Alzheimer's disease: from pathology to therapeutics

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ABSTRACT

Amyloid β peptides are the most characteristic neuropathological protein deposited in the brains of patients with Alzheimer's disease, which is implicated in its pathogenesis and deemed as the prime target for the disease-modifying therapy. In this talk, the molecular pathology of Alzheimer's disease, the most frequent cause of dementia in the elderly and often linked to traffic accidents, will be discussed in relation to the efforts to develop mechanism-based therapeutics for this devastating disease.

Deposition of amyloid β peptides (Aβ) as senile plaques is the most characteristic neuropathological feature of Alzheimer's disease (AD), which is implicated in its pathogenesis and deemed as the prime target for the disease-modifying therapy (DMT) [1] (Figure 1). Aβ deposition is determined by the production and clearance. Aβ is produced by sequential proteolytic cleavages by β- and γ-secretases. γ-Secretase, harboring presenilins (PS) as the catalytic center, forms the C terminus of Aβ that determines its propensity to aggregate: missense mutations in PS genes cause familial AD by altering the preferred γ-secretase cleavage sites in a way to increase production of pathogenic Aβ42 species [2,3]. γ-Secretase forms a hydrophilic pore within the membrane lipid bilayer, which enables the unique mode of intramambrane proteolysis to form Aβ, and inhibitors of β- and γ-secretases with different targets and mode of action are being developed. Aβ immunotherapy facilitates the clearance of Aβ from brain parenchyma through the activities of anti-Aβ antibodies with different characteristics. Efforts to clinically develop the DMTs for AD, including establishment of imaging and fluid biomarkers that surrogate the AD pathology through clinical studies like AD Neuroimaging Initiative (ADNI) and Japanese ADNI are currently underway.

J-ADNI was started in 2008, aiming at conducting a longitudinal workup of standardized neuroimaging, biomarker and clinico-psychological surveys [4] (Figues 2). The research protocol was designed to maximize compatibility with that of US-ADNI, including structural magnetic resonance imaging analysis for the evaluation of brain atrophy, fluorodeoxyglucose and amyloid positron emission tomography, cerebrospinal fluid sampling, *APOE* genotyping, together with a set of clinical and psychometric tests that were prepared to maximize the compatibility to those used in the North America. Japanese ADNI has recruited 545 participants (239 amnestic mild cognitive impairment (MCI), 152 normal aged and 154 early AD). A number of significant results, including the predictive values of amyloid markers (i.e., amyloid PET and CSF Aβ42) for conversion of MCI to AD, are being obtained and analyzed. ADNI activities world-wide will establish the rigorous quantitative descriptions of the natural course of AD in its very early stages. The data, as well as the methodologies and infrastructures, will facilitate the clinical trials of disease-modifying therapies for AD using surrogate biomarkers that will enable the very early treatment of AD, which will further be supported by J-ADNI2 focusing on preclinical AD population as well as early and late MCI.

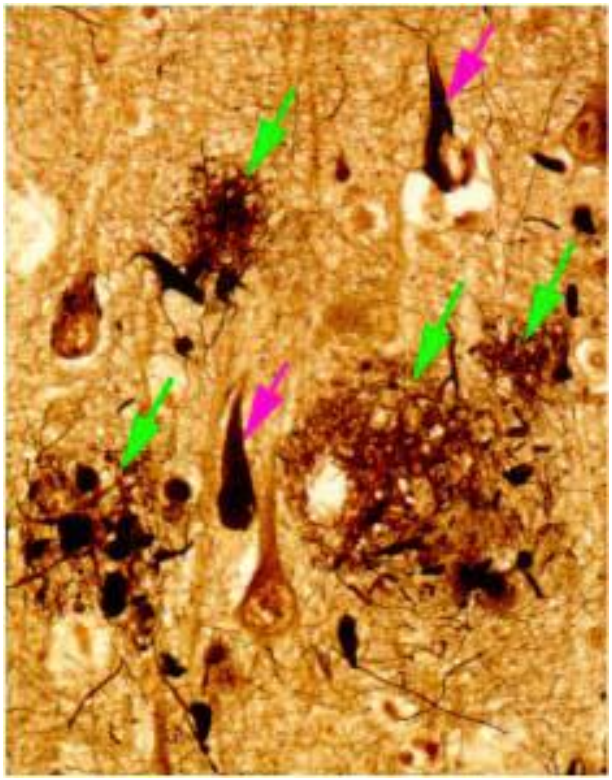

Figure 1. Neuropathology of Alzheimer's disease Green and pink arrows denote senile plaques (amyloid deposits) and neurofibrillary tangles, respectively.

AD and other types of dementias sometimes cause traffic accidents by wrong-way driving. Current status as well as causes of this type of traffic accidents will also be discussed.

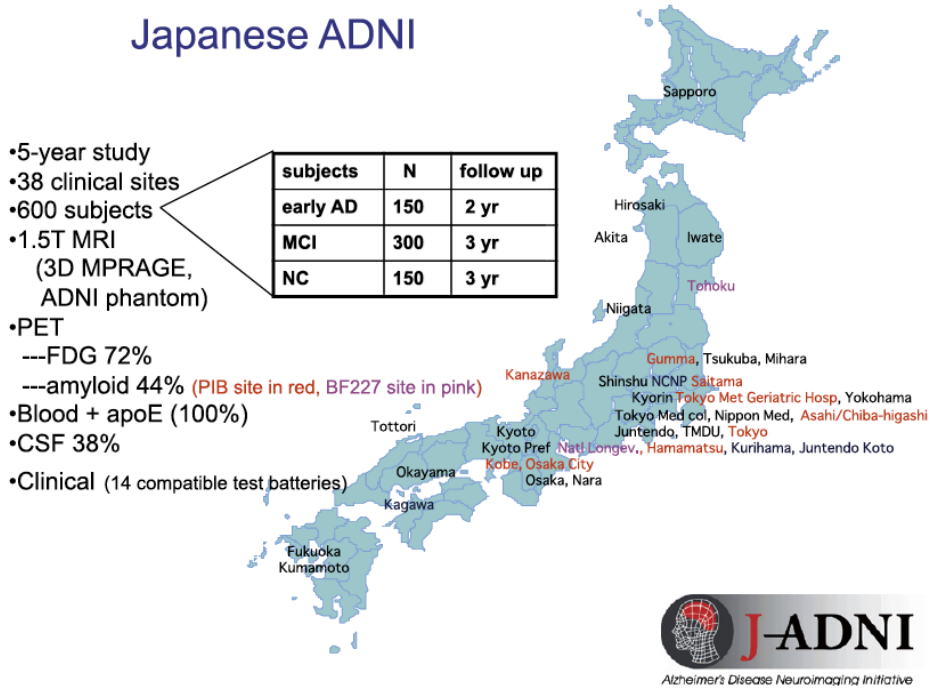

Figure 2. Overview of J-ADNI

References

[1] Iwatsubo T et al. ***Neuron*** (1994) **13**: 45-53
[2] Tomita T et al. ***Proc Natl Acad Sci USA*** (1997) **94**:2025-2030
[3] Takasugi N et al. ***Nature*** (2003) **422**: 438-441
[4] Iwatsubo T ***Alzheimer Dement*** (2010) **6**: 297-299