ELSEVIER

Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring ■ (2016) 1-10

Alzheimer's & Dementia

Neuroimaging

Association between Aβ and tau accumulations and their influence on clinical features in aging and Alzheimer disease spectrum brains: A [^{11}C] PBB3-PET study

Hitoshi Shimada[a,*], Soichiro Kitamura[a], Hitoshi Shinotoh[a,b], Hironobu Endo[a,c], Fumitoshi Niwa[a,d], Shigeki Hirano[a,e], Yasuyuki Kimura[a], Ming-Rong Zhang[f], Satoshi Kuwabara[e], Tetsuya Suhara[a], Makoto Higuchi[a]

[a]*Department of Functional Brain Imaging Research (DOFI), Clinical Research Cluster, National Institute of Radiological Sciences (NIRS), National Institutes for Quantum and Radiological Science and Technology (QST), Chiba-shi, Chiba, Japan*
[b]*Neurology Chiba Clinic, Chiba-shi, Chiba, Japan*
[c]*Division of Neurology, Kobe University Graduate School of Medicine, Kobe-shi, Hyogo, Japan*
[d]*Department of Neurology, Kyoto Prefectural University of Medicine, Kyoto-shi, Kyoto, Japan*
[e]*Department of Neurology, Graduate School of Medicine, Chiba University, Chiba-shi, Chiba, Japan*
[f]*Department of Radiopharmaceuticals Development, Clinical Research Cluster, NIRS, QST, Chiba-shi, Chiba, Japan*

Abstract

Introduction: Amyloid-β (Aβ) and tau accumulations may occur independently and concurrently as exemplified by primary age-related tauopathy and Alzheimer disease (AD), respectively. Interactions between Aβ and tau accumulations and their influence on clinical features, however, are still unclear.
Methods: Associations among clinical symptoms, gray-matter volume, regional tau, and Aβ deposition assessed by positron emission tomography with [^{11}C]pyridinyl-butadienyl-benzothiazole 3 and [^{11}C]PiB were evaluated in 17 AD, 9 mild cognitive impairment due to AD, and 28 PiB(−)-cognitive healthy controls (HCs).
Results: High tau burden was associated with aging and low-level education in PiB(−)-HC and AD-spectrum groups, and with high Aβ burden and low-level education in all subjects. It was not Aβ but tau accumulation that showed significant associations with cognitive performance even in PiB(−)-HC.
Discussion: The present study indicated aging and low-level education after Aβ would be enhancers for tau pathology, associated with neurodegeneration and cognitive impairment in healthy and diseased elderly individuals.

Keywords: Tau; Amyloid; Brain atrophy; Cognitive decline; Biomarkers; Alzheimer disease; MCI; Preclinical; Dementia; Aging; Cognitive reserve; Positron emission tomography; [^{11}C]PBB3; [^{11}C]PiB

1. Background

Senile plaques and fibrillary tau inclusions are neuropathological hallmarks of Alzheimer disease (AD) [1]. As represented by the "amyloid cascade" hypothesis [2], one of the most accepted models of the pathogenesis of AD, it has been considered by many that amyloid-β (Aβ) plays key roles in disease initiation and progression and that it would be a promising target for therapy and imaging. In fact, Aβ imaging by positron emission tomography (PET) has brought about major developments in dementia research and clinical trials. Aβ imaging enables us to make accurate differential diagnosis [3,4], predict disease progression [5], build a better understanding of the pathogenesis [6–9], and

*Corresponding author. Tel.: +81-43-263-8555; Fax: +81-43-253-0396.
E-mail address: shimada.hitoshi@qst.go.jp

http://dx.doi.org/10.1016/j.dadm.2016.12.009

evaluate therapeutic efficacies in clinical trials [10,11]. It remains unclear, however, whether Aβ pathology itself shows neurotoxicity in vivo and influences clinical features. Only a few studies have indicated significant associations between Aβ burden and clinical features in AD [12–14]. Furthermore, recent neuroimaging and neuropathological studies have revealed that some cognitively healthy elderly have abundant neocortical Aβ [15–18].

Tau pathology sometimes occurs concurrently (e.g., AD) with, and sometimes independently (e.g., non-AD tauopathies such as progressive supranuclear palsy, corticobasal degeneration, and primary age-related tauopathy (PART)) of Aβ [19,20]. Accumulating evidence has suggested that tau pathology has a close relation with neurodegeneration equal to or rather than Aβ pathology [21–23]. To assess the effect of tau pathology on neurodegeneration, previous studies had to use animal models, estimate from cerebrospinal fluid (CSF), or wait for postmortem autopsy. These approaches, however, have several limitations. In other words, specific differences, lack of information on location, and temporal interval between autopsy and clinical evaluation make it difficult to evaluate the effect of tau pathology on the human brain environment.

There has been a conspicuous progress in the development of PET agents for tau pathology, as exemplified by [^{18}F]AV-1451 (also known as [^{18}F]T807), [^{18}F]THK-5117, and [^{18}F]THK-5351 [24–26], along with our tau-binding ligand, [^{11}C]pyridinyl-butadienyl-benzothiazole 3 ([^{11}C]PBB3) [27]. Previous studies showed that tau PET imaging using these ligands were able to detect tau pathologies with high sensitivity and specificity even at an early stage and that those signals could reflect the disease severity [24,25,27]. In our present study, we could evaluate tau pathology as well as Aβ with PET imaging quantitatively with spatial information in vivo, together with clinical evaluation.

To elucidate the interaction between Aβ and tau accumulations and its influence on clinical features such as brain atrophy and cognitive decline, we performed a cross-sectional PET study using [^{11}C]PBB3 and [^{11}C]PiB for tau and Aβ imaging, respectively, in both cognitively healthy individuals and patients with cognitive impairments. We also performed voxel-based morphometry using three-dimensional T1-weighted magnetic resonance imaging (MRI) and psychological batteries for assessing brain atrophy and cognitive decline.

2. Methods

2.1. Participants

Clinically diagnosed patients with mild cognitive impairment (MCI) and AD were recruited from Chiba University Hospital and affiliated hospitals between July, 2011 and March, 2014. Clinical diagnoses of AD and MCI were based on the National Institute of Neurological and Communicative Disease and Stroke/Alzheimer's Disease and Related Disorders Association criteria [28] and Petersen's criteria [29], respectively. Cognitive healthy controls (HCs), consisting of age-matched elderly (oHC) and young (yHC) subjects under or equal to 40 years old as a reference standard group in evaluations of tau and Aβ accumulations, without a history of neurologic and psychiatric disorders, were also recruited from the volunteer association of the National Institute of Radiological Sciences (NIRS), and were without abnormalities in physical and neurological examinations. Because we intended to focus on the aging and AD-spectrum group, PiB(−) patients with dementia, patients with possible and probable dementia with Lewy bodies, six PiB(−) patients with MCI whose pathological backgrounds were expected to be heterogeneous and were excluded from the assay group. Two PiB(+) HCs were also excluded from the further analyses because of its small sample size.

Subjects underwent psychological evaluations including Mini–Mental State Examination (MMSE), clinical dementia rating (CDR) scale, and Wechsler memory scale revised logical memory II (WMSR LM-II) tests for assessing cognitive and functional impairment, Raven's colored progressive matrices (RCPMs) for assessing nonverbal cognitive impairment, and frontal assessment battery (FAB) for assessing frontal dysfunction.

Written informed consent was obtained from all participants and from spouses or other close family members when the participants were cognitively impaired. This study was approved by the institutional review board of NIRS, in accordance with the ethical code of NIRS and the ethical guidelines for clinical studies of the Ministry of Health, Labour and Welfare in Japan, as well as the Declaration of Helsinki. The study was registered with UMIN Clinical Trials Registry (UMIN-CTR; number 000009863).

2.2. PET data acquisition

[^{11}C]PBB3 and [^{11}C]PiB were produced as previously reported [27,30,31]. PET images were acquired with a Siemens ECAT EXACT HR+ scanner (CTI PET Systems, Inc., Knoxville, TN) with an axial field of view of 155 mm, providing 63 contiguous 2.46-mm slices with 5.6-mm transaxial and 5.4-mm axial resolution. For tau and Aβ imaging, 70-minute dynamic PET scans in three-dimensional mode were performed after an intravenous injection of [^{11}C]PBB3 (432 ± 59 MBq, specific activity 98 ± 51 GBq/μmol) or [^{11}C]PiB (381 ± 29 MBq, specific activity 83 ± 51 GBq/μmol), respectively, on the same day as MRI. [^{11}C]PBB3 was injected in a dimly lit condition to avoid its photoracemization [27,30]. Subjects were examined with their eyes closed and their ears unplugged in a quiet room, and their heads were restrained with a band extending across the forehead attached to the headrest. An examiner carefully monitored head