

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many of the biomarkers that provide insight into the underlying pathology of AD are not yet used in day-to-day patient care, these diagnoses reflect attempts to describe clinical syndromes in the absence of definitive proof of the underlying pathology. However, in combination with clinical methods and cognitive tests, cerebrospinal fluid (CSF) biomarkers can contribute to a more accurate assessment of both whether AD pathology is the likely cause or associated with cognitive impairment as well as whether AD pathology is present in the brain of someone who is cognitively normal. Perhaps more importantly, CSF biomarkers can now be useful for clinical trials and for clinicians to predict prognosis of individuals who have mild cognitive impairment/very mild dementia as well as for those who are cognitively normal.

The sampling of CSF represents the most direct and convenient means to study the biochemical changes occurring in the central nervous system. Therefore, CSF is an attractive resource for ongoing research into AD biomarkers. Implicated by biochemical and immunohistological studies of AD brain tissue, the major protein constituents of the hallmark pathological features of the disease ($A\beta_{42}$, tau and phosphorylated forms of tau) have emerged as the current leading diagnostic and prognostic fluid CSF biomarkers.

CSF Amyloid-β

Amyloid-β (Aβ) is a secreted peptide of unknown physiological function that is cleaved from the amyloid precursor protein (APP) by the sequential activities of β-secretase and γ-secretase enzymes. The majority of Aβ is produced in the brain and secreted into the brain extracellular space. Some fraction of CNS-produced Aβ diffuses into the CSF, appearing in modest concentrations (~10–15 ng/ml). Aβ occurs in multiple forms, including those ranging from 37 to 43 amino acids in length. Among these, $A\beta_{40}$ is the most abundant species, but $A\beta_{42}$ seems to be essential for initiating amyloid-β aggregation and is considered central to the amyloid cascade hypothesis of AD (Hardy and Selkoe, 2002). Of these two species, $A\beta_{42}$ has emerged as a useful biomarker for AD.

Although the finding is initially counterintuitive, the mean concentration of $A\beta_{42}$ in the CSF is significantly reduced by about 50% in subjects with AD relative to age-matched controls (Motter, et al., 1995 Sunderland, et al., 2003); this phenomenon is thought to result from deposition of the $A\beta_{42}$ in amyloid plaques, preventing its transit from the brain into the CSF (plaques acting as a sink). In support of this hypothesis, when ante-mortem CSF $A\beta_{42}$ concentrations are compared with results from amyloid imaging in the same individual or to post-mortem measurements of brain Aβ load, virtually all individuals with fibrillar Aβ deposits show low concentrations of $A\beta_{42}$ in the cerebrospinal fluid, independent of cognitive status (Fagan, et al., 2006 Fagan, et al., 2009 Fagan, et al., 2007 Jagust, et al., 2009 Tapiola, et al., 2009). Thus, CSF $A\beta_{42}$ can serve as a diagnostic and surrogate biomarker for Aβ deposition in the brain. Unlike CSF $A\beta_{42}$, CSF $A\beta_{40}$ levels are not different in individuals with AD compared with controls (Shoji, et al., 1998). The decrease in CSF $A\beta_{42}$ appears to precede amyloid retention as detected by amyloid imaging using compounds such as ^{11}C-labeled Pittsburgh compound B (^{11}C-PIB), signifying what is perhaps the first evidence of AD pathology in cognitively normal individuals (Cairns, et al., 2009 Fagan, et al., 2006 Fagan, et al., 2009). While CSF $A\beta_{40}$ does not differentiate individuals with AD from controls, CSF $A\beta_{40}$ has recently been shown to be decreased in a subset of subjects with cerebral amyloid angiopathy (CAA) (Verbeek, et al., 2009). $A\beta_{42}$ alone is less useful in differentiating AD from other dementias, since low levels have also been documented in patients with frontotemporal dementia (FTD), vascular dementia, and dementia with Lewy bodies (DLB), though it is possible it is low in many of these patients because of the concomitant presence of fibrillar Aβ deposits, such as occurs in the majority of individuals with DLB.

Despite its utility in the detection and differential diagnosis of dementia, CSF $A\beta_{42}$ does not correlate well with disease duration or severity. This is consistent with results from ^{11}C-PIB studies showing that amyloid retention does not change appreciably during the symptomatic stages of AD (Rowe, et al., 2007), and further supports results from pathological studies of AD; amyloid pathology occurs very early in the disease process and has relatively stabilized by the time the first clinical signs of dementia appear.

CSF Tau

Tau is a cytosolic protein predominantly expressed in neurons, wherein its primary function seems to be regulation of microtubule stability within the axon. This function is regulated by several different post-translational modifications, principally phosphorylation of numerous serine and threonine residues. In AD, hyperphosphorylated tau often fills the dystrophic neurites of neuritic plaques, and is the principle component of the paired helical filaments that constitute NFTs that are present in neuronal cell bodies. The precise forms of tau that appear in the CSF, and the mechanism or mechanisms by which they get there, are not entirely understood, but recent studies (Portelius, et al., 2008) demonstrate that virtually all domains of the protein are represented, and it is widely assumed (but not proven) that the major sources of increases in tau and phosphorylated tau in the CSF in AD are either due to synaptic/neuronal injury, cell death, or possibly neurofibrillary tangles.

Total (T)-Tau

Tau is the major protein component of intra-neuronal NFT and is elevated in the CSF in most patients with AD. In addition to the presence of tau in neurofibrillary tangles, it has been shown that tau levels in CSF can increase rapidly as a result of neuronal injury, and therefore, may indicate the severity of the underlying neurodegeneration (Blennow, 2004). Over 50 studies have demonstrated an increase in the concentration of total tau (t-tau) by approximately 2–3 fold in AD compared with non-demented elderly subjects (Blennow, et al., 2001). Elevation of CSF tau differentiates AD from non-demented, age-matched elderly with a sensitivity and specificity of ~90% (Sunderland, et al., 2003). As mentioned previously, tau elevation seems to occur at the early symptomatic stages of disease (MCI/very mild dementia) and in some cognitively normal individuals, where its levels correlate with the amount of amyloid deposition and together with Aβ42 predict cognitive decline (see below). Cognitively normal individuals with evidence of amyloid deposition and increased tau are likely to have preclinical AD (see below) (Fagan, et al., 2009). However, it is important to consider that tau elevation can be seen in other neurodegenerative diseases, potentially limiting the utility of tau alone in the differential diagnosis of AD (Arai, et al., 1997). Tau, as a marker of neuronal injury, can be transiently increased after any acute brain injury (such as stroke or trauma) (Hesse, et al., 2001). Moreover, tau levels seem to remain relatively stable throughout the clinically symptomatic period of AD (Sunderland, et al., 1999) and do not correlate well with dementia severity. Age might affect the CSF levels of tau; however, studies have been conflicting regarding the direction and significance of such an effect (de Leon, et al., 2007).

P-tau

Abnormal tau phosphorylation is present in neurofibrillary tangles and has been investigated as a marker of AD pathology. As many as 30 different phosphorylation sites of p-tau have been identified (Buee, et al., 2000), and ELISAs (enzyme-linked immunoassays) have been developed for at least 5 of them. Studies examining the utility of different forms of p-tau in the early diagnosis of AD, and in the differentiation from other causes of dementia, have consistently shown that p-tau 181 (Arai, et al., 2000), p-tau 231-235,or p-tau 396-404 (Hu, et al., 2002) offer at least equivalent diagnostic utility for AD as compared to total tau.

Studies comparing the diagnostic performance of different phosphorylation sites (p-181, p-199, and p-231) suggest that all three assays are equally effective in differentiating AD from non-demented controls. P-tau 231 may provide diagnostic specificity for AD and may improve the differentiation between AD and FTD (Buerger, et al., 2002), while there is some evidence that p-tau 181 improves the differentiation between AD and DLB (Hampel, et al., 2004). P-tau 396-404, and the ratio of p-tau 396-404/t-tau, but not tau alone, has been shown in one study to differentiate AD from vascular dementia (Hu, et al., 2002). In contrast to t-tau, p-tau does not appear to be increased secondary to acute brain injury, further adding to its diagnostic specificity.

Combination of Aβ42 and tau

Diagnosis

Based on current data, the use of CSF $A\beta_{42}$ alone but especially together with t-tau or p-tau181 is very useful in both diagnosis and prognosis of individuals with MCI/very mild dementia and also in predicting progression from cognitive normalcy to MCI/very mild dementia. This is likely due to the fact that the levels of the markers together can identify two aspects of AD pathology, plaques ($A\beta_{42}$) and tauopathy/neurodegeneration (tau).

The combination of $A\beta_{42}$ and T-tau or p-tau as a ratio or as an index provides the best discriminative value to date for individuals with AD compared to healthy controls of the same age, with a sensitivity of ~85–90% and a specificity of ~85–90% (Shaw, et al., 2009,Welge, et al., 2009) as verified by autopsy. Slightly lower sensitivities and specificities are seen with MCI/very mild dementia vs. age-matched controls; however, this is likely due to the fact that a somewhat larger percentage of patients diagnosed with MCI have an underlying diagnosis that is not AD (Fagan, et al., 2007, Shaw, et al., 2009). Lower specificities are obtained when these ratios are used to differentiate AD from other dementia etiologies.

Prognosis

Progression from MCI/very mild dementia to AD: Several studies have shown that either decreased CSF $A\beta_{42}$ or increased tau or phosphorylated forms of p-tau predict progression from MCI/very mild dementia to AD. However, ratios of tau/$A\beta_{42}$ and p-tau/$A\beta_{42}$ may be more predictive than an individual marker. The relative risk of progression from MCI to AD was increased in patients who had high tau, p-tau, and low $A\beta_{42}$ at baseline with 90% sensitivity and 100% specificity in one study (Arai, et al., 1997). An increased tau/$A\beta_{42}$ ratio was seen in 90% of individuals with MCI who later progressed compared to 10% of those who did not in a large longitudinal study of MCI patients followed for 18 months (Riemenschneider, et al., 2002). The combination of tau/$A\beta_{42}$ and the p-tau181/$A\beta_{42}$ ratio, in a longitudinal study of almost 200 subjects with average follow-up of 4-6 years, strongly predicted progression of MCI to AD (Hansson, et al., 2006). The utility of the AD CSF profile (defined by decreased $A\beta_{42}$ and increased tau) to detect progression from MCI to more advanced stages of AD was recently confirmed in a longitudinal study of 100 individuals with mild AD, 196 individuals with MCI, and 114 controls (Shaw, et al., 2009) as well as in a very large multicenter study of over 1000 subjects in both Europe and the US (Mattsson, et al., 2009). In a smaller study, both markers predict not only conversion from MCI to AD, but also the rate of progression of cognitive decline as measured by the clinical dementia rating (CDR) sum of boxes and neuropsychological test scores (Snider, et al., 2009). This is important as it is difficult to determine if an individual subject hits a qualitative clinical cutoff defined as impaired enough to now have “AD” instead of “MCI”. However, being able to predict the rate of clinical progression should be quite useful in future clinical trials of disease modifying drugs. Progression from cognitive normality to

MCI: The increased ratio of tau/Aβ_{42} and p-tau/Aβ42 in normal individuals has been associated with an increased risk of conversion from normal to MCI in 3 recent studies. In a study by Fagan et al., ~70 % of those with a high ratio, compared to only 10% of those with a normal ratio, converted from normal to MCI over a 3 year period (Fagan, et al., 2007). Li et al. reported that over a follow up of 42 months, all subjects who converted to MCI had elevated tau/Aβ_{42} ratios, while no conversions occurred in the normal ratio group (Li, et al., 2007). A larger study of 174 individuals that were enrolled initially as cognitively normal at the time of lumbar puncture has confirmed and extended these data (Craig-Schapiro et al., 2010). Although the current data come from relatively small sample sets, they suggest that over a 3–4 year period, the CSF tau/Aβ42 ratio is a very good marker of predicting conversion from cognitively normal to MCI/very mild dementia. Low levels of CSF Aβ_{42} alone in cognitively normal elderly is also predictive of conversion to MCI/very mild dementia; however, in the absence of an increase in tau or p-tau, the conversion time is significantly longer (3–8 years) (Gustafson, et al., 2007,Skoog, et al., 2003 Stomrud, et al., 2007). This is likely due to the fact that amyloid deposition alone in the absence of significant degeneration as marked by increased tau indicates an earlier phase of the AD pathological process. It appears that the subgroup of normal elderly with a high ratio of tau/Aβ_{42} have developed both Aβ deposition and neurodegeneration and represent individuals with preclinical AD.

Recommendation and Future Directions for use of CSF biomarkers for use in clinical trials

Clinical trials

1. For clinical trials in subjects with mild clinically defined cognitive abnormalities (MCI/very mild dementia), enrollment based on the use of CSF Aβ_{42}, tau, and p-tau would assist in several ways. First, by only enrolling individuals with a CSF Aβ_{42} below a cutoff score for that laboratory that indicates a greater than 90% chance of having brain amyloid deposition, this will ensure that almost all of the subjects being enrolled have AD and will exclude subjects that lack amyloid deposition. Second, by using cutoff cores for the tau/Aβ_{42} ratio or at minimum Aβ_{42} as entry criteria, it will ensure that most individuals enrolled will decline at an appreciable rate such that smaller number of subjects will be required per arm to determine whether there are significant effects of the treatment. Third, assessment of these markers over time may allow one to visualize a therapeutic effect (e.g. decreased tau) that might precede and ultimately correlate with a clinically beneficial effect such as reduced neurodegeneration.
2. Although the data are less extensive in cognitively normal subjects, they support enrollment of normal subjects with a high CSF tau/Aβ_{42} ratio into clinical trials with a goal of reducing conversion from normal to MCI/very mild dementia or in slowing cognitive decline as measured by neuropsychological test score performance. In untreated persons, such a biomarker result would predict conversion rates from CDR 0 to CDR>0 of ~50% over 3 years.

Future directions

1. Larger numbers of cognitively normal people should be followed over time to validate the usefulness of CSF Aβ_{42}, tau, p-tau, and the ratios as predictors of cognitive decline.
2. Especially for prognosis in both normal and those with MCI/very mild dementia, it will be useful to validate the CSF markers in larger, epidemiologic-based sample sets. In addition, it will be informative to combine both fluid and imaging

biomarkers to determine the most useful combinations of tests for diagnosis and prognosis.

3. From a technical standpoint, for a clinical trial to be conducted now using CSF biomarkers, it would be recommended to assess CSF markers in a single laboratory due to interlab variability. Assessment of these markers in multiple sites will require interlab standardization.

4. Other CSF biomarkers have been identified that may assist with diagnosis and prognosis. It will be important to determine if they provide added value to the current markers in appropriately assessed populations.

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Table

Levels of Evidence for AD Biomarkers

Marker type	Diagnosis of AD versus controls	Diagnosis of MCI versus controls	Prognosis: predicting progression from MCI to AD	Prognosis: predicting progression from cognitively normal to MCI or AD
CSF biomarkers	Primary studies - Sufficient evidence of a direct relationship[1] *	Primary studies - Sufficient evidence of a direct relationship[1] **	Primary studies - Sufficient evidence of a direct relationship[1] ***	Primary studies - Sufficient evidence of a direct relationship[1]

Levels of evidence are based on Categories of Association established and used by the Institute of Medicine for association between a biomarker and a specific health outcome (Committee on Health Effects Associated with Exposures During the Gulf War. Institute of Medicine, 2000): 1. Sufficient Evidence of a Direct Relationship: Evidence fulfills the guidelines for sufficient evidence of an association, is supported by experimental data in humans and animals, and satisfies several of the guidelines used to assess causality: strength of association, dose–response relationship, consistency of association, and a temporal relationship. 2. Sufficient Evidence of an Association: Evidence of association is sufficient to conclude that there is a positive consistent association, in human studies in which chance and bias, including confounding, could be excluded with reasonable confidence. It differs from category 1 because of the lack of experimental data in humans or animals that support the relationship. 3. Limited/Suggestive Evidence of an Association: Evidence is suggestive of an association between a biomarker and a specific health outcome in human studies, but the body of evidence is limited by the inability to exclude chance and bias, including confounding, with confidence. 4. Inadequate/Insufficient Evidence to Determine Whether an Association Exists: Evidence is of insufficient quantity, quality, or consistency to permit a conclusion regarding the existence of an association between exposure to a specific agent and a specific health outcome in humans.

* There are over 50 studies (including cross-sectional and longitudinal studies) for CSF tau, over 16 studies including longitudinal studies for CSF Aβ42, and over 5 studies including longitudinal studies for the combination of tau and Aβ42.

** Several studies indicate that CSF biomarkers can detect very mild dementia (MCI) with a sensitivity that is similar to that of more advanced AD.

*** There are several studies including studies with neuropathological confirmation of diagnoses.

¶ Evidence is limited to a small number of studies with methodological variations.