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Alzheimer disease biomarkers: Facing the complexity

Early clinic-pathological studies demonstrated that the two cardinal lesions associated with Alzheimer disease (AD), neuro brillary tangles (NFT) and amyloid deposits, have a di erential impact on cognition both at early and late stages of the neurodegenerative process. In contrast to ß-amyloid (Aß) deposition that occurs di usely in the human brain over 60 years of age, NFT formation follows hierarchical schemes of regional and cellular vulnerability a ecting rst the entorhinal cortex and parahippocampal formation before moving in adjacent neocortical association areas. Long before the emergence of nove imaging techniques, it was clear that Aß deposits correlate very weekly with cognition and downstream neurodegenerative biomarkers. In contrast, NFT and associated synaptic loss is strictly related to the loss of cognitive functions not only at late but also at early stages of AD. e last decade was characterized by the exponential increase of knowledge in the eld of AD predictive biomarkers and, most importantly, characterization of tracers for ß-amyloid (Aß). It is now widely acknowledged that amyloid deposits in positron emission tomography (PET) with Pittsburg compound B (PiB; a marker of Aß brillar deposits) precede dementia by 5-10 years, and PiB burden inversely correlates with concentration of Aß42 in the cerebro-spina uid. However, increased PiB burden was reported in nearly 20% to 30% of controls in the general population pointing to the fact that Aß deposition is not su cient to cause cognitive decline in AD. Moreover, the rate of Aß accumulation is not related to neurodegeneration at baseline and only 8% of controls display both decreased hippocampal volume and increased Pi signal. According to Jack's model, all of the aforementioned markers become positive well before dementia onset, and the one related to amyloid pathology already reach their plateau at the time of rst cognitive de cits. More recently, selective tau tracers became available for clinical research. Although a PiB equivalent is not yet ready for tau imaging, the recent development of ta tracers with higher selectivity, reduced non-speci c binding and improved tracer kinetics compared to the rst molecules raise increasing expectations among the scienti c community. Given the tight association between tau deposition, cognition and neurodegeneration, and unlike Aß imaging, tau imaging will be essential for assessing disease progression. Furthermore, the may help to resolve the controversy about the temporal sequence of tau pathology in AD. e new diagnostic criteria by Dubois and collaborators consider that the development of tau pathology, at least under its brillar forms, is a late phenomenon in AD dependent, at least partly, on the Aß deposition in prodromal states. Recent contributions showed that tau-related markers (but also structural MRI changes) might become positive in the absence of PiB deposits mainly in preclinical cases. Ultimately, tau imaging will provide the tool to change the landscape and explore whether or not presymptomatic administration of anti-Aß therapy impacts on the progression of tau pathology that determines the clinical expression of AD.

Biography

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