

Cerebrospinal fluid biomarkers for the diagnosis of Alzheimer's disease

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Abstract

The histopathological changes in the Alzheimer's disease (AD) brain begin years before the first clinical symptoms become apparent. Hence, reliable biomarkers have long been sought for the early diagnosis of AD, prediction of conversion to AD from mild cognitive impairment (MCI), identification of AD at the preclinical stage of AD, differentiation among AD, MCI and other types of dementia, and assessment of clinical trials for AD therapies; however, biomarkers of AD at various stages of development and clinical evaluation have so far not been established in clinical routine. Recently, revised diagnostic criteria have been proposed for AD dementia, MCI and preclinical AD from the National Institute on Aging (NIA)-Alzheimer's Association (AA) workgroups on diagnostic guidelines for AD. In each phase, the revisions are related to the incorporation of diagnostic biomarkers into the diagnostic criteria. Only the five most widely studied biomarkers of AD have been formally incorporated into the diagnostic criteria. The five biomarkers include: (i) abnormal tracer retention on amyloid imaging, (ii) decreased levels of the 42 amino acid form of β -amyloid ($A\beta_{1-42}$) peptide in cerebrospinal fluid (CSF), (iii) elevated levels of both total and phosphorylated tau (t-tau and p-tau, respectively) in CSF, (iv) decreased fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET), and (v) atrophy on structural magnetic resonance imaging (MRI). The former and latter two are biomarkers for $A\beta$ accumulation and for neuronal degeneration or injury, respectively; however, the role of biomarkers differs in each of these stages. In the preclinical AD stage, biomarkers are used to identify the presence of the pathophysiology of AD in research subjects with no or very subtle overt dementia symptoms, while, in both the MCI and AD dementia stages, clinical diagnoses are paramount and biomarkers are complementary.

There is a reduction of $A\beta_{1-42}$ in CSF by approximately 50% in AD patients, compared to age-matched non-demented controls, with diagnostic sensitivity and specificity levels ranging between 80 and 90%. CSF $A\beta_{1-42}$ levels are now considered to be the most sensitive single analyte for the detection of AD compared with cognitively normal elderly. Low levels of CSF $A\beta_{1-42}$ are already observed in subjects with MCI who are later converted to AD, and furthermore may predict a cognitive decline in healthy elderly individuals in whom AD dementia develops later. An increase in CSF t-tau in AD compared to elderly controls is consistently observed, with a sensitivity of 77% and a specificity of 91%. Similar increases in CSF t-tau are shown in patients with MCI who are at increased risk of AD. CSF levels of p-tau₁₈₁ and p-tau₂₃₁ proteins are also increased in AD and yield a sensitivity of 64 and 93% and a specificity of 86 and 94%, respectively, in discriminating AD from healthy controls. CSF p-tau yields a higher specificity than t-tau in diagnosing AD compared to other types of dementia. High CSF levels of p-tau significantly predict cognitive decline and subsequent conversion to AD in MCI subjects.

It should be noted that the ability of CSF biomarkers to discriminate AD from other types of dementia, especially vascular dementia (VAD), is still unsatisfactory. A combination of two CSF biomarkers, $A\beta_{1-42}$ and tau, seems to give significantly higher diagnostic accuracy than any biomarker alone; however, further studies are likely to be necessary to confirm whether a panel of biomarkers rather than single analytes has more ability