Biomarkers in the differential diagnosis of dementia

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Part 1: Cerebrospinal fluid (CSF) biomarkers in dementia

Chapter 2:

Perspectives of CSF biomarkers in dementia in the past, present and future
Valid diagnostic biomarkers are linked to neuropathology, be able to detect the disease early in its course and be able to distinguish it from other dementias, as well as being non-invasive and simple to use, inexpensive and not influenced by symptomatic drug treatment, with a sensitivity and specificity of more than 85%\textsuperscript{1}.

The first Alzheimer's disease (AD) cerebrospinal fluid (CSF) biomarkers were described more than two decades ago, using the ELISA methods, the INNOTEST assays for quantification of total-tau (T-tau), phosphorylated tau (P-tau) and amyloid-\(\beta\) (A\(\beta\))\textsuperscript{2,3}. In AD, increased levels of T-Tau and P-tau are found, together with a decreased A\(\beta\)42, what reflects the key elements of AD pathophysiology. This AD CSF profile has been validated in numerous subsequent papers with very consistent findings\textsuperscript{4}. High performance of the core AD CSF biomarkers for the diagnosis of prodromal AD is verified in several large multicentre studies such as the DESCRIPA study\textsuperscript{5}, the ADNI study\textsuperscript{6}, and the Swedish Brain Power study\textsuperscript{7}. The National Institute on Aging and Alzheimer’s Association (NIA-AA) working group has embedded the AD CSF biomarkers in their guidelines and clinical criteria of AD\textsuperscript{8}. Recently, the NIA-AA working group has defined AD as a pathological process, identified primarily by biomarkers grouped into amyloid-\(\beta\) deposition, tau pathology and neurodegeneration (A/T/N classification)\textsuperscript{9}.

CSF, with its matrix in proximity to the brain parenchyma and proteins secreted from the brain extracellular space, is accessible by lumbar puncture. The hypothesis of a decreased CSF A\(\beta\)42 with disease progression, is that the hydrophobic peptide aggregates and become sequestered in plaques, resulting in lower amounts remaining to be secreted to the extracellular space and CSF\textsuperscript{10}. CSF A\(\beta\)\textsubscript{1-42} and amyloid PET have been shown to be valuable measures of amyloid plaque pathology\textsuperscript{11} in inverse relation with lower CSF A\(\beta\)42 and higher positron emission tomography (PET) ligands binding to fibrillary A\(\beta\) in the brain\textsuperscript{12}. Although they are regarded as equal measures of amyloid plaques, they still show a mismatch in 6-21\% of MCI and dementia patients and in 17-21\% of cognitively healthy subjects\textsuperscript{13,14}. Is has been suggested this is due to different A\(\beta\) isoforms\textsuperscript{15}. A\(\beta\) isoforms present in CSF are A\(\beta\)\textsubscript{1-37}, A\(\beta\)\textsubscript{1-38} and A\(\beta\)40. A\(\beta\)40 is found around 10 times higher\textsuperscript{16} and is less diagnostic than A\(\beta\)42\textsuperscript{4}, although the CSF ratio A\(\beta\)42/A\(\beta\)40 has a higher performance to identify AD than single CSF A\(\beta\)42\textsuperscript{17}. CSF A\(\beta\)\textsubscript{1-37} and A\(\beta\)\textsubscript{1-38} were found to improve differentiation between AD and Fronto-temporal dementia (FTD) or dementia with Lewy bodies (DLB)\textsuperscript{18}. CSF T-Tau seems to reflect the intensity of neurodegeneration or severity of acute neuronal damage and is proposed as a non-specific ‘state marker’ of disease\textsuperscript{19}, predicting more rapid clinical disease progression\textsuperscript{20}. CSF p-Tau probably reflects the phosphorylation state of tau and is specific for AD\textsuperscript{21}. Recently, PET Tau-ligands has been developed to visualize Tau pathology, but the correlation with CSF Tau is still weak\textsuperscript{22}.

One limitation of the ‘core’ CSF biomarkers is the uncertainty how to interpret untypical biomarker patterns. Also, in late-onset AD the severity of neuropathological changes
varies and in higher ages, the level of changes overlaps with those found in cognitively unimpaired elderly\textsuperscript{23}. Another limitation of CSF biomarkers is the between-laboratory variability of 15-25\%, most pronounced for CSF Aβ\textsubscript{42}, according to the Alzheimer's Association quality control (QC) programme for CFS biomarkers\textsuperscript{24}. These differences may be caused by pre-analytical procedures (e.g. type of test tube for CSF collection or freeze-thaw schedule) or discrepancies in analytical- and/or manufacturing procedures between laboratories\textsuperscript{25}. Future developments for AD CSF biomarkers will be focus on fully automated laboratory analyser assays with stable and precise results between laboratories and the establishment of uniform cut-off values\textsuperscript{26}.

Another limitation is that a lumbar puncture is more invasive and CSF is less accessible than serologic markers. Blood brain biomarkers are a far more challenging matrix than CSF. This is caused by the facts that only a fraction of brain proteins enter the bloodstream. In addition, they may be degraded by proteases in the liver or cleared by the kidneys, and their measurement may be hampered by high levels of plasmaprotein\textsuperscript{27}. The recent technical developments of novel ultrasensitive immunoassays and mass spectrometry methods are promising for the development of new blood biomarkers\textsuperscript{26}. The technique is based on a single-molecule array (Simoa), with high analytical sensitivity (fg/ml) and reduced matrix interference\textsuperscript{28}.

Novel biomarkers focussing on additional aspects of AD pathology, such as synaptic dysfunction and degeneration, are called presynaptic biomarkers. Loss of synapses in grey matter regions of AD is correlated with the degree of cognitive impairment\textsuperscript{29}. Synaptic proteins in CSF are Synaptotagmin, rab3a, the presynaptic membrane protein SNAP-25 and the dendritic protein neurogranin\textsuperscript{30}. CSF Neurogranin, synaptotagmin-1 (SYT1) and SNAP-25 show promising results, but need validation in future studies\textsuperscript{31}. Neurofilament light (NF-L) is a Tau-independent CSF marker of non-specific general neuroaxonal degeneration\textsuperscript{32} and its increase is an inherent feature of AD, which predicts a more rapid disease progression\textsuperscript{33}. TREM2 (triggering receptor expressed on myeloid cells 2) is a CSF biomarker of microglial activation\textsuperscript{34}, recently reported in both dementia and MCI stages of AD and CSF TREM2 correlate with CSF Tau but not CSF Ab\textsubscript{42} concentrations, suggesting that microglial activation occurs in close connection with onset of neurodegeneration\textsuperscript{35}. The association of CSF sTREM2 with protective versus harmful microglial activation is presently unknown; longitudinal studies with repeated CSF samplings over time are needed to determine this\textsuperscript{36}.

Although CSF biomarkers can differentiate between AD pathology and other pathologies, there is still an absence of a specific CSF biomarker for other dementias. In case of FTD\textsuperscript{37}, neurofilament light has been identified as a promising biomarker candidate\textsuperscript{38}. For DLB, α-Synuclein was detected in cerebrospinal fluid (CSF)\textsuperscript{39} as potential biochemical biomarker for DLB, with conflicting results; Most studies showed lower CSF levels of total- α-Synuclein in PD and DLB compared to healthy controls and Alzheimer’s disease (AD), but other showed increased levels or no difference at all\textsuperscript{43}. The majority of the studies on biochemical biomarkers were cross-sectional, retrospective, and tested with
pathologically unproven subjects\textsuperscript{41,42}. Complicating methodological factors are the use of different antibodies and standard proteins in the immunoassays, patient selection, variation in pre-analytical processing and blood contamination from traumatic lumbar puncture\textsuperscript{40}. \(\alpha\)-Synuclein has different species in CSF and immunoassays for total \(\alpha\)-Synuclein (t-\(\alpha\)-syn) does not take into account its conformation or aggregation state. Early aggregated or soluble \(\alpha\)-Syn oligomers (o-\(\alpha\)-Syn) seems to be more neurotoxic and associated with PD and DLB neurodegeneration\textsuperscript{44}. Immunoassays for CSF o-\(\alpha\)-Syn is described to be a promising biomarker for the diagnosis band to monitor disease severity\textsuperscript{45}. Increased levels of soluble o-\(\alpha\)-syn are found in PD/ PDD and DLB patients, compared with other neurodegenerative diseases and healthy controls\textsuperscript{46}. Phosphorylated \(\alpha\)-Syn at serine 129 (pSer129-\(\alpha\)-Syn) is described as dominant pathological species of \(\alpha\)-syn in post mortem DLB\textsuperscript{43}, although pSer129-\(\alpha\)-Syn was not discriminative as CSF biomarker\textsuperscript{43}. \(\alpha\)-Synuclein in blood and saliva is investigated as potential biomarker, but did not differ between PD and healthy controls, neither correlate with CSF \(\alpha\)-Synuclein\textsuperscript{47,48}. Various research groups focus to identify ligands that have high \(\alpha\)-Synuclein potency and specificity as PET/SPECT ligands for imaging \(\alpha\)-Synuclein in vivo, but no suitable PET tracer has been reported yet\textsuperscript{49}.

The next two chapters are published articles (2010 and 2012) about CSF biomarkers (T-tau, P-tau and A\(\beta\)42, \(\alpha\)-Synuclein) and the potential to differentiate between AD and DLB.

References:


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