Where we are on the journey of Alzheimer’s biomarker development?

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Alzheimer’s disease (AD), a complex progressive neurodegenerative disease that is pathologically characterized by amyloid-beta (Aβ) plaques and neurofibrillary tangles (NTFs). Over several decades, AD biomarkers to detect these pathological hallmarks have been developed using cerebrospinal fluid (CSF) reflecting pathological changes in the brain. Aβ accumulation and neuronal loss in the brain during AD development lead to lower CSF Aβ and higher total tau and p-tau181, respectively. In 2010, the use of typical CSF biomarkers (i.e., CSF Aβ1-42, total tau and p-tau181) were incorporated in the diagnostic criteria for research. However, CSF AD biomarkers have several disadvantages for clinical application, including invasiveness of lumbar puncture. Furthermore, the measurement of CSF AD biomarkers using manual immunoassay platforms showed large inter-laboratory variability, which leads to the recent development of fully-automated immunoassay platforms and kits. In this presentation, we discuss the current efforts to encourage clinical application of CSF AD biomarkers by using fully automated immunoassay. In Koreans, we observed that CSF AD biomarkers measured by manual and automated immunoassay platform show strong intercorrelated agreement with Aβ-PET imaging. The Korean-specific Aβ-PET-based CSF biomarker cutoffs measured by automated immunoassay strongly predict progression of cognitive decline, which will provide the clinical utility of CSF AD biomarkers from fully-automated immunoassay platform. In addition, we discovered amyloidogenesis-associated plasma micro-RNAs (miRNAs) in Koreans, although the clinical diagnostic utility was limited. The selected miRNAs in plasma and in plasma extracellular vesicles showed activated Aβ production in neuronal cells and regulated the amyloidogenesis-associated target mRNAs. In summary, the clinical diagnostic utility from fully automated immunoassay platforms should be further evaluated in larger, more diverse cohorts for clinical application. miRNAs in blood compartment will be good candidates for development of non-invasive AD biomarkers and therapeutic strategies against AD.

Keywords: Alzheimer’s disease, Biomarker, Cerebrospinal fluid, micro-RNA, Amyloidogenesis