CSF biomarkers and their role in Alzheimer's disease

DOI:- https://doi.org/10.62772/APFCB-News.2022.1.4

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Amid the continued ageing of the global population, Alzheimer's disease is a serious and rapidly growing public health concern. The Asia Pacific region alone is estimated to have over 23 million cases today, and that figure is projected to be more than 70 million cases by 2050 [1]. While much attention is currently on a new therapeutic intervention recently approved by the FDA, clinical lab diagnostics will also be essential for helping to manage this growing crisis.

What are CSF biomarkers?

Multiple studies have shown the value of 3 core cerebrospinal fluid (CSF) biomarkers — β-amyloid 42 (αβ42), total tau (T-tau) and phosphorylated tau (P-tau) — within the diagnostic process for Alzheimer's disease. αβ42 levels are detected at lower concentrations in CSF and this change can already be seen at least 5 years before Alzheimer's disease is even formally diagnosed [2]. T-tau and P-tau, both markers for neuronal loss, are consistently found at increased levels above baseline [3].

CSF can be obtained through a lumbar puncture and its contents are taken to be a direct reflection of the brain's environment. Even so, CSF biomarkers are not widely used currently for clinical diagnosis. To date, there has not been any formal consensus on the established cut-off levels for the CSF biomarkers, but great effort is underway to agree on these cut-off values. Given the change to several clinical guidelines, such as the National Institute of Aging and Alzheimer's Association (NIA-AA) assessment that an Alzheimer's disease diagnosis can now be biologically based regardless of presence and severity of symptoms [4], as well as an external quality control programme by the Alzheimer's Association [5], there may now be room for greater use of CSF biomarkers in a clinical setting. If approved, the use of CSF biomarkers can also be increased with automation, reducing human handling and error.

The benefits of a timely diagnosis

Alzheimer's disease almost always starts with mild overlooked symptoms such as moments of forgetfulness, something easily attributable to age. At this point, the patient is most likely experiencing subjective cognitive decline; cognitive functions may be impaired but this cannot be confirmed solely through clinical assessments.

The next phase in this continuum is mild cognitive impairment (MCI), whereby clinical evidence via neuroimaging can be found. As MCI is also found in other neurodegenerative disorders, CSF biomarkers help with differential diagnosis. Given the time lag between physiological changes and clinical symptoms and given that MCI is a risk factor for Alzheimer's disease, the use of CSF biomarkers for timely diagnosis can impact the patient's experience with Alzheimer's disease.

Prior to CSF biomarkers, diagnosis of Alzheimer's disease relied on neuroimaging such as amyloid PET scans to detect amyloid plaques in the brain, a hallmark of Alzheimer's disease. However, this method has its limitations, ranging from late diagnosis to inaccessibility of equipment and specialised personnel. This could explain why 50 – 70% of patients do not even receive a formal diagnosis.

A timely diagnosis could allow for a definitive detection of Alzheimer's disease [6], and for applying intervention therapies or enrolment in clinical trials [7]. Outside of the clinic, patients are well informed and are able to make decisions about their own future, from deciding future living options to making appropriate legal arrangements. A timely diagnosis could also inform how healthcare systems in a country shape their policies for decades to come.

Potential use as companion diagnostics

CSF biomarkers have been used in clinical trials for disease-modifying therapies (DMTs) that aim to intervene in the clinical progression of Alzheimer's disease [8]. To appropriately stratify eligible patients for clinical trials, CSF biomarkers (and PET scans) are performed as confirmatory tests to show presence of physiological changes. With an increasing number of biomarker assays and progress in standardisation, CSF biomarkers could broadly support key milestones in clinical trials. A downside may be that multiple lumbar punctures may not be well tolerated by a patient, which drives the need for further research into developing blood-based biomarkers as an alternative.

Many studies have raised the potential benefits of timely diagnosis, including opportunities for earlier treatment or earlier intervention with DMTs. With a pharmacological agent on the market, this theoretical benefit now has the chance to become a reality. The advent of a new drug could provide an impetus for more healthcare practitioners to embrace the use of biomarkers for a definitive Alzheimer's disease diagnosis in their patients.

References

1) Dementia in the Asia Pacific Region 2014 Report, Alzheimer's Disease International.

2) Buchhave, P. et al. (2012) Cerebrospinal Fluid Levels of β-Amyloid 1-42, but Not of Tau, Are Fully Changed Already 5 to 10 Years Before the Onset of Alzheimer Dementia. Archives of General Psychiatry, 69(1), pp98.

3) Olsson, B., et al. (2016) CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. The Lancet Neurology, 15, pp673-684.

4) Alzheimer's Disease Diagnostic Guidelines, Dementia Resources for Health Professionals, National Institute of Health.

5) The Alzheimer's Association QC program for CSF and blood biomarkers.

6) Dubois, B. et al. (2016) Timely diagnosis for Alzheimer's Disease, A Literature Review on Benefits and Challenges. Journal of Alzheimer's Disease 49, pp617-631.

7) Lleo, A. et al. (2014) Cerebrospinal fluid biomarkers in trials for Alzheimer and Parkinson diseases. Nature Reviews Neurology, 11, pp41-55.

8) Horgan, D. et al. (2020) Biomarker Testing: Piercing the Fog of Alzheimer's and Related Dementia. Biomedicine Hub.