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Review Article

The impact of preanalytical variables on measuring cerebrospinal fluid biomarkers for Alzheimer's disease diagnosis: A review

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Abstract

Introduction: Cerebrospinal fluid (CSF) biomarkers have the potential to improve the diagnostic accuracy of Alzheimer's disease, yet there is a lack of harmonized preanalytical CSF handling protocols.
Methods: This systematic review summarizes the current literature on the influence of preanalytical variables on CSF biomarker concentration. We evaluated the evidence for three core CSF biomarkers: β-amyloid 42, total tau, and phosphorylated tau.
Results: The clinically important variables with the largest amount of conflicting data included the temperature at which samples are stored, the time nonfrozen samples can be stored, and possible effects of additives such as detergents, blood contamination, and centrifugation. Conversely, we discovered that there is consensus that tube material has a significant effect.
Discussion: A unified CSF handling protocol is recommended to reduce preanalytical variability and facilitate comparison of CSF biomarkers across studies and laboratories. In future, experiments should use a gold standard with fresh CSF collected in low binding tubes.

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1. Introduction

Alzheimer's disease (AD) can be characterized as a continuum with three main stages of symptoms: no cognitive symptoms in the preclinical population, mild cognitive symptoms in the prodromal population, and advanced clinical symptoms of dementia in fully developed AD [1,2]. Therapeutics in development to treat the underlying pathology of AD will likely have greatest clinical benefit early in the AD continuum before neuronal damage is widespread [3,4]. It is challenging to definitively diagnose early AD using clinical criteria alone [2]; however, biomarkers can detect changes in underlying neuropathology not only when mild cognitive symptoms are present [5–9] but also at preclinical stages [10–14].

1.1. The potential impact of biomarkers in AD diagnosis and research

While several definitions of biomarkers have been offered, an inclusive broad definition that we will adopt here is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or biological responses to a therapeutic intervention" [15]. Several physiological changes related to the pathogenesis of AD (such as neuritic plaques, tangles, and neuronal and synapse loss) have been well documented. These are accompanied by changes in the levels of some molecules, both in the brain and cerebrospinal fluid (CSF), several of which have been suggested as potential biomarkers in the field of AD for specific applications (e.g., diagnosis, treatment follow-up) [16].

Patients with AD have a characteristic profile of altered concentrations of three CSF core protein biomarkers: β-amyloid (Aβ) (1–42), total tau (tTau), and phosphorylated tau (pTau) [17–19]. While these biomarkers may be individually affected by non–AD-related pathologies, the combination of the three core biomarker changes is known as the CSF AD "signature" or "profile" [5,6,19–23].

Aβ(1–42) is the main peptide responsible for the formation of amyloid plaques that are associated with AD [24–26]. Currently, the only FDA-approved method to detect Aβ deposits within the brain is Aβ positron emission tomography (PET) [27]. However, several commercially available assays for measuring Aβ(1–42) (and other core AD biomarkers) in CSF are approved for diagnostic use in the European Union [28–31].

Brain amyloid pathology is correlated with abnormally low levels of Aβ(1–42) in the CSF [3,32–36]. There is high concordance of CSF Aβ(1–42) with Aβ PET status in both AD dementia and prodromal AD [5]. Low CSF Aβ(1–42) could be an early indicator of preclinical AD before amyloid deposition rises to levels visible by PET imaging [32,37]. Concordance is further improved by using the ratio of CSF Aβ(1–42)/(1–40), CSF pTau/Aβ(1–42), or CSF tTau/Aβ(1–42) [16,18,37–40]. The presence of an ε4 allele of apolipoprotein E (*APOE*), the strongest genetic risk factor for AD, is known to influence amyloid load as evidenced by both CSF Aβ(1–42) and amyloid PET [38–41].

CSF tTau may be increased following neuronal injury or degeneration and is associated with cognitive decline [42,43]. This may be due to a neurodegenerative disorder such as AD [44] but is also documented in other pathologies, for example, ischemic stroke [45] and Creutzfeldt-Jakob disease [46].

Hyperphosphorylated tau is an important component of neurofibrillary tangles, which are a pathological hallmark of AD [3,16,47]. High CSF pTau was reported to correlate with cortical tangle pathology in some [48,49] but not all [50] studies, whereas high levels of CSF pTau are consistently found in AD patients (up to 3.4-fold higher than healthy controls) [44]. The inclusion of pTau as a biomarker for AD together with Aβ(1–42) and tTau can help differentiate AD from normal aging and other diagnoses (e.g., Parkinson's disease, Creutzfeldt-Jakob disease, and some forms of non-AD dementia), and improve diagnostic [51,52] and prognostic [6,53,54] performance.

Research guidelines from the National Institute on Aging and the Alzheimer's Association [51,55] and International Working Group [52] recommend including core biomarkers in AD diagnostic assessment, while the European Academy of Neurology recommends CSF biomarker assessment to aid AD differentiation [56]. As well as having diagnostic potential, changes in the core AD biomarkers precede cognitive changes and predict clinical progression in patients with mild cognitive impairment [6,8,19,57,58] and effectively stratify patients for their risk of developing AD dementia [6,8,21,22,53,59]. Promisingly, these biomarkers also detect pathological changes associated with preclinical AD in cognitively healthy elderly individuals [14,54,60,61] and can enhance both differential diagnosis and prognostic stratification within AD populations.

Accurate, consistent, and reliable biomarker measurement remains a goal for researchers and clinicians alike but requires consensus to establish universal cutoff values. However, the significant variability documented in CSF biomarker measurements across research and clinical studies [3,41,62–64] has hampered these efforts. The