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Amyloid plaque imaging in vivo: current achievement and future prospects

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Abstract
Introduction Alzheimer's disease (AD) is a very complex neurodegenerative disorder, the exact cause of which is still not known. The major histopathological features, amyloid plaques and neurofibrillary tangles, already described by Alois Alzheimer, have been the focus in research for decades. Despite a probable whole cascade of events in the brain leading to impairment of cognition, amyloid is still the target for diagnosis and treatment.
Discussion The rapid development of molecular imaging techniques now allows imaging of amyloid plaques in vivo in Alzheimer patients by PET amyloid ligands such as Pittsburgh compound B (PIB). Studies so far have revealed high ^{11}C-PIB retention in brain at prodromal stages of AD and a possibility to discriminate AD from other dementia disorders by ^{11}C-PIB. Ongoing studies are focussing to understand the relationship between brain and CSF amyloid processes and cognitive processes.
Conclusion In vivo imaging of amyloid will be important for early diagnosis and evaluation of new anti-amyloid therapies in AD.

Keywords Positron emission tomography (PET) · Amyloid · PIB · Alzheimer's disease · Diagnostic marker

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Introduction

Alzheimer's disease (AD) is presently considered as the most devastating neurodegenerative disorder. The present cost of dementia for 29.3 million patients worldwide is estimated to be 315.4 billion US $ [1]. New data suggest that the number of AD worldwide will increase from 26.6 million in 2006 to 106.8 million in 2050 [2]. To tackle both the increasing societal costs and the burden on the patients and their families, great efforts are presently made to develop early diagnostic markers of AD. This will enable early drug intervention and hopefully find a cure of AD in the future.

The appearance of the neuropathological hallmarks of AD, senile plaque and neurofibrillary tangles, probably occur many years before the clinical symptoms of AD [3, 4]. As a consequence, within the aging population, subjects with no history of cognitive problems might show a sign of AD neuropathology at autopsy. Beta amyloid (Aβ 1–42) has been suggested as the primary cause of AD [5], but other ongoing processes, including oxidative stress, inflammatory reactions, microglia activations, tau phosphorylation and neurotransmitter impairment, to some extent, play a crucial role in the AD pathology [6].

The present study will focus on the recent attempts to develop in vivo amyloid imaging methods to understand the evolution of amyloid, which will be important for the development of early diagnostic markers and anti-amyloid treatment strategies in AD.

Amyloid imaging

More than 10 years ago, the development of amyloid ligands started, and the studies went from in vitro binding studies in

tissue homogenates from mice or human autopsy brain tissue to in vivo imaging studies in mice, monkey and humans. Many substances failed because of high unspecific binding and poor distribution to brain in experiment animals [7]. The small molecular strategy turned out to be most promising. Four amyloid positron emission tomography (PET) ligands, namely [^{18}F] 1,1-dicyano-2-[6-(dimethylamino)-2-naphtalenyl] propene or ^{18}F-FDDNP [8], *N*-methyl [^{11}C] 2-(4′-methylaminophenyl)-6-hydroxy-benzothiasole or ^{11}C-PIB [9], 4-*N*-methylamino-4′-hydroxystilbene or ^{11}C-SB13 [10] and 2-(2-[-dimethylaminothizol-5-yl] ethenyl)-6-(2-[fluoro] benzoxazole) or ^{11}C-BF-227 [11] have so far been applied in PET studies to AD patients. In vitro binding studies showed that FDDNP ligand bound to synthetic $A\beta_{1-40}$ with two binding sites, a high affinity site (0.12 nM) and a low-affinity site (1.9 nM), while binding studies with ^{18}F-FDDP in post-mortem AD homogenates showed a B_{max} value of 144 nM with K_d value of 0.75 nM [12, 13]. ^{18}F-FDDNP has also been found to bind to neurofibrillary tangles in human autopsy brain tissue [14]. ^{11}C-PIB showed two binding sites in human autopsy brain tissue, a high affinity binding site with B_{max} of 1,407 pmol/g and K_d value of 2.5 nM and a low-affinity binding site with B_{max} of 13 nM and K_d of 250 nM, respectively [15]. ^{3}H-SB-13 binding studies showed a B_{max} value of 14–45 pmol/mg protein with a K_d of 2.4 nM [16], while BF-227 demonstrated a K_i value of 4.3 nM to Aβ 1–42 fibrils [11].

Transgenic mice models overexpressing human mutant amyloid protein (APP) and amyloid pathology are valuable in AD research. PIB binding, however, was initially demonstrated in brain of APP transgenic mice [15, 17]. By increasing the specific activity of PIB, Maeda et al. [18] were able to elegantly show a similar regional binding of ^{11}C-PIB in transgenic mice brain sections as in autopsy brain slices from AD patients. The ^{11}C-PIB binding was also by found immunostaining to be colocalized with Aβ 40 and Aβ 42 [17].

Amyloid imaging in Alzheimer's disease

The first studies in humans with the PIB were performed in Uppsala, Sweden in 2002. The PIB compound was developed by William Klunk and Chester Matties at the Pittsburgh University. The first PET PIB imaging studies were performed in collaboration between the Pittsburgh University, USA, Karolinska Institutet and Uppsala University, Sweden. Sixteen mild AD patients recruited at Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, underwent imaging with ^{11}C-PIB and showed significantly higher PIB retention in the frontal, temporal, parietal and occipital cortices and the striatum (1.9–1.5 times differences) compared to healthy controls [9]. The retention of ^{11}C-PIB was low and similar in the pons and cerebellum of both groups [9]. An inverse significant correlation was observed between ^{11}C-PIB and cerebral glucose metabolism (^{18}F-FDG) [9]. The findings with ^{11}C-PIB have later been confirmed by several research groups [19–23]. It is estimated that more than 500 subjects now have been scanned with the PET amyloid imaging ligand worldwide. Figure 1 illustrates the high ^{11}C-PIB retention and the regional impairment in cerebral glucose metabolism (^{18}F-FDG) in two mild AD patients compared to a healthy control.

Time course of amyloid load in AD brain as studied by PET

What is the time course of amyloid deposition in AD brains? A 2-year follow-up study using ^{11}C-PIB showed no significant change in the PIB retention compared to baseline, although a decline in cerebral glucose metabolism was observed in all patients and especially in those who had deteriorated in cognitive function by more than 3 points on the MMSE during the follow-up period [24]. This finding was of course somewhat unexpected, because it had been assumed that the amyloid load would continuously increase in the brain during the progression of AD. The unchanged PIB retention at the 2-year follow-up suggests a different time course for the amyloid load compared to changes in the functional activity in the brain. It is possible that a maximum amyloid load in brain is reached almost in the prodromal stage of AD disease. This assumption is also supported by the high ^{11}C-PIB retention in mild cognitive impairment (MCI) patients [25–27]. Seven MCI patients who subsequently converted to AD showed high PIB retention in brain by PET at baseline, whereas none of the ten MCI patients with low PIB retention converted to AD after the 2-year follow-up [26]. The difference in ^{11}C-PIB retention between MCI converters and non-converters is illustrated in Fig. 2. The finding that MCI patients showed less impairment in cerebral glucose metabolism in comparison to PIB retention supports the assumption that amyloid represents an earlier event in the time course of AD pathology than metabolic changes. ^{18}F-FDDNP PET studies in MCI patients have also shown intermediate binding compared with AD patients and healthy controls [28]. It is known from histopathological studies that amyloid plaques can be present in the cerebral cortex of cognitive normal older subjects [29]. It was recently estimated that amyloid plaque could be visualized in 10% of normal elderly subjects [22]. Whether these normal elderly subjects will develop in AD has to be systematically investigated [23]. Interestingly, high ^{11}C-PIB retention and low cerebral glucose metabolism were recently reported in highly educated

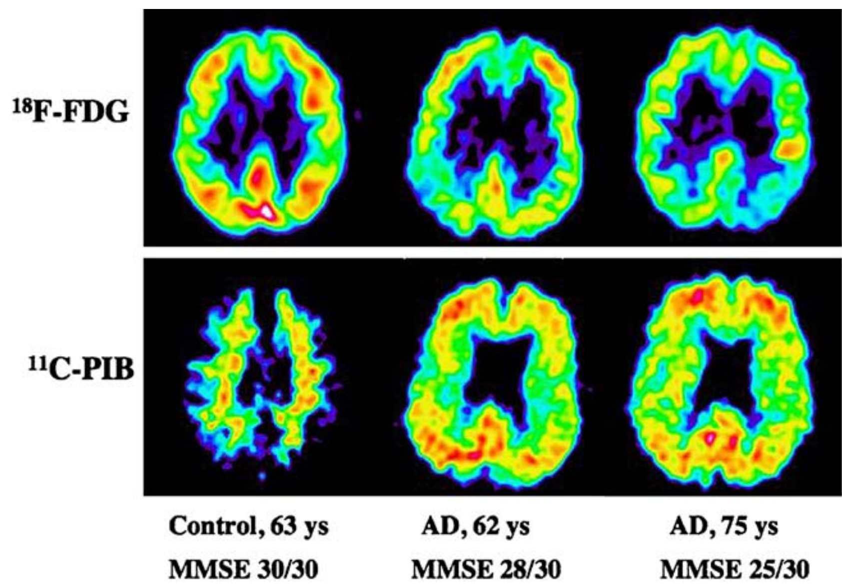

Fig. 1 Cerebral glucose metabolism (^{18}F-FDG) and ^{11}C-PIB amyloid imaging in two AD patients and one healthy control. The PET scans show ^{18}F-FDG and ^{11}C-PIB at a saggital section. *Red* indicates high, *yellow* medium, *blue* low ^{11}C-PIB retention. *MMSE* Mini-Mental-State-Examination, *ys.* years. Courtesy of Uppsala PET centre/ Imanet and Karolinska University Hospital Huddinge

AD compared to low-educated AD patients as a possible sign for a greater neuroplasticity in the highly educated group [30].

Brain amyloid imaging and cognition

It has generally been concluded from the autopsy studies in the literature that the quantified amyloid plaque pathology correlates less with cognitive function than neurofibrillary tangles and neurotransmitter activity. What is the finding in AD patients undergoing amyloid imaging with PET? A negative correlation has been observed between episodic memory test scores and cortical ^{11}C-PIB retention in MCI and AD patients [24, 26, 27]. Pike et al. [27] reported a strong correlation between episodic memory and ^{11}C-PIB binding for MCI patients, while the same correlation was weak for AD patients [27]. The latter finding might explain the often found poor correlation between reported clinical cognitive status and Aβ burden in autopsy brain tissue.

Brain amyloid imaging and CSF biomarkers

In a recent autopsy study, AD patients who prospectively had undergone magnetic resonance imaging (MRI) and cognitive testing before death showed less correlation between brain beta amyloid burden and atrophy than between density of neurofibrillary tangles and atrophy [31]. What is the correlation between amyloid measured in cerebrospinal fluid (CSF) and amyloid measured with PET in living AD patients? In a longitudinal follow-up of CSF biomarkers in

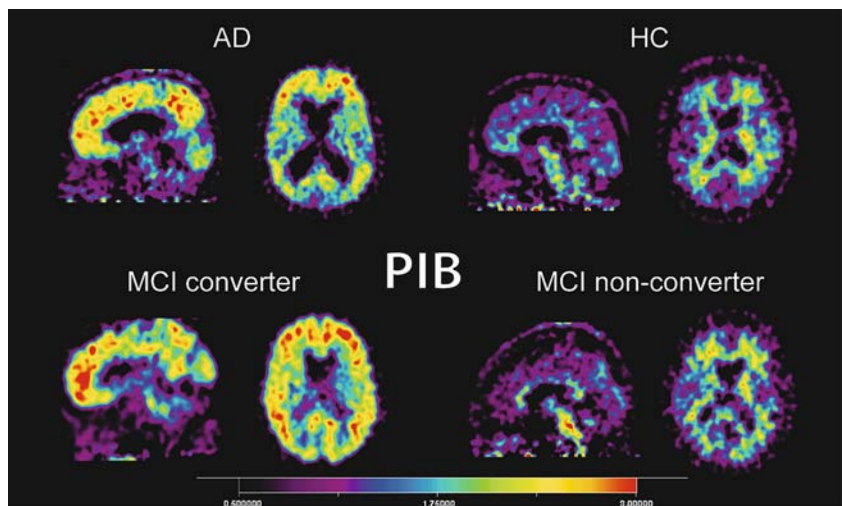

Fig. 2 ^{11}C-PIB retention in one MCI converter and one MCI non-converter compared with an AD patient and healthy control. The PET scans show ^{11}C-PIB retention at sagittal and longitudinal sections at the level of the basal ganglia. *Red* indicates high, *yellow* medium, *blue* low ^{11}C-PIB retention. Adapted from [26]

a cohort of community-dwelling volunteers of whom some were cognitively normal whereas one had very mild or mild AD, Fagan et al. [32] observed higher ^{11}C-PIB retention in subjects with low levels of CSF Aβ 1–42, while individuals with low PIB retention showed high CSF Aβ 1–42 levels [32]. A significant negative correlation has been observed between cortical PIB retention and CSF Aβ 1–42, while a positive correlation was observed between PIB retention and CSF tau in MCI patients [26]. Furthermore, systematic studies are needed to verify how closely brain amyloid plaque load correlates to CSF biomarkers.

Amyloid imaging in other forms of dementia

Some of the value for PIB, as future early diagnostic marker in AD, depends on the possibility to discriminate by PIB imaging between AD and other forms of dementia. In some recent studies, ^{11}C-PIB has been used in studies of patients with frontotemporal dementia (FTD). Rabinovici et al. [33] investigated 12 FTD patients with ^{11}C-PIB. Eight of the 12 FTD patients showed negative PIB scans, while four showed positive scans [33]. Two out of four patients with positive PIB scans showed FDG images consistent with AD [33]. Similarly Engler et al. [34] observed negative PIB scans in eight out of ten FTD patients investigated with ^{11}C-PIB, while two patients showed high PIB retentions. The FDG scans were consistent with the hypometabolism pattern seen in FDT patients [34]. Drzezga et al. [35] investigated eight subjects with semantic dementia who all showed negative PIB scans. It can, thus, be concluded that although six out of 28 patients with FTD and semantic dementia have shown high PIB retention, PIB may help to discriminate AD from FTD [33–35]. Post-mortem studies are needed to clarify whether PIB-positive FTD patients represent FTD/AD pathology or AD pathology mimicking FTD clinically. Johansson et al. [36] observed that patients with Parkinson's disease and normal cognition showed negative ^{11}C-PIB scans [36]. Among ten Parkinson patients who were classified as demented, eight patients showed PIB-negative scans, while two patients showed positive PIB scans and were considered more AD-like [37]. A high cortical PIB retention has been found in patients with Lewy body dementia [23]. In vitro binding studies with ^{11}C-PIB showed a binding to Aβ plaques and not to the Lewy bodies in the brain tissue [38]. High ^{11}C-PIB retention has also recently been reported in cognitively normal patients with advanced cerebral amyloid angiopathy (CAA) [39]. The retention of ^{11}C-PIB in the occipital cortex of CAA was interestingly enough greater than in AD patients [39]. As far as the authors know, no ^{11}C-PIB studies have been performed in vascular dementia.

Amyloid imaging for evaluation of anti-amyloid therapy

Different treatment strategies are presently tried to reduce the amyloid load in the brain of AD patients. Active and passive immunotherapy is in focus. The first trial (AN-1792) using an active immunization with Aβ 42 and an immunogenic adjuvant was suspended because of the occurrence of meningoencephalitis [40]. Surprisingly, MRI showed reduced brain volumes in immunized AD patients compared to placebo treated [41]. Post-mortem studies of immunized patients have shown reduced Aβ pathology with unchanged tau pathology [42, 43]. A reduced in vitro binding of ^{3}H-PIB was recently demonstrated in homogenates from autopsy tissue of immunized AD patient compared to untreated subjects [44]. A crucial question is the extent of Aβ pathology before immunization, because all amyloid studies, so far, have dealt with post-mortem brain tissue.

In vivo imaging of amyloid in patients undergoing anti-amyloid treatment has great potential for several reasons. In vivo PIB imaging before start of treatment would allow selection of patients with demonstrable high amyloid load in the brain. Repeated studies of ^{11}C-PIB retention during ongoing treatment allow detection of decrease in insoluble Aβ load in brain. Mathis et al. [44] suggested that a two-fold decrease in the test–retest variability, thus 10–20%, should be sufficient to detect a reduced Aβ load. Interestingly enough, a decreased ^{11}C-PIB retention in such range was observed after treatment with phenserine, an inhibitor of the formation of β-APP [45]. Immunization therapies are presently ongoing, where ^{11}C-PIB retention is measured both prior and during immunization. These studies will provide further understanding of the underlying mechanisms for anti-amyloid therapy.

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