

Biological markers of Alzheimer's disease

Biomarcadores da doença de Alzheimer

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ABSTRACT

The challenges for establishing an early diagnosis of Alzheimer's disease (AD) have created a need for biomarkers that reflect the core pathology of the disease. The cerebrospinal fluid (CSF) levels of total Tau (T-tau), phosphorylated Tau (P-Tau) and beta-amyloid peptide ($A\beta_{42}$) reflect, respectively, neurofibrillary tangle and amyloid pathologies and are considered as surrogate markers of AD pathophysiology. The combination of low $A\beta_{42}$ and high levels of T-tau and P-Tau can accurately identify patients with AD at early stages, even before the development of dementia. The combined analysis of the CSF biomarkers is also helpful for the differential diagnosis between AD and other degenerative dementias. The development of these CSF biomarkers has evolved to a novel diagnostic definition of the disease. The identification of a specific clinical phenotype combined with the *in vivo* evidence of pathophysiological markers offers the possibility to make a diagnosis of AD before the dementia stage with high specificity.

Keywords: CSF biomarkers, Alzheimer's disease.

RESUMO

O desafio de se estabelecer o diagnóstico precoce de doença de Alzheimer (DA) levou ao desenvolvimento de biomarcadores que reflitam os aspectos patológicos centrais da doença. As dosagens no líquido da proteína Tau total (T-Tau), Tau fosforilada (P-Tau) e peptídeo beta-amiloide ($A\beta_{42}$) no líquido cefalorraquidiano (LCR) refletem, respectivamente, as patologias Tau e amiloide, sendo consideradas como marcadores da fisiopatologia da DA. Os biomarcadores do LCR podem identificar acuradamente pacientes com DA em estágios precoces da doença, mesmo antes do desenvolvimento da demência. A análise combinada dos biomarcadores permite também fazer o diagnóstico diferencial entre DA e outras demências degenerativas. O desenvolvimento dos biomarcadores de DA conduziu a uma nova definição diagnóstica da doença. A identificação de um fenótipo clínico específico associado a uma evidência fisiopatológica *in vivo* provida por um biomarcador possibilita estabelecer, com alta especificidade, o diagnóstico de DA antes do estágio demencial.

Palavras-chave: biomarcadores do LCR, doença de Alzheimer.

BIOLOGICAL MARKERS OF ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is the most common form of dementia, accounting for approximately 50-60% of all cases¹. The most prominent feature of AD is the decline in cognitive function, with an early impairment of episodic memory². The incidence of AD increases with age and, due to the increasing aging of populations and life expectancy, the prevalence of AD continues to rise worldwide. In this scenario, AD

represents a major public health concern, with important social and economic outcomes³.

There is still no curative treatment for AD, but many ongoing trials are actually evaluating new therapeutic strategies on different molecular targets. Among several factors, the efficacy of these disease-modifying treatments will depend of early and accurate diagnosis⁴. These treatments should be more efficient if they are administered at early stages of the disease and in well-defined groups of patients, which requires accurate tools for the early diagnosis.

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Support: This work was partly funded by CNPq, Brazil.

Conflict of interest: There is no conflict of interest to declare.

Received 03 October 2013; Accepted 10 October 2013.

The challenges for establishing an early and accurate diagnosis have created a need for biomarkers, which may be defined as “an objective measure of a biological or pathogenic process that can be used to evaluate disease risk or prognosis, to guide clinical diagnosis or to monitor therapeutic interventions”⁵. These biomarkers for AD include both neuroimaging and biological parameters. In this review, we will only focus on cerebrospinal fluid (CSF) biomarkers and present data demonstrating their added-value when they are applied to the clinical diagnosis and evaluation of AD.

CSF BIOMARKERS AS EVIDENCE OF THE PATHOLOGICAL PROCESS

Ideally, a biological marker of AD should detect with high accuracy a fundamental feature of AD's pathology early in the course of the disease⁶. The core pathological hallmarks of the AD are the extracellular deposits of A β peptide and the intracellular accumulation of abnormally hyperphosphorylated tau protein. As the CSF is in direct contact with the extracellular space of the brain and also considering that the CSF usually reflects pathological changes in the brain, the CSF is an optimal source of pathophysiological markers^{5,7}. Currently, the main biological biomarkers employed in AD diagnosis are total Tau (Tau), the isoforms of phosphorylated Tau (P-Tau₁₈₁ and P-Tau₂₃₁) and β -amyloid peptide (A β ₄₂).

Some studies investigated the correlations between *antemortem* CSF biomarker levels (Tau, P-Tau and A β proteins) and AD-type neuropathologic changes in the brain^{6,8-10}. Data from these clinico-pathological studies showed that CSF levels of total Tau reflect the intensity of neuronal degeneration, while P-tau reflects tangle pathology. It has also been demonstrated that *antemortem* A β ₄₂ is inversely correlated with A β plaque counts at *post-mortem* examination⁹. Moreover, there is an inverse correlation between CSF A β ₄₂ levels and the overall retention of the amyloid tracer Pittsburgh compound B (PiB) with positron-emission tomography investigation^{11,12}.

These findings have been recently confirmed by a study that analyzed relationships between AD pathology in cortical brain biopsy and AD biomarkers in a series of 182 patients¹³, showing that the amount of amyloid plaques and hyperphosphorylated Tau in cortical brain biopsies are associated with low CSF A β ₄₂ and high CSF levels of Tau markers, respectively. It was also demonstrated a concordance of 94% between CSF markers and neuropathological diagnosis in a sample of patients from a memory clinic¹⁴.

Taken together, data from clinico-pathological studies support the view of CSF biomarkers as surrogate markers of the pathophysiological process of AD⁵.

SENSITIVITY AND SPECIFICITY OF CSF BIOMARKERS FOR ALZHEIMER'S DISEASE

During the last two decades, a multitude of studies has consistently demonstrated that AD patients exhibit a decrease in CSF A β ₄₂ and an increase in CSF Tau and P-tau when compared with healthy controls^{5,7,15}. Data provided by these studies confirm that each of these biomarkers differentiates AD patients from age-matched controls with 80-90% sensitivity and specificity^{5,7}.

The CSF A β ₄₂ levels are around 50% lower in AD patients than in aged-matched normal subjects¹⁶. The aggregation of A β protein in amyloid plaques and the consequent reduction of its availability in the CSF are the suggested mechanisms to explain the reduction of CSF A β ₄₂ levels in AD patients⁵. It should be noted, however, that a reduction of CSF A β ₄₂ levels may also occur in other diseases, such as Lewy body dementia, vascular dementia and cerebral amyloid angiopathy^{14,17,18}. Hence, although a decreased level of A β ₄₂ is characteristic of AD, it is not sufficient for an etiologic diagnosis of AD.

Tau is considered to be a non-specific marker of neuronal lesion associated to a variety of biological processes⁷. In AD patients, total Tau CSF levels are about three times higher than in age-matched controls¹⁶. Isolated high total Tau protein levels can also be detected in other acute neurodegenerative diseases and brain lesions, such as head trauma, stroke, and in Creutzfeldt-Jakob disease^{5,7,14}. On the contrary, P-Tau protein (subtypes P-Tau₁₈₁ and P-Tau₂₃₁) is the most specific biomarker of AD, being normal in non-AD diseases, including those in which Tau protein levels may be increased, such as Creutzfeldt-Jakob disease and stroke¹⁴.

It is well established that the best accuracy in the differential diagnosis between AD patients and controls is obtained with the combined analysis of two or more of the three main AD CSF markers (total Tau, P-Tau and A β ₄₂). Association of A β ₄₂ with Tau or P-Tau improves both sensitivity and specificity of AD diagnosis when compared to any of the markers alone. The value of the combined approach of CSF biomarkers was demonstrated by a study with neuropathological confirmation of the diagnosis, which showed that the ratio P-Tau/A β ₄₂ has a sensitivity of 91.6% and a specificity of 85.7% for AD diagnosis⁶. In order to consider the combined analysis of biomarkers, some ratios have been proposed, as the Innostest Amyloid-Tau Index (IATI), defined by the ratio $A\beta_{42}/(240+1.18 \times \text{Tau})$ ^{19,20}, the AD-CSF-Index²¹, and the ratios Tau/A β ₄₂ and P-Tau/A β ₄₂. An IATI score inferior to 1 has been proposed as suggestive of AD but, given the high prevalence (31%) of control subjects without cognitive impairment with this profile²², this cut-off does not seem to be specific.

CSF BIOMARKERS IN THE PRODROMAL STAGE (PRE-DEMENTIA) OF ALZHEIMER'S DISEASE

The pathophysiological process of AD starts decades before the clinical onset of the disease, with a gradual loss of synapses, axons and neurons that progress before the appearance of the first cognitive symptoms, most often episodic memory impairment²³. The dementia that characterizes the severe stage of the disease is thus preceded by a clinical phase in which the patients present memory impairment in an intermediate degree between age-matched normal controls and patients fulfilling clinical criteria for AD. This symptomatic prodementia phase is characterized by a preserved autonomy and may be referred as mild cognitive impairment (MCI)²⁴.

During the last decade, large cohort studies have consistently shown that an AD biomarker profile distinguishes with high accuracy (up to 95% sensitivity) MCI patients who will progress to AD from healthy controls and from MCI patients who will remain cognitively stable during the follow-up. These longitudinal studies showed that “MCI-converters” have a biological profile characterized by low $A\beta_{42}$ associated with high levels of CSF total Tau and P-Tau, while “MCI-stable” patients have a normal biomarker profile^{22,25-27}. Taken together, these data support the validity of CSF markers for identifying incipient AD among patients with mild cognitive impairment⁵. These patients with objective memory deficit, preserved autonomy and an AD signature at CSF analysis may be referred as “prodromal AD”²⁸.

Besides prodementia stages of AD, abnormalities on CSF measures can be eventually observed in subjects without cognitive complaints^{22,23}, which is in line with the current knowledge on AD pathophysiology. According to it, the first clinical symptoms of AD are preceded by a long pathophysiological process. It should be noted, however, that the accumulated data from clinical studies do not allow the assumption of progression from normal cognition to AD in asymptomatic subjects with any specific biomarker of AD²⁹. Therefore, at this time, the concept of “preclinical AD” is restricted only for research, and cannot be translated into a recommendation for the clinical practice²⁹.

THE PROGNOSTIC VALUE OF CSF BIOMARKERS

A series of studies investigated whether CSF biomarkers are correlated to clinical and imaging markers of AD severity. Data from a longitudinal study suggested that low $A\beta_{42}$, elevated Tau level and high Tau/ $A\beta_{42}$ are predictive of a faster cognitive decline during a follow-up of one year³⁰. Patients with extreme alterations in CSF biomarkers ($A\beta_{42}$ reduction and increased total Tau and P-Tau) appear to progress unfavorably, with a more severe cognitive decline, poor

response to anticholinesterase treatment and higher mortality³¹. CSF markers may also be useful to identify subgroups of AD patients with distinctive clinical and neuropsychological profiles which may be associated with more severe cognitive impairment^{32,33}.

Neuroimaging studies with structural brain MRI have also reported a significant positive correlation between the increased levels of Tau markers (total Tau and P-Tau) and the severity of hippocampal atrophy³⁴⁻³⁹. High levels of CSF total Tau and P-Tau seem also to be related to a faster progression of hippocampal atrophy³⁶⁻³⁸.

These data suggest that CSF markers may be predictive of the clinical severity in specific groups of AD patients. These findings, however, need further validation.

CSF BIOMARKERS FOR THE DIFFERENTIAL DIAGNOSIS BETWEEN ALZHEIMER'S DISEASE AND OTHER DEMENTIAS

The analysis of CSF biomarkers has been increasingly employed in the differential diagnosis between AD and other dementias^{14,40-44}. Data from different centers consistently confirmed that the combined analysis of the CSF biomarkers provides the best accuracy in the differential diagnosis between AD and other degenerative dementias^{14,40,42}. Particularly, the P-Tau/ $A\beta_{42}$ was the best biomarker for differentiating AD from the behavioral variant of frontotemporal lobar degeneration and from semantic dementia, with a sensitivity of 91.7% and 98.3%, respectively, and a specificity of 92.6% and 84.2%, respectively⁴². These results in terms of performance for the differential diagnosis between AD and frontotemporal lobar degeneration are in agreement with previous findings showing a specificity of 96.6% in a series of patients with diagnostic confirmation either by genetics or by *post-mortem* examination⁴⁰.

CSF biomarkers are also useful for identifying patients with focal atypical presentations of AD. In contrast to the typical amnesic profile “of the hippocampal type”, atypical focal forms of AD include non-amnesic focal cortical syndromes⁴⁵, such as posterior cortical atrophy (PCA), logopenic aphasia and the frontal variant of AD^{28,46-50} which exhibit characteristic histological lesions of AD-type pathology at *post-mortem* examination. For instance, AD-type pathology is the retained diagnosis in more than 80% of PCA cases at *post-mortem* examination^{46,51} and in almost 60% of patients with primary progressive aphasia (PPA)^{52,53}. In these groups of patients, data on biomarker assays are consistent with the pathological studies, as it was observed that 60% of PCA patients (9/15) and 61.5% (16/26) of aphasic subjects had an AD biological profile, with both altered Tau/ $A\beta_{42}$ and P-Tau/ $A\beta_{42}$ ratios⁴². Moreover, a concordance between CSF markers and amyloid imaging with PiB was reported

in a group of patients with PCA⁵⁴. Also interestingly, in a series of 34 patients with PPA who underwent both brain perfusion SPECT and lumbar puncture for CSF biomarkers, two distinct brain perfusion profiles were observed: PPA patients with an AD CSF profile presented a perfusion pattern similar to that observed in logopenic aphasia, and those PPA patients without an AD CSF biomarker profile showed a brain perfusion pattern similar to that has been described in semantic dementia⁵⁵. Indeed, other studies demonstrated that logopenic aphasia is associated with significant PiB uptake, while semantic dementia and non-fluent aphasia do not exhibit amyloidosis on molecular imaging^{56,57}, in agreement with the classification of logopenic aphasia as a focal variant of AD, and non-fluent APP and semantic dementia as language variants of frontotemporal lobar degeneration⁵⁸. AD pathology may also be observed in patients with behavioral presentation mimicking behavioral variant of frontotemporal lobar degeneration, the so-called frontal variant of AD^{46,48,59}.

Taken together, these data support using CSF biomarkers for identifying AD pathology in patients with atypical presentations. By identifying an underlying AD pathology in these patients, CSF biomarkers are useful as

their positivity may reorient the diagnosis and, hence, the therapeutics¹⁴.

FINAL REMARKS

The development of CSF biomarkers of AD led to a new diagnostic definition of the disease. The use of biological markers in association with the clinical approach opens the possibility to establish a diagnosis of AD before the dementia stage, differently from the previous National Institute of Neurological and Communication Disorders and Stroke - Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria⁶⁰. The core clinical criteria remain the main landmark of the diagnosis of AD in the clinical practice, but biological evidence provided by CSF increases the specificity of the diagnosis. By using CSF markers, it is now possible to establish an etiological diagnosis *in vivo*, which enables identifying patients at pre-dementia stages of the disease and patients with atypical focal presentations of AD⁵². This is crucial in the perspective of new disease-modifying drugs that will tackle specific pathophysiological targets.

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