atrophy due to their lack of amyloid fibril formation. In addition, the formation of neurofibrillary tangles as another late pathology may contribute to atrophy, as is evident in most dementia-like frontotemporal dementia, tangle dementia, and argyrophilic grain dementia. In either case, our findings clearly suggest that neurodegeneration does not correlate with cognitive decline, which reflects synaptic failure and which was probably caused by pathological Aβ oligomers [1]. This notion might be confirmed by a new method of imaging that detects Aβ oligomers and/or dysfunctional synapses.

Another unique point of our patients is the appearance of motor dysfunction. Typical sporadic AD rarely shows cerebellar ataxia and signs of pyramidal tract disturbances. Patients bearing presenilin-1 (PS-1) mutations exhibited spasticity of their legs, but they did not exhibit cerebellar ataxia [17]. Patients with spinocerebellar ataxia (SCA) showed not only spasticity and cerebellar ataxia, but also dementia [18–22]. In this regard, the clinical features of our patients were similar to those of SCA patients. The major difference between our patients and those with SCA is that SCA patients usually exhibit atrophy of the cerebellum in conjunction with the inability to walk, but our patients exhibited no apparent atrophy or hypoglucose metabolism of the cerebellum when they could not walk. The present ataxia in our patients may be caused by synaptotoxicity of Aβ oligomers that accumulated in the cerebellum and ataxia. This notion may be in part supported by the observation that PiB-retention signals were slightly detected in the cerebellum of our patients (fig. 4b, 7), since amyloid-binding dyes, including PiB, have been shown to recognize Aβ oligomers as well as amyloid fibrils. We speculate that the metabolism of Aβ oligomers and the vulnerability of neurons to Aβ oligomers in the cerebellum may be different from those in the cerebrum; Aβ oligomers could be cleared more efficiently and neurons are less vulnerable to Aβ oligomers in the cerebellum. Therefore, motor dysfunction associated with cerebellar ataxia is rarely observed in typical AD, whereas our patients, with higher levels of Aβ oligomers, exhibited these symptoms after a long period of time.

Recently, we reported on a novel mouse model of AD expressing the Osaka (E693Δ) mutation [23]. This transgenic mouse displayed an age-dependent intraneuronal accumulation of Aβ oligomers from 8 months of age but no extracellular amyloid deposits, even at 24 months. Aβ accumulation was detected not only in the cerebral cortex and hippocampus but also in the cerebellum. Their hippocampal-related synaptic plasticity and memory functions were impaired at 8 months, and the levels of the presynaptic marker synaptophysin in the hippocampus began to decrease with the same timing. Furthermore, abnormal tau phosphorylation was detected from 8 months, and neuronal loss in the hippocampus was observed at 24 months. These findings seem to support our speculation concerning the underlying mechanisms of the disease process in our patients described above. The CSF levels of Aβ1–42 in our patients were significantly lower than those in patients with typical AD, and CSF levels of total and phosphorylated tau were as high as those seen in patients with typical AD. These results suggest that Aβ accumulated in the brain parenchyma, possibly within neurons, and the pathological changes related to tau occurred in our patients, similar to that seen in our mouse model.

Lastly, it is a new and difficult challenge to distinguish clinical symptoms in AD that are caused by Aβ oligomers versus amyloid fibrils because of their simultaneous occurrence in the brain. Our patients, however, are presumed to possess only Aβ oligomers in their brains. Thus, the symptoms of our patients presented here are expected to reflect pathological functions of Aβ oligomers. Our findings suggest that Aβ oligomers primarily cause cognitive dysfunction in the early stages of the disease and, in some cases, elicit motor dysfunction through cerebellar ataxia in the late stages. Aβ oligomers can induce neurodegeneration that leads to brain atrophy, but it requires a long period of time of neuronal exposure to Aβ oligomers. We also found that brain atrophy does not correlate with cognitive impairment. Finally, we suggest that senile plaques are a less important target, but we acknowledge the practical view that plaques are currently a useful marker of disease progression. Thus, the pathological significance of senile plaque formation remains to be further studied in AD.

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Disclosure Statement

Competing interests: none. Patient consent: obtained.

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Pittsburgh Compound B-Negative Dementia—A Possibility of Misdiagnosis of Patients With Non-Alzheimer Disease-Type Dementia as Having AD

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Abstract

Amyloid imaging has been used to detect amyloid deposition in the brain. We performed Pittsburgh compound B (PiB)-positron emission tomography on 63 patients with dementia having cognitive decline or memory disturbance. In addition, we measured the patients' apolipoprotein E4 (apo E4) status and cerebrospinal fluid (CSF) levels of amyloid-β (Aβ)1-42, tau, and P-tau. Finally, the patients were diagnosed as having probable Alzheimer disease (AD) on the basis of their neuropsychological findings and because they met the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria. Among the patients diagnosed with probable AD, 10 patients were PiB negative. The CSF levels of P-tau and tau in PiB-negative patients were significantly lower than those in the PiB-positive patients. In addition, the CSF levels of Aβ1-42 in the PiB-negative patients were significantly higher than those in the PiB-positive patients. None of the PiB-negative patients were apo E4 carriers. These results suggest that the PiB-negative patient group included not only AD patients but also non-AD-type dementia patients. However, our finding is based on a relatively small number of patients and therefore should be replicated in a larger cohort. In addition, it will be necessary to categorize these participants by longitudinal follow-up and postmortem pathological examinations.

Keywords

PiB-PET, PiB-negative dementia, CSF biomarkers, non-AD type dementia

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Introduction

The neuropathological features of Alzheimer disease (AD) include the formation of extracellular senile plaques and intraneuronal neurofibrillary tangles. Amyloid-β (Aβ) protein is a major component of these senile plaques. Klunk et al reported that ^{11}C-labeled Pittsburgh compound B ([^{11}C]-PiB) has a high affinity for Aβ, and [^{11}C]-PiB has been used as an amyloid-imaging compound since their report was published.[1] ^{11}C-labeled Pittsburgh compound B-positron emission tomography (PET) has shown amyloid deposition in patients with AD and in some patients with mild cognitive impairment (MCI).[2] Furthermore, PiB does not bind to the neurofibrillary tangles or brain homogenates that are not associated with plaques.[3] In previous studies on non-AD-type dementia, PET did not show an increased [^{11}C]-PiB uptake.[4]

Among the patients clinically diagnosed with AD, some were PiB negative. In this study, we evaluated the cerebrospinal fluid (CSF) levels of biomarkers and the status of apolipoprotein E (apo E) in PiB-negative patients (PiB-negative dementia group). We compared the results of this study with those obtained from the studies on PiB-positive patients with AD.

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Table 1. The Demographic Characteristics and the Levels of Biomarkers in the Cerebrospinal Fluid (CSF) of Pittsburgh Compound B (PiB)-Positive and PiB-Negative Patients[a]

	PiB (+) AD	PiB (−) AD	*P* Value
N	21	10	
Gender	5 M, 16 F	5 M, 5 F	
Age	74.8 ± 3.1	77.3 ± 4.8	
Mean Mini-Mental State Examination (MMSE) score	22.5 ± 3.5	23.9 ± 2.5	
Pittsburgh compound B (PiB) mean cortical distribution–volume ratio (MCDVR)	1.56 ± 0.26	0.99 ± 0.15	.001
Cerebrospinal fluid (CSF) amyloid β (Aβ1-42; pg/mL)	385.7 ± 107.1	559.6 ± 243.3	.05
CSF P-tau (pg/mL)	107.1 ± 37.8	68.4 ± 46.7	.05
CSF total tau (pg/mL)	580.4 ± 222.6	277.9 ± 220	.01
Apolipoprotein E (apo E) E4 carriers (%)	13 (62%)	0	.001

[a] Table demographic data of Pittsburgh compound B (PiB)-positive and PiB-negative patients and the levels of biomarkers in their cerebrospinal fluid. The analysis was performed on only 21 of the 53 PiB-positive patients and on 10 PiB-negative patients.

Methods

Participants

We recruited 63 patients with AD from the Department of Geriatrics and Neurology, Osaka City University Hospital. These patients met the criteria for probable AD as defined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). Informed consent was obtained from all patients or their next of kin. This study was approved by the Ethics Committee of Osaka City University Graduate School of Medicine.

Positron Emission Tomography

We synthesized [^{11}C]-PiB using 2-(4′-aminophenyl)-6-hydroxybenzothiazole as the labeled precursor molecule. After an intravenous injection of [^{11}C]-PiB (150-300 MBq), we performed a 60-minute, dynamic, 3-dimensional list-mode emission scan without arterial sampling using an Eminence-B PET scanner (Shimadzu Corporation, Kyoto, Japan).

Magnetic resonance imaging (MRI) scans were aligned with corresponding PET images using the PMOD Image Fusion Tool (PMOD Technologies Ltd, Zurich, Switzerland). These images were reconstructed using a filtered back-projection algorithm with attenuation and scatter corrections. We used the Logan graphical analysis method to calculate each regional count (distribution–volume ratio [DVR]) with the cerebellum as a reference and using the frame summation of dynamic images for 40 to 60 minutes.[5] We selected the cortical regions in the frontal, parietal, precuneus, posterior cingulate, and lateral temporal lobes. The mean cortical DVR (MCDVR) is the mean of the DVR values in these regions. We defined the cutoff level of the MCDVR as 1.3, which was based on the distribution of DVR values of normal controls and patients who were diagnosed with PiB positive by visual inspection. Patients were judged to be PiB positive based on visual inspection by a single reader or if the MCDVR and DVR values obtained from at least 3 main cortical areas were higher than 1.3 each. The patients were judged to be PiB negative if they showed no or low PiB retention in most cortical areas and if the MCDVR values were lower than 1.3.

Biomarkers

The CSF samples were obtained from the L3/L4 or L4/L5 interspaces in the morning and were collected in 10-mL polypropylene tubes. The CSF samples were aliquoted into 0.5- or 1-mL polypropylene tubes and stored at −80°C until further analysis. We measured the levels of Aβ1-42 in the CSF using an enzyme-linked immunosorbent assay (ELISA) kit (Wako Pure Chemical Industries Ltd, Japan). We measured the levels of tau and P-tau 181 in the CSF using a sandwich ELISA kit (Innotest; Innogenetics, Belgium).

Statistical Analysis

Statistical analysis was performed using the commercially available software (SPSS, version 16.0 for Windows; SPSS Inc, Chicago, Illinois). Nonparametric tests were used because the variables were not normally distributed. Mann-Whitney test was used to compare the demographics of the patients in PiB-positive and PiB-negative groups.

Results

In this study, we observed that the levels of [^{11}C]-PiB uptake in 10 of the 63 patients with dementia who were clinically diagnosed with AD were as low as those in normal patients. These PiB-negative patients included 4 men and 6 women (mean age, 73.3 ± 7.4 years). We observed no differences between the PiB-negative and PiB-positive patients with AD (19 men and 34 women; mean age, 70.2 ± 8.3 years) with respect to clinical presentation, particularly in their neuropsychological features, including memory disturbances, visuospatial cognition, and executive function. The patients met the NINCDS-ADRDA criteria. We assessed the differences between the levels of CSF biomarkers and apo E status in 10 PiB-negative patients and the first 21 of the 53 PiB-positive patients who agreed to undergo the examination. The CSF levels of tau and P-tau in the PiB-negative patients were significantly lower than those in the

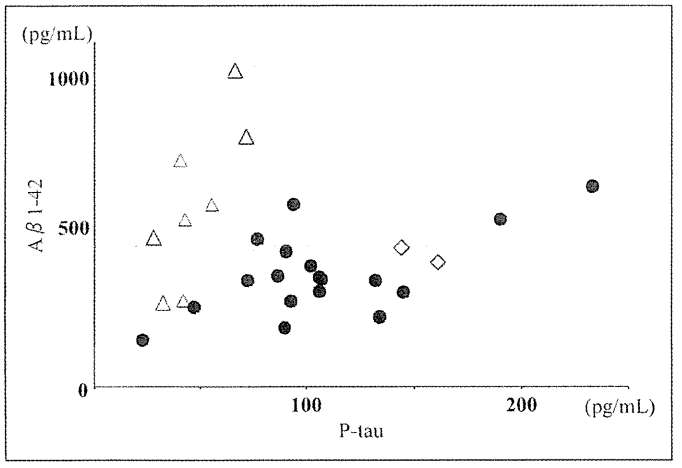

Figure 1. The closed circles (●) represent the Pittsburgh compound B (PiB)-positive patients. The other symbols (Δ, O) represent the PiB-negative patients. The lines indicate cutoff values in our laboratory.

PiB-positive patients, and the CSF levels of Aβ1-42 in the PiB-negative patients were significantly higher than those in the PiB-positive patients (Table 1). None of the PiB-negative patients was a carrier for the apo E4 genotype (Table 1). The CSF levels of P-tau in 8 of the 10 PiB-negative patients were within normal ranges and were lower than those in most PiB-positive patients (Figure 1, open triangles). Among the 8 PiB-negative patients, 6 were negative for each Aβ1-42, P-tau, and apo E4. Two patients had low CSF Aβ1-42 levels and normal P-tau levels, and 2 patients had high P-tau and Aβ1-42 levels that were just below the cutoff level (Figure 1, open diamonds). The 4 PiB-positive patients had normal Aβ1-42 levels.

Discussion

Our results indicate that low levels of Aβ deposition were observed in the neocortex of some patients clinically diagnosed with probable AD. We propose that, in these patients, the dementia can be referred to as PiB-negative dementia. This entity may include sporadic AD, familial AD, and other types of dementia such as dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), argyrophilic grain dementia (AGD), neurofibrillary tangle-predominant dementia (NFTPD), and hippocampal sclerosis. In our study, 6 PiB-negative patients were negative for Aβ1-42, P-tau, and apo E4. These patients were considered to have a pathological background different from that of the patients with AD, as described above. Since 2 PiB-negative patients had low Aβ1-42 and normal P-tau levels, we assumed that the CSF Aβ1-42 levels might have been lowered before an increase in PiB retention.

Two previous reports have shown that 2 patients diagnosed with sporadic AD on the basis of autopsy findings were PiB negative.[6,7] However, the Cairns case had a diagnosis of possible AD or low-probability AD because of the low densities of neuritic plaques and tangles. Rosen et al only performed a postmortem study and did not investigate in vivo PiB levels.

In our case, 2 cases, 2 PiB-negative patients, were diagnosed with AD because of the high levels of P-tau and low levels of Aβ1-42 in their CSF. Furthermore, we assumed that several other cases of PiB-negative dementia may be AD. These 2 cases indicate that PiB retention may be less sensitive than CSF Aβ1-42 levels. We had previously reported that patients with familial AD, who had a low tendency for Aβ aggregation, showed negative PiB staining.[8] In addition, we would like to emphasize that among the PiB-positive patients, 4 had normal Aβ1-42 levels, suggesting that PiB retention can increase before Aβ1-42 levels drop below the cutoff value.

Because some PiB-negative patients showed low CSF levels of P-tau and high CSF levels of Aβ1-42, these patients were thought to be non-AD-type patients with dementia. In our study, all PiB-negative patients showed AD-like neuropsychological characteristics; these patients showed no behavioral abnormalities like those in patients with FTD, and none of them met the diagnostic criteria for probable DLB.[9] In addition, it is difficult to differentiate between FTD or DLB and early-stage AD.[10] Previous reports have shown that the clinical features of AGD[11,12] and NFTPD[13,14] are indistinguishable from those of AD. In some cases, these diseases are characterized by gradually progressing dementia with prominent memory disturbances and considerable preservation of other cognitive functions. Therefore, we speculate that patients with non-AD-type dementia may be misdiagnosed as having AD, and some of the patients with non-AD-type dementia may have been included in our PiB-negative patient group.

It is necessary to consider several limitations of our study. First, the total number of patients with dementia was only 63, which is too small to determine the rate of PiB-negative patients in patients clinically diagnosed with AD. Further studies should be performed with a larger number of patients with dementia using the PiB-PET method. Second, we did not perform postmortem analyses and were therefore unable to confirm the diagnosis in these PiB-negative patients with dementia. Third, we evaluated our patients only by MRI and by the CSF biomarkers in this report. There are several other examinations that are used for the evaluation of patients with dementia, including fluorodeoxyglucose (FDG)-PET, volumetric MRI analysis, single photon emission tomography, and other neuropsychological evaluations.

In conclusion, our findings show that the PiB-negative patient group with dementia included patients with non-AD-type dementia; and in clinics and hospitals where PiB-PET cannot be performed, PiB-negative patients with dementia were misdiagnosed as having early-stage AD. Pittsburgh compound B-negative dementia should be accounted for when developing an anti-amyloid treatment of AD.[15] Further clinical studies are required to completely understand the pathological characteristics of such PiB-negative patients with dementia.

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Declaration of Conflicting Interests

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