What is the future for CSF biomarkers in the prediction of cognitive decline and Alzheimer's disease?

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Alzheimer's disease (AD) is the most common form of cognitive disorder in the elderly, and is a major health problem. It is now 100 years since Alois Alzheimer presented the first report on the disease, and described the characteristic findings of plaques and tangles in the cortical areas of the brain. Although it took almost 80 years until the molecular composition of these pathological hallmarks was revealed, knowledge on the molecular pathogenesis of AD has grown rapidly during the last two decades.

Plaques are made of aggregated β -amyloid ($A\beta$), which is a small peptide produced from the much larger amyloid precursor protein (APP), while tangles are made of an abnormally hyperphosphorylated form of the microtubule associated protein tau. Details on the metabolic pathways and enzymes resulting in production of $A\beta$ from APP and the mechanism of $A\beta$ aggregation and toxicity, as well as the kinases and phosphatases balancing tau phosphorylation, are now well known [1]. Intense worldwide research efforts have also been undertaken to translate these advances into therapeutic strategies. As a result, several promising drug candidates with disease-modifying effects, such as $A\beta$ immunotherapy and secretase modulators, are now being tested in several clinical trials. The promise of therapy has also created a need for biomarkers to enable the clinical identification of the disease at an early stage. Early diagnosis will be of great importance since disease-modifying drugs are likely to be most effective in the earlier stages of the disease, before neurodegeneration is too severe and widespread.

Cerebrospinal fluid biomarkers

Since the cerebrospinal fluid (CSF) is in direct contact with the brain extracellular fluid, biochemical changes in the brain will be reflected in the CSF. CSF biomarkers for AD should reflect the central pathogenic processes in the brain. Candidate biomarkers for these pathogenic

processes include total tau ($T\text{-}\tau$) as a marker for the neuronal degeneration, $A\beta_{42}$ as a marker for plaque formation and phosphorylated tau ($P\text{-}\tau$) as a marker for tau hyperphosphorylation [2].

To obtain CSF, a lumbar puncture (LP) must be performed. This has made the implementation of CSF analyses in AD research more difficult, since LP may be regarded invasive and has been avoided due to fear of complications in the form of post-LP headache. However, the use of small-size needles and atraumatic techniques has reduced the risk of this complication, and several large prospective studies have shown that the incidence of post-LP headache is marginal in elderly with cognitive disturbances [3–5]. This has made CSF analyses a rapidly expanding research field, and has paved the way for the introduction of LP in clinical routine use [5].

CSF biomarkers for AD diagnosis

The three candidate CSF biomarkers $T\text{-}\tau$, $P\text{-}\tau$ and $A\beta_{42}$ have been extensively evaluated in numerous scientific studies. Very consistently, all studies have found a marked increase in both CSF $T\text{-}\tau$ and $P\text{-}\tau$ accompanied by a marked decrease in $A\beta_{42}$ in AD cases with dementia (for review see [2,6]).

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The diagnostic performance of these CSF biomarkers to discriminate AD from non-demented aged individuals is high, with sensitivity and specificity figures of 80–90% [2,6]. Normal CSF levels are found in several important differential diagnoses, such as depression and Parkinson's disease, and $P\text{-}\tau$ especially aids to differentiate AD from other dementias, such as fronto-temporal dementia and Lewy body dementia [7,8].

CSF biomarkers to identify incipient AD in mild cognitive impairment

Mild cognitive impairment (MCI) is an age-related syndrome characterized by mild memory impairment, which can be verified by objective

measures, but without other cognitive symptoms indicative of dementia [9]. MCI is an etiologically heterogeneous disorder; many MCI cases have incipient AD (i.e., have early AD pathology and will progress to AD with dementia), while others have a benign form of MCI related to aging and, in some MCI cases, cerebrovascular disease may contribute to the memory impairment [9].

Recent research efforts on CSF biomarkers have been directed to evaluate biomarkers to identify incipient AD in patients with MCI [2]. Initial studies showed that the combination of T- τ and A β 42 have a high predictive power to identify incipient AD in MCI cases [2]. Recent studies with extended clinical follow-up periods show that the combination of all three CSF biomarkers (T- τ , P- τ and A β 42) may have a predictive value as high as 95% to differentiate MCI cases with progression to AD from stable MCI cases and MCI cases with other types of underlying pathology [10].

CSF biomarkers to identify AD preclinically

Some studies have also examined if CSF biomarkers may be useful to predict AD at the pre-clinical stage, that is, in elderly without any cognitive symptoms. Two population-based studies have found a significant reduction in CSF A β 42 in cognitively normal elderly people that later developed dementia [11,12]. In the same material, there was no significant change in CSF T- τ or P- τ in individuals that later developed AD [12 & Skoog I *et al.*, Unpublished Data].

‘CSF biomarkers, especially CSF A β 42, may predict preclinical AD in cognitively normal elderly individuals.’

A recent clinical study also found that CSF A β 42, but not T- τ and P- τ , predict cognitive decline in the healthy elderly [13]. Another study based on a clinical patient sample showed that both the CSF T- τ :A β 42 ratio and the P- τ :A β 42 ratio predict cognitive decline with high confidence [14]. These data show that CSF biomarkers, especially CSF A β 42, may predict preclinical AD in cognitively normal elderly individuals.

CSF biomarkers in treatment trials

Identification of the clinical effect of a drug using rating scales requires large patient materials and extended treatment periods in a slowly progressive disorder such as AD, especially for disease-modifying drugs with a potential to slow down the degenerative process, but without any

direct effects on the symptoms. These new types of drugs are often evaluated on AD transgenic mice, but these animal models have a low predictive power for treatment efficacy in patients with sporadic AD [1]. To bridge the gap between animal studies and large clinical trials, and to help select the most promising drug candidates, short-term pilot studies using biomarker information to detect desired biochemical drug effects may be a valuable approach.

‘...CSF biomarkers may be valuable tools in future treatment trials on disease-modifying drugs in AD.’

Treatment trials with acetylcholine esterase (AChE) inhibitors may serve as a proof-of-concept for the potential of CSF biomarkers to identify and monitor the biochemical effect of a drug in AD. Such studies have found a marked increase in CSF AChE activity during treatment, which is dose-dependent and may be linked to both the mechanism of action for the drugs and the clinical outcome [15,16]. By contrast, there is no change in CSF T- τ , P- τ or A β 42 during treatment with AChE inhibitors [16,17]. These data suggest that an adequate CSF biomarker is capable not only of identifying the biochemical effect of drugs, but also to differentiate between different compounds in a clinically relevant manner.

The very low intraindividual variability of T- τ , P- τ and A β 42 levels in studies with longitudinal CSF samples during 6 months and 2 years [17,18] also paves the way for use of these markers in clinical trials. At present, it is uncertain how CSF A β 42 might react upon treatment with efficacious amyloid-targeting drugs in man [19]. However, studies in transgenic mice suggest that reduced CSF A β 42 levels are to be expected for γ -secretase inhibitors [20], and acute administration of the γ -secretase inhibitor BMS-299897 in guinea pigs was found to reduce all cortical, CSF and plasma levels of A β [21]. These data give promise that CSF biomarkers may be valuable tools in future treatment trials on disease-modifying drugs in AD.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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