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# CSF Aβ1-42 combined with neuroimaging biomarkers in the early detection, diagnosis and prediction of Alzheimer's disease

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**Abstract** The development of validated, qualified, and standardized biomarkers for Alzheimer's disease (AD) that allow for an early presymptomatic diagnosis and discrimination (classification) from other types of dementia and neurodegenerative diseases is warranted to accelerate the successful development of novel disease-modifying therapies. Here, we focus on the value of the 42-residue-long amyloid β isoform (Aβ1-42) peptide in the cerebrospinal fluid as the core, feasible neurobiochemical marker for the amyloidogenic mechanisms in early-onset familial and late-onset sporadic AD. We discuss the role and use of Aβ1-42 in combination with evolving neuroimaging biomarkers in AD detection and diagnosis. Multimodal neuroimaging techniques, directly providing structural-functional-metabolic aspects of brain pathophysiology, are supportive to predict and monitor the progression of the disease. Advances in multimodal neuroimaging provide new insights into brain organization and enable the detection of specific proteins and/or protein aggregates associated with AD. The combination of biomarkers from different methodologies is believed to be of incrementally added risk-value to accurately identify asymptomatic and prodromal individuals who will likely progress to dementia and represent rational biomarker candidates for preventive and symptomatic pharmacological intervention trials.


*Keywords:* Alzheimer's disease; Mild cognitive impairment; Cerebrospinal fluid; Prodromal; Asymptomatic; Preclinical; amyloid β peptides; Aβ1-42; Neurochemical biomarkers; Imaging biomarkers; Combination of biomarkers; Positron emission tomography; Magnetic resonance imaging; Early diagnosis; Early detection

## 1. Introduction

Alzheimer's disease (AD) is a genetically complex, slowly progressive, and irreversible neurodegenerative disease of the brain. During decades of asymptomatic progression, multiple interactive systems, pathways, and molecular mechanisms contribute to the development of the early clinical prodromal stage with episodic memory deficits and to further decline and loss of general cognitive functioning during the final syndromal dementia stage [1]. The pathophysiology of AD involves the aggregation of amyloid β (Aβ) peptides with amyloid plaque formation and hyperphosphorylation of tau protein with deposition of neurofibrillary tangles (NFTs). The "amyloid cascade hypothesis" [2] or "amyloid deposition cycle" [3] remains the best accepted model for explaining AD. It states that the pathological cleavage of the amyloid precursor protein (APP), the excessive formation and aggregation of toxic soluble

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Aβ oligomers, and the deposition of insoluble fibrillar Aβ, with subsequent accumulation in diffuse to senile plaques, represent the opening events in AD pathogenesis [4,5]. These processes secondarily elicit a converging and self-propagating decompensatory, increasingly neurotoxic cascade, finally leading to synaptic integrity disruption and neuronal loss in definite areas associated with cognitive activities [3,6].

Despite enormous financial and scientific efforts, all therapeutics claimed to reduce amyloid production or aggregation tested so far have failed in Phase III clinical trials. Although these negative outcomes have at least in part begun to challenge the validity of the amyloid cascade hypothesis, it can be argued that the failure of the studies is not necessarily the result of a failed or null experimental finding, but it can also imply that the hypothesis has not been properly tested [7]. These trials have been performed on relatively advanced AD cases, and the large majority of cases have been enrolled without any biomarker evidence of AD pathology. Little evidence of clear effects with antibody approaches has been found [8]. However, it should be noted that available studies do not always take into account whether relevant analytes in cerebrospinal fluid (CSF) are consistently affected [9]. For this reason, the availability of in vivo biomarkers of key pathogenic events in AD should help to test and adjust the current hypotheses on AD pathogenesis.

In the article presented here, we will focus our attention on the role of the 42-residue-long Aβ isoform (Aβ1-42) biomarker in the CSF as the core biochemical marker for the amyloidogenic process in AD and discuss its role in combination with neuroimaging biomarkers in AD diagnosis.

## 2. Development of AD biomarkers

Studies in transgenic mouse models suggest that most new types of disease-modifying drugs for AD may be most effective early on in the process of Aβ aggregation and be less effective in later stages when there is severe plaque pathology and neurodegeneration [10]. Therefore, the characterization and identification of these early disease stages is assumed to be key to successful development of disease-modifying compounds. Because AD treatment in most clinical practices begins in the later stages, the neurodegenerative damage is so extensive that the approved therapies with cholinesterase inhibitors offer limited symptomatic relief. There is currently a global consciousness that delaying or inhibiting cognitive impairments has a bigger impact for public health and economics than providing a short-period symptomatic relief in the later stages [11]. In this regard, it has been estimated that interventions intended to slow down the clinical onset and progression of AD by 1 year would decrease its worldwide prevalence by 9 million cases in the year 2050, with approximately the whole decline attributable to decreases in persons requiring a high level of care [12]. Thus, one of the major challenges for academic research and economic opportunities for the pharmaceutical industry is to focus on early detection and prevention as a promising objective. This novel perspective for drug discovery requires the development of technologies to identify the disease earlier and delay the loss of memory for as long as possible [11]. At this time, no disease-modifying drug therapy for AD has been approved. Many compounds are presently being tested in clinical trials for therapeutic use in AD [13]; the success of these molecules in clinical trials may rely on the right stratification of patient groups and on the correct recognition of individuals with asymptomatic AD.

The recent revision [14,15] of the traditional clinical diagnostic criteria [16] by the International Working Group (IWG) for New Research Criteria for the Diagnosis of AD, which have defined several stages of disease progression, reflects growing recognition that the underlying neurobiology of AD begins several years before the appearance of clinical symptoms or impairments of function [17]. In this connection, in the year 2011, the National Institute on Aging-Alzheimer's Association workgroup (NIA-AA) published recommendations concerning the definition of the preclinical stages of AD [18], the diagnosis of "mild cognitive impairment (MCI) due to AD" (MCI-AD) [19], and the diagnosis of "dementia due to AD" (AD dementia) [20], which also assimilated information on biomarkers. As stated by the NIA-AA workgroup, the most important AD biomarkers should be classified into those associated with the Aβ peptide deposition pathway—including low levels of Aβ1-42 in the CSF and positive positron emission tomography (PET) amyloid imaging—and those linked to downstream neuronal degeneration or injury processes: elevated concentrations of CSF tau protein, both total tau (t-tau) and hyperphosphorylated tau (p-tau); decreased $^{18}$F-2-fluoro-2-deoxy-D-glucose (FDG) uptake on PET in the temporo-parietal cortex; and unbalanced atrophy on structural magnetic resonance imaging (MRI) in the medial, basal, and lateral temporal lobe and the medial parietal cortex [20].

The publication of such revised criteria represents a milestone in the continued history of efforts to illustrate the clinical-pathological aspects of AD. These revisions denote substantial progress in that attempt of adding new features that would improve the precision and accuracy of the differential diagnosis of AD [21]. The concept of prodromal stages of the disease contributed to strengthening the exploration for early biomarkers. Advances in cellular/molecular neurobiology and emerging imaging technologies promise to provide much needed surrogate markers to detect and monitor progression during the early clinically asymptomatic stages [22]. As a result, in this increasingly evolving context, the identification of a biomarker—or a combination of biomarkers—in biological fluids that may allow an early presymptomatic diagnosis as well as discrimination from other types of dementia is critically needed.

## 3. Aβ biomarkers for AD in CSF

Extracellular senile plaques are primarily composed of Aβ peptides, originating from the APP through sequential