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Featured Article

Japanese and North American Alzheimer's Disease Neuroimaging Initiative studies: Harmonization for international trials

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Abstract

Introduction: We conducted Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI) and compared the basic characteristics and progression profiles with those of ADNI in North America.
Methods: A total of 537 Japanese subjects with normal cognition, late amnestic mild cognitive impairment (LMCI), or mild Alzheimer's disease (AD) were enrolled using the same criteria as ADNI. Rates of changes in representative cognitive or functional measures were compared for amyloid positron emission tomography- or cerebrospinal fluid amyloid β(1–42)-positive LMCI and mild AD between J-ADNI and ADNI.
Results: Amyloid positivity rates were significantly higher in normal cognition of ADNI but at similar levels in LMCI and mild AD between J-ADNI and ADNI. Profiles of decline in cognitive or functional measures in amyloid-positive LMCI in J-ADNI (n = 75) and ADNI (n = 269) were remarkably similar, whereas those in mild AD were milder in J-ADNI (n = 73) compared with ADNI (n = 230).
Discussion: These results support the feasibility of bridging of clinical trials in the prodromal stage of AD between Asia and western countries.

Keywords: Alzheimer's disease; ADNI; Mild cognitive impairment; Biomarker; Amyloid PET imaging; Harmonization; Japan

1. Background

The significance of neuroimaging and fluid biomarkers in the early diagnosis and prediction of clinical progression during the very early stages of Alzheimer's disease (AD)

[1]The full membership of the Japanese ADNI investigators is listed at https://humandbs.biosciencedbc.jp/en/hum0043-j-adni-authors.

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has been highlighted [1], as pathogenic molecules causative to AD (e.g., amyloid β [Aβ]) were discovered, and therapeutic strategies against the neurodegenerative process of AD (i.e., disease-modifying therapies [DMTs]) have been developed [2]. Because of the recent failures in large-scale clinical trials of DMTs in AD patients at the dementia stage [3–5], the target population of DMT trials is being shifted to earlier stages, i.e., mild cognitive impairment (MCI) [6] or even the asymptomatic stage (i.e., preclinical AD [7]), where the clinical progression is expected to be slower, and the drug efficacies harder to evaluate.

To develop methods to detect the progression of AD in its early stages (i.e., MCI and mild AD) in a multicenter trial setting using neuroimaging (e.g., positron emission tomography [PET] scan, magnetic resonance imaging [MRI]), and biomarkers (e.g., cerebrospinal fluid [CSF]) and establish a database delineating the natural history of the early stage of AD, AD Neuroimaging Initiative (ADNI) has been conducted in North America since 2004. ADNI has firmly established the basis for the current global clinical trials of DMTs for AD in its prodromal and mild stages [8].

A dramatic increase in the elderly population and those suffering from AD is also a common and imminent issue in Asian countries, especially Japan, where patients are already being involved in global clinical trials for AD DMTs. However, there have not been any large-scale observational studies of the early stages of AD including MCI in the Asian population, which has its own ethnic characteristics (e.g., lower prevalence of apolipoprotein E (*APOE*) ε4 alleles [9], difference in language and cultures). Furthermore, to validate the ADNI data obtained primarily in Caucasian populations in the United States, a replication of the ADNI study in a second cohort, especially in a non-Caucasian population, has long been awaited. To this end, we initiated the Japanese (J-) ADNI study, closely discussing the harmonization of the protocol and procedures with the ADNI core members from 2006. We launched J-ADNI as a multicenter, longitudinal observational study using an almost identical protocol to ADNI's in 2008. We have recently made publicly available the J-ADNI database obtained from 537 individuals of AD, MCI, and normal cognition (CN), supported in a database (National Bioscience Database Center, Japan) available for worldwide data sharing. In this article, we describe the basic characteristics and clinical progression profiles of the J-ADNI population and compare the data with those of ADNI to determine if any differences exist between the Japanese and North American populations with the goal of international harmonization for clinical trials of DMTs for AD.

2. Methods

2.1. J-ADNI participants

Approval for the J-ADNI study protocol (UMIN000001374) was obtained from the local ethics committees or institutional review committees at the 38 participating clinical sites, including the principal investigator's site (The University of Tokyo). Informed written consent was obtained from all participants at each clinical site.

To characterize the clinical, neuroimaging, and biomarker measures in subjects with CN, late amnestic MCI [6] (LMCI), or mild AD in the Japanese elderly population, volunteer participants between the ages of 60 and 84 years fluent in Japanese were diagnosed and enrolled using generally identical inclusion and exclusion criteria to those of ADNI [10]. Briefly, the subjects with LMCI or AD both had memory complaints, whereas CN had none. On Mini–Mental State Examination (MMSE), the range for CN and LMCI was 24–30 and for AD, 20–26 (all are inclusive). The Clinical Dementia Rating (CDR) global score for CN was 0, LMCI was 0.5 (memory domain 0.5 mandatory), and the rating for AD was 0.5 or 1. Delayed recall of the Logical Memory IIA subscale of the Wechsler Memory Scale-Revised was used for a memory criterion with cutoff scores based on education: For CN subjects, ≧9 for 16 years of education, ≧5 for 10–15 years, and ≧3 for 0–9 years. For subjects with LMCI or AD, Logical Memory IIA scores were ≦8 for 16 years of education, ≦4 for 10–15 years, and ≦2 for 0–9 years. The subjects with LMCI had to be largely intact with regard to general cognition and functional performance and could not meet diagnostic criteria for a dementia diagnosis, thus they were classified as single- or multi-domain amnestic MCI. J-ADNI did not recruit participants with early MCI, so this ADNI group was excluded from analysis. The subjects with mild AD had to satisfy the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable AD [11]. Psychoactive drugs were prohibited or restricted as defined in the protocol, and exceptions were approved and recorded. The participant should have Hachinski Ischemic Score of ≦4, and should not be depressed (Geriatric Depression Scale score ≦6). Of 715 people assessed for eligibility, 537 met criteria and were enrolled (Fig. 1).

At baseline, the following cognitive and functional measures based on the National Alzheimer's Coordinating Center Uniform Data Set, as used in ADNI, were examined: Digit Span, Category Fluency, Trail Making A and B, Digit Symbol Substitution Test of the Wechsler Adult Intelligence Scale III, Boston Naming Test, Clock Drawing Test, Neuropsychiatric Inventory-Q, AD Assessment Scale-Cognitive Subscale (ADAS-Cog), and Functional Assessment Questionnaire (FAQ). Audio-Visual Learning Test was not performed in J-ADNI. Participants who were CN or MCI were evaluated every 6 or 12 months for 36 months, and those with AD for 24 months, as in ADNI. Clinical conversion from LMCI to dementia was primarily diagnosed by clinical site investigators at every visit and verified by an adjudication committee.

All subjects received a structural MRI scan at 1.5 Tesla signal strength based on three-dimensional magnetization-