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Short Communication

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The value of neuroimaging and biochemical markers in characterizing and identifying preclinical Alzheimer's disease

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The pathophysiological changes of Alzheimer's disease (AD) begin decades before the onset of clinical symptoms. AD, characterized by progressive and inevitable impairment of memory and other cognitive fields, has been considered as a long continuum including the stages of preclinical AD, mild cognitive impairment (MCI) due to AD and AD dementia. Given the vast loss of neuron and widespread brain atrophy in the stage of dementia, the opportunity of diagnosis and intervention should be focused on the prodromal AD and even the asymptomatic stage, such as preclinical AD. Preclinical AD, as a long process without specific clinical phenotype, may provide a critical phase for treatment targeting AD-related pathology and further monitoring of therapeutic effects.

Amyloid cascade hypothesis is thought to be associated with Alzheimer's pathologies (AP). The disrupted equilibrium involving production and elimination of Aβ oligomers initially contributes to the accumulation of soluble amyloid species, probably leading to the following neurodegeneration (e.g. abnormal tau, synaptic dysfunction, neuronal loss) and cognitive impairment. The National Institute on Aging and the Alzheimer's Association (NIA/AA) has proposed a conceptual framework and operational research criteria for preclinical AD based on the above-mentioned pathophysiological model, which suggests that Aβ accumulation becomes abnormal first. However, converging evidence shows that amyloidopathy is necessary but not sufficient to directly correlated with the appearance of AD clinical symptoms. Previous postmortem studies have investigated that some individuals with the pathophysiological features of AD may not have objectively cognitive decline during their lifetime. Furthermore, cognitive dysfunction closely in parallels with progressive worsening of neurodegeneration rather than Aβ accumulation and it is likely that only Aβ accumulation plus synaptic dysfunction and/or neurodegeneration constitute the critical link to the occurance of cognitive impairment. Taken together, the presence of just one biomarker responsible for AD may not trigger the characteristic clinical phenotype. Currently, Dubois et al. redefined the term of preclinical AD, indicating that both amyloid and tau pathology are necessary for further conversion to clinical AD, while an isolated amyloidopathy or tauopathy without any clinical symptoms only refers to a situation at risk for AD.

With the application of biomarkers derived from the cerebrospinal fluid (CSF) or neuroimaging, it is likely to identify individuals with high likelihood of developing AD at the asymptomatic stage. Various biomarkers could provide insight into the pathological information from different aspects to improve our understanding of AD. Biomarkers in the CSF are considered to have the ability to predict clinical evolution from the preclinical stage to the phase of AD dementia. Among individuals with subjective cognitive decline (SCD), who report great memory complaints without meeting the criteria for MCI recognized by standardized tests of cognitive performance, those with the pathological CSF ratio (Aβ42/phosphorylated-tau) like AD have more possibility to convert to dementia. Moreover, reduced concentrations of Aβ42 in the CSF are strongly related to increased Aβ deposition in the brain, which can be shown via the retention of special tracers using positron emission tomography (PET). For example, Snitz and colleagues found that individuals with greater cognitive complaints had significantly increased brain Aβ deposition in frontal, lateral temporal and parietal cortices than healthy controls. However, the limitations of above methods are relatively invasive and radioactive. Therefore, exploring noninvasive, economical and convenient biomarkers is of great benefits to promote the clinical application.

Recently, multimodal magnetic resonance imaging (MRI), including structural MRI, functional MRI and diffusion MRI, has attracted extensive attention due to its noninvasiveness and high resolution. For instance, there are evolving evidences that individuals categorized with SCD present a great similarity to a typical AD gray matter pattern, affecting initially the hippocampus and entorhinal cortex. Besides, topographically similar hippocampal subfield changes, especially in the lateral part (CA1) have been found in both SCD and AD patients. Moreover, in the longitudinal studies of SCD subjects, smaller hippocampal volume has been shown to exhibit the predictive power of future conversion to AD. Although there are similar structural changes like AD in the preclinical stage, structural MRI is just a promising technique for staging of high risk of progression. Diffusion MRI is another technique mirroring the white matter structural alterations. Current studies showed that widespread white matter damages represented by decreased fractional anisotropy (FA), increased mean diffusivity (MD) and increased radial diffusivity (RD) were reported in the SCD group and the FA values were between healthy controls and MCI patients.

Approximately 90% of AD occurs sporadically and multiple factors, such as cognitive reserve, apolipoprotein E (APOE), the cooccurrence

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of age-related brain diseases and environmental influences, may modulate the ultimate presence of AD clinical symptoms. Therefore, in the future, clinical trials focusing on the Aβ-modifying therapies ought to target the early pathological processes in the preclinical stage of AD and also take into comprehensive consideration above various influence factors.