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Neurochemical approaches of cerebrospinal fluid diagnostics in neurodegenerative diseases

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Abstract

Alzheimer's disease (AD), Parkinson's disease dementia (PDD)/Lewy-body disease (DLB), and frontotemporal dementia (FTD) are the major causes of memory impairment and dementia. As new therapeutic agents are visible for the different diseases, there is an ultimate need for an early and an early differential diagnosis. Since cerebrospinal fluid (CSF) is in direct contact with the central nervous system (CNS), potentially promising biomarkers might be seen there first.

In principle, two research approaches can be considered for the laboratory diagnosis of dementias: (i) the direct detection of disease specific protein like Aβ-peptide–oligomers in AD or α-synuclein-aggregates in DLB and (ii) the detection of surrogate markers that show an altered pattern of expression in early stages of the disease or are used in the differential diagnosis of other dementias and thus enable an exclusion diagnosis. Especially Aβ-peptides and tau-protein measurements seem to employ a combination of these approaches.

Until now it was shown that a combined determination of just these few markers (tau-proteins and Aβ-peptides) is already sufficient to achieve a high degree of diagnostic certainty in the diagnosis of AD. However although these markers seem to correlate with neuropathological changes and memory disturbances, these markers are not specific for a single form of dementia and further research is necessary to improve especially the early differential diagnosis of dementias.

Keywords: Laboratory diagnosis; Mild cognitive impairment; AD; Non-AD dementia; Cerebrospinal fluid

1. Introduction

During the last century alone, the population has shown a staggering increase in its proportion of elderly citizens. All epidemiological studies of dementia show a strong correlation between prevalence and age: in the age group 60–64 years the prevalence is below 1%; it then doubles approximately every 5 years reaching a prevalence of about 30% among those 90 years or older. The average overall prevalence rate of dementia lies between 8% and 10% with 6–8% of the population having moderate and severe dementia [1–4]. This percentage is important in terms of social policy because these disease stages also coincide with the need for permanent care. Several studies have shown that about 90% of moderately and severely demented individuals require permanent nursing home care [5,6].

Up to now, the prevalence of subclinical cognitive deficits which are not yet pronounced enough to meet current criteria for dementia but which are clearly demonstrable during neuropsychological testing and predict a decline in daily living functions have not been extensively studied. These deficits are of interest, however, because in 70% of all cases mild cognitive impairment leads to dementia. Especially in such a situation biomarkers which reflect the status of the disease or give a risk status of developing a dementia are needed. Studies report a prevalence between 17% and 27% in the age group of those 65 years and older [5,7–9].

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The most frequent type of dementia is Alzheimer's disease, which accounts for 60–75% of all cases [1,2,10]. As a result of neuropathological studies, dementia of Lewy-body type (DLB)[1] or dementia associated with Parkinson's disease (PDD) is increasingly being discussed as the second most common form of degenerative dementia in old age, accounting for 20–35% of all cases [11–13]. However, large population-based epidemiological studies to confirm this hypothesis are not available at present. Frontotemporal dementia (FTD) is possibly the second most common form in patients below the age of 65 years.

The clinical diagnosis of AD still relies on the demonstration of a dementia syndrome and the exclusion of other causes of dementia. One of the most important and challenging clinical tasks in dealing with AD is the diagnosis and differential diagnosis in a very early preclinical stage of disease. In addition to a clinical investigation, multiple sources of information are used in the diagnostic process, principally neuropsychological assessment, structural and functional neuroimaging as well as biochemical and genetic variables.

Cross-sectional and population-based studies have clearly shown that careful neuropsychological investigation is very sensitive for detection of cognitive dysfunction in the early clinical stage of AD and may even reveal very mild cognitive impairment up to 5 years before the clinical diagnosis of dementia can be established according to contemporary diagnostic standards [14,15]. In typical Alzheimer's disease, first cognitive change usually occurs within the domain of episodic memory and impairment in acquiring new information.

Histopathologically, extracellularly located senile plaques and intracellularly located Alzheimer's fibrils (neurofibrillary tangles, NFT) are diagnostically compelling. The senile plaques consist largely of Aβ-peptides [16]. These are cleavage products of the amyloid precursor protein (APP), a cellular membrane protein. For the neuropathological diagnosis, so-called neuritic plaques are required in the vicinity of which pronounced microglial proliferation and activation is seen [17]. The NFTsconsist of hyperphosphorylated tau-protein monomers, which have merged into filament pairs wound into a double helix [18,19]. The extent of the plaquepathology is then classified according to CERAD (Consortium to Establish a Registry of Alzheimer's disease) and the extent of the tau pathology according to Braak [20–22].

The second most common dementia is the dementia with Lewy-bodies (DLB) and dementia associated with Parkinson's disease (PDD). DLB usually presents with a clinical picture characterized by progressive cognitive impairment, spontaneous parkinsonism, and neuropsychiatric symptoms. Memory deficits are the initial complaint in 60–70%. On formal neuropsychological assessment, patients with DLB present language and memory deficits similar to those with AD, but they also reveal a fronto-subcortical profile with significant impairment on attentional tasks, psychomotor speed with general slowing of thought, and visuspatial functions that may help distinguish them from patients with AD [23]. Typically a majority of patients present fluctuations in cognitive performance and alertness, either in the form of episodic confusional states resembling delirium or transient periods of reduced consciousness. About 80% of patients experience spontaneously arising persistent and complex visual hallucinations. The clinical picture progresses rapidly to dementia.

At present there is one criteria-based approach to the diagnosis of DLB, namely the Consensus criteria for clinical diagnosis of DLB [24–26]. It requires a progressive cognitive decline amounting to dementia, fluctuating cognition, recurrent visual hallucinations, and/or spontaneous parkinsonism in the absence of any other medical condition leading to dementia. Reported sensitivity rates varied from 0.22 to 0.75, and specificity from 0.79 to 1.0, which means that the consensus criteria are appropriate for confirmation of diagnosis but are of limited value in screening for DLB. PDD patients are by definition patients developing a dementia after at least 1 year of Parkinson's disease. However, neuropathologically PDD and DLB cannot be differentiated.

There are no specific structural brain imaging features for DLB. It may show generalized cerebral atrophy, sometimes with frontal predominance and a less pronounced medial temporal lobe and hippocampal atrophy than in AD [27]. Functional brain imaging usually shows diffuse cortical decrease in blood flow, respectively, glucose metabolism and significant hypometabolism in medial and lateral occipital cortex that may serve as a differentiation from AD [28].

Neuropathologically brains of patients with DLB show cortical atrophy to a lesser extent than seen in AD. The

[1] *Abbreviations used:* AD, Alzheimer's dementia; ApoE, Apolipoprotein E; APP, amyloid precursor protein; BBTS, buffer system Multiphasic buffer system consisting of bicine/bistris/tris/sulfate; CERAD, "Consortium to Establish a Registry of Alzheimer's Disease"; neuropathological criteria for a standardized evaluation of amyloid plaques; CJD, Creutzfeldt–Jakob disease; CSF, cerebrospinal fluid; DSM-IV, "Diagnostic and Statistical Manual of Mental Disorders, fourth Edition"; catalog of criteria for diagnosis; EEG, electroencephalogram; ELISA, enzyme-linked immunosorbent assay; FCS, fluorescence correlation spectroscopy; FFI, fatal familial insomnia; FTD, frontotemporal dementia; ICD-10, "International Classification of Disease"; WHO diagnostic catalog; IPG-2D-PAGE, two-dimensional (2D) electrophoresis by focussing in the immobilized pH gradient (IPG) and SDS–PAGE as the second analytical dimension; DLB, Lewy-body disease; MALDI–TOF, "Matrix-assisted laser desorption ionization mass analysis" with "time-of-flight modus"—method for determining the amino acid composition of peptides or proteins; MRI, magnetic resonance imaging; MSA, multisystem atrophy; NFT, neurofibrillary tangles; NSE, neuron-specific enolase; PBS, polybuffered saline; PET, positron emission tomography; PHF, paired helical filaments; RNA, ribosomal nucleic acid; sAPPα, soluble APP ectodomain after α-secretase splicing; SDS, sodium laurylsulfate (ionic detergent); SDS–PAGE/immunoblot, SDS–polyacrylamide gel electrophoresis with Western immunoblot; SPECT, single photon emission computed tomography; vCJD, new variant Creutzfeldt–Jakob disease; WB, SDS–PAGE/immunoblot; WHO, World Health Organization; CNS, central nervous system.