Alzheimer's disease

Blood biomarkers for early diagnosis of Alzheimer's disease

Dr Veer Bala Gupta/ M.Sc. Ph.D.
Edith Cowan University, Joondalup , Western Australia

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The clinical symptoms of Alzheimer's disease (AD) occur decades before the pathology starts to appear. The classic hallmarks of AD are extracellular amyloid deposits and intracellular neurofibrillary tangles. More than 95% of AD patients suffer from the sporadic form of AD, however, there are well established genetic markers for early onset AD. The sporadic form of AD is known to have multifactorial aetiology and is influenced by various factors. Early prediction of AD is of great importance as the treatment strategies can be initiated early in the disease course. This becomes possible by detecting the disease much before the clinical symptoms become apparent by using AD biomarkers [1]. A biomarker is as an indicator of a disease process and the sensitivity and specificity of which are the most important factors that ultimately define the diagnostic utility of a biomarker. The evaluation of such reliable biomarkers is an important area of research in Alzheimer's disease and has led to the introduction of a diagnostic preclinical phase where the biomarkers are present in asymptomatic individuals [2].

Whilst there have been major advances in neuroimaging, in particularly amyloid beta (Aβ) imaging, its use as a routine diagnostic test is cost prohibitive. As such, attention has switched to the periphery and readily accessible biological material for AD biomarker research. Over recent years, cerebrospinal fluid (CSF) has been the major focus of proteomic biomarker discovery studies. However, CSF collection is a highly invasive procedure, hence difficult to implement in clinical routine and in clinical trials. Therefore, a strong interest exists for less invasive diagnostic approaches for AD such as blood derived biomarkers. An ideal AD blood biomarker should represent the associated pathological and biochemical changes occurring in the brain. AD blood biomarker research is still at an early stage of development and clinical evaluation before it can be integrated into clinical practice as a key diagnostic tool. The measurement and reliability of these blood biomarkers is limited by the physiology of blood brain barrier. Moreover, the biomarkers closely associated with disease pathology are found in very low concentrations in blood which is furthermore compromised by the complex biochemical nature of the fluid [3]. A major limitation with blood biomarker studies is the lack of reproducibility of the results.

The quest for finding biomarkers for AD started with studies involving a single biomarker such as, amyloid beta (Aβ) [4]. AD has a complex pathology involving several molecular pathways such as amyloid deposition, taupathy, oxidative damage, inflammation and metabolic changes. The markers of an underlying pathology in all these pathways can serve as markers for AD. There is definite need of a holistic approach in standardising these blood biomarkers for AD. Hence, it is crucial to investigate a panel of biomarkers to distinguish between healthy and AD participants and evaluating a broad range of proteins in different combinations.

Proteomics has gained the interest of researchers as a promising way to decode the biomarker mystery. However, a close interaction of various fields such as lipidomics, genomics and proteomics is required to achieve an optimal AD biomarker panel. This kind of "multi-omic" interdisciplinary approach will strikingly advance further biomarker discovery.

Further, different blood fractions may be appropriate to study particular sets of biomarkers because of the differences in the distribution of blood-based proteins. The source of the biomarker (plasma vs. serum) can have a large impact on the observed concentration of some proteins, including the ones that are of great interest to AD pathophysiology [5]. Recently, platelets are becoming increasingly popular in blood biomarker research because of their homogenous and compartmentalised nature. Both plasma and serum are very heterogenous in nature and have a complex and abundant pool of proteins such as albumin and IgG which can potentially interfere in achieving the required amount of sensitivity for the assay.

Researchers usually tend to use the general term "AD blood biomarker" for an early AD diagnosis; however there exists a huge need to have a separate set of signatures to identify different stages of AD such as pre-clinical, prodromal and clinical AD. A unique set of blood analytes is required to successfully predict the conversion of pre-clinical AD participants and also to differentiate controls from Mild cognitively impaired (MCI) progressors and the ones who do not progress to further cognitive decline. These set of biomarkers then should be validated against the other established clinical correlates such as t-

tau/Aβ42 ratio from CSF and neuroimaging, so that they can be integrated into the clinical practice. This will help in the speedy and accurate diagnosis of sporadic AD, and should be able to detect the disease progression, impact of therapeutic intervention, classification of different stages of AD and differentiating AD from other dementias.

The major benefit from a successful multiplex blood biomarker approach in AD would be to provide an inexpensive and minimally invasive diagnostic test capable of monitoring changes over time and responses to clinical interventions.

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