Neurol Sci (2012) 33:87–92
DOI 10.1007/s10072-011-0479-6

CASE REPORT

Two cases of dementias with motor neuron disease evaluated by Pittsburgh compound B-positron emission tomography

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Received: 1 August 2010 / Accepted: 11 January 2011 / Published online: 5 February 2011

Abstract We described the cases of two patients with dementia associated with motor neuron disease, the former with frontotemporal dementia (FTD) and the latter with Alzheimer's disease (AD), studied by the Pittsburgh compound B-positron emission tomography (PIB-PET). In the FTD patient, the PIB-PET revealed no amyloid accumulation in the cortex, whilst in the AD patient showed amyloid accumulation mainly in the frontal, parietal and lateral temporal lobes, besides the posterior cingulate gyrus and the precuneus. Thus, PIB-PET might facilitate the discrimination of different proteinopathies that cause neurodegenerative diseases, as dementia associated with ALS.

Keywords Pittsburgh compound B (PIB) · Amyotrophic lateral sclerosis · Alzheimer disease · Frontotemporal dementia · Motor neuron disease

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Introduction

Some motor neuron diseases (MNDs) are accompanied by cognitive impairment and occasionally confused with Alzheimer's disease (AD). Frontotemporal dementia (FTD) can occur clinically in patients with MND in approximately 2% of sporadic amyotrophic lateral sclerosis (ALS) cases; this condition is called as FTD-MND [1]. On the other hand, some studies suggest that from one-third to half of the ALS patients have some types of cognitive impairments, including AD, throughout the clinical course, and many studies have indicated an overlap between ALS and cognitive impairment [2].

It has been reported that FDG-PET is useful for the differential diagnosis of several types of dementia, especially AD and FTD. Recently, Pittsburgh compound B-positron emission tomography (PIB-PET) has been used to evaluate the degree of amyloid accumulation in the brain. In general, AD is characterized by the accumulation of amyloid in the cortex of the frontal, parietal, and lateral temporal lobes, whereas this type of accumulation is not specific for FTD. Therefore, the evaluation of the cortex using PIB-PET could help us to understand the origin of the cognitive impairment.

We conducted PIB-PET study in two cases of dementia associated with MND to confirm the clinical significance of the PET study.

Case report

Case report 1

A 61-year-old man presented with cognitive impairment with muscle atrophy and muscle weakness of the first

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

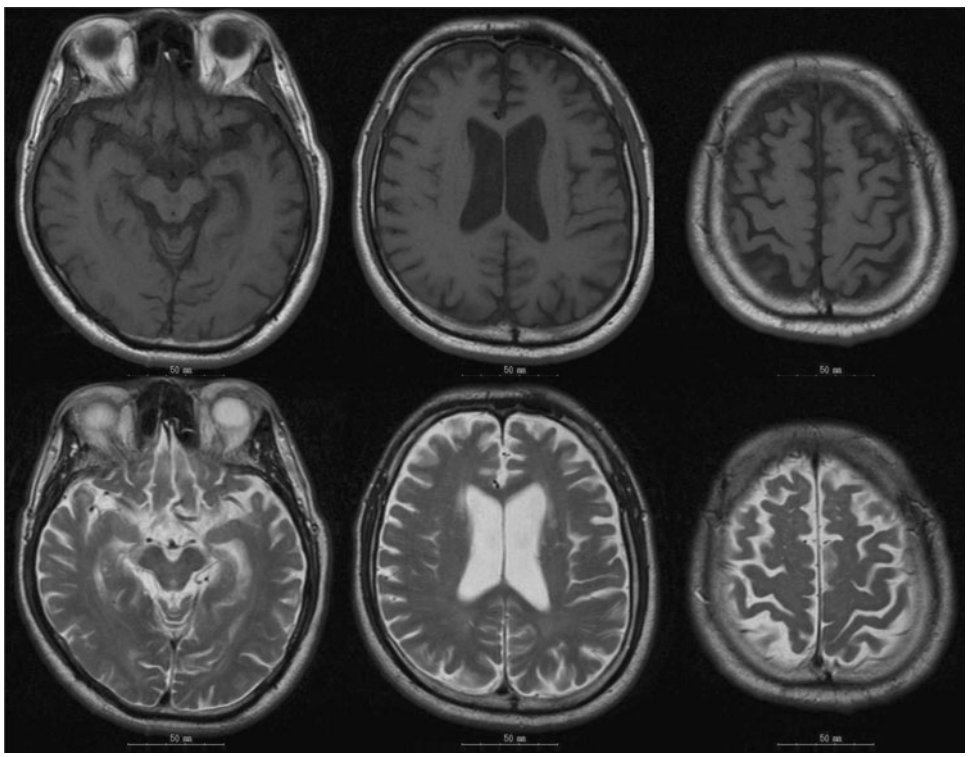

Fig. 1 Mild atrophy of both the frontal and parietal lobes and the left medial temporal area

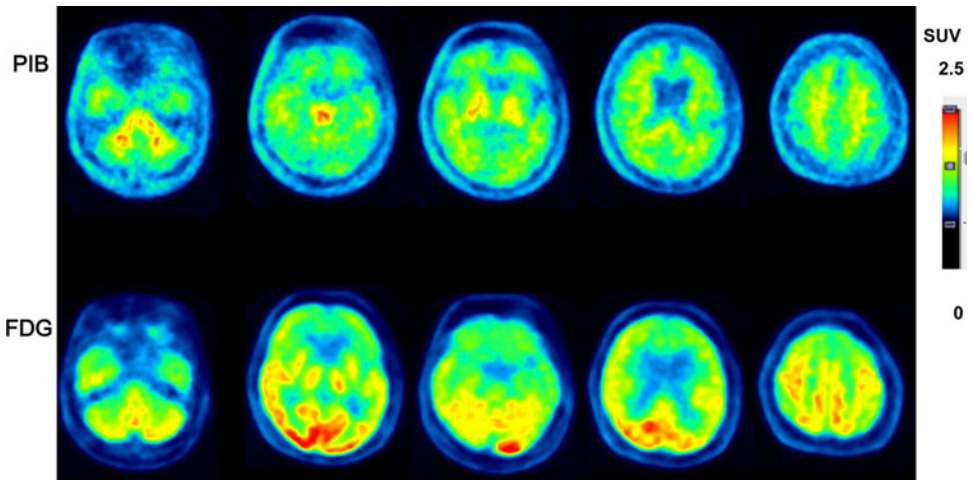

Fig. 2 *Upper panel* PIB-PET shows no accumulation of amyloids in the cortex. *Lower panel* FDG-PET shows decreased glucose metabolism in the frontal and temporal lobes with left-side dominancy associated with decreased metabolism in the right cerebellar hemisphere

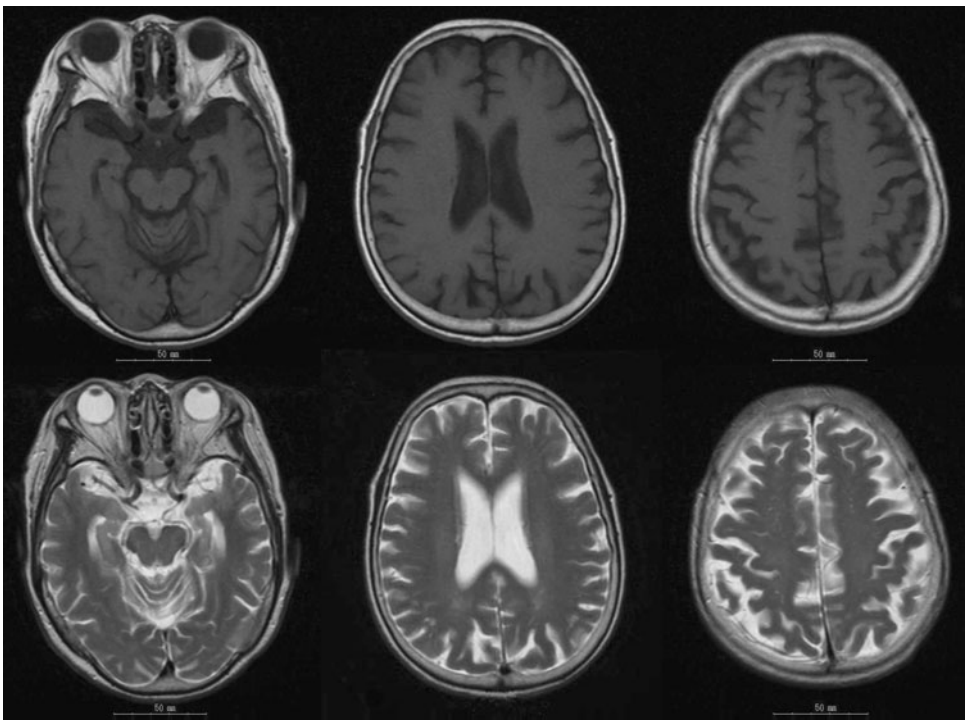

Fig. 3 Atrophy of bilateral medial temporal areas. Age-associated diffuse atrophy of the cerebral cortex

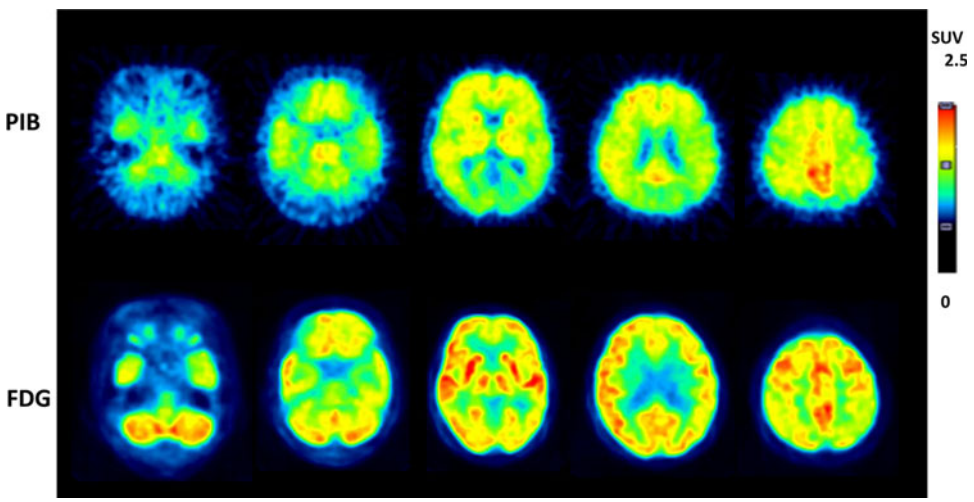

Fig. 4 *Upper panel* PIB-PET shows accumulation of amyloids mainly in the frontal lobe, anterior and posterior cingulate gyrus, precuneus, and also in the parietal lobe and lateral temporal lobe. *Lower panel* FDG-PET shows decreased glucose metabolism in bilateral parietal lobes with left-side dominancy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