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Molecular Neuroimaging in Alzheimer's Disease

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KEYWORDS

- PET • PiB • Alzheimer's disease
- Mild cognitive impairment

Dementia is a serious loss of cognitive ability in a previously unimpaired person beyond what might be expected from normal aging. Dementia that begins gradually and worsens progressively over several years is usually caused by neurodegenerative disease, that is, by conditions affecting only or primarily the neurons of the brain and causing gradual but irreversible loss of function of these cells. Worldwide increases in the number of people with dementia, the highest proportion of whom are affected by Alzheimer's disease (AD), have made its early diagnosis a major research and clinical priority. The cause of AD is unknown, but typical changes in the brain are neuronal loss, numerous globs of sticky proteins (β-amyloid [Aβ] plaques) in the spaces between neurons, a tangled bundle of fibrils within neurons (neurofibrillary tangles). Although it is still unclear what the relationship is between amyloid pathology and neuronal degeneration, progressive neuronal loss, and subsequent atrophy of various cortical gray matter structures, the most prominent hypothesis[1] for the cause of AD remains the amyloid cascade hypothesis, which holds that the Aβ peptide is the key to the initiation and progression of the disease. Pathologic studies are insufficient to validate this theory, because they are always inevitably cross-sectional and cannot determine how key events are temporally related to each other. During the past several years, amyloid imaging has established itself alongside magnetic resonance (MR) imaging and fluorodeoxyglucose (FDG)-positron emission tomography (PET) as a surrogate marker for the investigation of brain aging and dementia.

Functional neuroimaging, such as FDG-PET and brain perfusion single-photon emission computed tomography (SPECT), has been widely used for imaging biomarkers of AD. Recent advances in instruments have facilitated investigations of functional alterations in fine structures of not only cortical but also subcortical areas with high spatial resolution. Metabolic and perfusion reductions in the parietotemporal association cortex are recognized as a diagnostic pattern for AD. Outstanding progress in the diagnostic accuracy of these modalities has been achieved using statistical analysis on a voxel-by-voxel basis after anatomic standardization of individual scans to a standardized brain volume template instead of visual inspection or a volume-of-interest technique. In a very early stage of AD, this statistical approach revealed hypometabolism or hypoperfusion in the posterior cingulate cortex and precuneus. In some countries where FDG-PET has not yet been accepted for reimbursement for the detection of dementia in the health insurance system, more widely available brain perfusion SPECT has been used for the imaging diagnosis of AD. FDG-PET is superior to SPECT in diagnosing early AD because of its higher sensitivity and higher spatial resolution, and FDG-PET offers many advantages for detecting abnormalities in the AD brain. SPECT

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offers the advantages of lower cost and ease of access, which could lead to a large increase in the number of cases studied using this technique. Although FDG-PET shows more robust separation of patients with AD from healthy volunteers than SPECT, good correspondence of changes in the parietotemporal and posterior cingulate cortices and precuneus in mild to moderate AD is observed using voxel-based statistical image analysis between FDG-PET and SPECT.

Amyloid imaging allows for more rigorous quantification of the distribution and burden of amyloid, and enables direct comparison of these measures with simultaneously derived cognitive metrics in contrast to the significant delay between behavioral assessment and autopsy often seen in postmortem studies.

Among several compounds that have been developed for the imaging of amyloid, *N*-methyl-[^{11}C]2-(4′-methyl-aminophenyl)-6-hydroxybezothiazole or simply Pittsburgh compound-B (PiB)[2] is a derivative of the amyloid-binding dye thioflavin T and the most extensively validated tracer. It binds to aggregated, fibrillar Aβ deposits, such as those found in the cerebral cortex and striatum, but not to the amorphous Aβ deposits, such as those that predominate in the cerebellum. The first PiB-PET study in humans[3] was performed in patients with mild AD, in whom the uptake pattern was consistent with Aβ plaque deposition described in postmortem studies of AD brains. Postmortem studies of patients who showed increased PiB deposition during life showed high correlations between in vivo PiB accumulation and in vitro measures of Aβ pathology.[4,5] This article reviews the rapidly expanding literature applying PiB-PET to study cognitively normal volunteers and patients with mild cognitive impairment (MCI) and AD and summarizes the contribution of PiB-PET in understanding the association between amyloid plaques, aging, and dementia.

PiB-PET IMAGE ANALYSIS

Although visual reading of PiB images seems more accurate than that of FDG for identification of AD, better accuracy is obtained using a quantitative approach without requiring the expertise of readers.[6] PiB binding to Aβ plaque in the gray matter is specific and reversible, whereas PiB binding in the white matter is nonspecific and nonsaturable.[7] The relatively slow kinetics of PiB makes the specific PiB uptake in the gray matter prominent at later time points, which may impede the quantification of Aβ deposits because of the short half-life of ^{11}C-labeled tracer. To overcome this drawback in quantification, three-dimensional dynamic sampling of emission data for the whole brain is desirable, lasting 70 to 90 minutes after tracer injection. Application of the linear models developed by Logan[8] to these sampling data has become a standard calculation method for robust quantification in PiB studies (Fig. 1). Logan analysis is used to calculate the distribution volume of ligand tracers that have reversible binding kinetics. The choice of cerebellar cortex as a reference region that has no specific PiB deposition enables calculation of a distribution volume ratio (DVR) without arterial plasma data sampling as a slope of a graphical plot.[9] The DVR equals binding potential + 1. The pons can also be chosen as a reference area.[10] On the other hand, the standardized uptake value ratio (SUVR) has been proposed as a more feasible semiquantitative analysis than DVR (Fig. 2).[11] SUVR is calculated by computing the

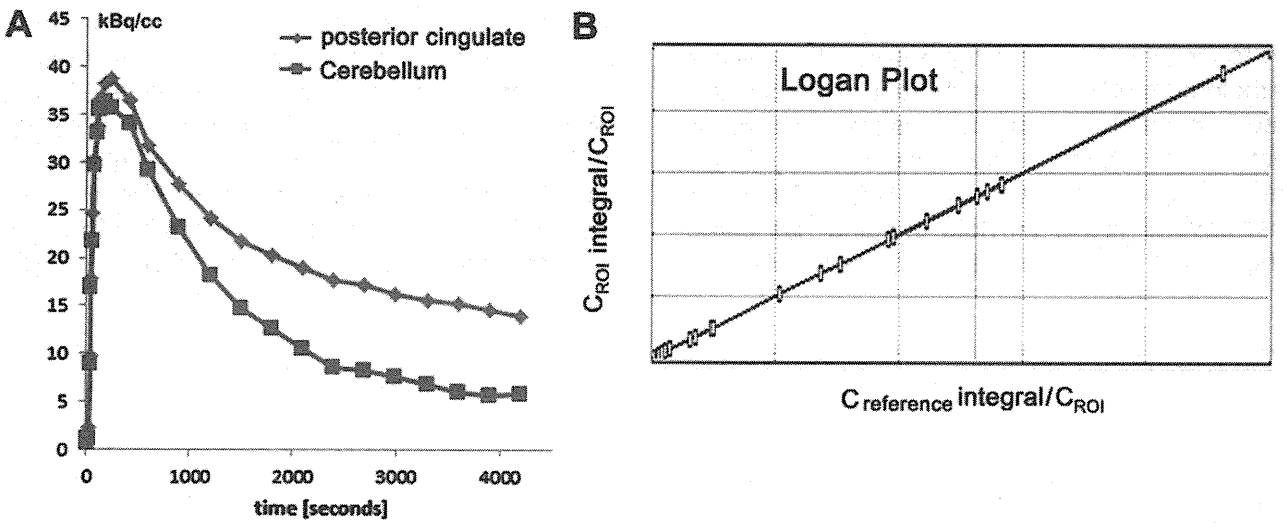

Fig. 1. Typical time-activity curves from dynamic PiB-PET studies from a patient with AD (*A*) and graphical analysis using a Logan plot (*B*). Using cerebellar cortex as input, the DVR in the posterior cingulate cortex is determined as a slope of a graphical plot without arterial plasma data sampling.

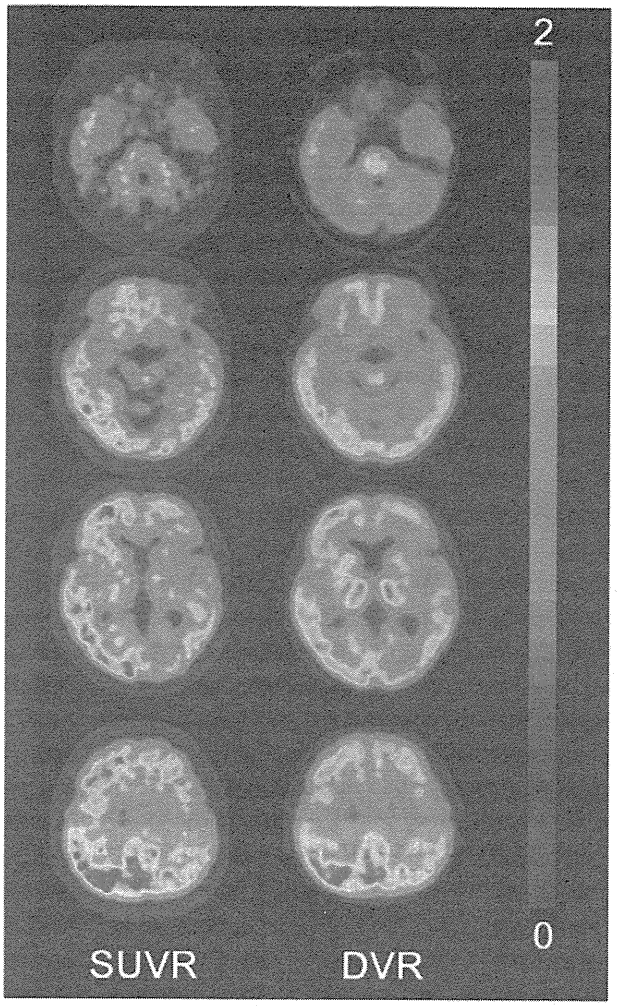

Fig. 2. Comparison of SUVR and DVR images. DVR provides better image quality than SUVR. A longer period of approximately 70 minutes is required for data acquisition for DVR compared with 20 minutes for SUVR.

region/cerebellum ratio at later time points. The optimal time range was studied by McNamee and colleagues[12]; their suggestion was to use a 40- to 60-minute period in studies limited by low injected dose, or a 50- to 70-minute period because of greater measurement stability, especially for longitudinal multisite studies (**Fig. 3**). The advantages of the SUVR approach are large effect sizes for AD and control group differences, and the possibility of obtaining the required data from a single short scan of 20 minutes. The disadvantages of this approach are the lower test-retest variability compared with the DVR approach and the potential for time-varying outcomes.[11] It also has the inherent bias of a tendency to overestimate PiB deposition.[12] The use of a standardized volume-of-interest template with spatially normalized PiB images to the same standardized space has been proposed as an automated voxel-based method for PiB deposition analysis.[13]

Regions that share a border with lower-binding or higher-binding structures are susceptible to partial volume effects because of a blurring caused by the low resolution of PET. Because gray matter, white matter, and cerebrospinal fluid (CSF) have different PiB uptake patterns, all gray matter boarders undergo partial volume effects. Atrophy of a region that increases the amount of neighboring CSF accentuates these partial volume effects. Applying partial volume correction to PiB-PET has been expected to increase the PiB deposition in atrophied gray matter and lead to more accurate quantification.[13,14] Partial volume correction is usually performed using segmented gray matter from three-dimensional MR imaging coregistered to PiB images.

PiB-PET IN NORMAL CONTROLS

Several autopsy studies have reported that significant Aβ deposits can be found post mortem in more than 30% of cognitively normal older individuals and that the extent of Aβ pathology may be indistinguishable from that found in AD.[15,16] In accordance with these autopsy results, several PiB-PET studies have consistently detected increased PiB binding in a subset of normal older volunteers (**Fig. 4**), with the proportion of PiB-positive cases ranging from 10% to 30% depending on the age of the cohort and the threshold for defining PiB positivity.[9,14,17–20] In contrast, increased binding has not been reported in young normal controls. Several studies suggest preferential PiB deposition in the prefrontal cortex and posterior cingulate/precuneus similar to the regions of earliest Aβ deposition noted in autopsy studies.[21] Some older controls show a distribution pattern of PiB binding that is essentially indistinguishable from that seen in AD. The high rate of PiB positivity in normal controls suggests that a positive PiB scan cannot be interpreted without a careful clinical evaluation and emphasizes that amyloid imaging alone must not serve as a surrogate for a clinical diagnosis of AD.

The most important risk factors for AD are age, family history, and heredity. The relationship between these risk factors and PiB deposition has been investigated using a voxel-based statistical analysis. Advancing age increases PiB-positive frequency in normal controls: 18% in those aged 60 to 69 years, rising to 65% in those older than 80 years.[22] The prevalence of Aβ deposition, as detected post mortem in cognitively normal subjects, exponentially increases with advancing age. The prevalence of PiB-positive normal controls increases with advancing age in a similar exponential fashion but precedes the postmortem study by 10 to 15 years. Aβ deposition seems almost inevitable with advancing age.

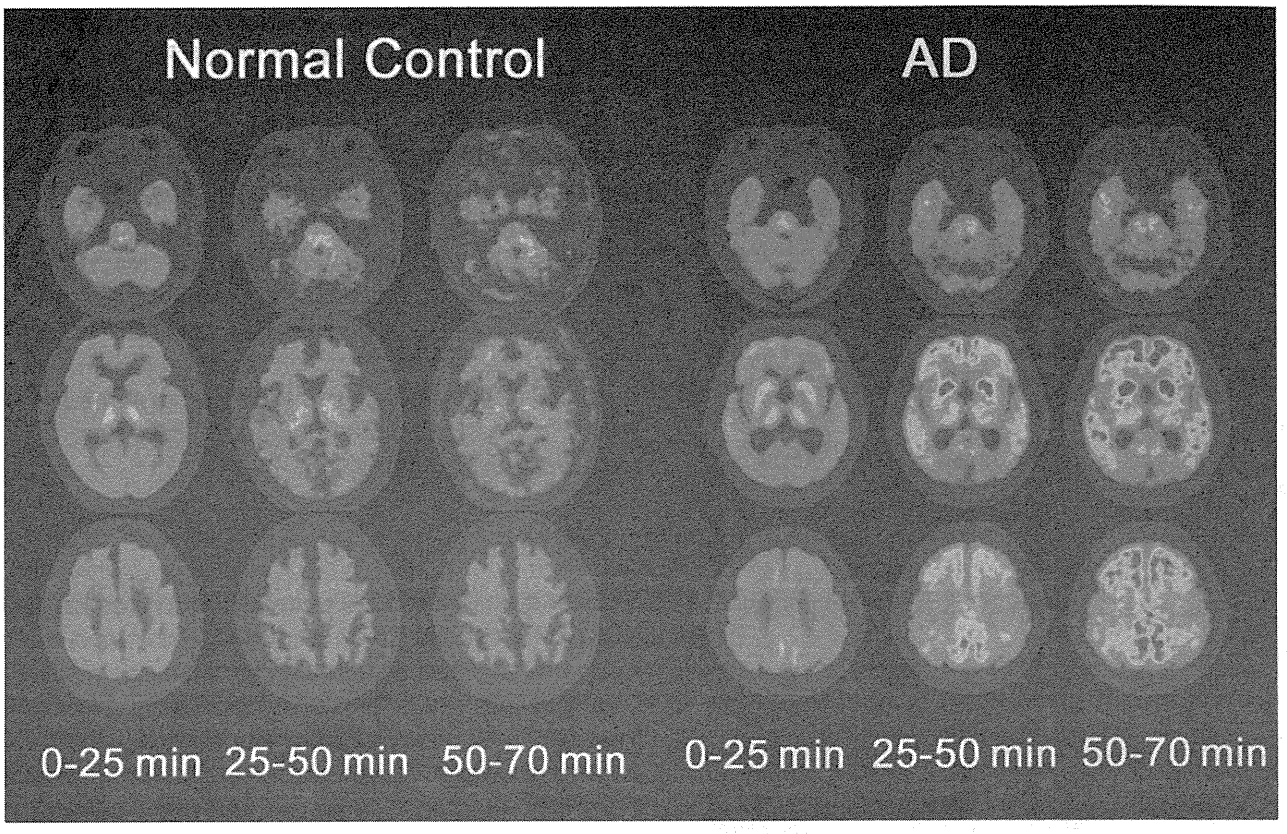

Fig. 3. SUVR images for the periods 0 to 25 minutes, 25 to 50 minutes, and 50 to 70 minutes for a control subject and a patient with AD. Note temporal changes in PiB distribution. The main factors determining PiB distribution changed from perfusion in an early phase to deposition in Aβ in a late phase. A control individual shows no accumulation in cerebral cortex but nonspecific accumulation in white matter in the late phase (PiB-negative). A patient with AD shows prominent PiB accumulation in the entire cerebral cortex except for occipital cortex and striatum in the late phase (PiB-positive). The cerebellar cortex shows very low accumulation in the late phase.

A recent study shows that normal controls with a parent affected by late-onset AD have increased PiB deposition in brain regions typically affected in patients with clinical AD compared with normal controls with no family history. In addition, significant parent-of-origin effects on Aβ deposition were found.[23] Normal controls with mothers affected by late-onset AD show increased and more widespread PiB deposition than those with affected fathers. Another recent study showed that PiB deposition in normal controls correlates with apolipoprotein E (APOE) ε4 gene dose, which is the best known genetic risk factor for AD.[24] The APOE4 allele increases the risk of the disease by 3 times in heterozygous individuals and 15 times in homozygotes. Emerging evidence suggests there may be other risk factors for AD. Epidemiologic studies suggest that cardiovascular risk factors such as increased blood pressure in midlife are associated with increased risk of AD in late life. Langbaum and colleagues[25] revealed that systolic blood pressure and pulse pressure were both positively correlated with PiB depositions. These preliminary findings provide additional evidence that higher BP, which is likely to reflect arterial stiffness during late midlife, may be associated with increased risk of presymptomatic AD. There is some evidence[26] that only angiotensin receptor blockers and angiotensin-converting enzyme inhibitors, and not other blood-pressure–lowering medications, are associated with reduced risk of AD. Antihypertensive treatments may protect against AD neuropathology, potentially by reducing vascular and arterial stiffness, thereby increasing blood flow to the brain and aiding in the removal of Aβ.

A major unresolved issue in AD research is whether cognitively normal people with amyloid deposition are on a trajectory toward AD, or whether the disease is benign in these individuals. Cross-sectional studies evaluating the influence of PiB binding on brain structure and cognition in older control individuals have yielded seemingly conflicting results. When individuals are dichotomized into PiB-positive and PiB-negative groups, most studies[9,18,19,27] have not found significant differences in cognitive performance, with the exception of a study[17] that found lower episodic memory scores in the PiB-positive group. In contrast, most studies that evaluated PiB deposition as a continuous variable have found significant negative correlations between PiB uptake and episodic memory

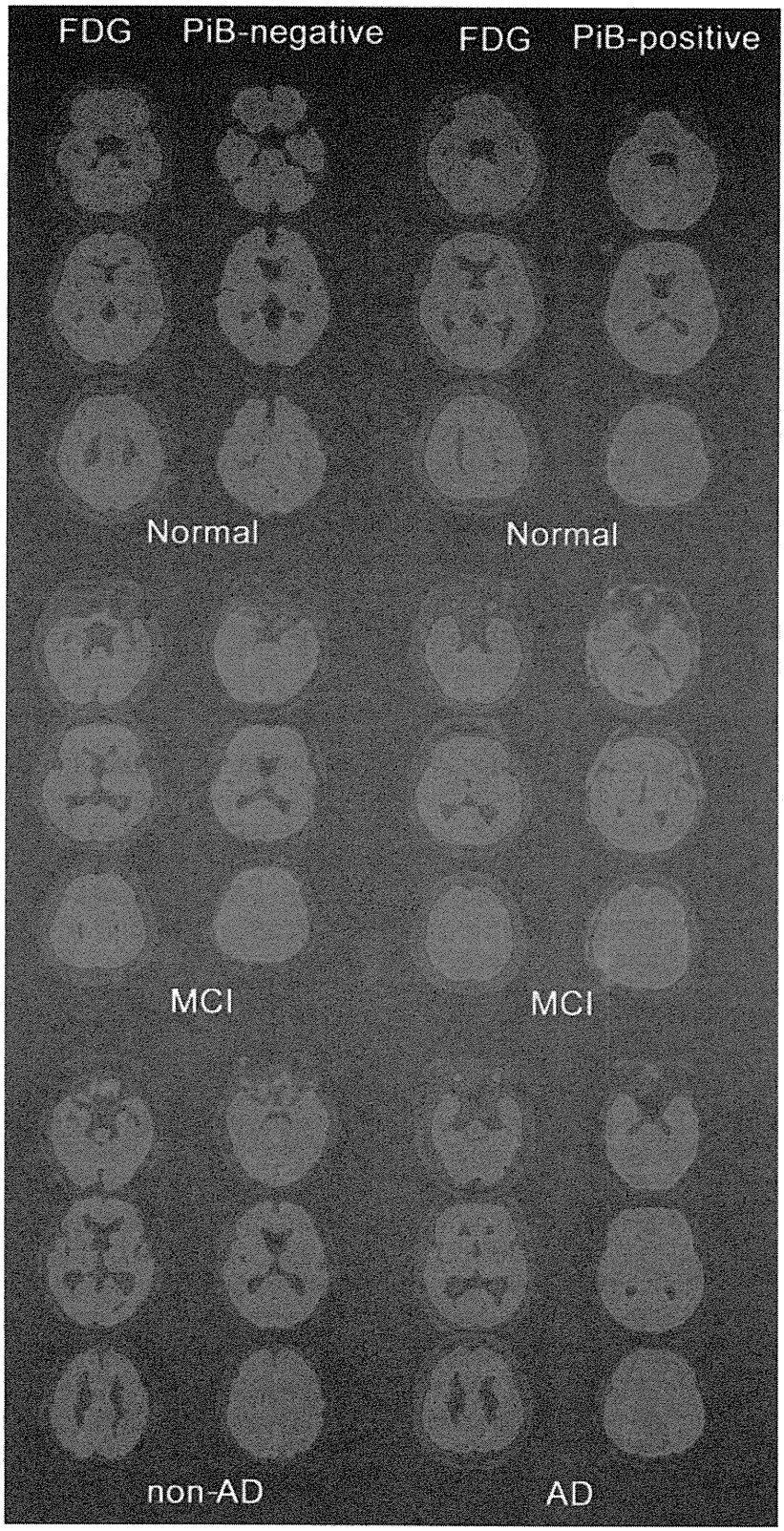

Fig. 4. Fluorodeoxyglucose and PiB-PET images in normal controls, MCI, patients without AD, and patients with AD. Both PiB-negative and PiB-positive findings are shown in normal controls and patients with MCI. PiB is useful for differentiating patients with and without AD.

scores. Mormino and colleagues[20] revealed significant correlations between PiB deposition and episodic memory, PiB deposition and hippocampal volume, as well as hippocampal volume and episodic memory. This observation suggests that declining episodic memory in older individuals may be caused by Aβ-induced hippocampal atrophy. Becker and colleagues[28] found the significant Aβ-associated cortical thinning particularly in parietal and posterior cingulate regions extending into the precuneus in a pattern consistent with early AD among nondemented older individuals. This

finding suggests that Aβ-associated neurodegeneration is manifest as cortical thinning in regions vulnerable to early Aβ deposition. Oh and colleagues[29] found that gray matter volume in the left inferior frontal cortex was negatively associated with amyloid deposition across all participants of nondemented older controls, whereas reduced gray matter volume was shown in the posterior cingulate among older controls with high amyloid deposition. This reduction of gray matter volume in the left inferior frontal cortex was associated with poorer working memory performance. The pattern of Aβ deposition as detected by PiB-PET shows substantial spatial overlap with the default mode network comprising a group of brain regions that typically deactivate during externally driven cognitive tasks.[30] Functional connectivity in the default mode network is altered with increasing levels of PiB uptake. These findings highlight structural and cognitive changes in association with the level of Aβ deposition in cognitively intact normal elderly individuals.

Longitudinal studies evaluating the relationship between PiB deposition and cognitive decline or brain atrophy have also yielded conflicting results. Dricoll and colleagues[31] examined associations between PiB deposition and brain volume changes in the preceding years in 57 nondemented individuals. Despite significant longitudinal decline in the volumes of all the regions investigated, no associations were detected between PiB deposition and regional brain volume decline trajectories in the preceding year, nor did the regional volume trajectories differ between those with highest and lowest Aβ burden. These findings suggest that Aβ load does not seem to affect brain volume changes in individuals without dementia. These investigators' observations are in agreement with existing reports on PiB deposition and brain volume loss. Jack and colleagues[32] investigated MR imaging and PiB studies at 2 time points, approximately 1 year apart, to gain insight into the sequence of pathologic events in AD. These investigators reported a dissociation between the rate of amyloid deposition and the rate of neurodegeneration late in life over 1 year of follow-up. Amyloid deposition proceeded at a constant low rate irrespective of clinical status, whereas neurodegeneration accelerated in association with clinical symptoms. These findings suggest that in nondemented elderly individuals, amyloid accumulation does not affect the rate of brain atrophy beyond that already observed as a part of the normal aging process. On the contrary, Villemagne and colleagues[14] reported that normal controls who progressed to MCI or AD over 38 months had significantly lower memory scores, higher baseline, and greater increase of PiB deposition than those normal controls who did not progress. Sojkova and colleagues[33] also found that longitudinal increases in Aβ deposition varied among individuals. This variability in the annual rate of change was affected by PiB deposition at the initial PET study, and increases were greater in nondemented older adults with an increased Aβ level compared with a minimal Aβ level at the initial evaluation. Furthermore a longitudinal cohort study[34] was performed to determine whether preclinical AD, as detected by PiB-PET in cognitively normal older adults, is associated with a risk of symptomatic AD. Twenty-three of 159 participants with a clinical dementia rating (CDR) of 0 progressed to CDR 0.5 at follow-up assessment. More increased PiB deposition highly predicted progression to CDR 0.5, with a hazard ratio of 4.85. These findings suggest that PiB deposition is not benign, because it is associated with progression to symptomatic AD.

PiB-PET IN MCI

Amyloid imaging can potentially identify patients with MCI who already show Aβ aggregation and are thus in the early clinical phase of AD, and separate them from patients with alternative causes for their cognitive impairment. Dividing patients with MCI into more biologically homogeneous groups may also facilitate their inclusion in clinical trials for AD-specific therapies, allowing these treatments to be tested in patients earlier in the disease course. Perhaps the correct use of antiamyloid monotherapies will be as a prophylactic given long before the onset of symptoms in people at risk of AD.[35]

Numerous studies in MCI have reported that PiB uptake is intermediate between AD and controls (see **Fig. 4**). However, PiB binding levels in MCI in most studies are bimodal, with most cases showing an AD-like uptake level, a few showing low control-level binding, and a few falling in the intermediate range. Overall, 52% to 87% of patients with MCI show increased PiB binding, depending on the criteria used to diagnose MCI and the threshold used to define PiB positivity.[11,14,17,18,20,27,36–38] Individuals meeting the criteria for amnestic MCI were more likely to be PiB positive than patients with nonamnestic MCI. Villemagner and colleagues[14] reported that progression of MCI to AD occurred in 67% of cases of MCI with high PiB deposition versus 5% of those with low PiB. Forsberg and colleagues[37] reported that 33% (7 of 21) of patients with MCI with increased PiB binding later at clinical follow-up converted to AD. Irrespective of MCI subtypes, longitudinal follow-ups reported that 5 of 13

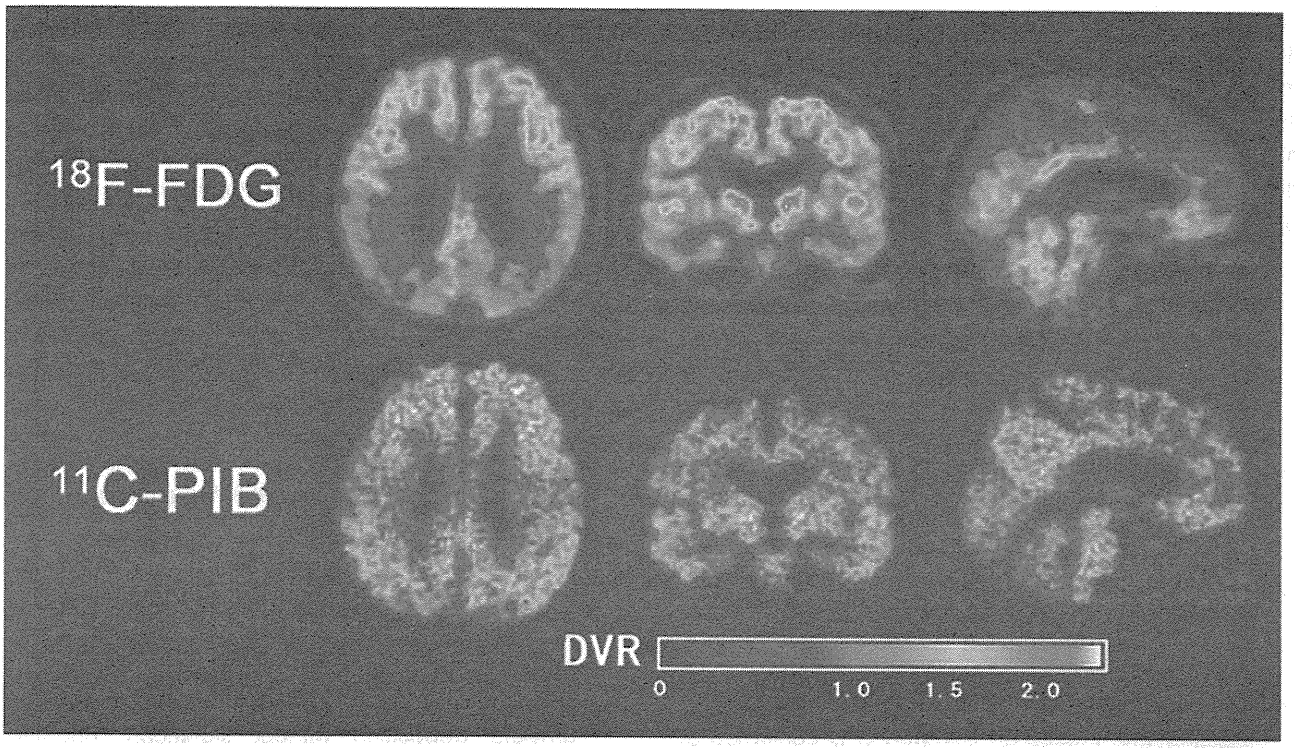

Fig. 5. Typical FDG and PiB-PET findings for AD in a 72-year-old male patient. His minimental state examination score was 18. Note high PiB deposition in the prefrontal cortex and posterior cingulate/precuneus, whereas FDG-PET showed decreased glucose metabolism in posterior cingulate/precuneus and bilateral parietal cortex.

amyloid-positive patients, but 0 of 10 amyloid-negative patients, converted to clinical AD.[38]

PiB-PET IN AD

The initial objective of amyloid imaging with PiB-PET focused on detecting Aβ amyloidosis in patients clinically diagnosed with AD. As expected, most patients with AD show increased PiB deposition (**Fig. 5**).[3,6,9,18,27,39] Using clinical diagnosis as a gold standard, the sensitivity of PiB-PET for AD has been reported as 80% to 100%, with most studies reporting sensitivities of 90% or greater. The significance of a negative PiB scan in a patient clinically diagnosed with AD is not yet clear because of the lack of postmortem data. The proportion of PiB-negative scans in AD is similar to the fraction of patients clinically diagnosed with AD at dementia referral centers who are subsequently found to have an alternative pathology at autopsy,[40] suggesting that many PiB-negative scans in AD may represent a true-negative. A pathology-confirmed false-negative PiB result has been reported,[41] involving a patient with Aβ plaques on frontal brain biopsy who showed low PiB binding when studied with PET 20 months later. Cairns and colleagues[42] reported a PiB-negative patient with reduced $A\beta_{42}$ and an increased level of tau in the CSF whose postmortem biochemical analysis met the neuropathologic criteria of AD. An inverse relation between PiB deposition and CSF $A\beta_{42}$ has been reported.[43] However, low levels of CSF $A\beta_{42}$ can occur in the absence of increased PiB deposition,[44] possibly because PiB may fail to bind to certain human amyloid confirmations, such as diffuse nonfibrillar plaque or concomitant Aβ oligomer formation. Therefore, although preliminary studies based on clinical diagnosis are encouraging, the precise sensitivity and specificity of PiB-PET for AD pathology need to be determined by further postmortem studies.

Patients with familial AD caused by presenilin-1 mutations show an atypical pattern of PiB deposition, with high uptake in the striatum and low cortical uptake.[45] Striatal binding is found in asymptomatic presenilin-1 mutation carriers, suggesting that striatal amyloid deposition may be an early feature of familial AD.

SUMMARY

PiB-PET shows potential for distinguishing AD from frontotemporal dementia[46] and AD from healthy controls, although specificity for the latter requires further examination. Amyloid imaging in healthy controls may detect those at high risk of future AD, identifying them as candidates for early preventive measures if and when they become available. A promising ^{18}F-labeled imaging marker[47] is currently available, which if successful will allow broader

application of amyloid imaging in clinical practice and research. The development of in vivo biomarkers for other critical elements of AD pathogenesis such as soluble Aβ and tau would further inform our understanding of the disease and assist in developing and testing disease-modifying therapies for AD.[48]

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新規アミロイドイメージング用トレーサー[^{18}F] FACT による認知症病態の検討

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【研究の背景】

アルツハイマー病における病理変化の一つであるβアミロイド沈着は、これに特異的に結合する放射性トレーサーおよびPET(Positron Emission Tomography)を用いてヒト生体において定量的に測定することができ、トレーサーとしてはピッツバーグ大学で開発された[^{11}C] PIB が国内外で広く使用されている。しかし、このトレーサーは[^{11}C] 標識のため放射能半減期が短く、PET 検査施設内にサイクロトロンなどの放射性医薬品製造設備を設置する必要があり、本格的な臨床応用のためには放射能半減期が比較的長い[^{18}F] 標識のアミロイド測定用トレーサーの開発が必要とされている。近年、我々の共同研究先である東北大学で開発された[^{18}F] 標識のアミロイド測定用トレーサー[^{18}F] FACT は、[^{18}F] 標識を実現すると同時に、脳内でのトレーサー動態がPET 測定に適したものであることが確認されている。一方、[^{18}F] FACT と類似の構造を有するトレーサーでは、アルツハイマー病における脳内特異的結合の分布が[^{11}C] PIB とは異なる傾向があることが報告されており、同じアミロイド測定用トレーサーであっても特異的結合部位に違いがあることなどが示唆されている。

【目的】

本研究では、[^{18}F] FACT を用いてアルツハイマー病における脳内アミロイド蓄積を定量的に評価し、トレーサーの特異的結合の程度やその脳内分布について同一人に施行した[^{11}C] PIB による測定結果と比較することにより、両トレーサーがそれぞれ反映する脳病理変化の差異を検討した。

【方法】

健常者 6 名、軽度認知機能障害(MCI)患者 2 名、アルツハイマー病(AD)患者 6 名を対象に[^{18}F] FACT および[^{11}C] PIB による PET 検査を同日に施行し、脳の形態画像を得るための頭部 MRI 検査も施行した。[^{11}C] PIB 静注後より 70 分間のダイナミックスキャンを施行し、スキャン終了 50 分後に[^{18}F] FACT を静注し 60 分間のダイナミックスキャンを施行した。大脳皮質領域に関心領域を設定して脳局所放射能濃度を体重当たり投与量で標準化した値(SUV)を計算した。次いで、T1 強調画像のセグメンテーション画像を用いた部分容積効果補正により単位灰白質量当たりの SUV を求め、小脳を参照領域として脳内放射能濃度比(SUVR)を計算した。

【結果】

それぞれの大脳皮質領域における SUVR の平均値は、[^{11}C] PIB では、健常者で 1.15-1.40、AD 患者で 3.10-4.91、[^{18}F] FACT では、健常者で 1.22-1.33、AD 患者で 1.58-1.70 であり、[^{11}C] PIB、[^{18}F] FACT 共にアルツハイマー病において高い大脳皮質への集積がみられた。また、[^{11}C] PIB および[^{18}F] FACT の集積には有意な正の相関がみられた。AD 患者における[^{11}C] PIB および[^{18}F] FACT の脳内分布には違いがみられ、後頭葉、海馬傍回では[^{11}C] PIB の集積が相対的に低値であり、前頭葉、頭頂葉では[^{11}C] PIB の集積が相対的に高値であった。

【考察】

[^{11}C] PIB、[^{18}F] FACT 共に白質における非特異的集積が高いため、MRI を用いた部分容積効果補正でこの影響を除外することにより、健常者と AD 患者での集積の差がより明らかとなった。AD 患者における[^{11}C]

PIBと[18F] FACTの集積の脳内分布には違いがみられたが、[18F] FACTはADの病態により深く関連するneuritic plaqueに主に結合し[1]、[11C] PIBはneuritic plaqueとdiffuse plaqueの両方に結合することが知られている。病理組織学的検討では前頭葉に比べ後頭葉ではdiffuse plaqueが相対的に少ないことも報告されており[2]、本研究で観察された[11C] PIBおよび[18F] FACTの脳内分布の差異はこれによく対応する。[11C] PIB、[18F] FACT共に脳内アミロイド蓄積を測定するトレーサーであるが、それぞれが反映する脳病理変化には違いがあり、両トレーサーの脳内分布の差異はこれを反映している可能性がある。

【臨床的意義・臨床への貢献度】

[18F] FACTはAD患者において必ずしも十分に高い集積を示さなかったが、ADの病態により深く関連するとされるneuritic plaqueに主に結合するという特徴がある。本研究により、反映する脳病理変化が異なるアミロイド測定用トレーサーを使い分けることで、認知症におけるより詳細な病態評価を行いうることが示唆された。βアミロイド沈着のPETによるイメージングは早期診断やアミロイド抗体療法などの治療効果判定の手段として研究されており、本格的な臨床応用へ向けて、病院外からのデリバリーでの供給が可能な[18F]標識のアミロイド測定用トレーサーの開発が国内外でなされている。今後、[18F] FACTの基本構造を用いてAD患者において十分に高い集積を示しうる新たなアミロイド測定用トレーサーが開発されれば、PETアミロイドイメージングによる認知症の客観的な早期診断法、鑑別診断法、治療効果判定法の確立に寄与していくものと思われる。

【文献】

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〔非売品〕

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病態理解と薬剤開発における アミロイドPET検査の現状

Current Status of Amyloid PET in Pathophysiological Research and Drug Development for Alzheimer's Disease

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石井賢二*

1. はじめに

アミロイドPETは生体におけるアミロイドβ（Aβ）の脳内蓄積を非侵襲的に可視化できる診断技術である。この技術が実用化したことにより、動物モデルや死後脳の病理学的検索によってしか知ることのできなかったAβ蓄積とAD発症との関係を生きたヒトを対象として検証することが可能となった（図1）[1]。特にAD発症前の経過が観察可能になったことで、ADの発症遅延・予防法の開発と検証もが視野に入るようになった。本講演ではアミロイドPETの現状と、その病態理解におけるインパクト、治療予防薬開発への展望について述べる。

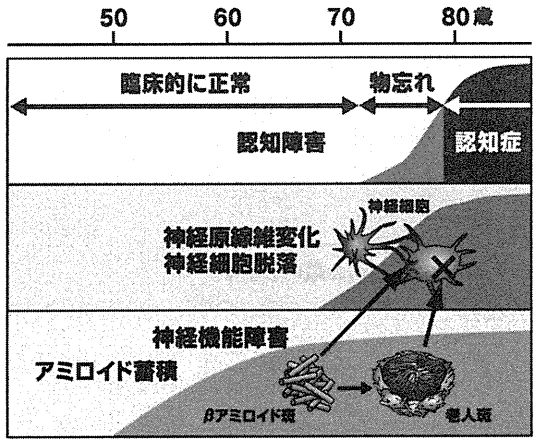

図1　アミロイドβは発症に先立って蓄積し始める

2. アミロイドPET診断薬の開発

現在臨床使用されているアミロイドPET診断薬（図2）はいずれもアミロイドの組織染色に用いられているコンゴーレッドやチオフラビンTの類似化合物である。これらのうちピッツバーグ大学で開発されたPittsburgh Compound-B（PiB）が集積の感度・特異性ともに優れ、標準診断薬として用いられている[2,3]。PiBは半減期が約20分と短い^{11}Cで標識されているため、普及や多数例での検査に制約がある。普及を目指し、半減期110分の^{18}Fで標識されたアミロイド診断薬の第Ⅲ相治験が現在行われている。PiBを用いた脳画像を図3に示す。上段は集積のな

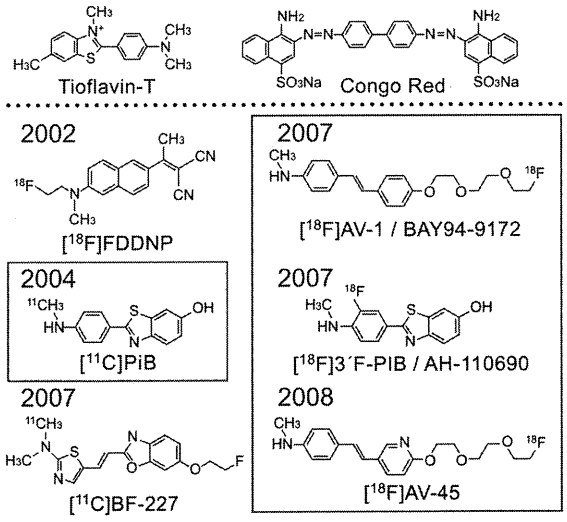

図2　Amyloid Probes for Human PET Study

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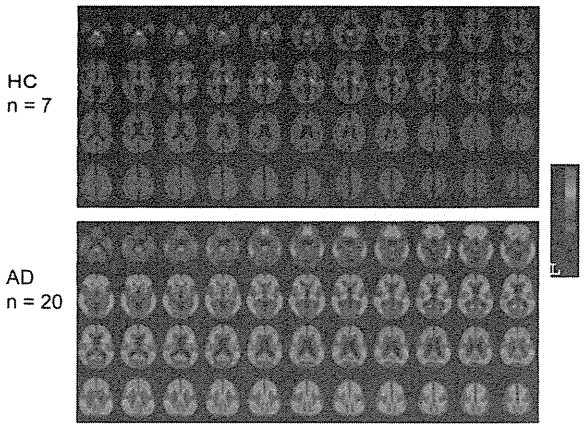


図 3　PiB の平均画像（投与後 50-70 分の後期画像）

い健常者の平均画像で、白質に少量の非特異的集積が認められるが皮質への集積は少ない。これに対し、下段の AD 患者脳では、白質のレベルを上回る集積が大脳皮質（主として連合野）に認められ、脳組織における Aβ沈着を表していると考えられる。

3. わが国のアミロイド PET の現状

現在全世界でアミロイド PET を実施している施設は 100 を優に超えるといわれているが、わが国では PiB が 15 施設で、東北大学で独自に開発された BF-227 が 4 施設で実施されている（図 4）[4]。J-ADNI 研究で得られた被験者 105 名の結果を図 5 に示す。健常者で約 20%、軽度認知障害（MCI）で約 60%、AD で約 90%の例でアミロイド陽性と判定された。健常者や MCI におけるアミロイド陽性例の中には将来 AD に移行する者が含まれていると考えられる。一方 AD の臨床診断でアミロイド陰性の者は臨床診断が誤りである可能性が高い。アポリポ蛋白 E（ApoE）の遺伝子型 ε4 は AD のリスクとして知られているが ε4 保有者は非保有者に比べアミロイド陽性率が際立って高いことがわかった（図 6）。

4. アミロイド PET の臨床的意義

アミロイド PET 陽性所見を持つ健常者（図 7）の中には将来 AD を発症する者を含んでいると推測される。Fotenos らはアミロイド陽性健常者と陰性健常者では前者の方が脳容積が有意に小さいことを示した（図 8）[5]。これは、アミロイド陽性者の中に脳萎縮が既に始まった者が含まれていることを示唆する。現時点でアミロイド陽性健常者の AD 発症の可能性やその時期を予測することはできない。しかしアミロイド陽性健常者を検索追跡することにより、AD の危険因子や予防因子を探索することができるであろう。また、リスクの高いアミロイド陽性健常者を対象として、発症予防を目的とした介入研究も始まろうとしている。アミロイド陽性者（cerebral amyloidosis）は高血圧や高脂血症と同様、症状がなくても深刻な疾患のリスクとして将来理解されるよ

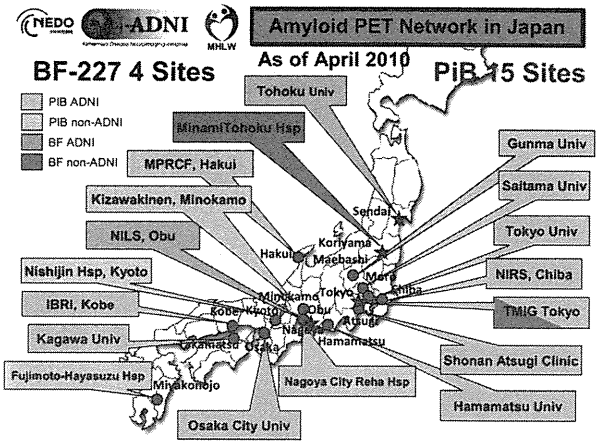
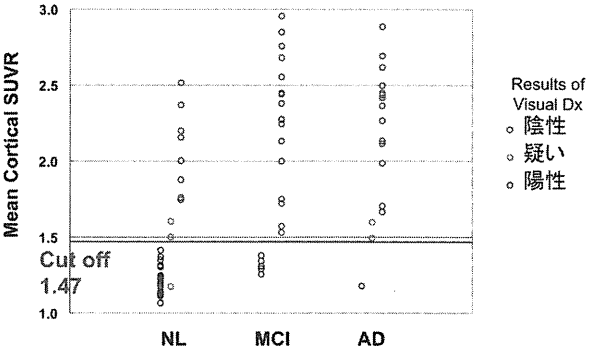


図 4　わが国におけるアミロイド PET 実施施設



As of Apr 4, 2010

図 5　Mean cortical PiB uptake: $SUVR_{50-70}$
By group and visual diagnosis

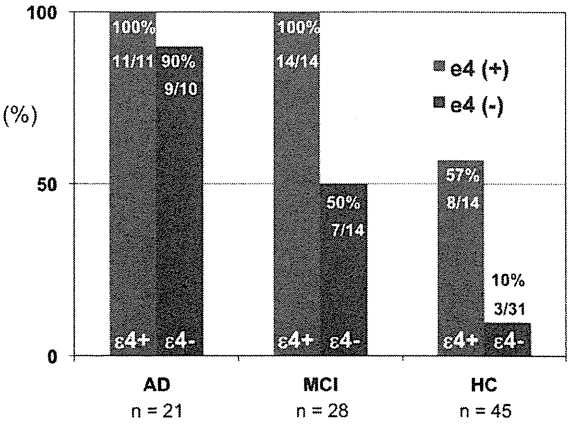


図 6　PiB positive (MCSUVR > 1.47) rate
by group and ApoE4

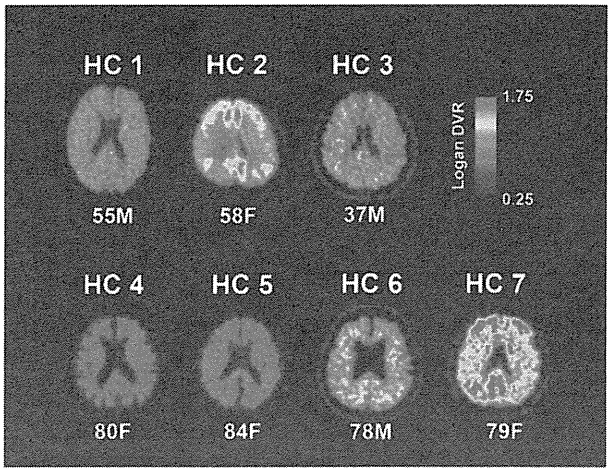
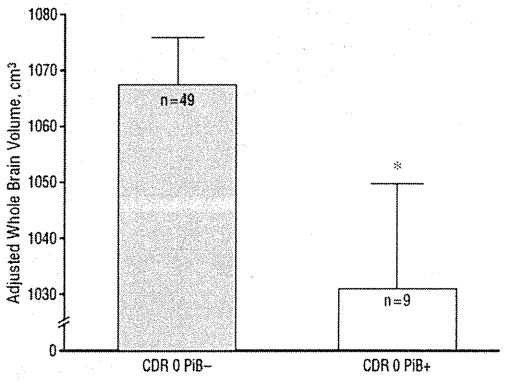


図 7　PiB in Healthy Controls



Fotenos et al. Arch Neurol 2008;65:113

図 8　PiB 陽性健常者は脳容積が有意に小さい

PiB陽性健常者の検討の意義

- 発症の危険因子および予防因子の探索
- 将来的な早期介入、発症予防へ
- PiB(+) = ADか？ No
  - preclinical AD
  - cerebral β-amyloidosis
- PiB(−) ≠ ADか？ Probably yes
- 現時点でアミロイドイメージングを検診として実施することは時期尚早

図 9

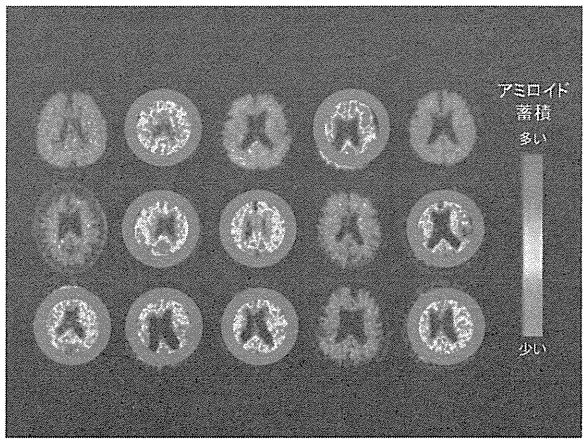


図 10　MCI におけるアミロイド蓄積

うになるかも知れない。しかし、予防法がある程度確立し、発症予測が正確になされるようになるまでは、「未発症の AD（preclinical AD）」として扱うことは倫理的に問題があり、アミロイド PET を検診に用いることは時期尚早である（図 9）。

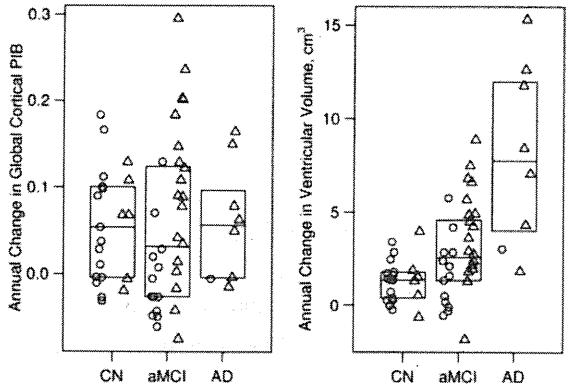
MCI では約 60-70%でアミロイド陽性者が認められ、これらは早期に高率に AD に移行する傾向があることがこれまでの追跡研究で明らかになりつつある。MCI における AD の発症予測が可能と考えられる（図 10）。

5. 根本治療薬治験とアミロイド PET

アミロイド PET でみたアミロイド集積は発症前かごく早期に既にプラトーに達しており、AD の必要条件あるいは発症を予測するマーカとしての意義があるが、病態（神経障害）の進展をよく表すマーカではない（図 11）。しかし、アミロイド蓄積の変化率が病期によってそれほど変わらないということは、アミロイド修飾治療薬の薬効を評価する上で重要な知見である[6]。最近、モノクローナル抗体アミロイド修飾薬 bapineuzumab が被験者脳のアミロイド集積を減らす効果があることが報告された（図 12）[7]。アミロイド修飾薬の治験において、アミロイド PET は対象者の選択と治療効果の判定の両者で用いることができる。

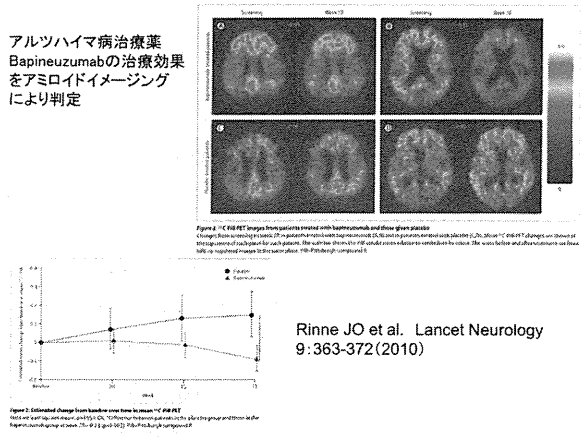
6. 各種脳疾患におけるアミロイド PET の意義

アミロイド PET は AD 診断に対して感度が極めて高いが特異性は低い。アミロイド PET 陰性であれば、アルツハイマー病の可能性をほぼ否定できる。従って、従来アルツハイマー病との鑑別が困難であった疾患の鑑別診断や病態理解に寄与できると考えられる。老年者タウオパチーやレビー小体型認知症の臨床研究がこれによって進展すると期待される（図 13）。



Jack et al. Brain 132:1355-1365 (2009)

図 11　PiB 集積と脳室容積の 1 年あたりの変化



Rinne JO et al. Lancet Neurology 9:363-372(2010)

図 12

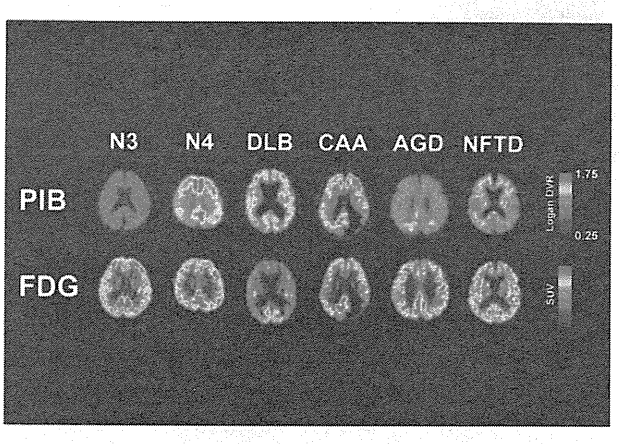


図 13　認知症関連疾患における PiB 集積

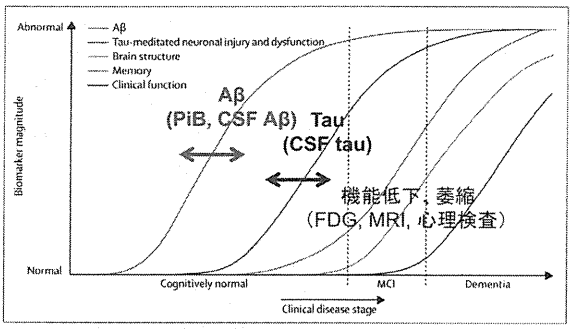


Figure 2. Dynamic biomarkers of the Alzheimer's pathological cascade
Aβ is identified by CSF $A\beta_{42}$ or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment.

Jack et al. Lancet Neurol 2010;9:119 を改変

図 14　アルツハイマー病進展における
バイオマーカの動き

7. AD における病態進展とバイオマーカー

これまでの臨床研究から AD の病態進展を反映するバイオマーカが明らかとなってきた。最も早期に動くのは Aβ 沈着を示すマーカであり（アミロイド PET、髄液 Aβ 1-42）、ついで髄液 tau や FDG-PET でみた代謝低下、MRI でみた海馬萎縮、そして心理検査指標や臨床症状が順次変化すると考えられる（図 14）。これらのバイオマーカを組み込んだ新しい臨床診断基準が提案される予定である[8-11]。

8. おわりに

アミロイド PET の実用化によってもたらされたアルツハイマー病の病態理解進展と、治療予防法開発への影響について述べた。今後は発症予防も含めた早期介入が焦点となる。そのためには、アミロイド陽性健常者における発症を予測するマーカが必要となる。また、タウやαシヌクレインのイメージングが実用化すれば、変性疾患の病態理解と克服に向けた研究が飛躍的に促進するであろう（図 15）。

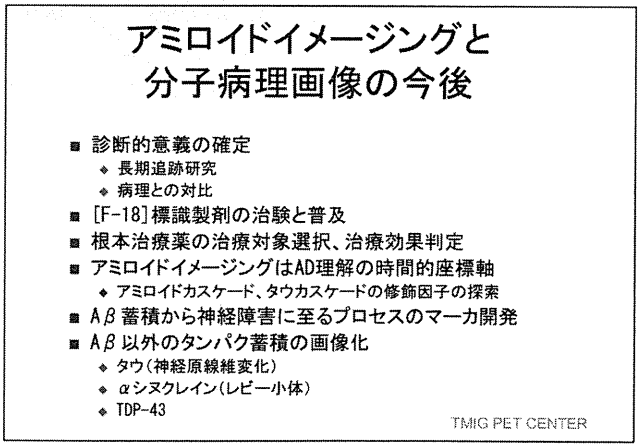


図 15

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Ⅱ．診断

2．画像診断（MRI，SPECT，PET）

石井　賢二

要　旨

認知症の正確な診断を行う上で画像診断は欠かすことができない．初期評価の段階で治療可能な疾患を鑑別するために，まず頭部X線CTまたはMRIを必ず施行すべきである．MRIによる萎縮の分布，脳血流SPECTやFDG-PETによる神経機能障害の分布，アミロイドPETによるアミロイドβ沈着の有無の情報は早期診断や鑑別診断にきわめて有用である．新しいAlzheimer病診断基準における画像の位置づけについても紹介する．

〔日内会誌　100：2116～2124，2011〕

Key words　認知症（dementia），MRI，SPECT，PET

はじめに

認知症の診断は，慢性進行性の臨床症状と認知機能の評価に基づいて行われ，長期の経過観察でより確実となり，最終的には病理所見によって確定するというのが従来の考え方であった．しかし近年，薬物や行動学的手法による治療法が進歩し，早期診断・早期介入の必要性が認識されるようになり，画像診断は認知症早期診断において欠かせないものとなった．更にAlzheimer病（AD）の病態研究が進み，臨床症状の顕在化に先立って，画像を含めたバイオマーカの変化により病態の存在やその進行をとらえることができるようになった．本稿では，認知症日常診療の流れの中での画像診断の役割について概説するとともに，モダリティ別ではなく疾患別にその診断的意義を解説する．また，今年改訂されたAlzheimer病臨床診断基準に沿った画像診断の役割について述べる．

1．認知症画像診断の流れ

認知症の画像診断として広く行われているのは，X線CT，MRI，脳血流SPECTである．認知症の診断プロセスにおいて，さまざまな脳の器質性疾患を鑑別してゆく必要があるので，X線CTまたはMRIはスクリーニングとしても必須であるが，正確な診断にはMRIを撮影することが推奨される．脳血流SPECTはMRIだけではわかりにくい脳機能（神経活動）や脳循環に関する情報を得ることができるので，脳動脈閉塞などの

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Dementia：Progress in Diagnosis and Treatment；Topics, II. Diagnosis；2. Neuroimaging diagnosis of dementia（MRI, SPECT and PET）.

Kenji Ishii：Positron Medical Center, Tokyo Metropolitan Institute of Gerontology, Japan.

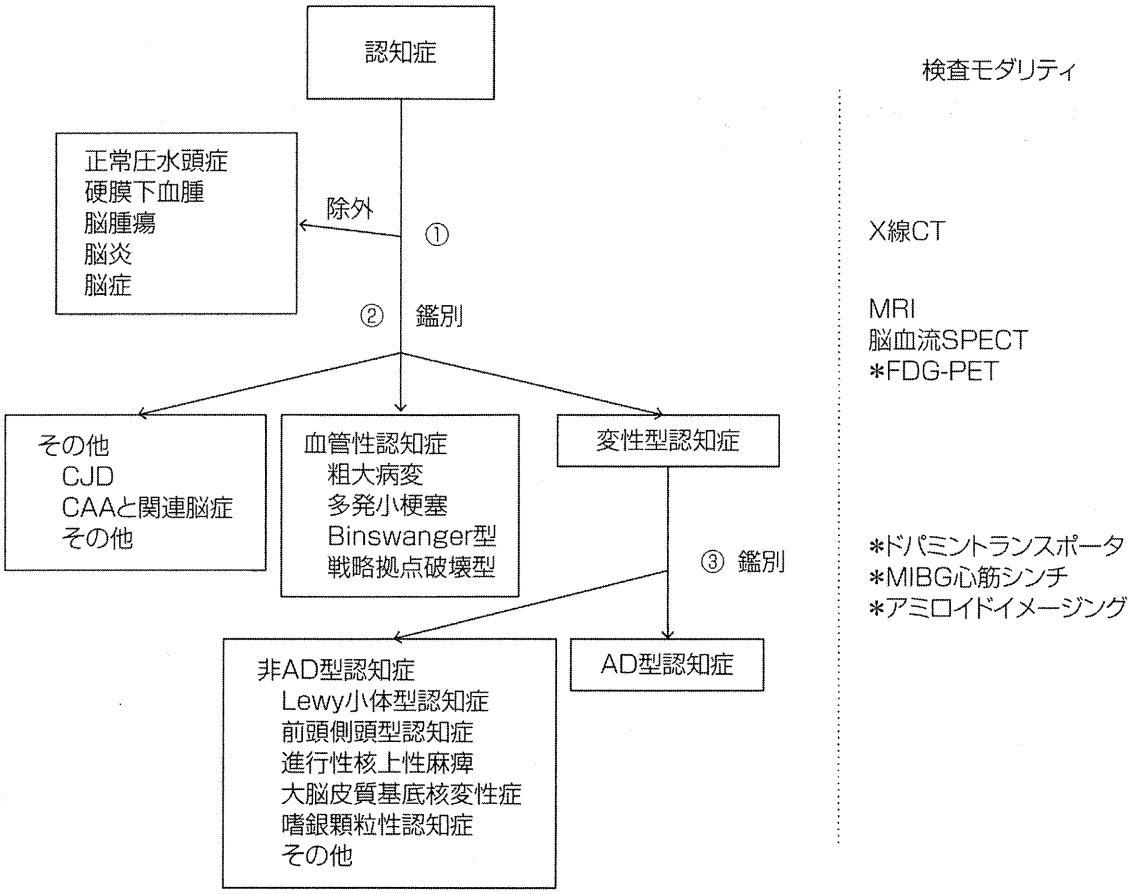

図 1. 認知症画像診断のスキーム

認知症診断の流れの中で，画像診断の位置づけを示す．初期評価の段階で，治療可能な疾患を除外することが最も重要である．慢性進行性の変性型認知症でも，画像診断の組み合わせにより，早期の診断も可能となる場合もある．＊はまだ保険適用が認められていない検査．

血管性病態を疑う場合や，AD，前頭側頭型認知症（FTD），Lewy小体型認知症（DLB）などの変性型の認知症を疑う場合には，鑑別に有用である．脳の萎縮や脳血流の低下を正常データベースと比較して分かりやすく表示する診断補助ソフト（MRIではVSRAD，脳血流SPECTでは3DSSPやeZISなど）も普及しており，これらの補助診断法が日常診断で既によく使われている．また，保険適応がまだないため普及していないが，将来有望な検査としてPETによる脳代謝測定（^{18}F-FDG）とアミロイドイメージングがある．^{18}F-FDG PETは脳の神経活動を反映した画像が得られるので，脳血流SPECTと同様の意味があるが，診断精度は^{18}F-FDG PETの方が優れており，保険適用と普及が望まれる．アミロイドイメージングは，ADの原因とされるアミロイドβ（Aβ）の脳内蓄積を画像化することのできる技術である．ADの早期診断に役立つと期待されているだけでなく，現在進められている根本治療薬の開発や，将来の発症予防に欠かせない技術として注目されている．認知症診断の中で適応は限定されるが，ADとDLBの鑑別診断には^{123}I-MIBG心筋シンチも有用であり，保険適用が望まれる検査である．

認知症の背景となる疾患はきわめて多彩であり，その中での画像診断の役割は，スクリーニングと詳細な質的診断の二つに分けて考えるべきである．初診時の画像評価の目的は，治療可