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Research Article

The cerebrospinal fluid "Alzheimer profile": Easily said, but what does it mean?

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Abstract

Background: We aimed to identify the most useful definition of the "cerebrospinal fluid Alzheimer profile," based on amyloid-ß$_{1-42}$ (Aβ$_{42}$), total tau, and phosphorylated tau (p-tau), for diagnosis and prognosis of Alzheimer's disease (AD).

Methods: We constructed eight Alzheimer profiles with previously published combinations, including regression formulas and simple ratios. We compared their diagnostic accuracy and ability

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to predict dementia due to AD in 1385 patients from the Amsterdam Dementia Cohort. Results were validated in an independent cohort (n = 1442).

Results: Combinations outperformed individual biomarkers. Based on the sensitivity of the best performing regression formulas, cutoffs were chosen at 0.52 for the tau/Aβ_{42} ratio and 0.08 for the p-tau/Aβ_{42} ratio. Ratios performed similar to formulas (sensitivity, 91%–93%; specificity, 81%–84%). The same combinations best predicted cognitive decline in mild cognitive impairment patients. Validation confirmed these results, especially regarding the tau/Aβ_{42} ratio.

Conclusions: A tau/Aβ_{42} ratio of >0.52 constitutes a robust cerebrospinal fluid Alzheimer profile. We recommend using this ratio to combine biomarkers.

Keywords: Dementia; Alzheimer's disease; Mild cognitive impairment; Cerebrospinal fluid; Amyloid-β_{1-42}; Tau; Biomarkers; Differential diagnosis; Predictive value

1. Introduction

The cerebrospinal fluid (CSF) biomarkers amyloid-β_{1-42} (Aβ_{42}), total tau, and tau phosphorylated at threonine 181 (p-tau) have been extensively studied in Alzheimer's disease (AD) [1,2,3,4,5,6,7,8,9]. They seem promising diagnostic biomarkers [10,11] and have now been included as evidence for AD pathology in the new research criteria for AD [12,13,14]. CSF biomarkers have not yet been implemented in clinical guidelines however, and the research criteria do not specify how exactly they should be used. This is partly due to the lack of standardization between centers, currently targeted in an international quality control program [15,16]. Furthermore, there is no consensus on what constitutes a "CSF Alzheimer profile." Previous studies are fairly consistent that combining biomarkers is superior to the use of a single marker to diagnose AD. However, some promote a simple ratio of two biomarkers [4,17,18], whereas others developed weighted regression formulas or other algorithms [1,5,6,7,9,19,20]. Most of these combinations were developed in single-center studies, hampering their generalization and implementation in clinical practice.

Our aim was to identify which of these previously published combinations constitutes the optimal CSF "AD profile," to answer the most relevant clinical questions in a memory clinic: to differentiate AD patients from cognitively normal subjects and other dementias and predict dementia due to AD in patients with mild cognitive impairment (MCI). We compared eight different combinations of biomarkers, previously coined to describe an AD profile, in a large cohort of patients from our memory clinic. To assess generalizability of the results, we repeated the analyses in an independent multicenter cohort.

2. Methods

2.1. Patients

We included 1385 patients from our memory clinic–based Amsterdam Dementia Cohort who received a diagnosis of subjective memory complaints, MCI, AD, or other dementia and had baseline CSF collected between October 1999 and November 2011. All patients underwent extensive dementia screening at baseline, with physical and neurologic examination, electroencephalography, magnetic resonance imaging, and laboratory tests. Neuropsychological assessment was performed in all patients and included at least Mini-Mental State Examination (MMSE) for global cognition, visual association test for memory, forward and backward Digit Span for attention and working memory, and Trail Making Tests A and B for mental speed and executive function. Tests are described in detail elsewhere [21]. Diagnoses were made by consensus in a multidisciplinary team without knowledge of CSF results. At any follow-up visit, patient history, neuropsychological tests, and physical and neurologic examination were repeated.

Probable AD (n = 631) was diagnosed according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association [22], and all patients met the core clinical National Institute of Aging–Alzheimer's Association (NIA-AA) criteria [14]. Other dementia diagnoses were made according to standard criteria: consensus criteria for frontotemporal lobar degeneration (FTLD; n = 121) [23], McKeith criteria [24] for dementia with Lewy bodies (DLB; n = 57), National Institute of Neurological Disorders and Stroke (NINDS)–Association Internationale pour la Recherche et l'Enseignement en Neurosciences [25] for vascular dementia (VaD; n = 40), criteria by Boeve et al. [26] for corticobasal degeneration (n = 15), and NINDS–Society for Progressive Supranuclear Palsy [27] for progressive supranuclear palsy (n = 25). Furthermore, there were three patients with alcohol dementia, two with Huntington's disease, three with normal pressure hydrocephalus, and one patient with CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). Three patients with Creutzfeldt-Jakob disease and extremely high tau values were excluded from further analyses. MCI was diagnosed according to the criteria by Petersen et al. [28], and all patients met the core clinical NIA-AA criteria [29]. MCI patients with follow-up of at least 1 year were included (n = 236). When all clinical investigations were