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Development of Blood-Based Biomarkers for Diagnostic and Monitoring of Alzheimer's Disease

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Abstract

Alzheimer's is the most prevalent form of age induced dementia in modern societies as a neurological disease. Dementia is a rising socio-economic and medical issue with increasing life expectancy. The effect of Alzheimer's disease, including age, sex (females are most likely affected), genetic factor, head injury and Down syndrome has been correlated with several factors. By 2050, the number of people 80 years of age or older would be projected at about 370 million in the world and 50% of people 85 years of age or older suffer from Alzheimer's disease. The disorder is distinguished by the buildup of extracellular amyloid β plaques, neurofibrillary tangles consisting of truncated and phosphorylated protein tau, dystrophic neurites, synapse and neuronal losses, and prominent Gliosis involving changes in morphology and function of astrocytes and microglia.

Keywords: Blood-based biomarkers • Diagnostics • Blood-brain barriers

Introduction

Considering the high prevalence of the disorder, alternatives such as blood-based biomarkers would represent a major development, even like screening tools to assess who should be referred for particular trials to the memory clinic, far from routine testing in general practise. Measurement of biomarkers for blood brain diseases faces a range of challenges requiring responsive and precise testing and thorough confirmation. The blood-brain barrier, which prohibit molecules from free transiting between the central nervous system and blood compartments, usually have brain dependent biomarkers at relatively low levels in the blood. Moreover, some of the Alzheimer's disease pathology-related biomarkers are expressed in non-cerebral tissues, which may confuse their blood measurements. In addition, heterophilic antibodies may also be found in the blood, which can show false high or low results. Therefore, biomarker tests aimed at one pathological alteration and biomarker panels which can represent tissue responses to these modifications will be helpful.

Blood based targeted biomarkers

In early plasma Aβ results described in the database of Alz-Biomarker showed no consistent variation in either Aβ42 or Aβ40 plasma in Alzheimer's disease. This result was primarily due to test-related difficulties; the measurements for plasma Aβ could be affected by matrix effects (mainly other plasma proteins that bind Aβ), and the analytical sensitivities of the first experiments could not minimise such matrix effects. An ultrasensitive Single molecule array (Simoa) test for Aβ42 has been published in 2011 [1]. In the dementia stage of Alzheimer's disease, plasma tau concentrations are elevated relative to cognitively normal control persons, assessed with ultrasensitive measures, but not as clearly than in the well replicated Cerebrospinal Fluid. The application of these results to intermediate participants in the mild cognitive impairment stage of the disease has no clarification with less consistent studies. However, in the most up-to-date paper Mielke and his collaborators explored the correlation between plasma t-tau, which had been identified by Simoa, and the cognitive deterioration of 458 participants in the Mayo Clinic Study on Aging [2]. The plasma neurofilament light (NfL) is a well-replicated biomarker for neurodegeneration of Alzheimer's disease. It is an intra-axonal structural protein that leaks into body fluids in an axonal injury regardless of cause Serum- or NfL plasma concentrations are strongly correlating with Cerebrospinal Fluid NfL and are increased by neurodegenerative conditions in many non-Alzheimer's diseases, and both in sporadic and familial Alzheimer's diseases [3].

Blood-based panels as biomarkers

Panels of markers have been suggested to surpass single candidate markers to diagnose, predict and characterise AD. For the classification of the disease and its pathology, multiple multivariate blood-based biomarker panels have therefore been suggested. A wide range of studies illustrate the successful use of multivariate protein marker panels in stratifying situations [4]. Blood-based biomarker panels are designed to estimate disease-related phenotypes, such as cognitive impairment, atrophy of the brains, neocortic Aβ deposition, following case-control studies. Both inflammatory marker and supplementary cascade proteins have been shown to have cognitive performance correlations, cognitive impairment and clinical progression.

Biomarker panels of miRNA

The area of epigenetics, with micro RNA (miRNA) gene regulation, is one such subject for biomarker discovery as well. miRNAs are transported in liposomes, HDLs, exosomes and other proteins that shield miRNA from degradation. The first panel report of 12 miRNAs can discriminate Alzheimer's disease against the controls with 93 percent accuracy. The panel was also able to identify AR patients with accuracies of 74 to 78 percent from Mild cognitive impairment, multiple sclerosis, parkinsonism, severe depression, schizophrenia and bipolar disorder. Additional trials of the panels of miRNAs revealed discrimination of 75 and 95 percent between Alzheimer's disease patients and controls. Nagaraj and his colleagues include a recent analysis of miRNAs as Alzheimer's disease biomarkers whereby 136 individual miRNAs between Alzheimer's disease and the control states in literature have been significantly altered [5].

Metabolomics

Recent developments, combined with a high-performance liquid/gas chromatography of the magnetic resonation and mass spectroscopy, allowed thousands of metabolites to be evaluated dynamically and represent functional networks of downstream genome shift, transcriptome and proteome. The two most influential metabolites were glycerophosphocholin and D-glucosaminide and metabolic changes in plasma that showed a distinction between controls and AD were also recorded. Another trial showed different

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metabolites in MCI participants who did not progress to AD over the next 2 years with a 2.4-dihydroxybutanoic acid motivated directly by this result [6].

Discussion and Conclusion

The field is gradually moving closer to the search of blood biomarker in AD as instruments are made more sensitive for the quantification of blood biomarkers and for the understanding and implementation of standardisation processes in the field of the sample processing. These changes tend to have shifted in recent literature to include single candidate metrics, which were also the subject of investigations from 10 to 15 years ago, away from multiplexed evaluation that was common around 5 years ago. Plasma Aβ42/Aβ40 ratio, tau and NfL are the markers most promising as the markers for AD, but promising evidence on new panels can reflect responses in tissue to AD-related diseases also exists. In order to understand their merits as potential screenings, diagnostic, monitoring or prognostic markers of the disease, replication and further studies are therefore needed.

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