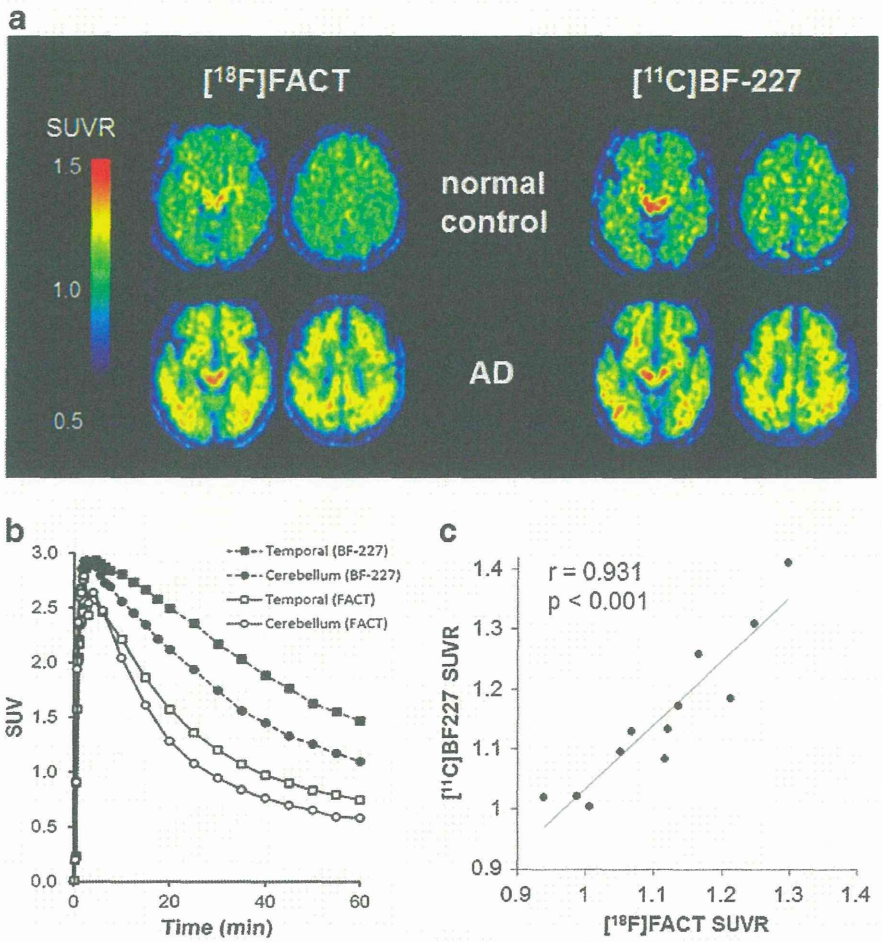

Fig. 5. **a** SUVR images (30 to 40 min postinjection) of [^{18}F]FACT and [^{11}C]BF-227 for a normal control subject (60-year-old man, MMSE score 30) and an AD patient (70-year-old woman, MMSE score 17). **b** Time activity curves of [^{18}F]FACT and [^{11}C]BF-227 in an AD patient (70-year-old woman, MMSE score 17). **c** Significant correlation between regional SUVR of [^{18}F]FACT and [^{11}C]BF-227 in two AD (70-year-old woman (MMSE score 17) and 79-year-old man (MMSE score 20)) and one normal control (60-year-old man, MMSE score 30) subjects (Pearson's r=0.931, P<0.001).

temporal, parietal, occipital, and anterior and posterior cingulate cortices were significantly greater in AD patients than in the normal controls (Table 4). In addition, the SUVRs for the lateral temporal, parietal, occipital, and anterior and posterior cingulate cortices were significantly greater in AD patients than in those with MCI. As shown in Fig. 6, averaged neocortical SUVR was also significantly greater in AD patients than in normal control subjects and MCI (P<0.05, Kruskal–Wallis test). MCI patients additionally showed significantly greater SUVR in the lateral temporal and frontal cortices than normal subjects, but not significant in other brain regions (P<0.05, Kruskal–Wallis

Table 4. Regional SUVR (30 to 40 min postinjection) and effect size measures of [^{18}F]FACT in ten normal controls and ten MCI and ten AD patients

	Normal control	MCI	AD	Cohen's d NC *vs.* AD
Frontal	1.00±0.10	1.09±0.04*	1.15±0.06*	1.82
Lateral temporal	1.05±0.08	1.13±0.06*	1.21±0.05*,**	2.40
Parietal	1.07±0.07	1.13±0.07	1.21±0.08*,**	1.86
Occipital	1.09±0.08	1.07±0.06	1.17±0.05*,**	1.20
Anterior cingulate	1.08±0.07	1.12±0.08	1.21±0.08*,**	1.73
Posterior cingulate	1.15±0.07	1.17±0.06	1.30±0.07*,**	2.14
Medial temporal	1.10±0.05	1.13±0.04	1.15±0.09	0.69
Striatum	1.31±0.11	1.30±0.06	1.35±0.12	0.35
Pons	1.55±0.15	1.57±0.10	1.54±0.09	0.08
White matter	1.50±0.21	1.47±0.11	1.52±0.13	0.12
Neocortex	1.04±0.07	1.12±0.05	1.19±0.05*,**	2.47

*P<0.05 (vs normal control group) and **P<0.05 (vs MCI group) by the Kruskal–Wallis test followed by Dunn's multiple comparison test

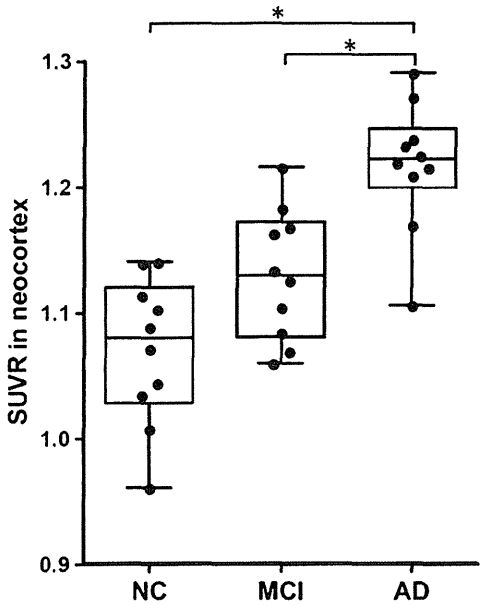

Fig. 6. Comparison of neocortical SUVR of [^{18}F]FACT among ten aged normal controls (NC) and ten mild cognitive impairment (MCI) and ten AD patients. The neocortical SUVRs are represented in a *box* and *whisker plot*. *P<0.05 by the Kruskal–Wallis test followed by Dunn's multiple comparison test.

test). The SUVR in the medial temporal cortex and striatum showed the tendency to be greater in AD patients, but this was not significant. The SUVR in the pons and white matter was nearly identical in AD, MCI, and normal subjects. Effect size value between AD and aged normal subjects was the highest in the lateral temporal cortex (2.40), followed by the posterior cingulate (2.14), parietal (1.86), frontal (1.82), and anterior cingulate (1.73) and occipital (1.20) cortices (Table 4).

Discussion

The current study demonstrated that [^{18}F]FACT PET can be used to detect AD pathology in AD patients and to confirm its absence in cognitively unimpaired elderly people. We previously reported the ability of [^{11}C]BF-227-PET to detect Aβ deposits in the brains of AD patients [15]. The current study has further demonstrated the binding preference of [^{18}F]FACT to dense Aβ plaques in the brains of AD patients. A similar pattern of tracer distribution was observed between [^{18}F]FACT and [^{11}C]BF-227 in AD patients, indicating that [^{18}F]FACT-PET could be substituted for [^{11}C]BF-227-PET for noninvasive detection of dense Aβ deposits in the brain of AD patients. The correlation of [^{18}F]FACT uptake *in vivo* and brain pathology at autopsy should be examined in the future. Our previous studies demonstrated the unique ability of [^{11}C]BF-227 to detect certain forms of prion and α-synuclein protein deposits [22, 23]. Further study will be required to validate the practical usefulness of [^{18}F]FACT-PET for noninvasive detection of these protein deposits.

When a neocortical [^{18}F]FACT SUVR of 1.145 (1.5 SD above control mean) was used as a cutoff, [^{18}F]FACT-PET scan achieved a sensitivity of 90 % (nine of ten) and a specificity of 100 % (ten of ten) in the discrimination between AD patients and normal subjects. In one exception, a 76-year-old female AD patient, MMSE score 24, showed no remarkable retention of [^{18}F]FACT in the neocortex. This is not surprising because approximately 10 to 20 % of patients diagnosed as probable AD reportedly fail to meet pathological criteria for AD at autopsy.

The amnestic subtype of MCI has a high risk of progression to dementia, and it may constitute a prodromal stage of AD [24]. Previous amyloid-PET studies demonstrated a substantial amount of neocortical tracer retention in 50 to 60 % of the MCI population, which is comparable to the level in AD patients [10, 17]. In our study, about half of the MCI patients had elevated neocortical [^{18}F]FACT retention, which was an intermediate level between the aged normal subjects and the AD patients. This finding is in accord with the previous neuropathological observation that the density of neuritic plaque increased as a function of increasing dementia severity [25]. The parent tracer [^{11}C]BF-227 showed neocortical retention to be a reliable indicator of disease progression in MCI subjects in our previous study [17, 19]. Therefore, PET imaging with [^{18}F]FACT is also expected to have a similar prognostic utility.

The amount of elevation of neocortical [^{18}F]FACT uptake in AD patients was approximately 14 to 15 %, far less than PiB and other ^{18}F-labeled amyloid-PET tracers. This is probably due to the relatively low binding affinity and B_{max} of this tracer with amyloid fibrils in comparison to that of PiB (K_d=1.02 nM, B_{max}=0.61) [26, 27]. There is considerable amount of tracer retention in the white matter, which reflects non-specific binding of the compound to myelin sheath. Because of modest specific binding of [^{18}F]FACT in the gray matter of AD patients, spillover from the white matter could reduce the sensitivity for detecting amyloid positive subjects. Use of early phase (30 to 40 min postinjection) images can compensate for this because the relatively stronger signals in the gray matter persist in this time interval. Partial volume correction may also be able to improve the discriminatory power of [^{18}F]FACT-PET by eliminating nonspecific signals in the white matter. Another method to improve the sensitivity for detecting specific signals in the brain is to create a statistical map by comparison with a normal control database [19].

One of advantages of [^{18}F]FACT over BF-227 is its rapid kinetic profile. [^{18}F]FACT showed faster washout from normal brain tissue than BF-227 (Fig. 5) probably because of the lower lipophilicity of FACT (LogP=1.99±0.02) as compared to BF-227 (LogP=2.29±0.02). The neocortical SUVR of [^{18}F]FACT reached a peak at 30 min post-administration. This characteristic would also contribute to reduced procedure and waiting times for PET scans.

Conclusion

We successfully developed a novel ^{18}F-labeled ethenylbenzoxazole derivative, [^{18}F]FACT, as a PET tracer for amyloid deposits. This tracer preferentially bound to dense Aβ plaques in AD brain sections, visualized cortical amyloid deposits in APP Tg mice, and demonstrated fast kinetics and significant retention of [^{18}F]FACT in sites with predilection for the deposition of dense amyloid plaques in AD patients during clinical PET imaging. [^{18}F]FACT PET distinctly distinguished AD patients from normal individuals. These findings suggest that [^{18}F]FACT may be usable for *in vivo* detection of dense Aβ plaques in AD brains.

Acknowledgments. This study was financially supported by the Special Coordination Funds for Promoting Science and Technology, the Health and Labour Sciences Research Grants for Translational research from Ministry of Health, Labour and Welfare, the Program for Promotion of Fundamental Studies in Health Science of the National Institute of Biomedical Innovation, and the Grant-in-Aid for Scientific Research (C) (20591432) from the Ministry of Education, Culture, Sports, Science and Technology of Japan. The authors appreciate the technical assistance of Dr. Shoichi Watanuki in the clinical PET studies.

Conflict of Interest. The authors declare they have no conflicts of interest.

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ORIGINAL ARTICLE: BIOLOGY

Brain accumulation of amyloid β protein visualized by positron emission tomography and BF-227 in Alzheimer's disease patients with or without diabetes mellitus

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Aim: Although diabetes mellitus (DM) is considered to be one of the most consistent risks for developing dementia, it is not known if the pathology in dementia patients with DM is similar to or distinct from typical pathological features of Alzheimer's disease (AD). To discover the mechanism of developing dementia in AD patients with DM in a living state, we studied the distribution of amyloid β (Aβ) protein of diabetic AD patients.

Methods: To evaluate the accumulation of Aβ, we examined 14 normal controls, four diabetic patients with AD and 11 non-diabetic patients with AD by positron emission tomography (PET) using BF-227, a currently developed Aβ tracer.

Results: The analysis of PET images among the three groups showed an abundant aggregated Aβ accumulation in the cerebral cortex of both AD patients with and without DM. The extent and distributions of BF-227 accumulation in diabetic AD patients were not significantly different from these of non-diabetic AD patients.

Conclusion: These results suggest that the degree and extent of Aβ deposition is not significantly different between AD with DM and AD alone. **Geriatr Gerontol Int 2013; 13: 215–221.**

Keywords: Alzheimer's disease, amyloid β-peptides, diabetes mellitus, positron emission tomography.

Introduction

Long-standing lifestyle-related disorders from midlife, such as diabetes mellitus (DM) and hypertension, as well as obesity, are likely to be prominent risk factors for developing dementia and Alzheimer's disease (AD).[1] In fact, it is often found that diabetic patients develop AD in their later stage of life. Several separate community-based studies suggest that DM might increase the risk of dementia and AD,[2] though the underlying mechanisms are still not clearly explained.

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AD is well characterized by an accumulation of misfolded proteins in the aging brain, which results in oxidative and inflammatory damage that in turn leads to energy failure and synaptic dysfunction.[3] In contrast, the impact of DM on the central nervous system (CNS) is not clearly understood.

Three major components related to type 2 DM that might underlie the effect of diabetes on the CNS in the development of AD are insulin resistance, hyperinsulinemia and hyperglycemia.[4] In addition to these three components, several other components are associated with the incidence of dementia or progression of cognitive decline. Whitmer *et al.* reported that severe hypoglycemic events were associated with a greater risk of dementia.[5] In addition, daily acute glucose fluctuations are also reported to be associated with cognitive decline.[6] Leptin, adiponectin and glucagon like peptide-1 (GLP-1) have recently been mentioned as potential factors that

are associated with the development of AD.[7–10] These components are not fully independent of each other, and it is unlikely that the impact of DM on the CNS depends exclusively on a single component. Which components play the major role might depend on the patient's clinical history and the present state of DM.

Each of these components are thought to act on several different pathways that are important in the pathophysiology of AD, either indirectly, through inflammation or the development of vascular disease, or directly, through effects on amyloid and tau metabolism, and the formation of advanced glycation end-products (AGE).[11] (Fig. 1)

Autopsy results in an epidemiological study concluded that macroscopic brain infarcts are more common in people with DM than those without the disorder, as well as microvascular changes.[12] In contrast, the reported incidence of Alzheimer's pathology in the brains of people with diabetes varies between studies. There are several contradictory papers reporting the relationship between DM and AD. Beeri *et al.* have reported that type 2 DM is inversely associated with AD pathology; that is, diabetic patients with dementia have a significantly lower density of senile plaques than non-diabetic patients with dementia.[13] Matsuzaki *et al.* reported that hyperinsulinemia and hyperglycemia caused by insulin resistance are positively associated with the pathology of AD.[14] In the autopsy population of the Honolulu-Asia Aging Study, the occurrence of neurofibrillary tangles and amyloid plaques in the hippocampus and cortex in people without the apolipoprotein E (*APOE*) ε4 allele were similar to those with and without DM. However, as for *APOE* ε4 carriers, these lesions were more common in people with DM than in people without DM.[12] It was also reported that DM is related to generating atherosclerosis and cerebral infarction, but not directly to AD pathology in diabetic patients with dementia.[15,16] Autopsy findings are usually a mixture of many changes occurring during the living state, so the findings do not necessarily reflect the changes that are clinically relevant.

Interaction between medication for DM, especially the effect of insulin use, and AD neuropathology should be considered as well, as the population of insulin users showed a much higher risk of developing dementia in a cohort study.[17] Biessels *et al.* showed significantly fewer amyloid plaques in diabetic patients who received both insulin and oral antidiabetic medication, as compared with diabetic patients with other medication statuses or non-diabetic subjects. The effects of diabetes medication were specific to amyloid plaques, as the extent of neurofibrillary tangles pathology was not associated with diabetes medications.[18] However, these findings are derived from autopsies, and it is not certain if the same results can be gained from living human brains.

Several neuroimaging studies reported that DM is a risk factor for silent and symptomatic brain infarcts seen with magnetic resonance imaging (MRI),[19,20] and DM is also associated with cortical and subcortical atrophy.[21–23] As functional imaging, it is well known that reductions in regional cerebral glucose metabolic rate (CMRglu), as measured by fludeoxyglucose F 18 positron emission tomography (FDG-PET), are associated with increased AD risk and can be observed years before the onset of dementia.[24,25] Baker *et al.* reported that insulin resistance in persons with normal cognition and prediabetes or early diabetes without treatment is associated with reductions in CMRglu measured with FDG-PET.[26] However, previous radiological studies had limitations on discussing the pathological mechanism, as the modalities used were not directly linked to Alzheimer's pathology. No studies have been carried out regarding a pathobiological link between DM and AD in living human subjects.

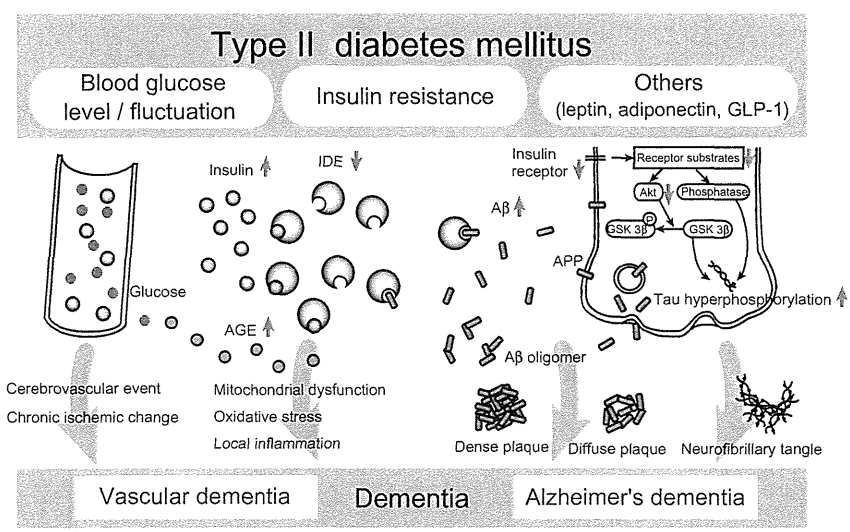

Figure 1 The possible pathological mechanisms associated with the impact of type 2 diabetes mellitus (DM) on the central nervous system (CNS). The major components of DM are described in the second column (only the three major components are described for easier understanding, though several other components are mentioned). Just below the column, the possible mechanism of developing dementia in type 2 DM. Aβ, amyloid β protein; AGE, advanced glycation end-products, APP, amyloid precursor protein; GLP-1, glucagon like peptide-1; GSK-3β, glycogen synthase kinase 3β; IDE, insulin degrading enzymes.

Table 1 Demographic data of the study participants

	Diagnostic group Normal control	AD alone	AD with DM
n	14	11	4
Sex (male/female)	7/7	4/7	2/2
Age	64.5 ± 2.9	78.5 ± 3.9	77.5 ± 5.2
MMSE	29.9 ± 0.1	20.5 ± 0.8	19.4 ± 2.8
ApoE ε4 allele (%)	0.12	0.35	0.37
HbA_{1c} (%)	5.7 ± 0.1	5.8 ± 0.1	7.2 ± 0.4

AD, Alzheimer's disease; DM, diabetes mellitus; HbA_{1c}, glycated hemoglobin; MMSE, Mini-Mental State Examination.

In order to clarify etiology and dementia subtypes in diabetic patients, we took a unique approach to visualize amyloid β protein (Aβ) deposition by positron emission tomography (PET) in living diabetic patients with dementia. The Aβ accumulation is successfully and non-invasively visualized by a recently-developed novel amyloid imaging probe called BF-227.[27–31] We used this tracer and applied it to "diabetic" and "non-diabetic" patients with clinically-diagnosed AD, to obtain more insights into differences in the extent and distribution of Aβ accumulation between diabetic and non-diabetic groups.

Methods

A total of 14 normal controls (NC), four diabetic patients with AD (AD with DM) and 11 non-diabetic patients with AD (AD alone) were examined. All the dementia patients were clinically diagnosed as probable AD according to the clinical criteria by "the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association".[32] Brain MRI (1.5 Tesla; General Electric, Fairfield, CT, USA) was carried out on all the participants to exclude other causes of dementia. All the DM types of diabetic patients with AD were type 2. The study protocol was approved by the Committee on Clinical Investigation at Tohoku University School of Medicine and the Advisory Committee on Radioactive Substances at Tohoku University. After a complete description of the study to the patients and subjects, written informed consent was obtained.

The PET procedure using BF-227 is described elsewhere.[28,31] BF-227 and its *N*-desmethylated derivative (a precursor of [^{11}C]BF-227) were custom-synthesized by Tanabe R&D Service (Osaka, Japan) [^{11}C]BF-227 was synthesized from the precursor by *N*-methylation in dimethyl sulfoxide using [^{11}C]methyl triflate. The [^{11}C]BF-227 PET study was carried out using a PET SET-2400W scanner (Shimadzu, Kyoto, Japan). After intravenous injection of 211–366 mBq of [^{11}C]BF-227, dynamic PET images were obtained for 60 min with each subject's eyes closed. Standardized uptake value (SUV) images of [^{11}C]BF-227 were obtained by normalizing tissue radioactivity concentration by injected dose and bodyweight. Regions of interest (ROI) were placed on individual axial MR images in the cerebellar hemisphere, striatum, frontal, lateral temporal, medial temporal, parietal, occipital, anterior and posterior cingulate cortices. The ROI information was then copied onto dynamic PET SUV images, and regional SUV were sampled using Dr.View/LINUX software (AJS, Tokyo, Japan). Because there were neither senile plaques nor glucose hypometabolism in the cerebellum of AD patients, the ratios of regional SUV to cerebellar SUV (SUVR) were calculated as an index of [^{11}C]BF-227 retention. Neocortical SUVR was calculated by averaging SUVR in the frontal, lateral temporal, parietal and posterior cingulate cortices. Apolipoprotein E genotyping was carried out as previously described.[33]

The difference of Neocortex SUVR between the group of AD with DM and other groups was assessed with Student's *t*-test. The performance of diagnostic indices to discriminate among groups was assessed using receiver operating characteristic (ROC) analysis. Areas under ROC curves (AUC) were calculated and compared using GraphPad Prism Software (GraphPad Software, San Diego, CA, USA). Statistical significance was defined as $P < 0.05$.

Results

The clinical features of the three groups, NC, AD alone and AD with DM, are described in Table 1. Severities of dementia assessed by Mini-Mental State Examination were not significantly different between AD alone and AD with DM. Three patients were treated with only oral DM medications (patient A glimepiride + pioglitazone; patient B glimepiride + metformin + voglibose; patient

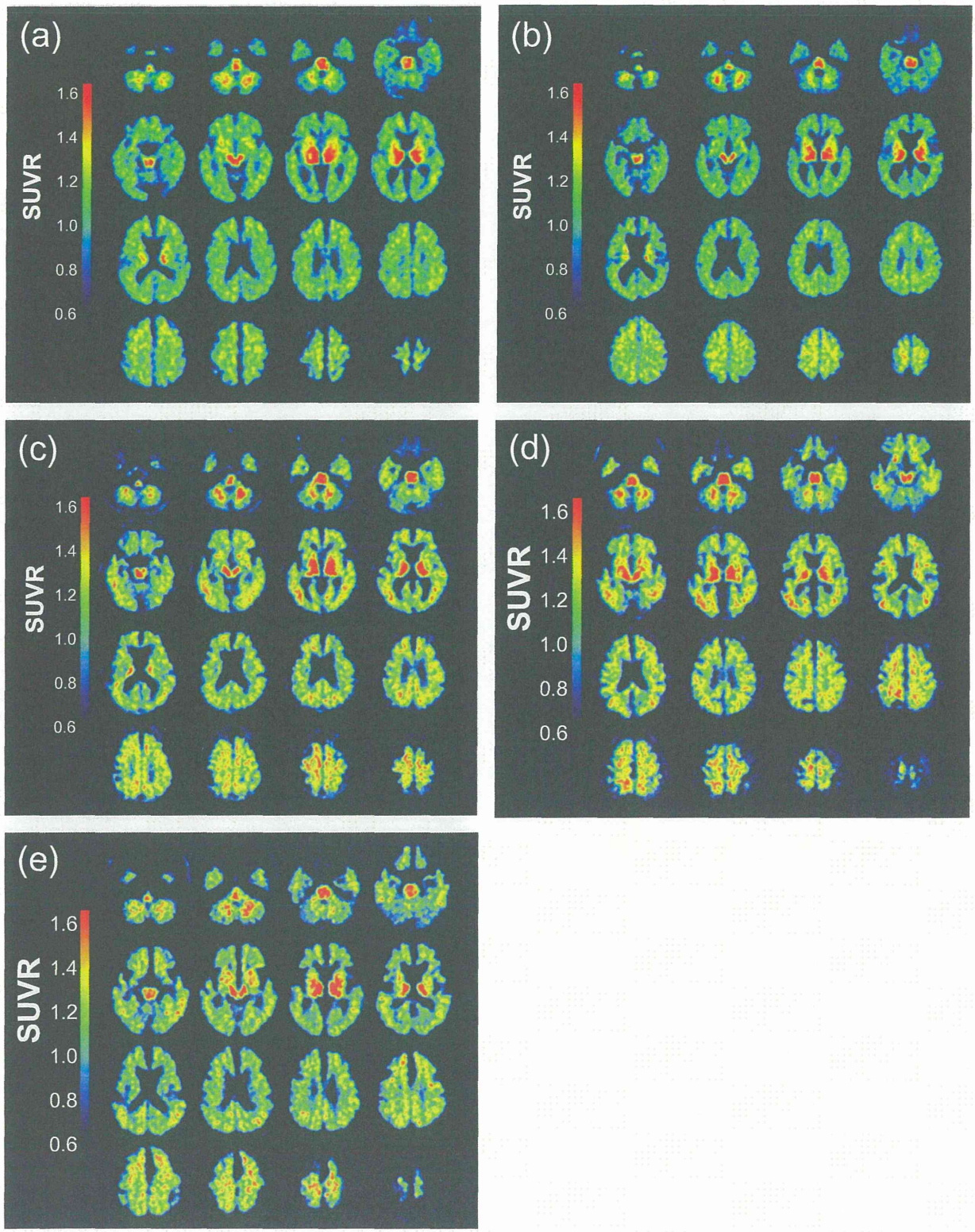

Figure 2 Representative BF-227 positron emission tomography images of each diagnostic group. (a) Normal control without diabetes mellitus (DM; 67-years-old, male, no complication; neocortical ratios of regional standardized uptake value to cerebellar standard uptake value ratio [SUVR] = 1.122). (b) Normal control with diabetes mellitus (67-years-old, female, insulin user; neocortical SUVR = 1.012). (c) Alzheimer's disease (AD) alone (75-years-old, female; neocortical SUVR = 1.230). (d) AD with DM (79-years-old, female, insulin user; neocortical SUVR = 1.240). (e) AD with DM (78-years-old, male, non-insulin user; SUVR = 1.18).

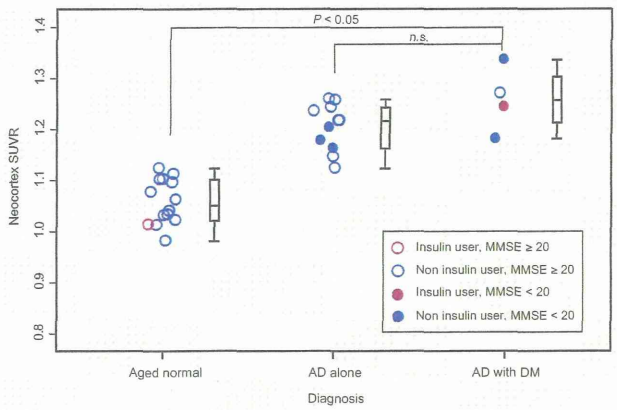

Figure 3 Box and scatter plots of ratios of regional standardized uptake value to cerebellar standard uptake value ration (SUVR) values with BF-227 in aged normal, Alzheimer's disease (AD) alone and AD with diabetes mellitus (DM) participants. Each circle indicates the mean SUVR from the mean neocortex. Red colored circle represents insulin user, whereas blue colored circle represents non-insulin user. There are no DM patients in the aged normal group shown with the blue circle. The filled circle represents the participants with Mini-Mental State Examination score less than 20. Although both AD with DM and AD alone showed significantly higher SUVR than the normal control group ($P < 0.05$), the difference between AD with DM and AD alone was not significant (n.s.).

Table 2 Characteristics of insulin users

	Subject 1 (no. 4) (normal cognition)	Subject 2 (no. 6) (AD patients)
Age	67	79
Sex	Female	Female
MMSE	28	21
ApoE genotype	3/3	3/3
CSF total tau (pg/ml)	–	334
BMI	24.7	19.8
HbA_{1c} (%)	7.6	8.2
Medication	Insulin only	Insulin, metformin
Hypoglycemic event	several	none
Duration of insulin use (years)	11	7

AD, Alzheimer's disease; BMI, body mass index; CSF, cerebrospinal fluid; HbA_{1c}, glycated hemoglobin; MMSE, Mini-Mental State Examination.

C metformin + voglibose), whereas only one AD with DM patient used insulin in addition to metformin. One DM patient was present in the normal control group. This patient in the control group had no oral medication. Insulin injection was the only medication.

MRI scans showed no or very few ischemic or hemorrhagic lesions observed in any of the participants. These small lesions were not strategic. White matter lesions (both periventricular and deep white matter) are all less than mild according to the Fazekas criteria (data not shown).[34]

After we obtained demographic information, we analyzed PET images with BF-227 among the three groups, and representative brain PET images are shown in Figure 2. As indicated in the figure, both the patients with AD alone and AD with DM showed significantly more robust retention of BF-227 than NC. Statistical analysis showed a significantly higher SUV-R of BF-227 ($P < 0.05$) in the cerebral cortex of AD alone and AD with DM than NC, as shown in Figure 3. Neocortical SUV-R of BF-227 in AD alone and AD with DM are not significantly different. Both the patients with AD alone and AD with DM showed increased BF-227 uptake in frontal, temporal, parietal, occipital and cingulated gyrus. The pattern of uptake was similar between the DM patients with insulin use and those without the use of insulin (Fig. 2). A similar pattern of uptake between insulin users and non-insulin users was seen both in the control group and the AD with DM group.

The clinical profiles of the two insulin users are shown in Table 2.

Discussion

The present study had two major findings. First, the uptake of BF-227 was significantly higher in both AD groups than that of the normal control group, regardless of DM complication. Second, the amount and pattern of the uptake was not affected by the use of insulin, both in the control group and the AD with DM group.

The first result that the severity and extent of the deposition did not differ significantly between the two groups suggests that both AD with DM and AD alone have robust deposition of senile plaques or typical AD pathology. In addition, all the participants we examined showed no or very few vascular lesions observed with MRI, indicating that we could exclude vascular dementia. The present result showed that the cause of developing dementia in DM patients cannot be fully explained by vascular mechanism. From the results of previous studies,[13,14] we assumed that either extra or less deposition of amyloid plaques would be seen in the brain of AD patients with DM complication. However, the brains of AD patients with DM showed a similar pattern and severity of the amyloid deposition to that seen in the brains of AD without DM complication. One possible explanation is that some kinds of protein that cannot be detected by BF-227 play a more important role than the classical aggregated plaque. Soluble

Aβ oligomers, which cannot be detected by BF-227, were shown to lower insulin receptor responses to insulin and cause substantial loss of neuronal surface insulin receptors.[35] Another possibility is that the additional effect of DM complication appears mainly through the increase in phosphorylation of tau, instead of an increase of Aβ plaque.

The second result of AD patients is in conflict with those reported by Beeri *et al.*[18] According to their conclusion, the AD patient with insulin and metformin use (subject 4 in Fig. 2) should have shown fewer senile plaques (lower uptake) as compared with diabetic patients with other medication status or non-diabetic subjects. One explanation for this inconsistency is that he/she was an *APOE* ε4 non-carrier. The occurrence of neurofibrillary tangles and amyloid plaques in people without the *APOE* ε4 allele were similar to those with and without DM in the autopsy population of the Honolulu-Asia Aging Study.[12] It is assumed that the effect of insulin and other medication use on reducing the plaques might only be effective in reducing the extra deposition of amyloid plaques in *APOE* ε4 carriers.

It was also found that the insulin user with normal cognition (subject 2 in Fig. 2) showed no difference in uptake. This subject was not obese, and started insulin injections 11 years before she undertook the PET procedure. Her glycohemoglobin level was 7.6%, and she had experienced several hypoglycemic events just before participation in the present study. From these clinical features, we assume that one of the main components of her DM were fluctuations of her blood glucose level (hyperglycemia and hypoglycemia). The interaction with ApoE ε4 might also be thought to be an explanation.

A limitation of the present study was that we could not adjust some factors, such as age, due to the small sample size. Because of the small sample size, the present study should be treated as a preliminary report. In addition, we could not measure the value of their homeostasis model assessment ratio, which is one of the key indicators of insulin resistance. We could not measure this indicator of insulin users, because they already had started insulin before admission to our clinic. Further studies are required to clarify the present report.

In conclusion, the present study provided new and important preliminary findings that a similar pathomechanism, which is the deposition of robust aggregated Aβ in the brain, is shared in both AD with DM and AD alone.

Disclosure statement

The authors declare no conflict of interest.

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血液症候群(第2版)

—その他の血液疾患を含めて—

III

X　血漿タンパクの異常

アミロイドーシス

局所性アミロイドーシス

脳アミロイドーシス

工藤幸司
荒井啓行

X 血漿タンパクの異常

アミロイドーシス
局所性アミロイドーシス

脳アミロイドーシス

Cerebral amyloidosis

工藤幸司[1]
荒井啓行[2]

Key words：脳アミロイドーシス，アルツハイマー病，preclinical AD

はじめに

脳アミロイドーシス(cerebral amyloidosis)とは脳へのアミロイド沈着が認められる疾患であり，沈着するアミロイドにより疾患特性が存在する．例えばアミロイドβタンパク(Aβ)は，アルツハイマー病(Alzheimer's disease: AD)および脳アミロイドアンギオパチー(cerebral amyloid angiopathy: CAA)において，また異常型プリオンタンパクはプリオン病(prion disease)においてそれぞれ観察される．

本稿では，主としてADにつき述べてみたい．

1．アルツハイマー病(AD)

ADにおける近年の話題で最も我々を驚かせたのは2010年7月ハワイで開催された国際アルツハイマー病学会(International Conference on Alzheimer's Disease 2010: ICAD2010)において，アメリカの2つの機関，すなわちNational Institute on Aging(NIA)とAlzheimer's Association(AA)から提案された新しいAD診断基準であったことに，異を唱えるAD研究者は少ないであろう．両機関はADをpreclinical AD，MCI due to ADおよびAD dementiaの3つの時期に分け，それぞれに新しい診断基準を提案した(提案の最終バージョンは2011年に公表)[1-4]．それらの提案の中で我々が驚かされたその本体は，臨床症状が認められなくてもAD特有の病理像を検出できたらpreclinical AD[4]として病気に組み入れるという新しい概念を提示されたことであった(ただし，この概念はあくまでもresearch criteriaとのこと)．学会でこれを最初に聞いたときは，'あっ，またアメリカに負けた！日本の社会ではこのような概念は提案できないだろうし，受け入れられないだろうなあ．これで彼らはまたまた日本の前を走り続けるのだろうなあ'が感想であった．

2011年に公表されたpreclinical ADに関する文献[4]の内容を紹介すると，図1は主としてpreclinical ADにおけるバイオマーカーとそれらのスタート時点およびその後の経過を示しているが，ADのバイオマーカーとして最も初期(stage 1)に検出できるそれはAβである．具体的なバイオマーカーとしては，アミロイドイメージング用陽電子断層撮影装置(positron emission tomography: PET)プローブとPETによって判明する主として患者脳灰白質におけるAβ蓄積量の増加，および脳脊髄液中のAβ1-42の低下である．preclinical ADを更に詳しく定義しているのが表1(文献[4]には記載されていない．2010年秋頃NIAおよびAAのホームページからリンクできたが，現時点では不可能)である．これにはpreclinical ADのstage 1はasymptomatic cerebral amyloidosisと記載されており，更に同表から各stageにおけるバイオマーカーの詳細を追跡することができる．

両機関がこの提案，特にpreclinical ADという新しい概念を導入するに至った経緯について，

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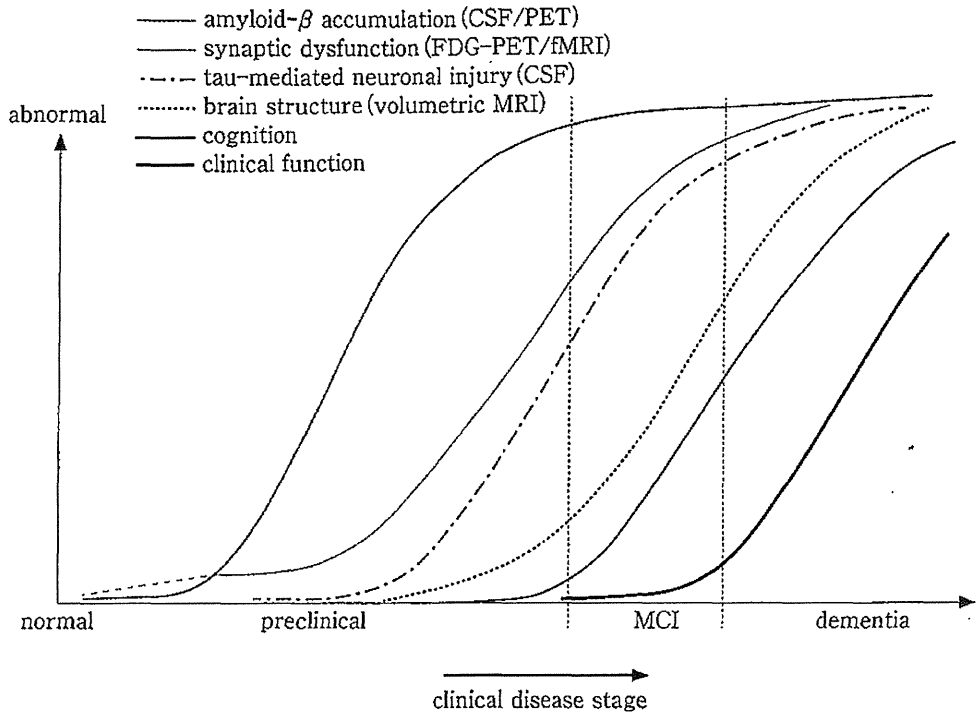

図1 アルツハイマー病，特にpreclinical ADにおけるバイオマーカーとそれらの発現時期(文献[4]より引用)

著者らは以下のように推察している．2008年6月以降，セクレターゼ阻害薬類，ワクチン，抗体をはじめとするいわゆる根本治療薬の治験成績が次々と公表された．多くの研究者，臨床家はこれらの介入によって少なくとも臨床症状の進行はストップする，と予測していたものと思われるが，それらの結果は我々の期待を大きく裏切るものであった．その中でも特に落胆させられたのはAβワクチンによって脳内Aβがクリアーされた患者においても，認知症の進行は食い止めることができなかったという2008年，Lancetの報告であった[5]．

これらの成績をどのように解釈するかであるが，まずこれらの薬物はADの治療薬とはなりえないとする立場をとるのが一般的と考えられる．一方，Aβの蓄積が始まる極めて早期にこれらの薬物を処方したならばADの一連の病理像の連鎖をスタート時点(=Aβ蓄積スタート時点)付近で断つことができ，その後のAD発症を抑制できる可能性があると推測することもできる．近年，この推測が正しいかもしれないことが示唆される報告も散見されている．すなわち，抗Aβ抗体bapineuzumab[6]やgantenerumab[7]により脳内Aβは減少することがアミロイドイメージング用PETプローブ[^{11}C]PiBを用いた試験によって確かめられており，また抗Aβ抗体solanezumabでは軽度のADにおいて認知機能低下の進行抑制(進行のストップではない)が認められたとのプレス発表がなされている[日本イーライリリー：https://www.lilly.co.jp/pressrelease/2012/news_2012_135.aspx].

2. Preclinical ADとアミロイドイメージング

臨床症状の全くみられないpreclinical ADを拾い上げるためには，現時点では図1および表1のstage 1に示されているように脳内Aβをを PETで画像化するか，または脳脊髄液中のAβ1-42の低下を指標にするかであるが，本稿では前者について概説したい．

脳内Aβ蓄積を画像化するためには，いわゆるアミロイドイメージング用PETプローブが

表1　National Institute on Aging(NIA)およびAlzheimer's Association(AA)提案による preclinical AD の診断基準

Operational Research Criteria for Defining Preclinical AD

1. biomarker evidence of amyloid-β accumulation(stage 1=asymptomatic cerebral amyloidosis)
   a. elevated tracer retention on PET amyloid imaging and/or low $A\beta_{42}$ on CSF assay
2. biomarker evidence of synaptic dysfunction and/or early neurodegeneration(stage 2=evidence of amyloid positivity+presence of one or more additional AD markers)
   a. elevated CSF tau or phospho-tau
   b. hypometabolism in an AD-like pattern(i.e. posterior cingulate, precuneus, and/or temporo-parietal cortices) on FDG-PET
   c. cortical thinning/grey matter loss in AD-like anatomic distribution(i.e. lateral and medial parietal, posterior cingulate and lateral temporal cortices) and/or hippocampal atrophy on volumetric MRI
3. evidence of subtle cognitive decline, but does not meet criteria for MCI or dementia (stage 3=amyloid positivity+markers of neurodegeneration+very early cognitive symptoms)
   a. demonstrated cognitive decline over time on standard cognitive tests, but not meeting criteria for MCI
   b. subtle impairment on challenging cognitive tests, particularly accounting for level of innate ability or cognitive reserve but not meeting criteria for MCI

必要であるが，これらの中で最も使用頻度の高いプローブはピッツバーグ大学Klunkら—General Electric社の[^{11}C]PiBである．アミロイドイメージングはAD診断の強力なツールとして認められつつあるが，一方では想定外のデータも得られた．それを[^{11}C]PiBを例に紹介すると，2008年7月シカゴでの国際アルツハイマー病学会に先駆けて開催されたADNI(Alzheimer's Disease Neuroimaging Initiative) meetingにおいて健常高齢者の53％が[^{11}C]PiB陽性者であったという驚くべき報告がなされた．AD発症率は65歳以上人口の4-6％と考えられているが，ADNIの報告はADおよびMCI患者を除いた高齢者の53％が[^{11}C]PiB陽性であったということである．また2009年11月，仙台での第28回日本認知症学会に引き続き開催された'World Wide ADNIの展望'においても，特にアメリカでの健常高齢者の約40％が[^{11}C]PiB陽性とのことであった．これら以外にも多くの報告で健常高齢者における無視できない[^{11}C]PiB陽性者が存在することが確かめられている．

なぜこのような問題点が浮き彫りにされるかについては，以下のように説明できると著者らは考えている．すなわち健常高齢者，MCIおよびAD患者のいずれにおいてもAβ蓄積にはかなりのばらつきが存在するために，言い換えると健常高齢者においてもMCIおよびAD患者を凌ぐ，またMCI患者においてもAD患者を凌ぐAβ蓄積を示す個体が無視できない割合で存在するために多くの偽陽性者がみられ，プローブの集積と認知症尺度との間に相関がみられないのであろう．

ここまで書いてきたら次の予想がつくのかもしれないが，そう，健常高齢者における[^{11}C]PiB陽性者はまさにpreclinical AD患者とニアリーイコールと著者らは考えている．それでは，どれほどの患者数が存在するかというと，[^{11}C]PiB陽性者は健常高齢者の20-50％と著者らは見積もっている．高齢者を65歳以上とすると，我が国および先進国ではそれぞれ現時点で約3000万人および約2億人の65歳以上人口が存在し，またこれを基に算出されるpreclini-

表2 65歳以上人口とpreclinical AD患者数の推移
(preclinical AD患者数は65歳以上人口の20-50%として算出)(単位:万人)

		2005年	2010年	2015年	2020年
日本	65歳以上人口	2,560	2,944	3,312	3,532
	preclinical AD患者数	512-1,280	589-1,472	662-1,656	706-1,766
先進国	65歳以上人口	18,564	19,532	21,563	23,778
	preclinical AD患者数	3,713-9,282	3,906-9,766	4,313-10,782	4,756-11,889

(日本2005年データは総理府平成22年版高齢社会白書,それ以外は2008国連World Population Prospects[http://esa.un.org/unpp/]より引用)

cal AD患者数は我が国および先進国ではそれぞれ現時点で約590-1470万人および約3900-9770万人と推測され(表2),今後これらの患者数はますます増加することは確実である.

しかし,これらの数値(preclinical AD患者数)と実際のAD患者数との間には大きな隔たりがあることに気づくことは容易である.前述したように,AD発症率は65歳以上人口の4-6%であるが,6%としても我が国では約180万人,先進国では1200万人のAD患者しか存在しないことになるが,preclinical AD患者数は実際のAD患者数を大きく上回っている.そして更に指摘されるのは,現時点ではどのようなpreclinical AD患者がADに進行するかの情報は全くといってよいほど我々の手許にはないことである.更にpreclinical ADの検診・予防的介入に要する経費(日本では保険が適用されるか否か)および倫理上の問題などが挙げられる.これらがNIAおよびAA提案の問題点と思われる.

3. Preclinical ADと今後の展望

preclinical ADという新しい概念の導入,またpreclinical ADを拾い上げるためにアミロイドイメージングを活用することについて,当初は必ずしも多くの賛同が得られていなかったことも確かであり,NIAおよびAA提案の直後にフォーブス,ニューヨークタイムス,CNNなどにおいて批判的な記事,番組が流されていた.しかしアメリカのダイナミズムはpreclinical ADを対象とした試験,すなわち,A4(Anti-Amyloid Treatment in Asymptomatic AD),DIAN(Dominantly-Inherited Alzheimer Network),API(Alzheimer's Prevention Initiative)をスタートさせている.NIAおよびAA提案から2年以上経過したが,当初の懸念,批判はかなり薄れ,DIANプロジェクトにおいては発症20年以上前から家族性ADではバイオマーカーが動いている[8]らしいことが明らかにされた.

以上より,症状が顕在化するはるか以前のpreclinical ADの時期から予防的に介入することのみによってADに陥ることを防止でき,またこのスキームを実現させるためには,症状を指標とする臨床治験からバイオマーカーを指標とするそれへの転換が必要であろう.

4. 脳アミロイドアンギオパチー,その他アミロイドーシスにおけるアミロイドイメージング

脳アミロイドアンギオパチーのアミロイドの主な成分はAβ1-40である[9]ことから,AD診断用アミロイドイメージング用PETプローブによって比較的容易に脳血管アミロイドを描出することができる.脳アミロイドアンギオパチー患者における[11C]PiB PET画像と,死後脳の抗Aβ抗体染色およびPiB染色とが一致する[10]こと,AD患者における同プローブの集積像と異なり,脳アミロイドアンギオパチー患者では後頭皮質に比較的高い分布がみられる[11]ことなどが報告されている.アミロイドイメージング用PETプローブ[11C]BF-227を用いた研究では遺伝性プリオン病であるゲルストマン・ストロイ

スラー・シャインカー病(Gerstmann-Sträussler-Scheinker disease)患者脳において異常型プリオンタンパク[12]を，また，familial transthyretin-related全身性アミロイドーシス患者の心臓に集積したアミロイド[13]を描出できることが報告されている．

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