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CSF Biomarkers

Cerebrospinal fluid biomarkers in Alzheimer's disease: Diagnostic accuracy and prediction of dementia

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Abstract

Introduction: Guidelines for the use of cerebrospinal fluid (CSF) biomarkers in the diagnosis of Alzheimer's disease (AD) establish that each laboratory must use internally qualified cutoff values. We determined the concentrations of biomarkers that discriminate cases from controls and combinations that predict the progression to dementia in a Brazilian cohort.

Methods: Concentrations of amyloid-beta peptide ($A\beta_{1–42}$), total tau (T-tau), and ^{181}Thr-phosphorylated-tau (P-tau) were determined in CSF samples from 184 older adults (68 mild cognitive impairment, 41 AD, 34 non-AD cognitive impairment, and 41 controls) by the INNO-BIA AlzBio3 assay.

Results: Cutoff values discriminating AD from controls are as follows: $A\beta_{1–42}$: 416.0 pg/mL (sensitivity [SE]: 83%, specificity (SP): 70%); T-tau: 76.7 pg/mL (SE: 82%, SP: 67%); P-tau: 36.1 pg/mL (SE: 83%, SP: 49%); $A\beta_{1–42}$/P-tau <9.53 (SE: 88%, SP: 78%); and $A\beta_{1–42}$/T-tau <4.13 (SE: 80%; SP: 80%). Combining values $A\beta_{1–42}$ <416.5 pg/mL and $A\beta_{1–42}$/P-tau <9.5 best predicted the conversion in 2 years (Cox regression: hazard ratio 7.24 [2.09–25.06], $P = .002$, SE: 74%, Sp: 73%).

Discussion: Our findings are in line with most of the available evidence in this field; yet, our cutoff values are different from those derived from other laboratories.

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

1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia, affecting >35 million people worldwide [1]. The neuropathologic hallmarks of AD are the neuritic plaques and neurofibrillary tangles, which, respectively, arise from the extracellular deposition of the amyloid-beta (Aβ) peptide and from the intracellular accumulation of hyperphosphorylated tau protein in neurons. The pathophysiological changes that cause cognitive, functional, and behavioral impairment in AD allegedly start several years or perhaps decades before the onset of clinical symptoms [2]. Molecular and neuroimaging markers portray the presence of AD pathology [3–5]; therefore, AD biomarkers may play an important role in the diagnostic workup of patients with cognitive impairment, particularly among those with clinical symptoms compatible with prodromal AD [6].

Over the past years, multicenter task forces invested substantial resources in the integrated study of clinical, genetic, biochemical, and neuroimaging markers of AD and their relationship with clinical symptoms and rate of disease

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progression [7]. Many efforts have been expended to determine the specific pattern of changes that is found in AD and the predictive value of such findings in the diagnosis of predementia AD. The so-called "AD signature in the cerebrospinal fluid (CSF)" subsumes decreased concentrations of the $A\beta_{1-42}$ peptide [8] and increased concentrations of total tau (T-tau) [9] and hyperphosphorylated tau (P-tau) [10]. Studies have shown an average decrease of 50% in CSF $A\beta_{1-42}$ levels in AD compared with cognitively normal elders, along with a 300% increase in T-tau and a 200% increase in P-tau [5,11,12]. This set of biomarkers were accepted as proxy, in vivo evidence of the AD pathology, and incorporated into the revised diagnostic criteria of the National Institute of Neurological Disorders and Stroke, Alzheimer's and Related Disorders disease as supporting features to the diagnostic of AD [13], including its predementia and preclinical stages [14]. In combination, these biomarkers have a sensitivity (SE) and specificity (SP) profile in the 85%–95% range for the diagnosis AD at prodromal and dementia stages [15].

The availability of this technology reinforces the use of AD biomarkers in the selection of more homogeneous samples of patients for research purposes, particularly intervention trials with antidementia drugs. The translation of this method into a diagnostic tool for clinical purposes is expected in the near future, particularly to support the prediction of dementia among patients with subtle memory symptoms [15]. Therefore, it is relevant to determine the biomarker profile that distinguishes individuals at risk of AD among those diagnosed with mild cognitive impairment (MCI). The aim of the present study was to determine CSF concentrations of $A\beta_{1-42}$, T-tau, and P-tau and the respective cutoff scores that best discriminate normal elders from patients with AD, as well as the combination of values that predicts the conversion from amnestic MCI to dementia in a cohort of older adults.

2. Methods

2.1. Subjects and assessment

The present study was conducted at the psychogeriatric clinic of a tertiary, university-based hospital in Brazil (Institute of Psychiatry, Faculty of Medicine, University of São Paulo). A total of 184 older adults were enrolled after signing informed consent. The study was approved by the local Ethics Committee and conducted under the tenets of the Helsinki Declaration. The study was designed to include a cross-sectional assessment of the whole sample at baseline, followed by the longitudinal reassessment of nondemented participants at 12-month intervals. Initial assessment was performed by psychiatrists and a neurologist through the Brazilian version of the structured interview for Cambridge mental disorders of the elderly examination [16], which provides scores for cognitive test Cambridge (CAMCOG), and mini-mental state examination (MMSE) [17]. Neuropsychological assessments were performed by trained neuropsychologists and included the Fuld object memory evaluation (FOME) [18], the trail making test (TMT) A and B [19], and the short cognitive test (SKT) [20,21]. In view of the variability in educational level of the subjects in the sample, the cutoff scores of neuropsychological tests are also adjusted for age and educational level. To rule out cases with comorbid major depression, participants were assessed with the 21-item Hamilton depressive scale [22] and euthymia was defined as a score <8. All participants underwent blood tests (complete blood count, blood chemistry, thyroid function, blood lipid profile, folic acid and vitamin B12 dosage, and syphilis test), and neuroimaging (magnetic resonance imaging) studies, to exclude metabolic and vascular etiologies for MCI and dementia. Additional information on the assessment protocol can be found in previous publications from our group [23,24]. Clinical diagnoses were established at consensus meetings, taking into account all clinical and laboratorial information gathered by a multidisciplinary team including physicians (psychiatrists, a geriatrician, and a neurologist), neuropsychologists, physical therapists, speech therapists, occupational therapists, and gerontologists.

The patient sample comprised 41 demented patients with mild AD [25], 68 subjects with MCI [26], and 34 patients with cognitive impairments due to other neuropsychiatric conditions, namely 17 with major depression [27], 6 with bipolar disorder [27], and 11 patients with non-AD neurodegenerative disorders (frontotemporal dementia, Huntington disease, multiple system atrophy, Lewy body dementia, and corticobasal degeneration). The comparison group comprised 41 healthy older adults with no evidence of cognitive impairment or psychiatric disorder at the time of clinical and neuropsychological assessment. Healthy controls were recruited with the aid of internal and media advertisements. We also included older adults who volunteered to join our cohort after becoming aware of this initiative from information provided by other participants in the study and their relatives. In any case, volunteers were only included in the cohort as healthy controls in the absence of any relevant memory complaints, medical comorbidities, and psychiatric history and if they had a normal performance in neuropsychological tests.

Healthy controls and subjects with MCI were annually reassessed (mean duration of follow-up: 24 ± 11 months) and had their diagnostic status adjusted depending, respectively, on the onset of cognitive deficits (incident MCI) or the progression from MCI to dementia. MCI subjects with conversion to AD during follow-up were reclassified as having MCI-AD. MCI subjects remaining cognitively stable over time were designated as having stable MCI (MCI-S). Conversion from MCI to incipient dementia was characterized by objective measures of functionality with the Brazilian version of the direct assessment of functional status [28,29].

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