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Review Articles

Clinical utility of cerebrospinal fluid biomarkers in the diagnosis of early Alzheimer's disease

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Abstract Several potential disease-modifying drugs for Alzheimer's disease (AD) have failed to show any effect on disease progression in clinical trials, conceivably because the AD subjects are already too advanced to derive clinical benefit from treatment and because diagnosis based on clinical criteria alone introduces a high misdiagnosis rate. Thus, well-validated biomarkers for early detection and accurate diagnosis are crucial. Low cerebrospinal fluid (CSF) concentrations of the amyloid-β ($A\beta_{1-42}$) peptide, in combination with high total tau and phosphorylated tau, are sensitive and specific biomarkers highly predictive of progression to AD dementia in patients with mild cognitive impairment. However, interlaboratory variations in the results seen with currently available immunoassays are of concern. Recent worldwide standardization efforts and quality control programs include standard operating procedures for both preanalytical (e.g., lumbar puncture and sample handling) and analytical (e.g., preparation of calibration curve) procedures. Efforts are also ongoing to develop highly reproducible assays on fully automated instruments. These global standardization and harmonization measures will provide the basis for the generalized international application of CSF biomarkers for both clinical trials and routine clinical diagnosis of AD.

Keywords: Cerebrospinal fluid; Biomarkers; Alzheimer's disease; β-Amyloid; Tau protein; Mild cognitive impairment

1. Introduction

Alzheimer's disease (AD) is a complex progressive neurodegenerative disease affecting approximately 14 million people in Europe and the United States [1,2], including almost one-half of the population aged >85 years (43%) [2,3]. In the early stages, the pathologic changes in AD primarily affect the medial temporal lobe, subsequently progressing to neocortical-associated areas [4,5]. The hallmarks of the disease are neuritic plaques composed of the amyloid-β peptide (Aβ) and neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein (P-tau) [5].

The neuropathology of underlying AD starts decades before the appearance of clinical symptoms [6–10], and evidence suggests that AD should be considered as having three main stages: (1) presymptomatic, (2) "prodromal" with mild symptoms (mainly disturbances in episodic memory), and (3) symptomatic with dementia [11]. In many cases, mild cognitive impairment (MCI) can be considered a "transitional zone" between the cognitive decline seen in normal aging and the cognitive dysfunctions of AD dementia. Although as many as 10% to 20% of patients with MCI progress to AD per year [12], other causes of MCI include cerebrovascular disease, polypharmacy,

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depression, excessive alcohol/drug use, and neurodegeneration unrelated to AD [13].

The diagnosis of mild AD dementia—and especially prodromal AD—remains difficult on purely clinical grounds [11,14], although there is some evidence that specific memory tests identify the amnestic syndrome of the hippocampal type [15,16]. The accuracy of current clinical AD diagnostic methods to predict pathologic diagnoses (in the absence of biomarker information) is generally low; sensitivities have been reported to range from 71% to 88% and specificities from 44% to 71%, depending on the specific histopathologic diagnostic criteria used [17]. In addition, reports from large clinical trials of drug candidates with disease-modifying potential show that 10% to 35% of clinically diagnosed AD cases with mild-to-moderate dementia have negative amyloid positron emission tomography (PET) scans [18]. This means that a large proportion of individuals in these trials have no or little Aβ pathology in the brain and thus do not have the disease for which the drug is to be tested, adversely affecting the ability to identify a beneficial clinical effect of the drug. The accuracy of clinical diagnosis is probably even lower in the very early clinical stages of the disease (i.e., in patients with prodromal AD). This variable and relatively poor performance is particularly troubling given the high level of expertise of the clinicians in the specialized AD centers making the diagnosis, and the diagnostic accuracy in primary or secondary care settings is likely to be even lower.

In the last two decades, there have been intensive efforts to develop disease-modifying drugs to counteract the progression of AD. Because initiating treatment with these agents early in the disease continuum is expected to provide the greatest long-term benefits, there is a critical need for further progress in the development and validation of diagnostic tools to accurately identify patients with early AD dementia (and especially prodromal AD) for inclusion in clinical trials [14]. Aside from the need for biomarkers to identify patients for inclusion in registration trials of disease-modifying agents, once these drugs are approved for widespread use, diagnostic tools will also be required to recognize prodromal AD patients and provide appropriate treatments in routine clinical practice.

The use of magnetic resonance imaging (MRI), ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET), amyloid (Aβ) PET [19,20], and candidate fluid biomarkers for AD has been investigated extensively for a number of years [21]. Like MRI, FDG PET has demonstrated sensitivity for AD identification at the MCI [22] and even the normal stages of cognition [7,23], but these modalities are not pathologically specific. Amyloid PET has demonstrated some specificity for AD lesions [24], but the sensitivity of this modality continues to be investigated.

Although protein content is lower in cerebrospinal fluid (CSF) than in serum, CSF is an ideal source for developing viable biomarkers in AD as it directly interacts with the extracellular space in the brain, thus potentially reflecting the associated biochemical/pathologic changes [25]. As a result, CSF biomarkers have been become accepted and adopted to varying degrees for the clinical diagnosis of AD in different countries. Indeed, the European Federation of Neurological Societies (EFNS) guidelines recommend routine CSF analysis in the differential diagnosis of atypical AD characterized by prominent early deficits rather than episodic memory [1]. Although the International Working Group and, later, the National Institute on Aging and the Alzheimer's Association (NIA-AA) suggest that CSF biomarkers may add diagnostic value, they do not at present advocate the use of AD biomarker tests for routine diagnosis as they believe that further research, validation, and standardization are required and because access to biomarkers is restricted in some settings [11,26].

An international Expert Committee meeting was held in April 2012 to discuss the development and validation of CSF diagnostic assays and the optimization of their use as in vitro diagnostic tools, with a particular emphasis on the employment of CSF biomarkers to identify patients with prodromal AD. This meeting was held with the unrestricted support of Roche Diagnostics. This article summarizes the conclusions from that meeting and is not meant to be a guideline or a position article. The authors take full responsibility for the manuscript and the industrial partner did not advise or interfere with its content. The article aims to stimulate the international community to focus on the role and utility of CSF biomarkers for the diagnosis of prodromal AD.

2. Which CSF biomarkers are the most appropriate?

Although a multitude of CSF biomarkers for specific pathologic changes and nonspecific markers of oxidative damage or inflammation in AD patients have been proposed, many of them have only been reported in single publications and the results have been difficult to replicate. The most consistent findings have been obtained with the $A\beta_{1\text{-}42}$ peptide ($A\beta_{42}$), total tau (T-tau), and P-tau [21,27,28].

It is important to determine how the change in the CSF levels of these proteins relates to the pathology or neurochemical disturbances in the AD brain. It has been shown that the level of $A\beta_{42}$ in postmortem ventricular CSF shows an inverse correlation with plaque load in cortical regions [29], a finding that has been replicated in later studies [30] and in biopsied brain from living subjects [31]. In addition, decreased CSF concentrations of $A\beta_{42}$ have been found to correlate with high retention of Pittsburgh Compound B using PET [30,32–36]. Taken together, these studies show that in AD patients, the reduction in CSF $A\beta_{42}$ reflects deposition of the peptide in plaques in the cortex. It is likely, however, that other pathologic processes will also generate low CSF levels of $A\beta_{42}$. In support of this, low levels of CSF $A\beta_{42}$ are also detected in a proportion of cases with plaque-negative Creutzfeldt-Jakob disease (CJD) and in patients with bacterial meningitis [37,38].