dorsal interosseus; the condition had been progressive since October 2007. On admission to our hospital in 2008, the score for Hasegawa's Dementia Scale-Revised (HDS-R) was 11/30, and that for Mini-Mental State Examination (MMSE) was 15/30, in which recent memory, verbal recall, and orientation were mainly affected. Frontal signs such as forced laughter, personality disorder, and depressive mood were also observed. In addition, atrophy of the tongue, fasciculations in the thigh, and weaknesses of the distal muscles of the upper limbs, mainly in the first dorsal interosseus were observed. Jaw and knee reflexes were hyperactive, and both snout and tonic planter reflexes were present. However, sensory deficits were not detected. His medical history was unremarkable, and he had no family history of neurological diseases. He was diagnosed as the clinically probable ALS with the El-Escorial criteria [3] and refused the treatment with riluzole and had no treatment. Nerve conduction studies (NCS) were normal, while needle electromyography (EMG) studies showed both spontaneous activities and diffuse neurological changes in the extremities and trunk; these symptoms were compatible with MND. Magnetic resonance imaging (MRI) showed mild atrophy in both the frontal and parietal lobes and in the left hippocampus (Fig. 1). PIB-PET indicated no accumulation of amyloids in the cortex, while PET with 18F-fluorodeoxyglucose (FDG-PET) indicated depressed metabolism of glucose in the frontal and temporal lobes (Fig. 2); these signs were compatible with FTD. These findings suggested that the patient had FTD-MND.

Case report 2

A 79-year-old woman presented with cognitive impairment which had been progressive since September 2005. She developed bulbar palsy, including dysarthria and dysphagia, since December 2007 and March 2008, respectively. Initial evaluation in 2005 revealed that her HDS-R score was 25/30 and MMSE score was 25/30. The neurologic examination was normal. The diagnosis was mild cognitive impairment and, after 3 years, HDS-R was 21/30 and MMSE was 24/30, with disturbances in both recent memory and orientation. Atrophy and fasciculation of the tongue were observed, while mild muscle atrophy and weakness of the neck and both the upper limbs were observed. Deep tendon reflexes in both the upper limbs were hyperactive, and snout reflex was present. However, there were no sensory deficits. Her medical history was unremarkable, and she had no family history of neurological diseases. NCS were normal, whereas needle EMG studies revealed high amplitude, long duration, and polyphasic spontaneous activities in the upper extremities, although spontaneous activities were not found. These findings suggest that this patient was compatible to the clinically probable laboratory- supported ALS with the El-Escorial criteria [3] with the one lesion showed the upper and lower motor signs. Brain MRI showed mild atrophy in both the left and right hippocampus and diffuse atrophy in the cerebral cortex consistent with her age (Fig. 3). PIB-PET indicated accumulation of amyloids mainly in the frontal lobe, anterior

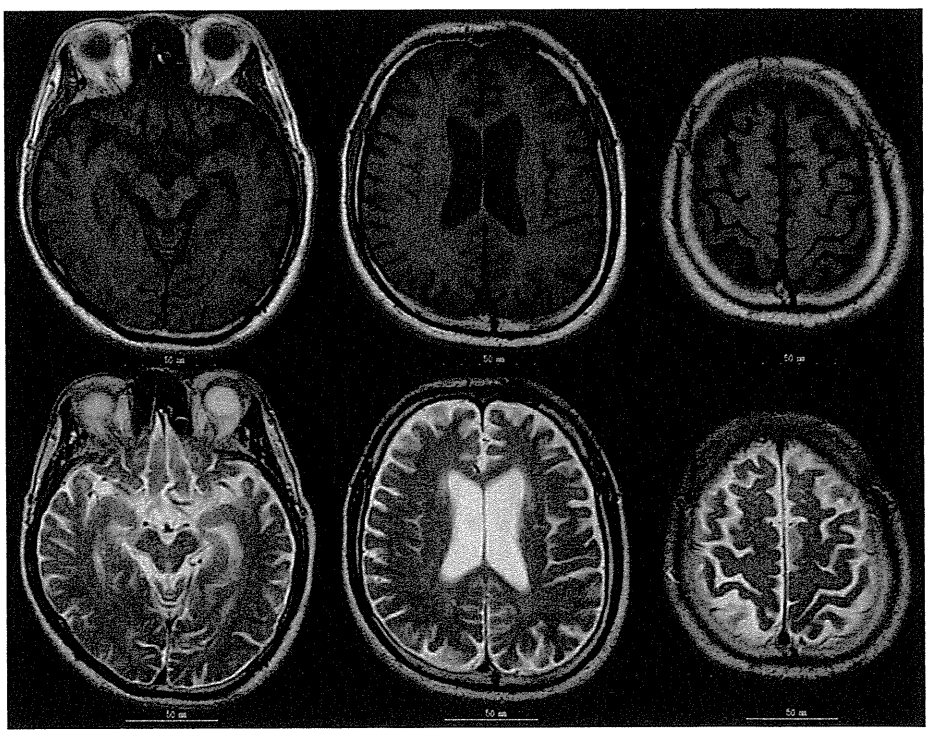

Fig. 1 Mild atrophy of both the frontal and parietal lobes and the left medial temporal area

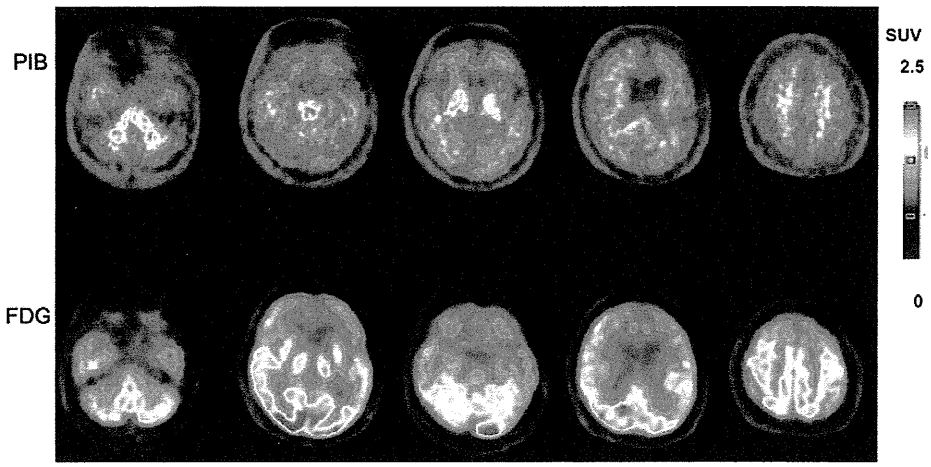

Fig. 2 *Upper panel* PIB-PET shows no accumulation of amyloids in the cortex. *Lower panel* FDG-PET shows decreased glucose metabolism in the frontal and temporal lobes with left-side dominancy associated with decreased metabolism in the right cerebellar hemisphere

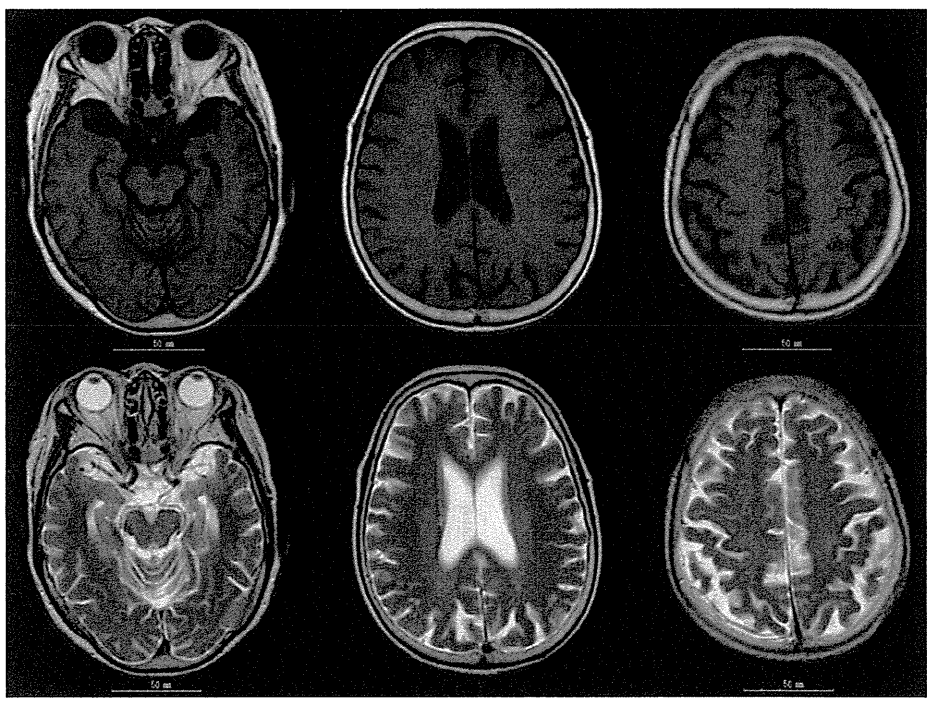

Fig. 3 Atrophy of bilateral medial temporal areas. Age-associated diffuse atrophy of the cerebral cortex

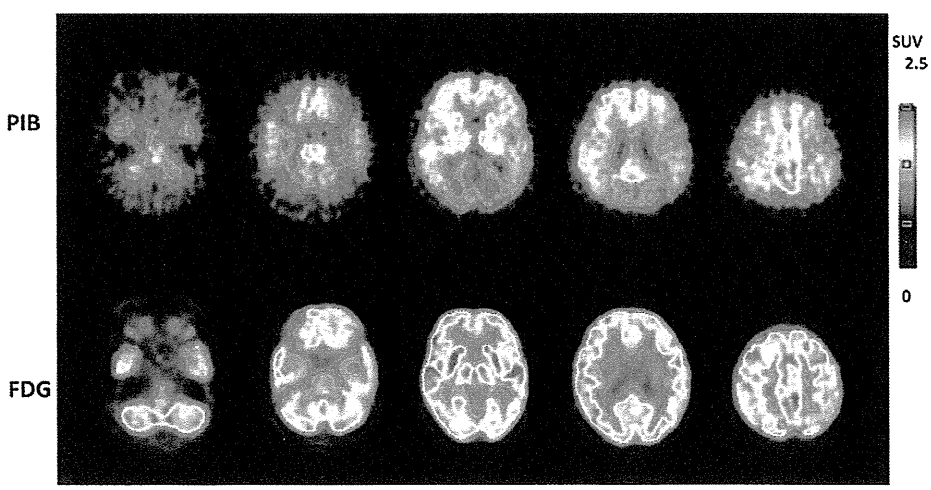

Fig. 4 *Upper panel* PIB-PET shows accumulation of amyloids mainly in the frontal lobe, anterior and posterior cingulate gyrus, precuneus, and also in the parietal lobe and lateral temporal lobe. *Lower panel* FDG-PET shows decreased glucose metabolism in bilateral parietal lobes with left-side dominancy and left lateral temporal lobe [15–23]

Table.1 Previous and present cases of motor neuron disease associated with dementia

	Tsuchiya et al. [15] 1	Ishihara K et al. [16]	Tsuchiya et al. [17] 2	Yokota O et al. [18]	Yamamoto et al. [19]	Yamamoto et al. [19]	Matsuda et al. [20]	Osoegawa et al. [21]	Yamashita et al. [22]	Rusina et al. [23]	Rusina et al. [23]	Present case 1	Present case 2
Clinical features													
Age of onset (years)	69	52	30	48	51	64	65	56	72	68	62	61	79
Age of emergence of dementia (years)	70	52	30	48	51	64	67	58	73	69	62	61	79
Age of emergence of motor neuron disease (years)	69	52	44	53	54	64	67	56	72	68	62	61	81
Duration (years)	2	7	15	6	4	4	3	4	1.5	20 months	2		
Sex	Female	Female	Female	Female	Male	Female	Male	Male	Female	Female	Male	Male	Female
Initial symptoms	Dysarthria and gait disturbance	Speech difficulties	Abnormal behavior	Abnormal behavior	Personality change	Personality change	Motor aphasia	Muscle weakness	Bulbar palsy	Bulbar palsy and motor impairment	Bulbar palsy and cognitive impairment	Cognitive impairment, muscle atrophy, and muscle weakness	Cognitive impairment
Prominent symptoms	Bulbar palsy and gait disturbance	Bulbar palsy	Bulbar palsy	Bulbar palsy and gait disturbance	Bulbar palsy	Bulbar palsy and gait disturbance	Bulbar palsy	Muscle atrophy and muscle weakness	Bulbar palsy	Muscle weakness	Muscle weakness	Muscle atrophy and muscle weakness	Bulbar palsy
Upper motor neuron signs	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(−)	(+)	(+)	(+)	(+)	(+)
Family history	(−)	(−)	(−)	(−)	(−)	(−)	(−)	(−)	Unknown	(−)	(−)	(−)	(−)
Part of brain atrophy													
Frontal lobe	(−)	(−)	(+)	Unknown	Bilateral	Bilateral	Bilateral					Bilateral	(−)
Temporal lobe	Right	(−)	(+)	Unknown	Bilateral	Right	Bilateral					(−)	(−)
Caudate nucleus	(−)	(+)	(+)	Unknown	(−)	(−)	(−)					(−)	(−)
Hippocampus	(−)	(−)	(−)	(−)	(−)	(−)	(−)					Left	(+)
Histological features													
Tau pathology	(−)	(−)	(−)	Neurofibrillary tangles in the frontal and temporal lobe	(−)	(−)							
Ubiquitin-positive inclusions	(+)	(−)	(+)	(−)	(+)	(+)							
Diagnosis	FTD-MND	FTLD associated with MND	†FTD-MND	‡FTLD associated with §MND	FTD-MND	FTD-MND	FTD-MND	Alzheimer's disease with FTD-MND	Alzheimer's disease associated with MND	Alzheimer's disease associated with MND	Alzheimer's disease associated with MND	FTD-MND	Alzheimer's disease associated with MND

† *FTD-MND* frontotemporal dementia with motor neuron disease, ‡ *FTLD* frontotemporal lobar degeneration, § *MND* motor neuron disease

and posterior cingulate gyrus, precuneus, and also in the parietal and lateral temporal lobes. FDG-PET indicated depressed metabolism of glucose in both the parietal lobes and in the left lateral temporal lobe (Fig. 4). These findings suggested that the patient had AD since 2005, and had slowly progressive MND since 2007.

Discussion

The novel PET tracer ^{11}C-PIB has a high affinity for fibrillar amyloid beta protein (Aβ). Klunk W et al. [4] reported that the in vitro 2-(4′-methylaminophenyl) benzothiazole (BTA-1) binding was over tenfold higher in the AD brain than in the normal brain, and that the majority (94%) of the binding was specific for amyloid, and high-affinity BTA-1 was observed only in the AD brain gray matter. However, Aβ accumulation is one of the pathologic hallmarks of AD, but not of frontotemporal lobar degeneration (FTLD), as shown in the criteria proposed by McKhann et al. [1] in 2001; according to the criteria, FTLD is classified into three major groups depending on the presence or the absence of tauopathy and ubiquitinopathy. Alternatively, according to the criteria proposed by Cairns et al. [5] in 2007, FTLD is classified in terms of the presence or the absence of the 43-kDa transactive response (TAR) DNA-binding protein (TDP-43 or TARDBP), which was identified by Arai T et al. [6]. ^{11}C-PIB binds specifically to fibrillar Aβ in AD brains, but shows a low binding affinity to brains from patients with non-Aβ dementias, including FTLD. PIB-PET demonstrated significantly higher ^{11}C-PIB retention in the gray matter of AD patients than that of FTLD patient [7]. In a previous study conducted on 30 ALS patients, 50% had Aβ plaques at histopathological examination; however, of the seven cases without cortical motor neuron inclusions, only two had neuritic plaques [8].

Table 1 summarizes previous and present cases of MND associated with dementia. In 7 of the 8 cases of FTLD associated with MND, including FTD-MND, the age of onset ranged from the half of the fifth to the half of the sixth decade of life, as in our case 1. The mean age of onset of FTLD with MND was 55.6 ± 15.9 years, whereas that associated with MND varied around 50 years. About the cognitive features, most patients with FTD/ALS show almost the same cognitive and behavioural impairments of FTD patients.

There are some cases where the clinical course of FTD is similar to that of AD, and vice versa; hence, clinical course is not helpful in confirming the diagnosis. Reñé et al. [9] reported that MRI showed frontal and/or temporal atrophy in 62% of the FTLD cases, and single-photon emission computed tomography (SPECT) showed frontal and/or temporal hypoperfusion in 75% of the FTLD cases. It has been reported that FDG-PET is useful in the differential diagnosis of AD from FTLD with more than 85% sensitivity and specificity [10]. Recently, Zhou [11] reported the efficacy of the differential diagnosis of AD from variant form of FTD with the resting state functional magnetic response imaging (RS-fMRI). On the other hand, the accumulation of amyloids is observed in AD but not in FTLD. Our study showed that AD associated with ALS showed positive PIB scans, whereas FTD-MND showed negative scans. In some cases, neither the clinical course nor radiological analyses other than functional neuroimaging techniques are useful in discriminating AD from FTD, especially in the initial stage of the disease.

Recently, the TDP-43 protein has been identified as the cause of FTD/ALS [6] and the mutation of SOD1 gene has been already reported as the cause of familial ALS [12]. Some mutations of the TDP-43 gene may contribute significantly to the aggregation and forming amyloid structures inducted by the C-terminal fragments of the TDP-43 [13]. On the other hand, the SOD1 mutant increased aggregation propensity and formation of amyloid like fibrils [14]. Because these studies suggest that their mutation affect the amyloid formation in the brain of the FTLD patients, we have to consider the possibilities of these mutations affect to our PET data. In the future, we would like to analyze the presence of these mutations of our patients' gene.

Our study suggests that PIB-PET can be considered as a useful tool to discriminate the different proteinopathies that cause neurodegenerative diseases, as dementia associated with ALS.

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Clinical Course of Patients with Familial Early-Onset Alzheimer's Disease Potentially Lacking Senile Plaques Bearing the E693Δ Mutation in Amyloid Precursor Protein

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Key Words
Alzheimer's disease · Clinical features · Amyloid β · Magnetic resonance imaging · Positron emission tomography · Mutation

Abstract
Background/Aims: Oligomeric amyloid β (Aβ) is currently considered to induce Alzheimer's disease (AD). We examined 2 patients with familial AD who possessed the Osaka (E693Δ) mutation in amyloid precursor protein. To the best of our knowledge, these patients are the first AD cases presumably affected with Aβ oligomers in the absence of senile plaques, and they support the Aβ oligomer hypothesis. ***Methods:*** We evaluated the clinical course, neuropsychological data, cerebrospinal fluid biomarker levels, magnetic resonance imaging (MRI) scans, fluorodeoxyglucose-positron emission tomography (PET) scans, and Pittsburgh compound B (PiB)-PET images of these patients. ***Results:*** In the early stages, these patients developed memory disturbances in a similar rate to patients with sporadic AD. Despite their memory disturbances, both patients showed only limited brain atrophy on MRI and little amyloid accumulation on PiB-PET. Subsequent to the development of memory disturbances, both patients suffered from motor dysfunction, probably due to cerebellar ataxia, and, within a few years, the patients fell into an apallic state. ***Conclusions:*** Familial AD patients with Osaka (E693Δ) mutation show severe dementia, cerebellar ataxia, and gait disturbances.

Background

The oligomer hypothesis of AD suggests that the soluble oligomers of amyloid β (Aβ), but not the amyloid fibrils, initiate synaptic and cognitive dysfunction in patients with Alzheimer's disease (AD) [1–6]. However, there is no direct evidence that these mechanisms cause dementia in humans. Recently, we identified E693Δ, which is a novel amyloid precursor protein (APP) mutation, in patients with AD and of Japanese lineage [7]. This mutation consists of the deletion of codon 693 (GAA) in the APP gene, which encodes glutamate-22 in the Aβ sequence. The resultant mutant Aβ (E22Δ) showed a unique aggregation property of enhanced oligomerization but no fibrillization. In support of the finding that the mutant Aβ failed to form a fibrillar structure, patients with this

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mutation were amyloid-negative on Pittsburgh compound B (PiB)-positron emission tomography (PET) imaging. In addition, the mutant Aβ inhibited hippocampal long-term potentiation more potently than did wild-type Aβ in rats in vivo. These findings suggest that the Osaka (E693Δ) mutation contributes to AD by enhancing the formation of synaptotoxic Aβ oligomers, and not of amyloid fibrils, providing genetic evidence for the oligomer hypothesis described above.

In our opinion, patients with the Osaka (E693Δ) mutation are therefore expected to exhibit pure features of the Aβ oligomer-induced neuropathology in their brains and of the Aβ oligomer-associated clinical symptoms because the pathophysiology underlying their disease is free from the influence of amyloid plaques. However, the patients with this mutation presented in this paper are still alive, and, therefore, no autopsy data is available to date. Thus, in the present study, we describe the detailed clinical features of these patients and discuss the possible contribution of Aβ oligomers to the clinical symptoms of AD. We believe that the precise clinical description of these patients will provide useful insights into dementia.

Methods

Positron Emission Tomography

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

Magnetic resonance imaging (MRI) scans were coregistered with the respective PET images using the PMOD image-fusion tool (PMOD Technologies Ltd., Zurich, Switzerland). The PET images were reconstructed using a filtered back-projection algorithm for attenuation and scatter corrections. According to the study performed by Lopresti et al. [8], in which the frame summation of the dynamic images was recorded for 40–60 min, Logan graphical analysis was used for determining the regional counts (distribution volume ratio, DVR = binding potential + 1) using the cerebellum as the reference region. For this purpose, the cortical lesions occurring in the frontal, parietal, and lateral temporal lobes, the gyrus rectus, and the precuneus regions were selected. The mean cortical DVR (MCDVR) was the mean of the DVR values of these lesions [9]. Positive PiB binding indicated that the visible cortical PiB accumulation was higher than that of the white matter or that the MCDVR of the cortex was larger than the cutoff index obtained at our institute.

Neuropsychological Evaluations

Neuropsychologists administered a set of neuropsychological test batteries that included a Mini-Mental State Examination (MMSE), a Rivermead Behavioral Memory Test (RBMT), a Clock Drawing Test (CDT) [10], a Category Cued Memory Test (CCMT) [11], a Verbal Fluency Test (VFT) [12], a Scenery Picture Memory Test (SPMT) [13], a Block Design Test (BDT), a subtest of the Wechsler Adult Intelligence Scale-Revised, and the Trail Making Test (TMT) part A and B. For the CDT, the subject was asked to draw a clock with all of its numbers on a blank piece of paper and indicate the time as 10 after 11. We used the 10-point scoring system by Rouleau et al. [10] to score the exam. The CCMT, a modified version of Buschke's Double Memory Test that was reported previously, is a verbal memory test that contains 16 words from 8 categories and uses category cues during encoding and recall. In the CCMT, only cued recall, and not free recall, was tested. The score consisted of the number of items recalled correctly with the maximum score being 16. In the VFT, the subject was instructed to name as many vegetables, animals, and words that start from the letter 'ka' as possible, each within 1 min. The score was the total number of items mentioned. The SPMT is a newly developed, quick, and effective memory test that uses a line drawing of a scene of a living room in a house where 23 objects that are commonly observed in daily life are drawn on a piece of A4-sized paper. The test consisted of 2 trials (Pict-1 and Pict-2).

Results

Patient 1

Patient 1 was a Japanese woman who was the proband of a highly consanguineous pedigree with hereditary dementia (fig. 1). She first experienced memory disturbances at the age of 55 and visited our hospital at the age of 57. Her MMSE scores (fig. 2) and MRI (fig. 3) and fluorodeoxyglucose (FDG)-PET (fig. 4a) images were rather normal. However, the three-dimensional stereotactic surface projection (3D-SSP) analysis showed hypometabolism of FDG in the posterior cingulate cortex, which is similar to that seen in patients with sporadic AD (fig. 4a) [14]. The levels of Aβ1–42 and Aβ1–40 in the patient's cerebrospinal fluid (CSF) were 22 and 390 pg/ml, respectively (normal values in our institute: Aβ1–42, >450 pg/ml). Based on a very small drop in her MMSE score and her own claims, the patient was diagnosed with mild cognitive impairment.

However, familial AD was suspected in the patient because of her pedigree's history of hereditary dementia. We therefore performed a genetic analysis on her and her family members under the agreement of informed consent and identified a novel mutation (E693Δ) in APP. She had homozygous alleles of this mutation, whereas her unaffected elder and younger sisters, who were 62 and 53 years old, respectively, bore heterozygous alleles.

At the age of 59, patient 1's MMSE score decreased to 22. According to the Diagnostic and Statistical Manual for Mental Disorders, 3rd edition-revised, and the Na-

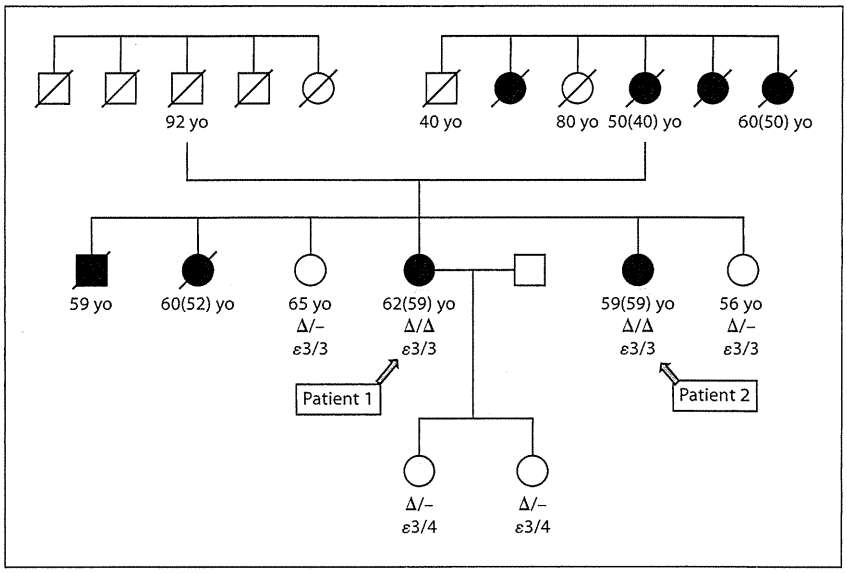

Fig. 1. Pedigree chart of the family carrying the E693Δ mutation. The numbers indicate the ages of the family members at the time of death, at the time of the investigation of the gene, or at the time of the onset of the disease. The Δ denotes the deletion of E693. The affected patients were homozygous for this mutation. The ε denotes the Apo E genotype. yo = Years old.

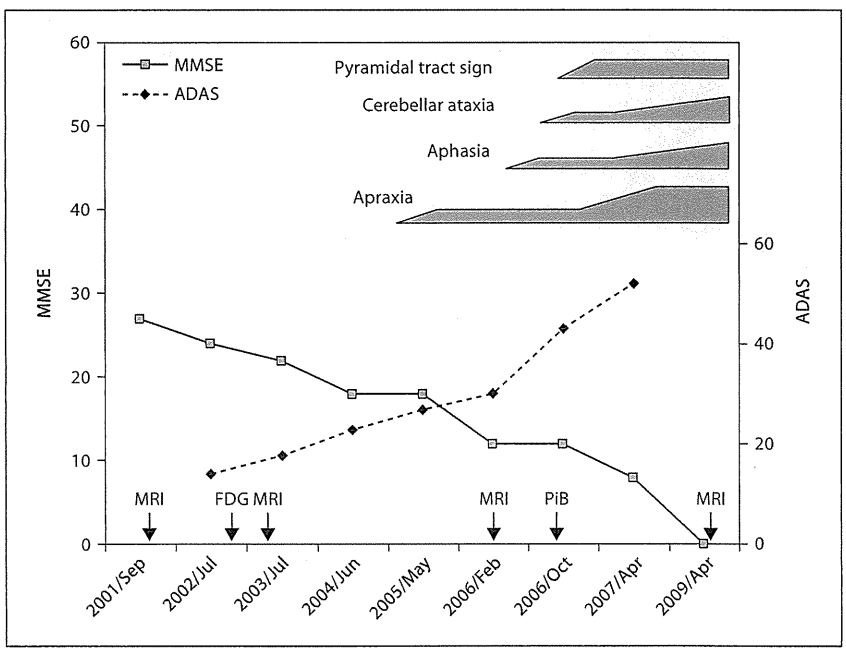

Fig. 2. Chart of the clinical course of patient 1. MMSE scores are graphed against the Alzheimer's Disease Assessment Scale (ADAS) scores. After the patient was diagnosed with mild cognitive impairment, her cognitive level declined gradually. Three years later, the patient developed apraxia and gait disturbance due to ataxia.

tional Institute of Neurological and Communicative Disorders and Stroke-AD and Related Disorders Association (NINCDS-ADRDA) criteria, she was diagnosed with AD, and treatment with donepezil was started.

Two years later, she showed dramatic changes in her clinical symptoms at the age of 61. Her MMSE score decreased to 12. She developed cerebellar ataxia, gait disturbances, apraxia, positive signs of pyramidal tract disturbances, including hyperreflexia of the patellar and Achilles tendons, and a positive sign of pathological reflex and spasticity in the lower extremities, none of which had been observed before. These features are unusual for patients with AD.

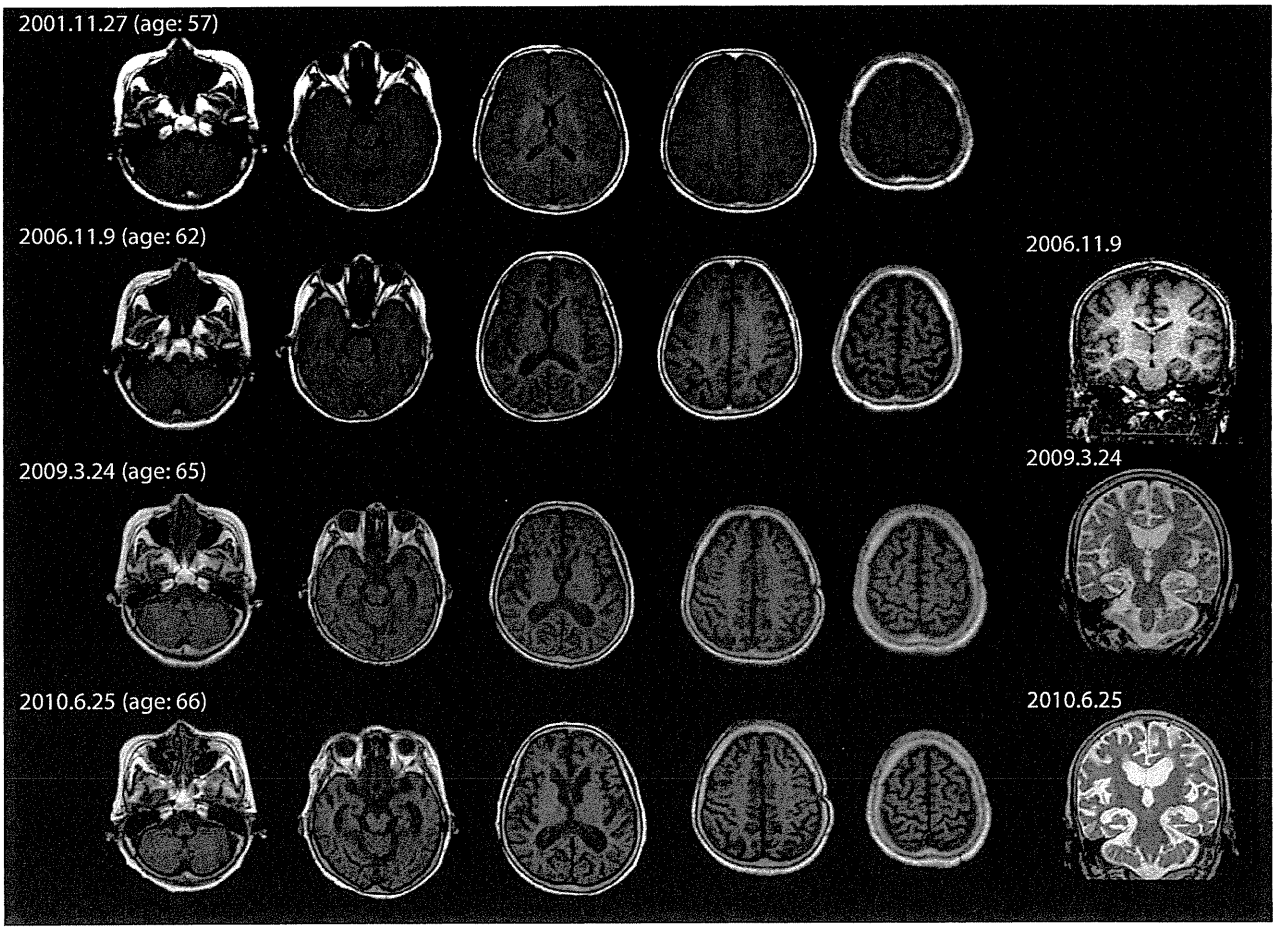

Fig. 3. MRI scans for patient 1 at the ages of 57, 62, 65, and 66. At the first visit, the MRI scans revealed no atrophy of the hippocampus. At the mid-stage of the disease (when the patient was 62), MRI images revealed slight worsening of the atrophy. After the patient entered the apallic state, atrophies of the hippocampus and the cerebral cortex were evident, but atrophy of the cerebellum was not detected.

Her cognitive impairment became very severe at the age of 62 when she had an MMSE score of 5. Nevertheless, an MRI scan revealed only mild parietal lobe atrophy (fig. 3) and no significant atrophy in the hippocampus. In addition, a [^{11}C]PiB-PET scan revealed almost no amyloid accumulation in the cortex (fig. 4b). An FDG-PET scan showed decreased glucose metabolism throughout the brain of patient 1 except in the motor and sensory cortices and in the cerebellum (fig. 4c). At the age of 63, she became unable to walk by herself, and she fell in her house several times. After a chronic subdural hemorrhage due to a fall, she became bedridden, and her cognitive dysfunction worsened.

At the age of 65, her general status was comparable to that of a patient with apallic syndrome. MRI scans revealed moderate atrophy of the hippocampus, mild atrophy of the cerebrum, and mild dilatation of the third and lateral ventricles (fig. 3). It is noteworthy that, despite the severity of her cognitive dysfunction, only mild atrophy was detected in the cerebrum, which is in contrast to patients with sporadic AD who usually show severe atrophy in this region. CSF biomarker levels of Aβ and tau were highly indicative of AD. For instance, her CSF levels of Aβ1–42 and Aβ1–40 were 4.1 and 242.8 pg/ml, respectively, which were very low compared with published values in the US AD Neuroimaging Initiative study [15] and in a Japanese cohort study [16]. Moreover, the levels of

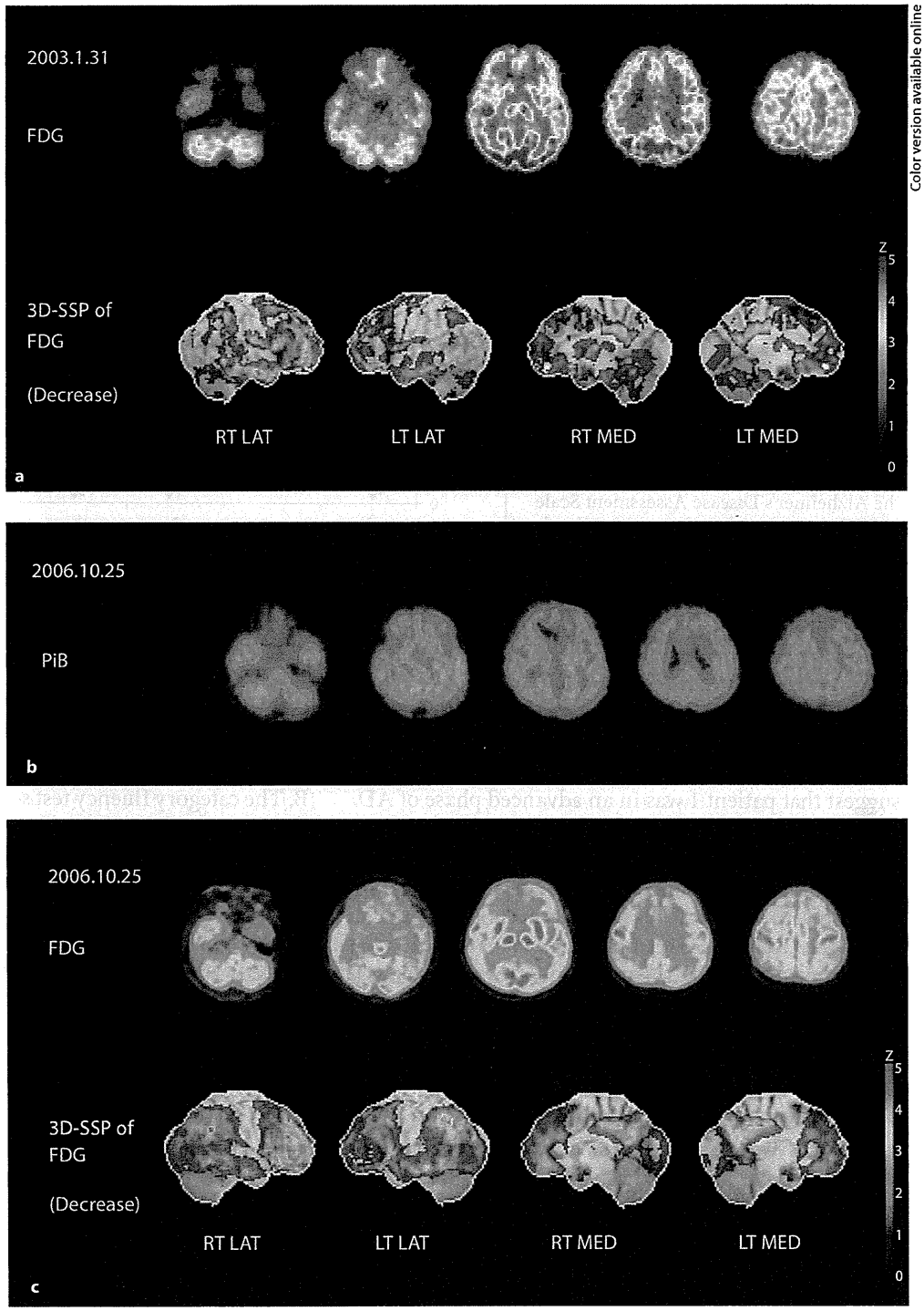

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Fig. 4. a FDG and the 3D-SSP analysis of patient 1 showed FDG hypometabolism in the posterior cingulate cortex, which was similar to that seen in patients with sporadic AD (arrow). **b** PiB-PET images of patient 1. No accumulation of amyloid is seen in her brain. **c** FDG and 3D-SSP analysis images of patient 1, 3 years later than those in **a**. 3D-SSP reveals decreased glucose metabolism throughout the patient's brain, except in the motor and sensory cortices and in the cerebellum.

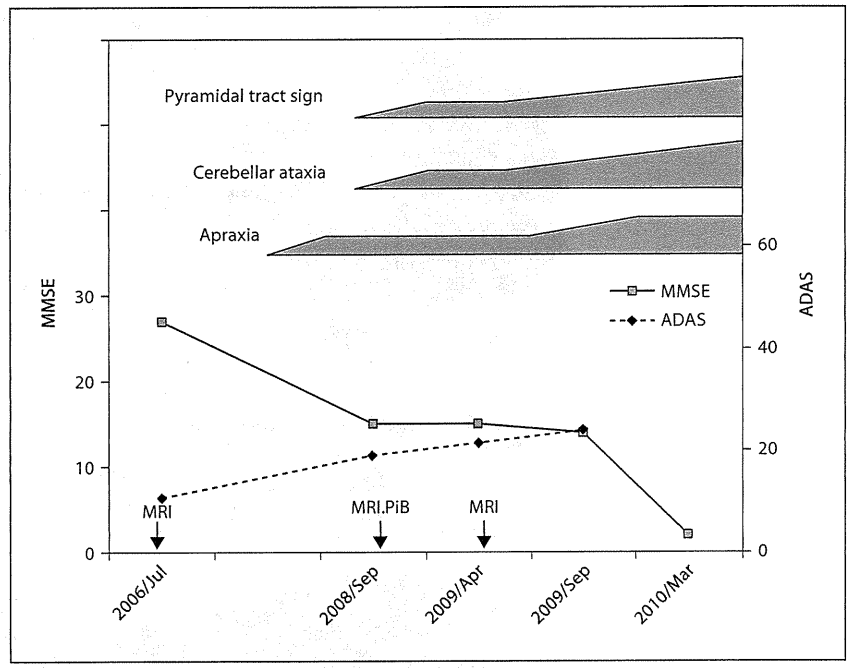

Fig. 5. Chart of the clinical course of patient 2. MMSE scores are graphed against the Alzheimer's Disease Assessment Scale (ADAS) scores. After the patient developed cerebellar ataxia, apraxia, and positive signs of pyramidal tract disturbances, her cognitive level declined rapidly.

total tau and phosphorylated tau in her CSF were 628 and 87.2 pg/ml, respectively (normal values in our institute: tau, <400 pg/ml; p-tau, <75 pg/ml). These values alone suggest that patient 1 was in an advanced phase of AD.

Patient 2

Patient 2 was the younger sister of patient 1 (fig. 1). She was carefully followed because she had homozygous alleles of the Osaka (E693Δ) mutation. When we found her homozygous mutation, she was 55. At that time, she was very thoughtful and polite to us and did not show any mental or behavioral abnormalities.

She experienced memory disturbances at the age of 59 and, hence, underwent a checkup at our hospital. However, her MMSE was 27 at that time. After that, her memory gradually worsened, and she was prescribed donepezil by her home doctor half a year later. Her condition worsened, and she again visited our hospital at the age of 61. She could speak fluently, but her MMSE score was 15 (fig. 5). A domain-specific cognitive evaluation was performed. Her recent memory was decreased to a score of 1 on the CCMT, 3 on the Pict-1, and 4 on the Pict-2 (table 1). The patient's visuospatial function showed mild to moderate decline, and her scores on the CDT and BDT decreased to 9 and 10, respectively. Her answer on the CDT showed distortion of the hour-hand of the clock, and both hands were the same length. She showed an apparent decrease of her executive function with the results of 113 s on the TMT-A, and she was unable to do the TMT-B. The category fluency test showed relative preservation, and she could name 13 vegetables and 11 animals in a minute. She had a mild depressive mood with a score of 7 on the Geriatric Depression Scale. Her naming ability was relatively preserved with a score of 16 out of 17 on the RBMT naming subtest. These results suggest that her cognitive decline was compatible with moderate AD due to the obvious abnormalities in her recent memory and her general cognitive decline without predominant decline in executive and visuospatial functions. Similar to patient 1, she exhibited cerebellar ataxia, gait disturbances, and signs of disturbances in the pyramidal tract at the age of 61. An MRI scan revealed only mild cortical atrophy (fig. 6). A [^{11}C]PiB-PET scan revealed no amyloid accumulation in the cerebral cortex (fig. 7). These clinical features were very similar to those of patient 1. The levels of Aβ1–42 and Aβ1–40 in her CSF were 9.5 and 285.2 pg/ml, respectively, and those of total tau and phosphorylated tau were 856 and 152 pg/ml, respectively. Again, these values alone suggested that patient 2 was in an advanced phase of AD similar to patient 1. At the age of 62, she could barely walk, even with the assistance of her family, and her MMSE score was 12.

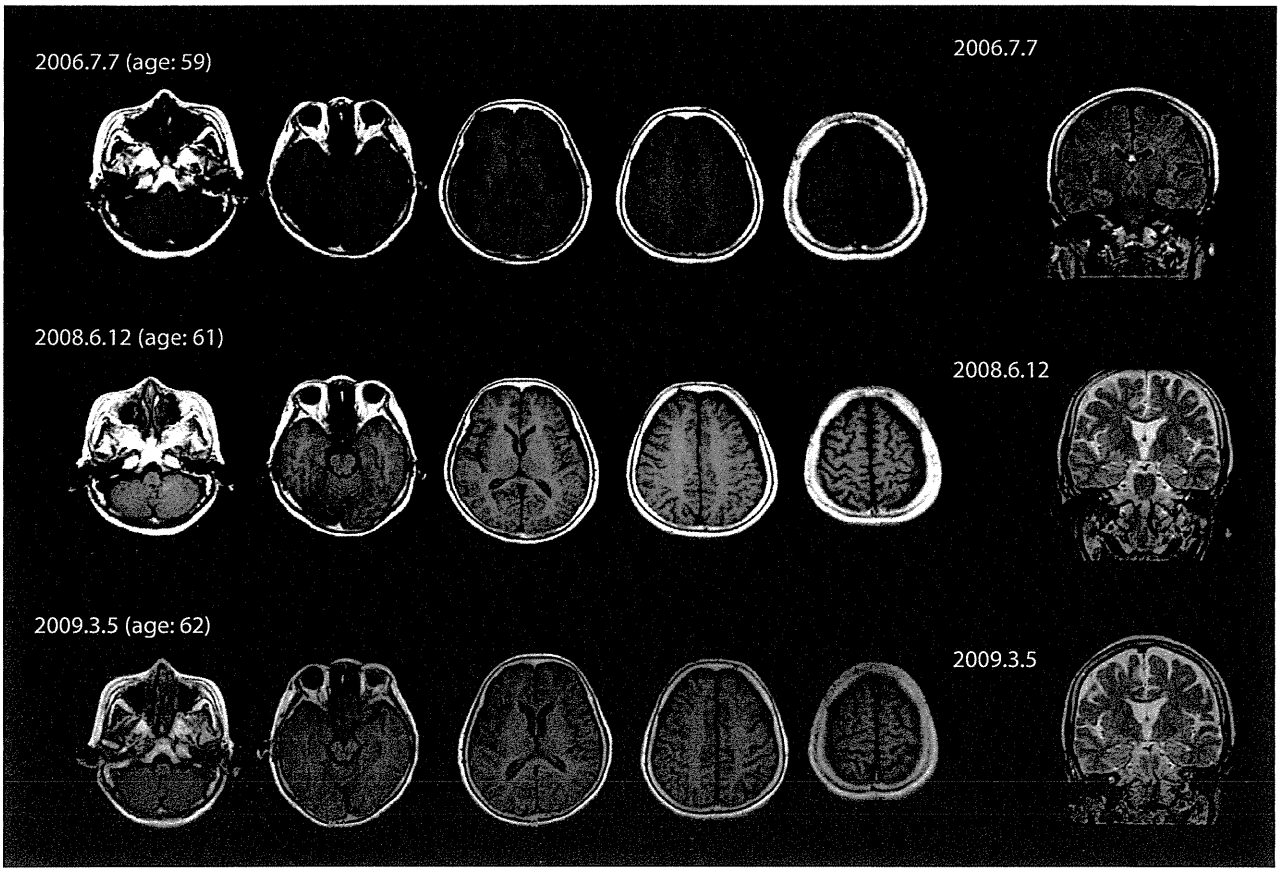

Fig. 6. MRI of patient 2 at the ages of 59, 61, and 62. The first MRI scan showed no atrophy of the brain. After her cognition decreased, her MRI images revealed slight cortical atrophy and no atrophy of the hippocampus.

Table 1. Neuropsychological evaluation in patient 2

Cognitive function	Test	Her score/maximum	Normal range
	MMSE	15/30	≥24
Recent memory	CCMT	1/16	≥9
	Pict-1	3/23	≥12
	Pict-2	4/23	≥15
Visuospatial function	CDT	9/10	≥10
	BDT	10/61	≥31
Attention, executive function	Category fluency (vegetable)	13	≥11
	Category fluency (animal	11	≥11
	Letter fluency ('ka')	7	≥11
	TMT-A	113	≤43
	TMT-B	NA	
Depressive state assessment	Geriatric Depression Scale	7	<5

The data suggest that the patient developed memory disturbances and a loss of visuospatial function and executive function similar to that seen in patients with sporadic AD.

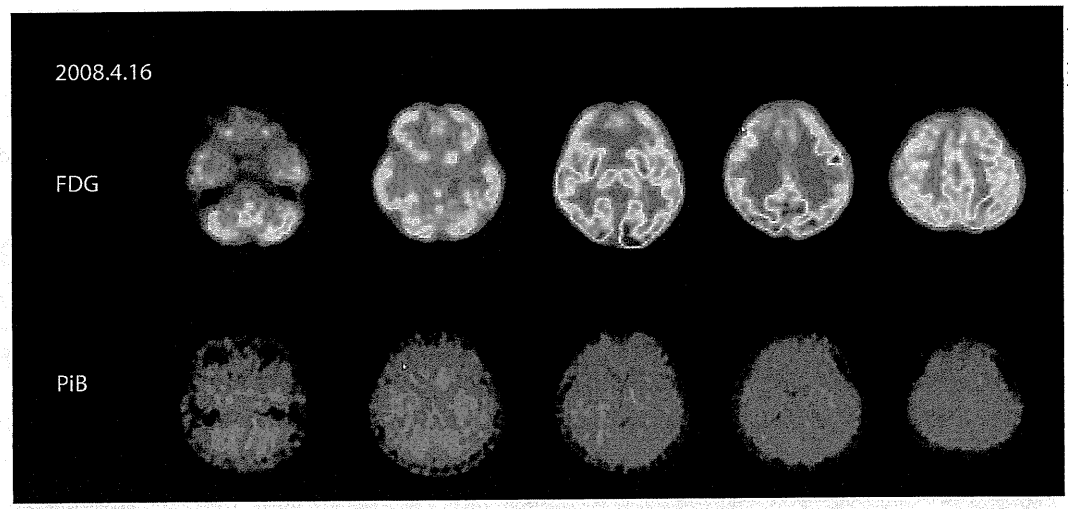

Fig. 7. FDG- and PiB-PET images of patient 2. PiB-PET images show no accumulation of amyloid in her brain, similar to that seen in patient 1.

Discussion

We report here on 2 cases who were sisters in the same pedigree, who were both carrying an APP E693Δ mutation, and who possessed the same genotype of apolipoprotein E (ε3/3ε3). Both of these cases had a variant type of AD. They developed very similar symptoms and showed a similar progression of the disease. In the early stages of the disease, they exhibited only memory disturbances, but they soon lost their visuospatial cognitive and executive functions. However, neither evident brain atrophy nor evident amyloid deposition was seen in the cortex. In the late stages, these patients displayed mild to moderate brain atrophy and unexpected motor dysfunction. These clinical features are unique and distinctive compared to patients with typical AD in several aspects.

First, our patients showed an apparent discrepancy between their cognitive impairment and apparent brain atrophy on MRI images. They first exhibited memory disturbances without any distinct atrophy. Similar observations were unexpectedly limited from our experiences in patients with AD when we considered their clinical dementia scales. The 3D-SSP analysis of the FDG-PET of patient 1 showed glucose hypometabolism in the posterior cingulate cortex, which is similar to that seen in patients with sporadic AD at the very early stages. This means that the mechanisms underlying the neuronal damage caused by the oligomers mimicked what happens in sporadic AD patients, and it caused the AD-like symptoms of these patients in their early stages. After the early stage, the rate of memory disturbance progression in these patients was apparently faster than that seen in sporadic AD cases. However, at this stage, brain atrophy was not apparent.

In our opinion, we speculate that both the memory disturbances and the subsequent brain atrophy were caused by Aβ oligomers due to synaptic failure, but the resulting neuronal death required a longer period of time of cellular exposure to the Aβ oligomers. Compared with typical AD, we expect that our patients possess higher levels of Aβ oligomers in their brains, and they therefore exhibited memory disturbances at earlier ages. However, since the Aβ oligomer-induced neurodegeneration required a long time, brain atrophy occurred only in the late stages. The second 3D-SSP analysis of FDG-PET of patient 1 showed severe hypoglucose metabolism throughout the brain except in the motor and sensory cortices and cerebellum, even though she could not walk due to cerebellar ataxia. In typical AD, the concentrations of brain Aβ oligomers increase gradually, and neurons are exposed to Aβ oligomers for a long time before the disease onset, which leads to eventual neurodegeneration. Once Aβ oligomers reach a certain level, patients display memory disturbances, and in the clinic, their brain atrophy is observed simultaneously. However, we cannot exclude the possibility that amyloid fibrils, rather than Aβ oligomers, primarily contribute to brain atrophy, and, thus, our patients did not possess significant

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.

Acknowledgment

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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

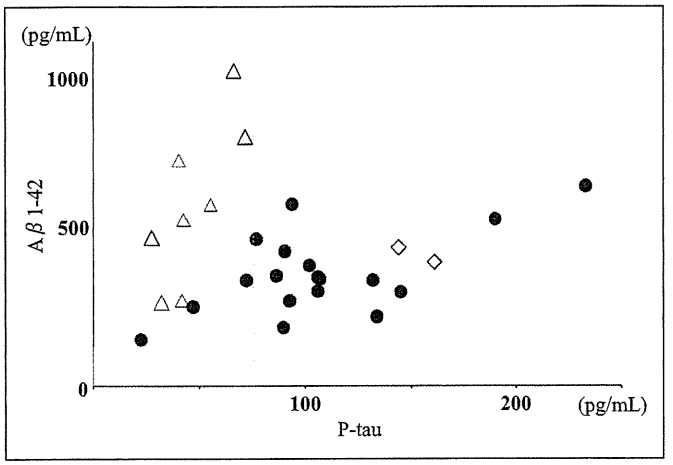

Figure 1. The closed circles (●) represent the Pittsburgh compound B (PiB)-positive patients. The other symbols (Δ, ○) represent the PiB-negative patients. The lines indicate cutoff values in our laboratory.

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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