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Editorial

Alzheimer's Disease Research in Japan: A Short History, Current Status and Future Perspectives toward Prevention

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Alzheimer's disease and Dementia is endemic in Japan

A recent report from the Hisayama study, a representative regional cohort in Japan, showed that the lifetime risk of dementia in the Japanese elderly population has exceeded 50%, in which >50% of all dementia cause is comprised by Alzheimer's disease (AD) (1). The total number of individuals with dementia in Japan is more than >5 million, and the global costs of dementia is estimated to exceed 14.5 trillion yen (equivalent to ~133 billion USD). Thus, there is an urgent and compelling need for the prevention of dementia, especially that of AD.

As an introduction to the excellent pieces of papers on AD prevention featured in this special issue, here we try to briefly overview the history, current status and future perspectives of AD research in Japan.

Dawn of the molecular neuropathology of AD in Japan

A milestone discovery that brought about a breakthrough in AD research dates back to mid 1980s: Yasuo Ihara and Nobuyuki Nukina identified hyperphosphorylated species of tau as an integral component of paired helical filaments in AD brains (2). This finding boosted the progress in molecular neuropathology of tau protein in Japan, ranging from the clinical and neuropathological studies of amyotrophic lateral sclerosis and parkinsonism-dementia complex uniquely observed in the Kii peninsula, which shares common features to that of Guam (3), to the development of a series of tau-oriented fluid and PET biomarkers (4-6).

Next came the molecular characterization of amyloid β peptides (Aβ), especially that of Aβ that initially get deposited in amyloid plaques of AD brains (7). The invention of sandwich ELISAs making use of antibodies that selectively discriminate the C-terminal extent of Aβ opened up venues for the development of plasma-based Aβ biomarkers (8,9), as well as characterization of unique APP mutations affecting the Aβ aggregation (10). Finally, the identification of presenilin polypeptides as the determinant of Aβ42 overproduction (11) led to the structure-function analyses of the presenilin complex that represents the catalytic subunit of γ-secretase (12).

Delineating the AD trajectories toward disease-modification: J-ADNI and A4 studies

As the pathomechanisms of AD are being elucidated, establishing methods to detect the progression of AD in its early stages (e.g., mild cognitive impairment; MCI) in a multicenter trial setting using neuroimaging and fluid biomarkers, and building up a database delineating the natural history of the early stage of AD, have become paramount toward the ultimate goal of precise evaluation of the efficacy of disease-modifying therapies (DMTs). For this purpose, AD Neuroimaging Initiative (ADNI) has been conducted in North America since 2004, which has set a firm basis for the current global clinical trials of AD. In 2007, the Japanese (J-) ADNI study was launched as a multicenter, longitudinal observational study using an almost identical protocol to ADNI's. J-ADNI was successfully concluded in 2014, making the J-ADNI database obtained from 537 individuals with AD, MCI, and normal cognition available for worldwide data sharing (13). Notably, profiles of decline in cognitive or functional measures in the prodromal AD population in J-ADNI and North American ADNI were remarkably similar, supporting the feasibility of bridging of clinical trials in prodromal AD between Asia and western countries (13). Also, J-ADNI sample repository has provided researchers with precious resources including genome; in this issue, Mano and colleagues have clearly shown that peripheral blood BRCA1 methylation positively correlated with the major Alzheimer's disease risk factors in the J-ADNI participants (14).

The second stage of J-ADNI (J-ADNI2/AMED preclinical AD study) was planned to focus on the preclinical (asymptomatic) and prodromal AD stages with biomarker verification of AD pathology. Senda and colleagues show the PET and biomarker profiles of the preclinical and prodromal cohort; importantly, this study represents the first academic multicencer tau-PET study

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in Japan utilizing flortaucipir as a tracer (15).

Currently, the anti-amyloid treatment in asymptomatic AD (A4) study is being conducted in 1169 preclinical AD participants from North America, Australia and Japan as a double-blind, randomized trial for 4.5 years using solanezumab as a prevention drug candidate, and the screening, pre-randomization data have been shared for research (16). Making use of the ADNI, J-ADNI and A4 screen data, Sato and colleagues propose a novel approach to predict preclinical AD (17). In view of the forthcoming series of preclinical AD trials using new AD DMTs (e.g., the AHEAD study), a method for efficiently recruiting individuals with preclinical AD is mandatory. To this end, we have started a collaboration with the Trial Ready Cohort for the Prevention of AD (TRC-PAD) in the US, and launched a trial ready cohort for preclinical AD in Japan, by combining a web-based, screening registry (J-TRC webstudy) and an in-person longitudinal study implementing cognitive assessments by Preclinical AD Cognitive Composite (PACC), amyloid PET (either by florbetapir or flutemetamol) and blood testing (J-TRC onsite study). Sato and colleagues have employed machine learning models fitted to the A4 screen data, to predict the amyloid PET results from the J-TRC webstudy data (18). Such an attempt will facilitate and ensure the effective recruitment of preclinical AD participants toward the upcoming prevention trials.

Non-pharmacological intervention into the lifestyle and modifiable risks

In addition to the pharmacological intervention approaches using DMTs in the early stages of AD, multi-domain interventions targeting modifiable risk factors for dementia in the lifestyle of older adults as evidenced by epidemiological studies is attracting enormous attention, since the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) has demonstrated that a multidomain lifestyle intervention (i.e., dietary counseling, physical exercise, cognitive training, and vascular risk monitoring) as a large randomized controlled trial can ameliorate cognitive decline in older adults at increased risk of developing dementia (19). In 2019, Arai, Sakurai and colleagues at the National Center for Geriatrics and Gerontology in Aichi have initiated the Japan-Multimodal Intervention Trial for Prevention of Dementia (J-MINT) as a member of the WW-FINGERS Network, sponsored by the Japan Agency for Medical Research and Development and the Ministry of Economy, Trade and Industry, Japan, aiming to verify whether multi-domain intervention consisting of management of vascular risk factors, group-based physical exercise and self-monitoring of physical activity, nutritional counseling, and cognitive training, could prevent the progression of cognitive decline in the Japanese elderly population (20). Another unique feature of the J-MINT trial is that the implementation of relevant interventional measures is led by private sectors, headed by SOMPO care Inc.

Successful interventions into the life-style to prevent cognitive decline and dementia in humans readily elicit reverse-translational approaches to elucidate the mechanism whereby metabolic stress aggravates AD pathophysiology in model animals. Wakabayashi and colleagues have characterized the effects of diet-induced insulin resistance on amyloid pathology (21), and shown that diet-induced and age-related endoplasmic reticulum stress can be attenuated by the administration of tauroursodeoxycholic acid, a chemical chaperone compound applicable to humans (22). Such an interplay between the translational and reverse-translational studies will facilitate the development of effective combinatorial interventions that retards the symptomatic and pathophysiological progression of cognitive decline in the elderly.

Future perspectives on the social implementation of research outcomes on dementia

The original contributions published in this special issue represent the favorable combinations of basic and clinical, as well as pharmacological and non-pharmacological approaches aiming at preventing AD and dementia, that are currently underway in Japan. Lastly, we would like to emphasize that the optimal coordination of the academic activities with different disciplines, often with those of private sectors, has been supported by the unique scholarly activities of the Japan Society for Dementia Research, the principal academic society on dementia comprised of a wide variety of members, e.g., from neurology, psychiatry, geriatrics, basic and social sciences. Development of prevention therapies on AD and dementia is a huge task on humans of the 21st century, which should involve multiple sectors, i.e., academia, industry, government, non-profit organizations, society, and individuals threatened to cognitive decline, under the spirit of public-private partnership, toward the ultimate goal of reducing the burden of cognitive decline on human being.

Conflict of interests: The author declares there are no conflicts.

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