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Special Section: Blood-based biomarkers for Alzheimer's disease and related dementias

Blood-based biomarkers for Alzheimer's disease and related dementias: Keys to success and things to consider

During the last two decades, considerable progress has been made in the field of fluid and imaging biomarkers for neurodegenerative dementias. As a result, the most recent research and clinical guidelines (the National Institute on Aging and Alzheimer's Association, International Working Group 2, National Institute for Health and Care Excellence) incorporate cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers in the diagnostic criteria of dementia and mild cognitive impairment due to Alzheimer's disease (AD) [1–3]. However, as both CSF and amyloid PET examinations require expert knowledge and are of limited availability outside specialized memory clinics, there is no doubt that blood tests would be much easier to implement in clinical medicine and as screening tools when recruiting patients for clinical trials.

However, there are several issues, both biological and technical, with the measurement of biomarkers for neurodegenerative dementias in blood. First, a biomarker that has its origin in the central nervous system (CNS) has to cross the blood-brain barrier to be detected in the periphery, and if the concentration in CSF is low, it will be even lower in the blood. Second, if the biomarker is not specific for the CNS but also expressed in peripheral tissues, the contribution from the CNS will potentially be hard to detect, given the high biological background caused by non-CNS sources. Third, the broad dynamic range of the plasma proteome, which is dominated by plasma proteins, such as albumin and immunoglobulins, with only minute amounts of CNS-derived proteins, presents an analytical challenge [4]. Fourth, heterophilic antibodies may be present in blood, which may interfere in immunoassays [5]. Fifth, the analyte of interest may undergo proteolytic degradation by various proteases in plasma [6]. Sixth, clearance of the biomarker by the liver or the kidneys, diurnal variation, and plasma volume changes may introduce significant variability.

In spite of all these challenges, there has been considerable progress in the field. Ultrasensitive high-precision assays that allow for the accurate determination of a ratio of 42 to 40 amino acid-long amyloid β (Aβ42/Aβ40) can now detect cerebral β-amyloidosis (determined by amyloid PET) with 70–90% diagnostic accuracy [7–11], which is almost as good as the corresponding CSF test [12]. Serum or plasma neurofilament light (NfL) is emerging as a reliable biomarker for neurodegeneration and neuronal injury, irrespective of underlying cause [13]. Promising results also exist for plasma p-tau, measured using a sensitive immunoassay with electrochemiluminescence detection [14]. Several large replication studies, showing robust correlations of plasma p-tau concentration with CSF p-tau and amyloid PET results, were presented during the Alzheimer's Association International Conference 2019 with publications in preparation. Promising results have also been published in regards to multimarker plasma proteomic profiles that may be used to detect cerebral β-amyloidosis in AD [15].

How come this field has developed in such an unexpectedly good way? The most important explanation is probably improved analytical sensitivity and specificity of the biomarker assays. Recent technological breakthroughs now allow for biomarker measurements in the subfemtomolar concentration range. This means that small amounts of CNS-derived proteins can be isolated and quantified from the complex blood matrix in a reliable manner. The matrix can also be diluted to remove some of the interfering factors described previously. Much more attention has also been paid to preanalytical sample handling, and consensus protocols regarding this have been published [16,17]. Finally, it is essential to remember that modern biomarker research is now performed on much more well-characterized cohorts than only 5–10 years ago. The reference standard used to classify study participants nowadays often includes, in addition to careful clinical examination, advanced neuroimaging and molecular markers of AD pathology. Researchers are increasingly making sure that their control group is amyloid free, whereas the AD group is amyloid positive using amyloid PET or the CSF Aβ42/Aβ40 ratio. In addition, from a basic technical point of view, many of the blood tests now

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contain blockers of heterophilic antibodies. From both a research and a clinical standpoint, the variation of many candidate blood biomarkers for neurodegenerative dementias is also carefully examined now, taking into account kidney and liver function, body constitution, and diurnal variation.

This special issue of *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring* is a follow-up on the article series on blood biomarkers for AD published 3 years ago [18]. The rationale to develop another special issue on this particular topic stems from the enormous research intensity in the field. In this special issue, we present the reader with articles on single and multiplexed biomarkers targeting different neurodegenerative pathologies, including traumatic brain injury and dementia with Lewy bodies. Although the majority of the manuscripts in this issue are reflecting on tau- and Aβ-related processes, we also include novel compelling findings focused on complement proteins and work reflecting fields of lipidomics and metabolomics.

We have every reason to believe that the blood-based biomarker toolbox will undergo further expansion during the coming years and move toward clinical implementation. There is a lot more work to be performed, however, particularly regarding biomarkers for non-AD neurodegenerative diseases. We anticipate seeing such markers emerging during the coming years, and hopefully, these will facilitate drug development and allow for efficient drug selection and dose finding, once we have disease-modifying drugs to prescribe.

Henrik Zetterberg[a,b,c,d,*]
Liana G. Apostolova[e,f,g,h]
Peter J. Snyder[i]
[a]Department of Psychiatry and Neurochemistry
Institute of Neuroscience and Physiology
The Sahlgrenska Academy at the University of Gothenburg
Mölndal, Sweden
[b]Clinical Neurochemistry Laboratory
Sahlgrenska University Hospital
Mölndal, Sweden
[c]Department of Neurodegenerative Disease
UCL Institute of Neurology
London, United Kingdom
[d]UK Dementia Research Institute at UCL
London, United Kingdom
[e]Department of Neurology
Indiana University School of Medicine
Indianapolis, IN, USA
[f]Department of Radiology and Imaging Sciences
Center for Neuroimaging
Indiana University School of Medicine
Indianapolis, IN, USA
[g]Department of Medical and Molecular Genetics
Indiana University School of Medicine
Indianapolis, IN, USA
[h]Indiana Alzheimer Disease Center
Indiana University School of Medicine
Indianapolis, IN, USA
[i]Ryan Institute for Neuroscience
University of Rhode Island
Kingston, RI, USA
*Corresponding author. Tel.: +46 31 3430025; Fax: +46 31 419289.
E-mail address: henrik.zetterberg@clinchem.gu.se

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