nonspecific white matter retention, the diagnostic value of Aβ imaging, and the role of Aβ pathology in disease generation. However, the editorial by Moghbel and colleagues brings into question the very feasibility of imaging Aβ in the brains of living humans [1]. Many of the issues raised in the editorial have been extensively researched and discussed in various scientific venues and publications over the past decade. However, it may be worthwhile to communicate these findings to a larger community, including scientists not active in this particular field of research. Thus, to avoid further misunderstandings and foster discussion based upon common grounds of knowledge in the future, we will try to address the issues raised by Moghbel and colleagues point by point and summarize the corresponding evidence in the following order: (1) alleged anomalies in the distribution of Aβ radiotracers, (2) perceived difficulties in visualizing Aβ plaques, (3) concerns about the binding properties of Aβ radiotracers to plaques, and (4) questions regarding the theoretical basis of Aβ imaging.

Alleged anomalies in the distribution of Aβ radiotracers

Moghbel and colleagues point out two issues regarding the regional distribution of Aβ radiotracers. One is a limitation of all existing Aβ radiotracers: nonspecific white matter retention. This phenomenon is well known, having previously been demonstrated in in vitro studies with human brain (see Fig. 4 of [2], Figs. 1C&D of [3], and Fig. 2 of [4]), in animal studies, (see Fig. 3 of [5]), and from the very beginning of in vivo human studies (see Fig. 3B of [4]). In hundreds of subjects, it has been shown that the level of this

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nonspecific white matter retention does not differ between Alzheimer's disease (AD) patients and normal controls [6–9]. Given that regional cerebral blood flow in white matter is approximately 40–50% of that in neocortex [10, 11], slower clearance of tracers [12] likely contributes to Aβ radiotracer retention in white matter [4, 13]. This nonspecific retention continues to represent a challenge to optimizing the analysis of Aβ imaging positron emission tomography (PET) data. It is true that spillover can occur from this nonspecific retention into neighboring gray matter (and vice versa when gray matter contains high amounts of fibrillar Aβ). However, it should be mentioned that due to the relatively small width of the cortical gray matter, which can be below the resolution of a PET scanner, the partial volume effect is not a problem unique to Aβ imaging but affects PET imaging procedures of the brain in general. Furthermore, in Fig. 2 of Moghbel et al., a representation of the partial volume effect is given that is not appropriate for Aβ imaging. Moghbel et al. refer to work in malignant lung lesions where the intensity differences are indeed huge and "overwhelming" [14]. In contrast, the typical retention of Aβ radiotracers in gray matter is not a small fraction of an overwhelming level of white matter retention as depicted, but at least comparable to threefold higher in typical Aβ-positive scans. Nevertheless, it is clear that the white matter uptake and the corresponding partial volume effects may lead to inaccuracies in the precise quantification of cortical tracer retention and thus assessment of cortical Aβ. While common to all Aβ radiotracers, this is more noticeable in currently published studies using ^{18}F-labeled Aβ radiotracers, which appear to generally show somewhat higher white matter retention as compared to ^{11}C-labeled Pittsburgh Compound-B (PiB) [4, 7, 9, 15–17]. However, this limitation has not proven to be a major hurdle to the quantitation of Aβ deposits in cortical gray matter, neither in the in vivo/postmortem cross-validation studies, nor in studies on the predictive value of the Aβ imaging findings, with regard to future cognitive decline. Nevertheless, there is room for further improvement in this context with regard to the development of tracers with less white matter retention and of image evaluation techniques (such as partial volume correction algorithms/volume of interest-based techniques for selective identification of gray matter uptake) [18–20]. Finally, it needs to be emphasized that for many clinical purposes, answering the question of the general presence of Aβ pathology in the brain with YES or NO by visual assessment will be of higher priority than absolute quantification and localization of these abnormalities. For example, in routine clinical practice, fluorodeoxyglucose (FDG) PET data of the brain are read without partial volume correction and the interpretation is usually established without absolute quantification of the findings.

A second alleged discrepancy between Aβ tracer retention and Aβ pathology—the claim that the frontal lobes do not harbor very high Aβ deposition in AD—is contradicted by a wealth of existing data. Thal et al. have clearly demonstrated heavy and early frontal Aβ deposition [21]. In their classic 2002 paper, this group (led by Heiko Braak) stated that in the earliest phase of Aβ deposition (phase 1) "*there are Aβ deposits in the frontal, parietal, temporal, or occipital neocortex*" [21] and Fig. 2 of this group's 1997 paper based on the examination of 2,661 brains clearly shows early and predominant basal frontal and anterior temporal Aβ deposition [22] (Fig. 1).

Numerous other neuropathological studies recapitulate these findings. In fact, the lead author of the paper that Moghbel et al. lean upon most heavily [23] later published a report showing that very high plaque density is found in the frontal cortex in AD [24]. An even more recently published work by this group demonstrated good correlation of an ^{18}F Aβ tracer to pathologically determined Aβ load in biopsies of the frontal cortex [25]. Despite the fact that neuropathological studies consistently detect a high Aβ plaque load in frontal cortex, neuropathological measures of percent plaque area are only semiquantitative and are complicated by variations caused by the fluorescence properties of the dyes used or secondary reactions used to amplify Aβ-antibody binding. Therefore, this may not be the most appropriate comparison to Aβ imaging. A more appropriate postmortem analysis would be truly quantitative assessments such as enzyme-linked immunosorbent assay (ELISA) analysis of Aβ load [26, 27]. In their benchmark study of 79 postmortem brains, Näslund et al. clearly show that frontal cortex typically contains two- to fourfold higher levels of total Aβ than temporal, entorhinal, parietal, or visual cortices [26]. In summary, the contention by Moghbel and colleagues that the frontal lobe is not a prominent site of Aβ deposition is inconsistent with the current state of knowledge regarding the neuropathology of AD.

The suggestion by Moghbel and colleagues that congophilic angiopathy (CAA) could be responsible for Aβ tracer retention in the frontal cortex also does not follow from the neuropathology literature. Several studies (including a recent one they cite [28]) clearly identify the occipital lobe as the site of highest Aβ deposition in CAA, but the occipital lobe is one of the lowest neocortical sites of Aβ radiotracer retention in AD [6, 29].

Moghbel et al. also claim that structural and functional changes such as regional atrophy, hypoperfusion, or hypometabolism should serve as a predictor of regional Aβ pathology. However, evidence that these processes are associated with regional postmortem Aβ pathology is sparse. For example, while brain atrophy may indeed occur in some areas of the brain affected by Aβ pathology, the data suggest that these abnormalities are sequential, and that Aβ deposition precedes synaptic dysfunction and neuronal loss [30–32], which are then evidenced as structural

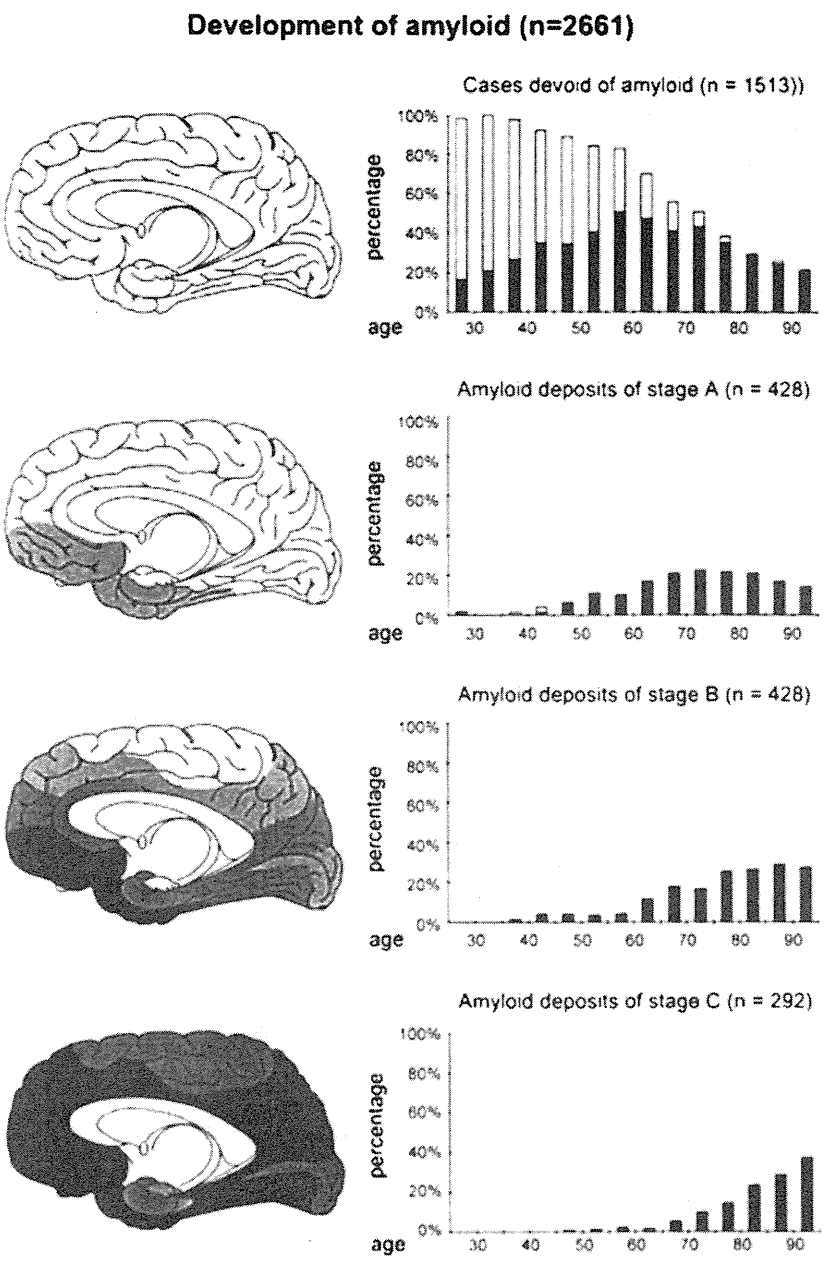

Fig. 1 "Development of amyloid deposits in 2,661 nonselected autopsy cases. The first line displays the frequency of cases devoid of changes in relation to the total number of cases in the various age categories. The second, third, and fourth lines are similarly designed, and show the evolution of the AD-related changes. The dark areas of the columns refer to subgroups showing the presence of neurofibrillary changes." (reproduced with permission from *Neurobiol Aging*, [22])

changes [33]. This may very well explain the regional discrepancies between patterns of atrophy and Aβ deposition detected by in vivo imaging studies [34]. At any rate, these considerations revolve around the interaction of different neurodegenerative pathologies and do not relate to the value of Aβ imaging to accurately measure the presence of Aβ in the brain.

The strongest proof of the feasibility of Aβ imaging to accurately measure Aβ deposition in vivo is founded on a wealth of detailed Aβ PET-neuropathology correlative studies that demonstrate the close match between in vivo Aβ radiotracer retention and postmortem Aβ pathology as assessed by ELISA, immunohistochemistry, Bielschowsky silver staining, or quantitative in vitro assessment of tritiated PiB binding [25, 35–43] (Fig. 2). Further support is added by the fact that high retention of Aβ radiotracers closely corresponds with: (1) low CSF Aβ levels, (2) presence of the apolipoprotein E ε4 allele, and (3) increasing age [44–47].

To make this argument even stronger, those subjects with a different regional distribution of Aβ in the brain such as those carrying one of the mutations associated with autosomal dominant AD [48–50], or familial British dementia [51], or subjects with posterior cortical atrophy [52–55] or CAA [56, 57] show a different regional distribution of PiB retention. If the retention of Aβ radiotracers was determined by nonspecific factors as much as Moghbel and colleagues suggest, then all scans would look relatively similar. The sharp distinction between the regional pattern of PiB

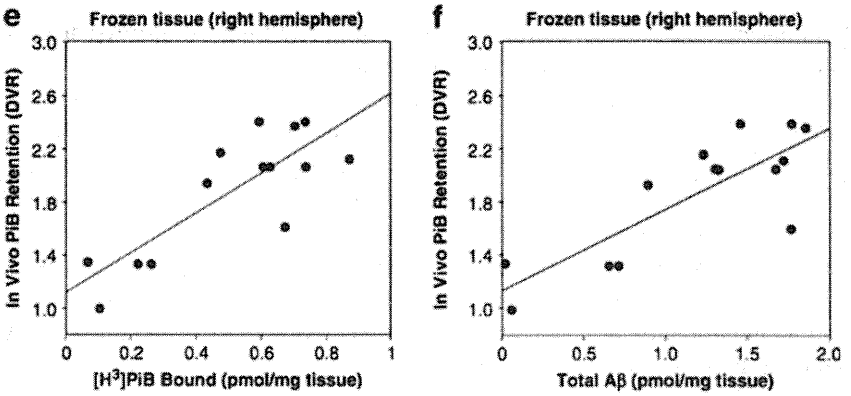

Fig. 2 Correlations of the in vivo PiB distribution volume ratio (*DVR*) values with postmortem quantifications of [^{3}H]PiB binding (*E*) and total insoluble Aβ ($Aβ_{1-40}$+$Aβ_{1-42}$) peptide levels (*F*) in 19 brain regions from fresh-frozen tissue from the right hemisphere of the same Alzheimer's disease subject. (reproduced with permission from *Brain*, [36])

retention in many presenilin-1 mutation carriers [48] and sporadic AD (Fig. 3)—corresponding to the known patterns of Aβ aggregation in their brains—makes a convincing argument for specific Aβ-driven retention of Aβ PET tracers.

Perceived difficulties in visualizing Aβ plaques

Moghbel and colleagues raise the concern that Aβ plaques in the brain are too small to allow in vivo imaging by means of PET. This argument would not only render Aβ imaging as impractical, but it would argue against the possibility of imaging structures/processes of even smaller size (i.e., molecular imaging in general), such as neuronal glucose metabolism (regularly imaged with FDG) or the receptor density on cell membranes. Aβ imaging does not attempt to resolve an individual 50–100 μm Aβ plaque. That futile effort would indeed be thwarted by the limited resolution of PET and the partial volume effects described. However, partial volume effects not only decrease the signal within a small structure such as a plaque due to low-signal bleed-in, but partial volume effects also increase the signal in the plaque penumbra by high-signal bleed-out. The net effect is a blurring of the signal on a submillimeter scale, but without significant loss of total signal on a larger scale. Like any other PET technique, Aβ imaging assesses the *average concentration* of Aβ radiotracer binding sites within a region of interest. Just as one dopamine receptor would be swamped by neighboring receptor-free tissue but millions of dopamine receptors produce a strong ^{11}C-raclopride signal in the striatum, also millions of fibrillar Aβ deposits produce a signal that is easily detectable in Aβ-laden parts of gray matter.

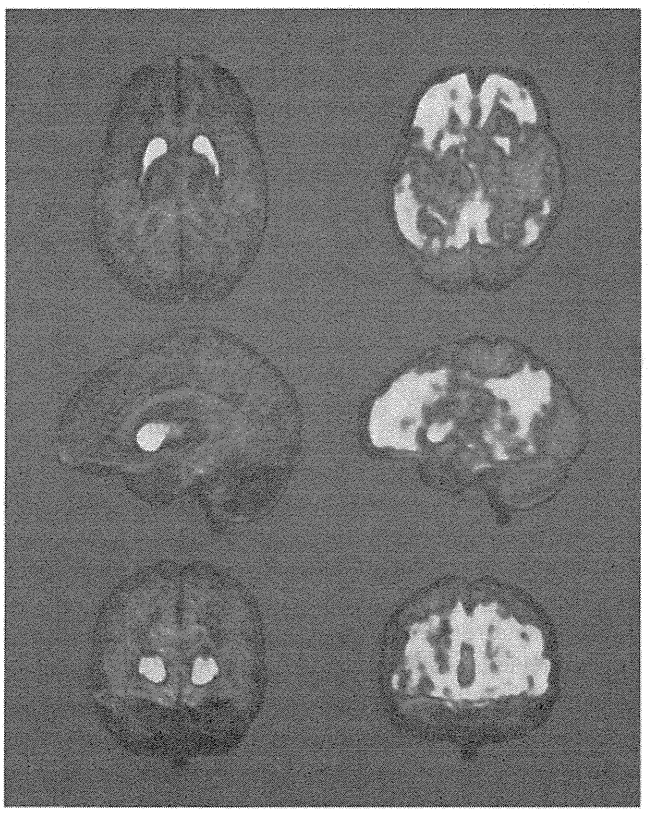

Fig. 3 Comparison of the regional distribution of PiB retention in a presenilin-1 mutation carrier (*left*) and a sporadic case of AD (*right*). The MRI is shown in *gray* and PiB retention is overlaid in a hot metal scale on transaxial (*top*), sagittal (*middle*), and coronal images (*bottom*)

Another concern brought up by Moghbel and colleagues is based on the surprising and unsupported assumption that the mass of Aβ in mild cognitive impairment (MCI) would be 60-fold less than (i.e., 1–2% of) that in AD, thus not possibly providing enough target structures for successful imaging. This assumption is not supported by data of neuropathological studies. In contrast, the quantitative postmortem data of Näslund et al. showed that subjects who die at the Clinical Dementia Rating (CDR) 0.5 stage (typically considered MCI) had an Aβ load 25–76% of that seen in patients with established dementia (CDR of 1.0 or greater) [26].

Even in groups of autopsy cases consisting of early or mild-moderate AD, neocortical amyloid markers are not significantly different when compared to those in MCI cases [58]. A recent review summarized the extent of amyloid pathology in MCI relative to cognitively normal people and early AD [59].

There is ample Aβ in the neocortex of AD and MCI patients and many normal controls to be detected with Aβ

radiotracers. The nominal concentration of Aβ in AD frontal cortex is ~3 μM [26, 27, 60], which is about twofold the number of PiB binding sites measured in vitro under saturating conditions [60] (and in the mid-nanomolar range under non-saturating conditions [61]). This is several orders of magnitude higher than the concentration of many receptors successfully assessed by PET. A recent paper demonstrated that, even under non-saturating conditions, there are about the same number of binding sites available in frontal and temporal cortex in postmortem human AD tissue [~60 fmol/mg tissue (~60 nM)]. The authors concluded that "*the observed binding of [^{11}C]PIB to amyloid plaques in vitro in human AD tissue, but not in healthy controls, is in correspondence with in vivo studies of patients with AD. This radiotracer is therefore very suitable in the early diagnosis of AD and can be used for the detection of pathological changes before there is a significant loss in cognitive function.*" [61]. This, along with the high affinity of the PET radiotracers for Aβ, renders the concerns about visualizing Aβ plaques inconsistent with a wealth of existing data.

Concerns about the binding properties of Aβ plaques

Moghbel and colleagues also propose that there may be "*inherent difficulties of targeting fibrillar amyloid plaques, which are not as well-defined as the soluble forms of the protein.*" Since the soluble (including oligomeric) forms of Aβ are not well defined at all, it is difficult to interpret this concern. In principle, conversion of a number of available binding sites from a soluble to a more solid or immobile status would be expected to increase the binding of a suitable ligand. For example, decreasing the mobility of receptors by fixation to a solid support can increase the binding of ligands [62, 63] because of decreased entropy and increased rebinding of small molecule ligands [64]. Currently, there are no data to support the idea that Aβ radiotracer binding to insoluble Aβ fibrils is fundamentally different than any other binding interaction of a radioligand with specific binding sites on other proteins (many of which are relatively immobile because they are embedded in membranes). In fact, the binding of Aβ radiotracers to Aβ fibrils shows typical, reversible binding properties in in vitro kinetic binding analyses [18].

The authors point out that no in vivo studies using high doses of unlabeled Aβ PET ligand to compete off the specifically bound Aβ radiotracer have been performed to validate the specific and reversible nature of binding in humans. This is true and will likely remain true for two reasons: (1) the nominal concentration of Aβ radiotracer binding sites is on the order of 1 μM in AD cortex [26, 27, 60], requiring micromolar levels of unlabeled ligand to effectively compete off the Aβ radiotracer; and (2) none of the Aβ tracers have been approved for human use at the doses required to achieve micromolar levels in brain. While it might be possible to perform such studies in animals, there are significant problems using Aβ radiotracers in transgenic mouse models of AD [60, 65], although some of these problems may be possible to overcome [66].

A more pertinent concern that Moghbel et al. correctly point out is that there are different tertiary forms of Aβ deposited in brain, such as the amorphous deposits in cerebellum which have very low affinity for all Aβ radiotracers. This conformational variability also may come into play in autosomal dominant forms of AD [48, 67] and in early stages of Aβ deposition [37], but the significance of non-fibrillar Aβ in typical, sporadic, late-onset AD is unknown. Studies assessing the selectivity of PiB for other aggregated misfolded proteins present in AD, such as tau/neurofibrillary tangles [36, 68] and α-synuclein/Lewy bodies [69, 70] utilizing in vitro methods that are more pertinent to PiB binding in vivo, have shown that in vivo cortical retention of ^{11}C-PiB primarily reflects fibrillar Aβ deposits. The potentially differential affinity of the Aβ tracers to various forms of Aβ deposits does not necessarily affect the clinical utility of Aβ imaging. For example, the case mentioned by Moghbel and colleagues [37] did not meet two commonly used sets of neuropathological criteria for AD [71, 72], because only sparse neuritic plaques and neurofibrillary tangles were present, although the case did meet the older Khachaturian criteria [73]. Nevertheless, it is important to keep in mind that different conformations of Aβ deposits in the brain [74] may affect the binding pattern of the tracers and that Aβ imaging modalities may not recognize all types of Aβ pathologies with equal sensitivity. This may be an interesting area of future research, to further improve the understanding of the quantitative information provided by in vivo Aβ imaging methods. However, any additional insights in this regard would rather lead to assigning a more specific information to the Aβ imaging signal than putting the general utility of this method into question.

Questions regarding the theoretical basis of Aβ imaging

Finally, Moghbel and colleagues broaden their concerns well beyond issues related to PET imaging by questioning the Aβ cascade hypothesis itself. This would imply that if Aβ deposition is not causative of AD, it is not worth measuring. In this context, it is important to draw a clear distinction between the value of Aβ imaging and the merits of the Aβ hypothesis—a hypothesis that remains supported by the bulk of existing data [75]. The basic feasibility of imaging AD pathology in vivo should not be confused with a discussion of the causal relevance of Aβ in AD. In isolation, Aβ imaging is not diagnostic, it is agnostic—that

is, agnostic to the role of Aβ deposition in AD. Aβ imaging was intended to assess the pathology of AD in vivo. This tool may ultimately be used to help prove or disprove the Aβ hypothesis of AD. The Aβ cascade hypothesis, though important, is not highly relevant to the feasibility and validity of Aβ imaging since, by definition, Aβ deposition remains a pathological hallmark of this disease.

Further, Moghbel et al. suggest that if Aβ deposition is causative, then the levels of Aβ in brain should correlate with cognition. Again, Aβ imaging is not a tool to assess cognition. In contrast, it may represent a tool to detect Aβ pathology independently and in particular before the onset of clinically significant cognitive symptoms. For example, a number of studies that have demonstrated the predictive value of Aβ pathology in subjects with MCI with regard to subsequent cognitive decline support this notion [76–79]. The long-recognized discrepancy between cognitive impairment and Aβ plaque burden in the brain [80] may be explained by three factors: (1) a dissociation in timing between early disease events and subsequent events that are more directly related to cognition [81]; (2) cognitive changes may be more related to the long-term, cumulative effects of soluble, oligomeric forms of Aβ (not apparent by routine neuropathology or imaged by current PET tracers) [82, 83]; and (3) the importance of cognitive reserve in the modulation of symptoms in the presence of brain pathology [84, 85].

Moghbel and colleagues further discuss the "*noteworthy rates of false-positive and false-negative PET scans using amyloid tracers*" [1]. This appears to reflect conceptual misunderstanding and terminological imprecision. A person with a positive Aβ PET scan who is negative for clinical AD should not be regarded as a "false-positive" but rather correctly classified as an "Aβ-positive" non-demented subject. This was clarified in the original report using PiB PET [4] as follows, "*Therefore, at the outset, it may be best to not equate amyloid deposition to clinical diagnosis. Rather than as a method of diagnosis, it might be best to first think of PiB retention more fundamentally as a method to detect and quantify brain β-amyloidosis, a term first used in reference to AD by Glenner* [86]." Aβ imaging simply detects cerebral β-amyloidosis. It does not provide a diagnosis by itself. It is only one tool to be used along with clinical assessment and other biomarker modalities to enhance our ability to provide earlier and more accurate diagnoses. The "false-positives" and "false-negatives" to which Moghbel et al. refer are mismatches between the presence of cerebral β-amyloidosis and symptoms of dementia. They are not false-positives and false-negatives for the presence of Aβ. The latter can only be determined by PET-neuropathology correlations and to date, there have been essentially no reported false-positives and only the rare false-negatives that would be expected when comparing an in vivo technique with a highly sensitive tissue stain [41, 87].

Summary

We acknowledge that there are a number of caveats with regard to the clinical value of Aβ imaging. This includes disorders other than AD which may show Aβ deposition (such as dementia with Lewy bodies), the unknown time to conversion in healthy Aβ-positive persons or the relative plateauing of the Aβ burden in later stages of disease [79, 87–90]. However, these caveats are not related to the proven functionality of the tracers and should not hamper the application and further evaluation of in vivo Aβ imaging with PET.

The fact that Aβ deposits can be detected by Aβ imaging in vivo is, in our opinion, a fact substantiated by a wealth of peer-reviewed data. ^{18}F-Labeled Aβ imaging radiotracers may be approved for clinical use in the near future. If so, this will be the first PET radiopharmaceutical developed commercially and the first PET tracer approved for clinical use by the US Food and Drug Administration (FDA) since FDG. As such, it represents a landmark moment in the field of molecular imaging and should encourage further commercial investment and development in the field. The functionality, sensitivity, and specificity of Aβ plaque imaging agents has by now been demonstrated in a level of detail and reliability (including in vivo-to-postmortem autopsy correlations) that has not been required or provided for most other imaging tracers clinically used today. Many of the concerns raised by Moghbel and colleagues in their current editorial in the *European Journal of Nuclear Medicine and Molecular Imaging* have been resolved previously, and we attempted to summarize the available information on these issues, to allow a future rational discussion on common grounds of knowledge. As is the case for any clinical test, Aβ imaging does not represent a perfect tool and some justified concerns remain, such as the nonspecific white matter retention or the effects of atrophy and partial volume on quantification. However, none of these concerns reasonably question the general feasibility of Aβ imaging or have been demonstrated to hamper the value of this procedure for detection of fibrillar Aβ pathology. A discussion regarding clinical indications for Aβ imaging is as welcome and important as the debate about the causal role of Aβ pathology in the genesis of AD. However, both of these topics clearly need to be treated independently from the feasibility of Aβ imaging itself. Thus, we believe that the remaining issues do not justify a call to slow the clinical development of these radiotracers and to withhold the availability of this technology from those it could potentially help. In contrast, we believe that hindering the progress of this exciting new molecular imaging approach could send an erroneous and discouraging signal to groups interested in the development of other new diagnostic agents. The inability to obtain the information provided by Aβ imaging would most certainly slow

down the urgently needed progress in understanding the basics of neurodegeneration and in the development of new approaches aiming to treat these devastating disorders. Aβ imaging has been repeatedly held up as one of the major successes of the past decade in the fight against AD. Thus, rather than to unnecessarily question the general feasibility of Aβ imaging, we believe we should vigorously foster the application of this unique new tool to improve our understanding of AD pathophysiology, to aid clinical diagnosis, and to advance the development of effective therapy.

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Conflicts of interest This response represents a consensus opinion of all coauthors, is meant to apply to all current amyloid PET tracers equally, and is not meant to favor any one particular tracer over any other. Two coauthors (WEK and CAM) have a conflict of interest based on being coinventors of an amyloid imaging tracer licensed by GE Healthcare, several coauthors (AD, MDI, KI, WJJ, KAJ, WEK, VJL, CLM, CAM, AN, RCP, EMR, CCR, RAS, KVL, VLV, and MWW) have been paid consultants to or received research grant support from one or more of the companies developing commercial amyloid imaging tracers (AstraZeneca, Bayer Schering, GE Healthcare Merck and/or Avid/Lilly) and one coauthor (DJB) holds a part-time position as a Senior Neurologist with GE Healthcare. Six coauthors have no conflicts of interest relative to amyloid PET tracers (BTH, CRJ, RAK, TJM, JCM, DJS).

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CASE REPORT

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

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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

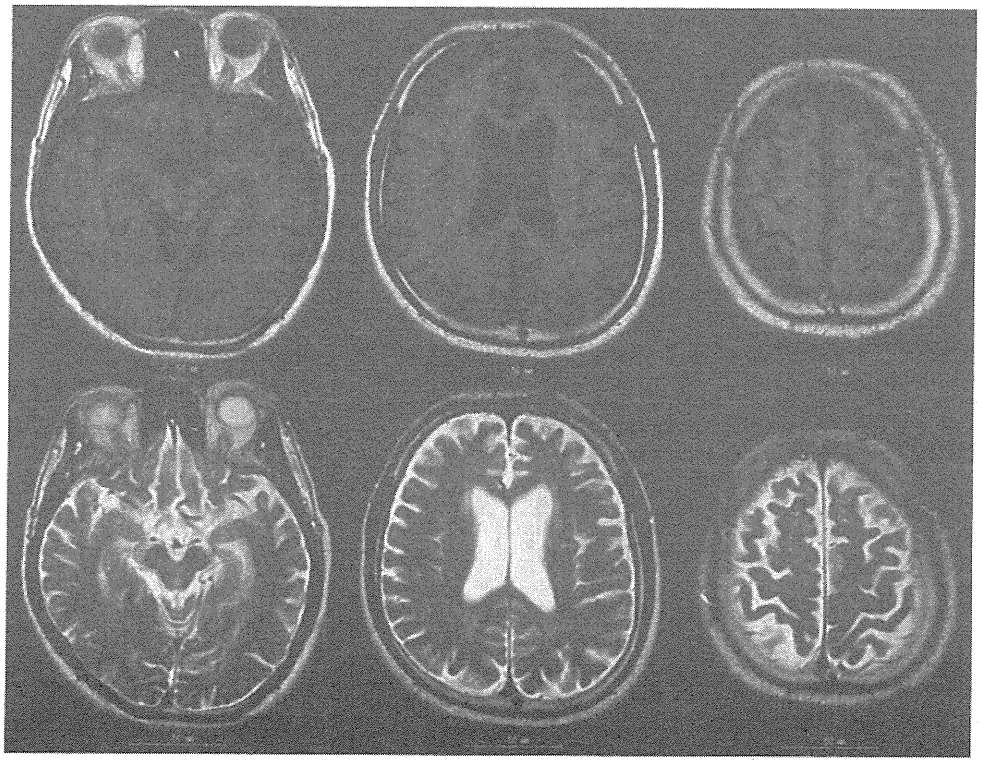

Fig. 1 Mild atrophy of both the frontal and parietal lobes and the left medial temporal area

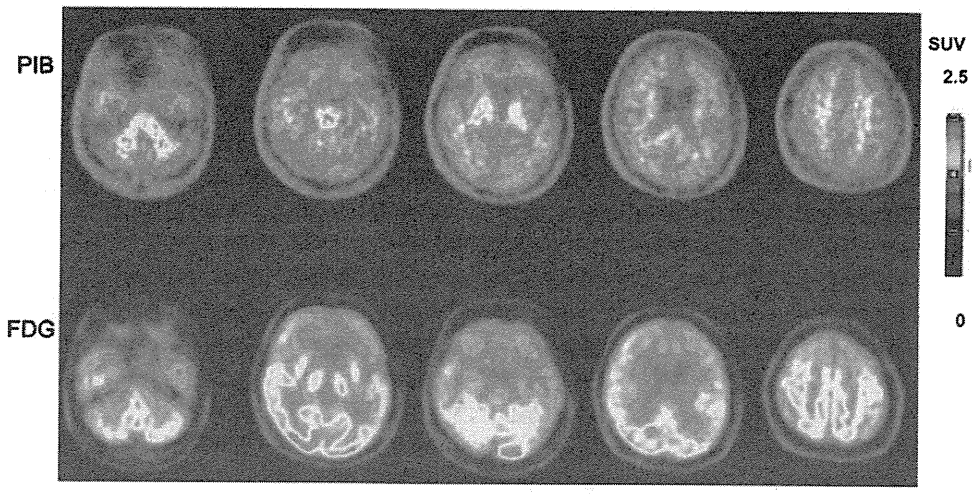

Fig. 2 *Upper panel* PIB-PET shows no accumulation of amyloids in the cortex. *Lower panel* FDG-PET shows decreased glucose metabolism in the frontal and temporal lobes with left-side dominancy associated with decreased metabolism in the right cerebellar hemisphere

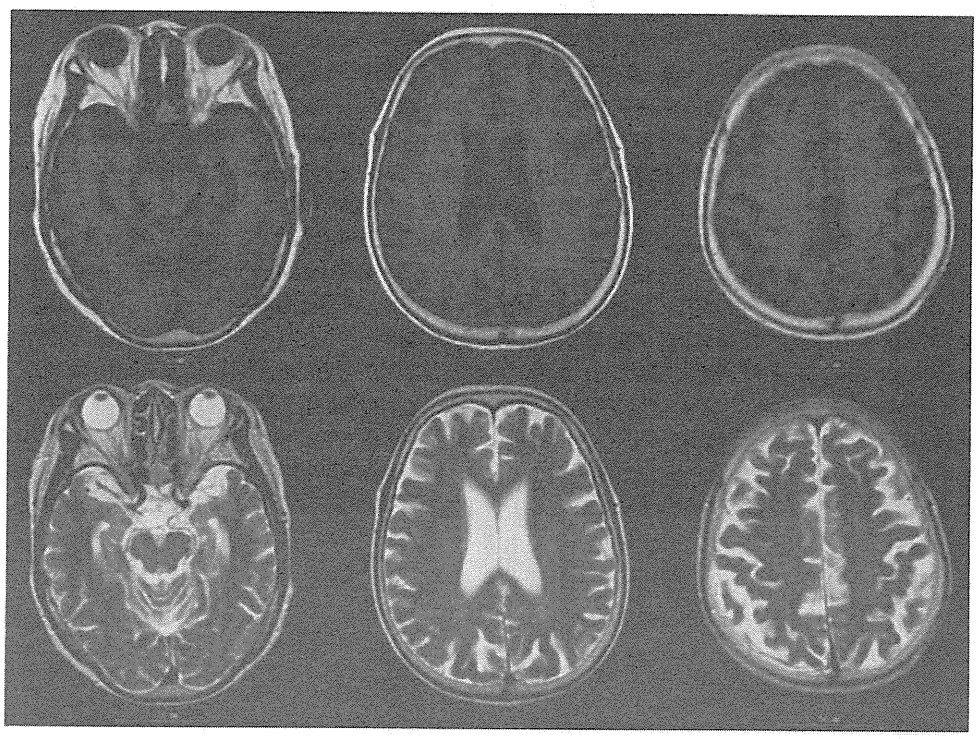

Fig. 3 Atrophy of bilateral medial temporal areas. Age-associated diffuse atrophy of the cerebral cortex

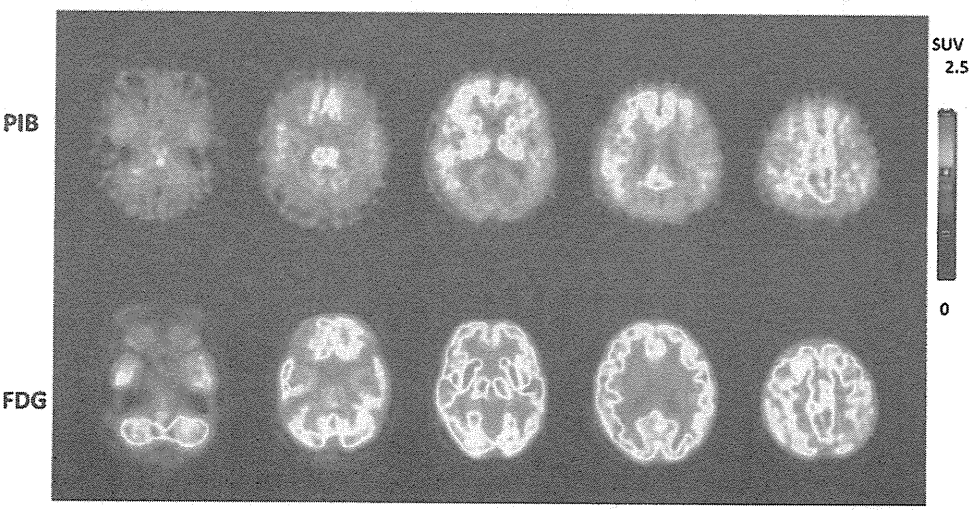

Fig. 4 *Upper panel* PIB-PET shows accumulation of amyloids mainly in the frontal lobe, anterior and posterior cingulate gyrus, precuneus, and also in the parietal lobe and lateral temporal lobe. *Lower panel* FDG-PET shows decreased glucose metabolism in bilateral parietal lobes with left-side dominancy 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 ± 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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Evaluation of Therapeutic Response to Donepezil by Positron Emission Tomography

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Abstract

Background

Donepezil hydrochloride (Donepezil) is an acetylcholinesterase inhibitor (AChEI) that is used for the symptomatic treatment of Dementia of the Alzheimer's Type (DAT). Recently, the effects of AChEI in patients with DAT have been investigated using positron emission tomography (PET) or single photon emission computed tomography (SPECT). This study is to evaluate the usefulness of fluorine-18-fluorodeoxyglucose (FDG)-PET in assessing the therapeutic response of Donepezil to DAT using Regions of Interest (ROI) analysis.

Methods

The participants included eleven outpatients diagnosed as having DAT according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-Ⅳ). The patients were performed FDG-PET before initiating Donepezil therapy and after 12 weeks of medication. Cognitive change was measured using the Japanese version of the Alzheimer's disease Assessment Scale cognitive subscale (ADAS-J cog) and the group was divided into Responders and Non-responders based on these results. We used FDG-PET to investigate glucose metabolism of the brain and measured FDG uptake in the ROI set in each lobe of the brain. Then the ratios of the post-treatment uptake to pre-treatment uptake were determined.

Results

In the Responders, the mean ratios in the frontal, temporal, occipital, parietal, and temporoparietal lobes were 2.18, 1.62, 1.15, 1.12, and 1.09 respectively. The mean ratios of the Non-responders were 0.69, 0.88, 0.75, 0.98, and 0.68 respectively. Significant differences were found between the ratios of the Responders and Non-responders in the frontal and occipital lobes ($p<0.05$).

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Conclusions

These findings suggest that FDG-PET could be useful for the evaluation for monitoring response to Donepezil.

Key Words: Donepezil; FDG-PET; Alzheimer; ADAS-J cog; ROI analysis

Introduction

Donepezil hydrochloride (Donepezil) is a highly centrally selective inhibitor of acetylcholinesterase (AChE) which is used for the symptomatic treatment of Dementia of the Alzheimer's Type (DAT). Acetylcholinesterase inhibitors (AChEIs) have an effect that delays the progression of cognitive dysfunction in DAT and occasionally improves cognitive function[1-5]. Although cognitive improvement occurs in 12% to 60% of the patients across the agents[4,6], AChEIs have not been effective for some patients with DAT regardless of disease stage[1,3-5]. Furthermore, it is not easy to evaluate the therapeutic response of Donepezil to patients with DAT for various reasons such as clinical symptoms or progression of the disease. Therefore, an index for a more objective evaluation of the therapeutic effect of AChEIs on patients with DAT is needed.

It has been established that regional metabolic rates for glucose assessed by fluorine-18-fluorodeoxyglucose-positron emission tomography (FDG-PET) in patients with DAT provides a sensitive, in vivo metabolic index of DAT[7]. Many studies have reported that reduced cerebral blood flow (CBF) and metabolism are observed firstly in the temporoparietal brain regions and the posterior cingulate cortex of patients with DAT. Recently, the effect of AChEIs in patients with DAT have been reported using PET or single photon emission computed tomography (SPECT)[4,5,8-13].

We examined the usefulness of FDG-PET in assessing the therapeutic response to Donepezil in patients with DAT using Regions of Interest (ROI) analysis.

Methods

The subjects of this study were eleven right-handed outpatients (3 men, 8 women; age range, 61-84 y; mean age, 72.1 y) diagnosed as having DAT by the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-Ⅳ)[14] (Table 1). The inclusion criterion of this study was a dementia severity below grade 2 on the Clinical Dementia Rating (CDR) scale. In order to evaluate cognitive function, the Revised Hasegawa Dementia Scale (HDS-R: score 0-30, with 0 being the most severe)[15] was used to all subjects with DAT. The HDS-R has been used exclusively in East Asian countries as a screening test for DAT. The optimal cut-off scores of the HDS-R for mild DAT are 20/21 in Japan. We assessed cognitive change using the Japanese version of the Alzheimer's disease Assessment Scale cognitive subscale (ADAS-J cog)[16]. This reliable and valid neuropsychological test of cognition has 11 items which test a variety of domains, including spoken language ability, comprehension of spoken language, recall of test instructions, word-finding difficulty, following commands, naming, orientation, ideational and constructional praxis, word recall, and word recognition. This test can be administered in approximately 40 minutes. Maximal impairment on the ADAS-J cog is indicated by a score of 70, with lower scores indicating less severity. We defined patients

Table 1. DSM-Ⅳ Diagnostic criteria for Dementia of the Alzheimer's Type

A. The development of multiple cognitive deficits manifested by both
  (1) memory impairment (impaired ability to learn new information or to recall previously learned information)
  (2) one (or more) of the following cognitive disturbances:
    (a) aphasia (language disturbance)
    (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
    (c) agnosia (failure to recognize or identify objects despite sensory function)
    (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in Criteria Al and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. The course is characterized by gradual onset and continuing cognitive decline.

D. The cognitive deficits in Criteria Al and A2 are not due to any of following:
  (1) other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
  (2) systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B_{12} or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
  (3) substance-induced conditions

E. The deficits do not occur exclusively during the course of a delirium

F. The disturbance is not better accounted for by another Axis I disorder (e.g., Major Depressive Disorder, Schizophrenia).

DSM-Ⅳ, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

whose total score on ADAS-J cog changed by more than −1 point as Non-responders and those under −1 point as Responders. None of the participants in this study had diabetes mellitus. Each patient had undergone brain perfusion SPECT with Tc 99m-ethyl cysteinate dimmer before this study. To confirm the diagnosis of DAT, each SPECT image was analyzed using the easy Z-score imaging system (eZIS)[17]. The Institutional Review Board of Osaka City University Hospital approved this study protocol, and informed consent was obtained from each patient and his or her family representative after a detailed explanation of the study.

All patients had fasted for at least 4 hours before PET scanning. Each patient underwent the first PET scan before the first dose of Donepezil. After the first PET examination, patients received 3 mg/day of Donepezil for the first 2 weeks, and then received 5 mg/day thereafter if tolerated. A second PET scan was completed after 12 weeks of Donepezil therapy. FDG was produced with the NKK-Oxford superconducting cyclotron and NKK synthesis system. A HEADTOME Ⅳ SET-1400W-10 (Shimadzu Corp., Japan), which has 4 detector rings providing 7 contiguous slices at 13 mm intervals, was employed for PET studies. The effective spatial resolution was 14 mm in Full Width Half Maximum. Before emission scanning, transmission scans were performed with a $^{68}Ge/^{68}Ga$ ring source for attenuation correction. Images were obtained from 40 to 55 minutes after intravenous injection of 185-370 MBq FDG after a 4-hour fast.

Five regions of interests (ROIs: circles 3 pixels in diameter) were placed on each area of FDG uptake within the left and right frontal, temporal, temporoparietal, parietal, occipital lobes, and cerebellar hemisphere. FDG uptake in ROIs on each lobe was measured, then divided by the mean count in the cerebellum normalized by the mean count per pixel in each ROI. These regions are shown in Figure 1. To evaluate the therapeutic effect of Donepezil, we calculated the ratio of the mean count after treatment to the count before treatment.

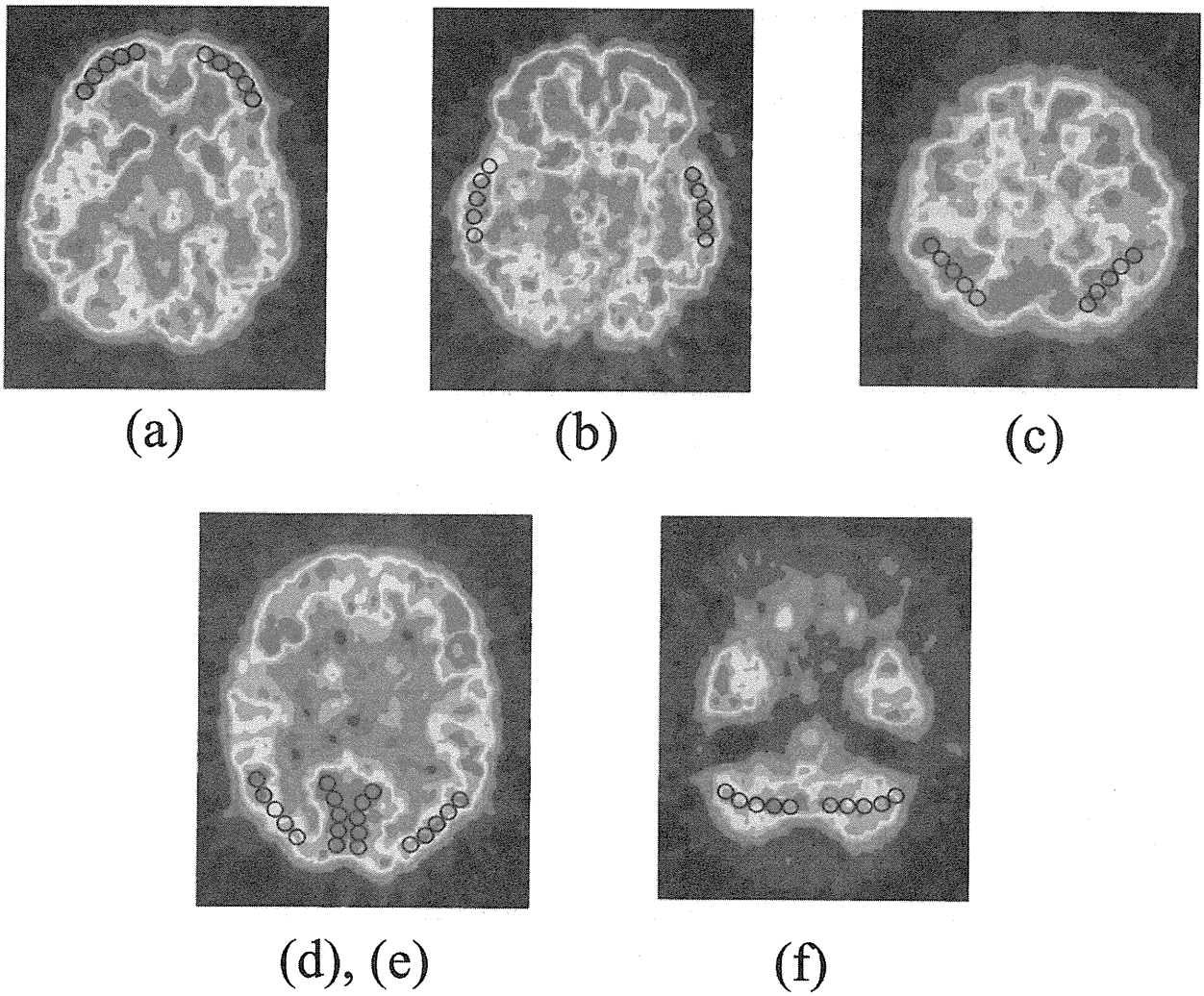

Figure 1. Five pairs of regions of interest (ROIs: circles 3 pixels in diameter) placed on the left and right frontal (a), temporal (b), parietal (c), temporoparietal (d), and occipital (e) lobes. Cerebellar reference regions were defined on the bilateral cerebellum (f).

Statistical analysis was performed with SPSS for Windows 16.0 (SPSS Japan, Tokyo, Japan). Categorical variables, such as gender, were compared with chi-square and Fisher-exact tests. We used the Mann-Whitney U-test to compare clinical characteristics and the ratio of the mean count after treatment to the count before treatment between Responders and Non-responders. All statistical tests were two-tailed and reported at $p<0.05$.

Results

Table 2 shows the demographic and clinical characteristics of Responders and Non-responders divided according to the changes of total scores of ADAS-J cog. Of the 11 patients, 7 were Responders and 4 were the Non-responders. There were no significant differences between Responders and Non-responders with respect to patient age, age at disease onset, duration of DAT/dementia, years of education, HDS-R score or total score on ADAS-J cog before treatment. In addition, chi-square analysis did not show any significant difference between the groups with regard to gender distribution or family history of dementia. The average change in the total score on ADAS-J cog in the Responders was –6.27, while in Non-responders, it was 4.25. All