BIOMARKERS OF ALZHEIMER'S DISEASE

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Introduction. Twenty years ago, there was not much discussion on if, or why, there is a need of biomarkers for Alzheimer's disease (AD). At that time, "probable AD" was diagnosed using the exclusion criteria published in 1984 by the Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association. Further, the diagnosis could not be set until the patient had reached the relatively advanced stage of clinically overt dementia. At that time, no biomarkers (e.g., amyloid PET scans or CSF tests amyloid-β (Aβ) or tau) for positive identification of AD pathology were available, so this was the only possible way to make the diagnosis.

Following the development of the first methods to measure the core AD cerebrospinal fluid (CSF) biomarkers total-tau (T-tau), phosphorylated tau (P-tau) and the 42 amino acid form of amyloid-β ($A\beta_{42}$), there has been an enormous expansion of this scientific research area. Today, it is generally acknowledged that these biochemical tests reflect several central pathophysiological features of AD and contribute diagnostically relevant information, also for prodromal AD. In this article in the 20th anniversary issue of the Journal of Alzheimer's Disease, we review the AD biomarkers, from early assay development to their entrance into diagnostic criteria.

The aim. To consider the significance of biomarkers of Alzheimer's disease for early diagnosis of the pathology.

Materials and methods. Information material was used (experimental articles, data of practical medicine) on traditional and new biomarkers of Alzheimer's disease and their determination methods.

Research results. One important component of AD pathologic change and pathophysiology is synaptic dysfunction and degeneration. Synapses are the central communication units in the neuronal networks the brain. Synapses consist of a pre-synaptic domain, where synaptic vesicles that contain the neurotransmitters that are released upon activation are located. Neurotransmitter release is a process regulated by a delicate machinery of specific pre-synaptic proteins. After release to the synaptic cleft, neurotransmitters bind to post-synaptic receptors at the dendritic spines and activate a cascade of molecular events to advance the neuronal signal. Synaptic dysfunction and degeneration are likely the direct cause of the cognitive deterioration in AD.

A large body of literature supports a marked degeneration and loss of synapses in grey matter regions in AD, also in the early disease stages. Importantly, severity of synaptic loss is more tightly correlated with degree of cognitive impairment than either plaque or tangle counts, and synaptic degeneration has been suggested as the best anatomical correlate of cognitive deficits in AD. Further, experimental animal studies suggest that both Aβ fibrils and diffusible Aβ oligomers may disturb dendritic spines by distinct mechanisms. In addition, tau hyperphosphorylation and microglia activation may also contribute to spine loss. Thus, synaptic biomarkers in CSF may serve as tools to explore this important aspect of AD pathophysiology in man, and to examine the link between effects on AD molecular pathology and cognitive symptoms by novel drug candidates with disease-

modifying potential. Synapses are plastic structures in the brain and, potentially, synaptic markers would change rapidly in response to successful treatment.

After developing novel monoclonal antibodies to measure neurogranin by ELISA, high CSF levels were found to predict prodromal AD in MCI. High CSF neurogranin in AD dementia and prodromal AD has been confirmed in several subsequent papers, including in the ADNI study. High CSF neurogranin also correlates with future rate of hippocampal trophy measured by MRI and rate of metabolic reductions on FDG-PET. Interestingly, a recent study suggests that high CSF neurogranin may be specific for AD, and not found in other neurodegenerative disorders such as frontotemporal dementia, Lewy body dementia, Parkinson's disease, progressive supranuclear palsy, or multiple system atrophy. A recent large study confirms that increased CSF neurogranin levels is found in AD dementia and prodromal AD, but not in other neurodegenerative disorders such as frontotemporal dementia, Lewy body dementia, Parkinson's disease, progressive supranuclear palsy, corticobasal degeneration, or amyotrophic lateral sclerosis

Conclusions. The last 20 years have seen an enormous expansion in research on fluid biomarkers for AD. The core AD CSF biomarkers T-tau, P-tau, and Aβ42 (and Aβ42/40 ratio) have been evaluated in hundreds of clinical neurochemical studies with extraordinary consistent results, showing high diagnostic accuracy both for AD dementia, but importantly also for prodromal AD. These biomarkers have undergone a phase of standardization and new assay versions on fully automated instruments show excellent analytical performance. The core AD biomarkers are today part of research diagnostic criteria, and we foresee an increased use of these diagnostic tests in clinical routine practice. The AD CSF biomarker toolbox has been expanded with novel biomarker reflecting additional aspects of AD pathology, such as synaptic dysfunction.

We envision further validated assays reflecting other pathologies common in age-related neurodegenerative disorders, e.g., Lewy body and TDP-43 pathology, reaching the stage of clinical applications in the coming years, so that CSF biomarkers can be part in a personalized medicine approach to the clinical evaluation of patients with cognitive disturbances. Last, we hope that blood biomarkers may be implemented as screening tools in the first-in-line clinical evaluation of this group of patients.