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Dementia-2014: Neurochemical dementia diagnostics for the early diagnosis of Alzheimer's disease: State-of-the art and the perspectives

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Neurochemical Dementia Diagnostics (NDD) is a routine diagnostic tool in the evaluation of the patients with cognitive impairments, such as those with Alzheimer?s disease (AD). Currently, two groups of biomarkers analyzed in the cerebrospinal fluid (CSF) are taken into consideration: amyloid ? (A?) peptides and Tau proteins, along with the hyperphosphorylated forms of the latter (pTau). The analyses of these two groups of biomarkers can reveal pathologic alterations as early as twenty years before the onset of the clinical symptoms. In mild cognitive impairment (MCI), NDD can reliably predict which persons are at risk to convert to AD. The role of biomarkers of amyloid ? deposition in the brain tissue (including the CSF concentrations of A?42), as well as the biomarkers of neurodegeneration (including the CSF concentrations of Tau/pTau proteins), is reflected in the currently proposed diagnostic criteria for AD and MCI. Current further directions in the development of NDD include: (a) search for novel biomarkers with improved analytical or diagnostic performance, (b) optimization of the analysis of the biomarkers already available (for example, by improved quality control and inter-laboratory comparison of results), (c) applications of novel technologies enabling better management of patients samples, for example application of multiplexing technologies, and (d) search for biomarkers in the blood.

Neurochemical biomarkers for diagnosing dementias principally rely on the soluble correlates of well known neuropathological features that characterize the underlying neurodegenerative diseases. This provides the unique chance to detect and track the disease even though clinical signs may not be observed. The probable diagnosis of neurodegenerative disorders is mainly based on clinical criteria, while definite diagnosis can only be made by neuropathological examination. Misdiagnosis is a frequent problem of clinical dementia diagnostics during the patient's lifetime; consequently neurochemical biomarkers for diagnosing dementias have gained enormous importance within the last decade.

The neuropathological hallmarks of AD are senile plaques and neurofibrillary tangles. Since their first microscopic description, proteomic analyses from postmortem brain tissue have increasingly clarified the molecular composition of these structures. Aggregated forms of amyloid-β peptides and hyperphosphorylated tau protein form senile plaques and neuro fibrillar tangles (NFTs) respectively.

The diagnostic value of these biomarkers for AD, especially regarding separation from nondemented controls (NDCs), has been proven in numerous studies with sensitivities and specificities of 80–90% [Blennow, 2004]. Accordingly, the characteristic concentrations of these biomarkers have been added as supportive attributes to the revised diagnostic criteria for AD.

Neurochemical biomarkers for diagnosing dementias are currently under intensive investigation and the field is rapidly expanding. The main protagonists and the best defined among them are cerebrospinal fluid levels of Aβ42, tau and its phosphorylated forms (p-tau). In addition, novel cerebrospinal fluid biomarkers are emerging and their multiparametric assessment seems most promising for increasing the accuracy in neurochemical dementia diagnostics. The combined assessment of Aβ42 and p-tau has recently shown value for diagnosing prodromal states of Alzheimer's dementia, that is, mild cognitive impairment. Disease-specific biomarkers for other degenerative dementias are still missing, but some progress has recently been made. As lumbar puncture is an additional burden for the patient, blood-based neurochemical biomarkers are definitely warranted and promising new discoveries have been made in this direction. These diagnostic developments have implicit therapeutic consequences and give rise to new requirements for future neurochemical.

Aggregated Aβ peptides, Aβ42 in particular, form the main part of the extracellular deposited amyloid plaques which are regarded as the central neuropathological attribute of AD [Glenner and Wong, 1984]. Aβ peptides emerge from the enzymatic processing of the β-amyloid precursor proteins (APPs) [Kang et al. 1987] through β and g secretases [Haass and Selkoe, 1993]. One of the possible physiological functions of the APP under discussion is a participation in the cell–cell and matrix interaction. The resulting Aβ peptides vary between 28 and up to 43 peptides amino acid length in their carboxyterminal appearance, while the aminoterminus can be shortened by two to ten amino acids. The aggregative potential of the Aβ peptides positively correlates with the length of their carboxyterminus and negatively with the length of the aminoterminus. A detailed analysis of amyloid-plaques' composition revealed an extensive rate of aminoterminally shortened Aβ peptides as well as the carboxyterminal endings 40 (x-40) and 42 (x-42). Moreover, the degree of posttranslational oxidation influences the aggregation characteristics of the peptides.

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