Table 1. Demographics and Clinical Data

Carrier	Mutation	Age, y	Family Age at Onset, Mean	Years From Onset	Sex	Mini-Mental State Examination Score	Clinical Dementia Rating	Neocortex SUVR[a]
PSEN1$_a$	L219P	36[b]	54	−18	F	30	0.0	0.54
PSEN1$_b$	dE9	38[b]	44	−6	F	29	0.0	0.80
APP	V717I	48[b]	54	−6	M	28	0.5[b]	1.24[b]
PSEN1$_c$	L219P	62	65	−3	M	29	0.5[b]	0.96[b]
PSEN1$_d$	Y115C	52[b]	49	3	F	22[b]	1.0[b]	1.39[b]
PSEN1$_e$	C236T	55	58	−3	M	...	3.0[b]	0.76
PSEN1$_f$	L85P	31[b]	26	5	M	...	3.0[b]	0.72
PSEN1$_g$	L173S	45[b]	37	8	F	...	3.0[b]	0.93[b]

Cohort		Mean (SD)			Female-Male Ratio	Mean (SD)	Mean (SD)	Mean (SD)
HC (n=30)	...	69.8 (6.6)	...	...	18/12	29.3 (0.9)	0.0 (0.0)	0.60 (0.08)
Sporadic AD (n=30)	...	73.6 (9.4)	...	...	14/16	22.1 (5.0)[b]	1.2 (0.7)[b]	1.21 (0.18)[b]

Abbreviations: AD, Alzheimer disease; Ellipsis, not applicable; HCs, healthy control subjects; SUVR, standardized uptake value ratio.
[a]The mean of the $SUVR_{pons}$ for frontal, cingulate, parietal, lateral temporal, and occipital cortex.
[b]Significantly different from HCs (*z* score, >2).

risk factors for AD.[6,7] The main feature of *APP*, *PSEN1*, and *PSEN2* mutations (involved in different steps of the APP processing pathway) is increased production and deposition of Aβ, especially $Aβ_{42}$.[8,9] Despite some clinical heterogeneity associated with *PSEN1* mutations,[10,11] these various genetic mutations lead to increased levels of Aβ in the brain before symptoms arise.[11]

Amyloid β-peptide imaging with positron emission tomography (PET) allows early and accurate diagnosis of AD.[12,13] Pittsburgh Compound B (PiB), the most widely used amyloid tracer, provides quantitative information on Aβ burden in vivo, which has led to new insights on Aβ deposition in the brain. The use of this technique has shown a robust difference in PiB retention between healthy control subjects (HCs) and subjects with AD[12,13] and has demonstrated inverse correlations of Aβ burden with glucose hypometabolism in some brain regions,[14] cerebrospinal fluid $Aβ_{42}$,[15] and rate of cerebral atrophy.[16] About 25% to 35% of asymptomatic age-matched HCs present with cortical PiB retention that correlates with subtle memory impairment and greater risk of cognitive decline, likely representing preclinical AD.[17-19] Two previous studies[20,21] reported high striatal PiB retention in *PSEN1* mutation carriers, while a third study[22] reported a novel *APP* mutation in which Aβ remains in an oligomeric form showing mild cortical PiB retention. From these few studies, it is difficult to infer the significance of PiB retention in asymptomatic mutation carriers. Therefore, it is crucial to examine more patients with familial AD (FAD) having early-onset or variable mutations to better define the role of Aβ in this population and its association with cognitive status.

The objectives of the study were as follows: (1) to evaluate the pattern of PiB retention in subjects with distinct but different autosomal dominant mutations associated with FAD vs that in age-matched HCs and subjects with probable sporadic AD (SAD), and (2) to correlate Aβ burden as measured by PiB with available clinical and cognitive data, and (3) to compare the regional brain patterns of PiB retention and fluorodeoxyglucose F 18 (FDG) uptake.

METHODS

PARTICIPANTS

Written informed consent for participation in this study was obtained from all subjects or caregivers before imaging. The study was approved by the Austin Health (Melbourne, Australia) human research ethics committee and by the Osaka City University Medical School (Osaka, Japan) institutional ethics committee.

Eight subjects who were carriers of *APP* or *PSEN1* mutations were studied using PiB and FDG PET imaging. All subjects were aware that they were carrying a mutation linked to AD. Specific mutations are listed in **Table 1**.

PiB and FDG PET studies of mutation carriers were compared with those of a well-characterized cohort of 30 HCs and 30 subjects with probable SAD. The latter subjects met the criteria for probable AD as outlined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association.[23]

Subjects underwent a neurologic examination. In addition to the Clinical Dementia Rating (CDR) and the Mini-Mental State Examination (MMSE), subjects without complete impairment underwent various neuropsychological tasks designed to assess a broad range of cognitive domains, although no specific test to assess striatal function was administered.

IMAGING PROCEDURES

All subjects underwent T1-weighted magnetic resonance (MR) imaging for screening and subsequent coregistration with PET images. Each subject received approximately 370 megabecquerels (MBq) of PiB by intravenous injection over 1 minute. Imaging was performed in Melbourne for the *PSEN1*$_{a-e}$ (as listed in Table 1) and *APP* mutation carriers (Allegro PET camera; Phillips, Amsterdam, the Netherlands) and in Osaka for the *PSEN1*$_{f,g}$ mutation carriers (Eminence-B PET imaging system;

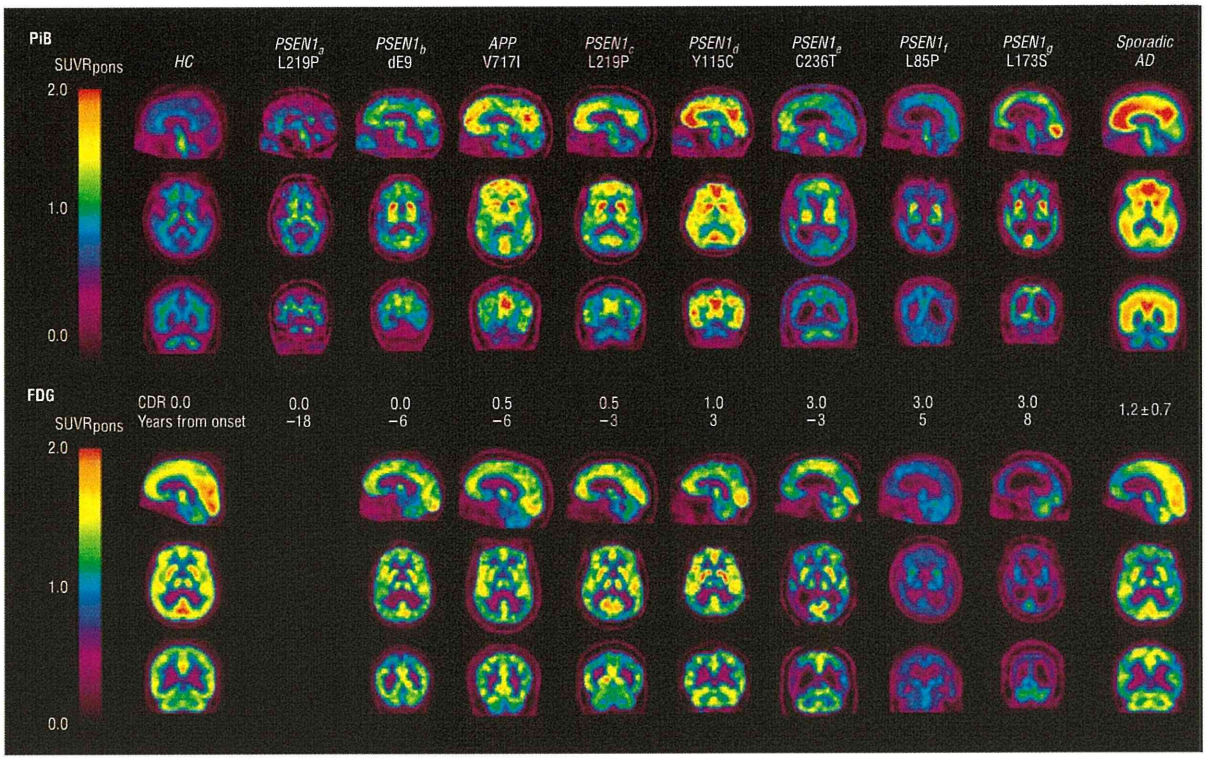

Figure 1. Positron emission tomography (PET) images. Representative parametric sagittal, transaxial, and coronal Pittsburgh Compound B (PiB) PET (top) and fluorodeoxyglucose F 18 (FDG) PET (bottom) images of 8 mutation carriers, as well as representative images of the healthy control (HC) and probable sporadic Alzheimer disease (AD) cohorts. Subjects are arranged according to their Clinical Dementia Rating (CDR) and years from onset for their respective pedigrees. All mutation carriers show high PiB retention in the striata, as well as in the ventrofrontal and posterior cingulate or precuneus areas in most of them. There was no clear pattern of FDG hypometabolism across the subjects studied. SUVR indicates standardized uptake value ratio.

Shimadzu, Osaka, Japan). A 20- to 30-minute emission acquisition was then performed in 3-dimensional mode starting 40 minutes after injection of PiB. In 7 of 8 subjects, static FDG images were obtained 45 minutes after injection of approximately 250 MBq of FDG.

IMAGE ANALYSIS

Coregistration of PET images was performed using a computer program (SPM5; [Statistical Parametric Mapping 5]; Medical Research Council Cognition and Brain Sciences Unit, Cambridge, England),[24] and an MR imaging-defined region-of-interest template was then applied to PET images. The mean standardized uptake value (SUV) was obtained from the region of interest for cortical, subcortical, and cerebellar regions.

Because of the reported presence of plaques in the cerebellar cortex of patients with FAD,[25] PiB retention and FDG uptake were normalized to pons radioactivity to generate standardized uptake value ratio pons ($SUVR_{pons}$). Regional PiB and FDG PET imaging $SUVR_{pons}$ of mutation carriers were then compared with those of a well-characterized (although significantly older) cohort of 30 HCs without evidence of Aβ deposition in the brain (PiB negative) and 30 subjects with probable SAD.

STATISTICAL ANALYSIS

z Scores exceeding 2 were considered significantly different from HCs or subjects with probable SAD. Correlations were assessed using Pearson product moment correlation analyses. Group data are expressed as the mean (SD).

RESULTS

Demographic data for mutation carriers and for the HC and probable SAD cohorts are given in Table 1. All symptomatic mutation carriers had onset of cognitive decline within the expected range of their respective pedigrees. At the time of PET imaging, 3 subjects had severe impairment, and it was impossible to obtain MMSE scores.

The pattern of PiB retention in all mutation carriers, independent of mutation type, differed from that in subjects with probable SAD, with higher PiB retention in the striatum among the mutation carriers (**Figure 1**). Older mutation carriers had higher striatal PiB retention. **Table 2** gives the regional $SUVR_{pons}$ of mutation carriers vs HCs and subjects with probable SAD. Another common feature was high PiB retention in the prefrontal, orbitofrontal, and gyrus rectus regions in most (6 of 8) mutation carriers (Figure 1). Despite their sharing the same *PSEN1* mutation (L219P) (Table 1), the degree of PiB retention was higher and more widespread in the 62-year-old subject closer to the age at onset for his pedigree, while PiB retention was restricted to the caudate nuclei in the 36-year-old subject (18 years away from the age at onset for her pedigree). A cortical PiB retention pattern similar to that usually seen in SAD was observed in 2 women with dementia (the 45-year-old $PSEN1_g$ mutation carrier and the 52-year-old $PSEN1_d$ mutation carrier) and in 2 men without dementia (the 48-year-old *APP*

Table 2. Individual Cerebral Regional Pittsburgh Compound B Retention $SUVR_{pons}$ in Familial AD, 30 HCs and 30 Subjects With Probable Sporadic AD

Location	*PSEN1*$_a$ L219P	*PSEN1*$_b$ dE9	*APP* V717L	*PSEN1*$_c$ L219P	*PSEN1*$_d$ Y115C	*PSEN1*$_e$ C236T	*PSEN1*$_f$ L85P	*PSEN1*$_g$ L173S	Mean (SD) HCs	Mean (SD) Sporadic AD
Frontal	0.53	0.91[a]	1.32[a]	1.04[a]	1.50[a]	0.84[a]	0.63	0.87[a]	0.59 (0.10)	1.30 (0.23)
Orbitofrontal	0.57	0.82[a]	1.34[a]	1.01[a]	1.40[a]	0.88[a]	0.68	0.89[a]	0.61 (0.09)	1.26 (0.22)
Gyrus rectus	0.70	0.92[a]	1.31[a]	1.17[a]	1.65[a]	0.93[a]	0.57	1.01[a]	0.62 (0.09)	1.34 (0.27)
Anterior cingulate	0.62	0.91[a]	1.31[a]	1.17[a]	1.53[a]	0.77	0.76	1.02[a]	0.63 (0.11)	1.30 (0.21)
Posterior cingulate	0.58	0.81	1.65[a]	1.17[a]	1.65[a]	0.73	0.82[a]	0.95[a]	0.62 (0.09)	1.33 (0.19)
Parietal	0.54	0.81[a]	1.00[a]	0.81[a]	1.34[a]	0.68	0.73	1.00[a]	0.55 (0.09)	1.14 (0.20)
Occipital	0.47	0.72	0.91[a]	0.68	1.14[a]	0.74	0.74	0.96[a]	0.64 (0.07)	0.96 (0.17)
Lateral temporal	0.51	0.68	1.24[a]	0.94[a]	1.34[a]	0.66	0.66	0.95[a]	0.59 (0.08)	1.17 (0.20)
Mesial temporal	0.56	0.60	0.80[a]	0.69	0.83[a]	0.50	0.55	0.42[a]	0.61 (0.07)	0.82 (0.11)
Caudate nuclei	1.04[a]	1.37[a]	1.76[a]	1.46[a]	1.97[a]	0.70[b]	1.19[a]	1.59[a]	0.64 (0.10)	1.32 (0.27)
Putamen	0.76	1.15[a]	1.25[a]	1.34[a]	1.57[a]	0.96[a]	1.15[a]	1.38[a]	0.63 (0.08)	1.16 (0.22)
Thalamus	0.63	0.82	1.19[a]	1.06[a]	1.28[a]	0.82	0.72	1.04[a]	0.72 (0.07)	1.03 (0.16)
Midbrain	0.88	0.95	0.96	0.88	0.98	0.90	0.80	0.92	0.87 (0.10)	0.96 (0.09)
Cerebellum	0.47	0.47	0.63[a]	0.65[a]	0.59	0.62[a]	0.65[a]	0.51	0.48 (0.06)	0.52 (0.09)
Striatal	0.90[a]	1.26[a]	1.50[a]	1.40[a]	1.77[a]	0.83[a]	1.17[a]	1.49[a]	0.63 (0.09)	1.24 (0.26)
Neocortex[c]	0.54	0.80[a]	1.24[a]	0.96[a]	1.39[a]	0.76	0.72	0.93[a]	0.60 (0.08)	1.21 (0.18)

Abbreviations: AD, Alzheimer disease; HCs, healthy control subjects; SUVR, standardized uptake value ratio.
[a] Significantly different from HCs (z score, >2).
[b] Severe caudate nuclei atrophy.
[c] The mean of the $SUVR_{pons}$ for frontal, cingulate, parietal, lateral temporal, and occipital cortex.

mutation carrier and the 62-year-old *PSEN1*$_c$ mutation carrier). Half of the mutation carriers demonstrated significantly higher cerebellar PiB retention than that in HCs (Table 2).

Although global and regional FDG uptake was lower in most symptomatic mutation carriers (**Table 3**), there was no common pattern of FDG uptake among the subjects studied (Figure 1). Three subjects (the *PSEN1*$_e$, *PSEN1*$_f$, and *PSEN1*$_g$ mutation carriers) showed marked global glucose hypometabolism in which reduced FDG uptake was associated with severe brain atrophy, while the *PSEN1*$_e$ mutation carrier demonstrated asymmetric FDG uptake but less atrophy on MR imaging than that in the other 2 subjects. Three other subjects (the *PSEN1*$_b$, *APP*, and *PSEN1*$_c$ mutation carriers) showed an almost normal pattern of FDG uptake. The *PSEN1*$_d$ mutation carrier had lower FDG uptake than that among HCs in the parietal cortex, as is usually observed in SAD, and had high FDG uptake in the anterior cingulate, lateral temporal, and striatum (Table 3).

Striatal and cortical PiB retention was not associated with mutation type, disease severity, or cognitive impairment (**Figure 2**). In contrast to PiB findings, the FDG posterior cortical index correlated with MMSE score (r=0.85, P=.02), CDR (r=−0.84, P=.02), and years from onset for the respective families (r=−0.78, P=.04). There was no regional or global correlation between PiB retention and FDG uptake. Given the dichotomy of the CDR and the MMSE score, mutation carriers were separated into 2 subgroups according to their disease severity (MMSE score >20 or ≤20 and CDR >2 or ≤2) for further comparison. There was no significant difference between the subgroups in striatal or neocortical PiB retention, while the most cognitively impaired subgroup (MMSE score ≤20 and CDR >2) had significantly lower striatal FDG uptake (P=.03) and FDG posterior cortical index (P=.01).

COMMENT

In vivo amyloid PET imaging has allowed new insights on Aβ deposition in the brain, facilitating research into the causes, diagnosis, and future treatment of dementias in which Aβ may have a role.[12,13,26] We examined the pattern and degree of PiB retention in familial cases with *PSEN1* and *APP* mutations. All mutation carriers showed some degree of increased PiB retention. Although the degree of cortical retention was generally lower than that usually observed in SAD, the striatal retention was remarkably high. Early onset and rapid progression of the disease indicate that other factors besides Aβ deposition have a role in the cognitive impairment process in FAD, in which Aβ upregulation and deposition represent an early and necessary but not sufficient immediate cause of cognitive decline.

The pattern of PiB retention was similar to that reported in 2 previous studies[20,21] of *PSEN1* mutation carriers. Postmortem studies[21,27] of patients with FAD had shown Aβ deposits in the striatum. The high PiB retention in the striatum is difficult to reconcile with the clinical phenotype given the similar symptoms in SAD, in which this pattern of retention is not observed. However, this pattern is constant across different mutation types, and it has been proposed that Aβ deposition in FAD starts in the striata.[20] High striatal PiB retention was accompanied by significant retention in the frontal regions, although the retention was not as high as that observed in SAD. As in a high percentage of HCs, PiB retention is observed in the frontal and posterior cingu-

Table 3. Individual Cerebral Regional Fluorodeoxyglucose F 18 Uptake $SUVR_{pons}$, in Familial AD, 30 HCs, and 30 Subjects With Probable Sporadic AD

Location	*PSEN1*$_a$ L219P	*PSEN1*$_b$ dE9	APP V717L	*PSEN1*$_c$ L219P	*PSEN1*$_d$ Y115C	*PSEN1*$_e$ C236T	*PSEN1*$_f$ L85P	*PSEN1*$_g$ L173S	Mean (SD) HCs	Mean (SD) Sporadic AD
Frontal	NA	1.32	1.40	1.30	1.43	1.23	0.80[a]	0.89[a]	1.43 (0.23)	1.20 (0.16)
Orbitofrontal	NA	1.32	1.45	1.35	1.36	1.26	0.81[a]	0.88[a]	1.42 (0.18)	1.21 (0.13)
Gyrus rectus	NA	1.37	1.42	1.48	1.58	1.29	0.82[a]	0.95[a]	1.39 (0.15)	1.24 (0.12)
Anterior cingulate	NA	1.44	1.38	1.37	1.55	1.40	0.91[a]	1.03[a]	1.37 (0.17)	1.17 (0.14)
Posterior cingulate	NA	1.46	1.55	1.45	1.48	1.36	0.82[a]	1.01[a]	1.62 (0.19)	1.24 (0.18)
Parietal	NA	1.25	1.32	1.01	1.05	1.02	0.79[a]	0.87	1.37 (0.26)	1.06 (0.24)
Occipital	NA	1.45	1.40	1.15	1.37	1.37	0.80[a]	1.00	1.45 (0.22)	1.22 (0.21)
Lateral temporal	NA	1.32	1.41	1.26	1.47	1.10[a]	0.81[a]	0.86[a]	1.39 (0.14)	1.07 (0.16)
Mesial temporal	NA	1.02	0.99	0.96	1.17	0.82	0.79[a]	0.54[a]	1.05 (0.13)	0.95 (0.12)
Caudate nuclei	NA	1.61	1.39	1.51	1.86	1.27[b]	1.06[a]	1.04[a]	1.61 (0.20)	1.47 (0.20)
Putamen	NA	1.63	1.60	1.62	1.93	1.56	1.08[a]	1.13[a]	1.68 (0.17)	1.57 (0.15)
Thalamus	NA	1.30[a]	1.47	1.72	1.73	1.66	0.88[a]	1.15[a]	1.70 (0.13)	1.49 (0.14)
Midbrain	NA	0.90[a]	0.92[a]	1.25	1.22	1.26	0.93[a]	0.96[a]	1.25 (0.12)	1.16 (0.14)
Cerebellum	NA	1.33	1.20	1.22	1.47	1.37	1.01[a]	1.17	1.33 (0.15)	1.26 (0.15)
Striatal	NA	1.62	1.50	1.57	1.90[a]	1.47	1.07[a]	1.09[a]	1.64 (0.12)	1.51 (0.17)
Posterior cortex[c]	NA	1.34	1.42	1.24	1.33	1.16	0.80[a]	0.92[a]	1.46 (0.17)	1.15 (0.16)

Abbreviations: AD, Alzheimer disease; HCs, healthy control subjects; NA, not applicable; SUVR, standardized uptake value ratio.
[a] Significantly different from HCs (z score, >2).
[b] Severe caudate nuclei atrophy.
[c] The mean of the $SUVR_{pons}$ for posterior cingulate, parietal, and lateral temporal cortex.

late regions of a significant proportion of cognitively unimpaired or minimally impaired mutation carriers. These findings in mutation carriers are in agreement with postmortem findings showing that a high percentage of nondemented older individuals have amyloid plaques (with deposits occurring well before the onset of dementia)[28,29] and with evidence indicating that neuropathologic changes precede the clinical phenotype by many years.[30,31]

At least 3 of 8 mutation carriers in our study demonstrated marked atrophy on MR imaging. Most extrastriatal PiB retention was confined to the ventrofrontal regions, with 4 mutation carriers showing a pattern of cortical PiB retention similar to the pattern observed in SAD.

Semiquantitative measures of Aβ burden are usually generated by normalizing the regional SUV to the cerebellar cortex, a region unaffected by senile plaque deposition in SAD.[32] In contrast, mutation carriers in our study showed a pattern of Aβ deposition different from that of subjects with probable SAD, with higher PiB retention in the cerebellum of mutation carriers reflecting cerebellar Aβ deposition (Table 2).

Postmortem measurements of the distribution and density of diffuse and neuritic Aβ plaques have not consistently correlated with the degree of cognitive impairment in AD.[33,34] The best correlation has been observed with neurofibrillary tangles and soluble levels of Aβ.[35,36] While the exact mechanism by which Aβ might produce synaptic loss and neuronal death is controversial,[1,37] it is likely that PiB retention in nondemented individuals[13,17-19,38] and in cognitively unimpaired or minimally impaired mutation carriers reflects preclinical AD in a classic neuropathologic view.[31] This "delay" in the manifestation of the phenotype may be attributed to different idiosyncratic or cellular susceptibility or vulnerability to Aβ, variations in Aβ conformation affecting toxicity or PiB binding, or both.[39-42] There is also the issue of mutation type, whereby some *PSEN1* mutations are more aggressive and evolve faster than others, while others are associated with movement disorders such as spastic paraparesis or extrapyramidal signs. Larner and Doran[11] have reviewed the phenotypic manifestations of some of the *PSEN1* mutations discussed herein. These hypotheses would justify early involvement of the striatum and would help explain why some older individuals with significant Aβ burden are cognitively unimpaired, while others with genetic predisposing factors (despite lower Aβ burden) have already developed the full clinical AD phenotype.

Regarding PiB binding to different Aβ species with or without posttranslational modification or in a fibrillary oligomer or monomer form, it has been reported that PiB binds with higher affinity to one kind of N-terminal–truncated $Aβ_{1-42(43)}$ species in senile plaques, specifically that truncated at position 3 (Aβ3[pE]), displaying a 5-fold higher affinity for $Aβ3(pE)_{1-42(43)}$ than for $Aβ_{1-42(43)}$.[43] This is relevant to PiB binding because, besides the usual senile and diffuse plaques observed in SAD, cotton wool plaques are observed in the brains of *PSEN1* mutation carriers.[27,44] Cotton wool plaques are generally large with a clear rim and are composed mainly of neuropil elements and $Aβ_{42}$ species, ubiquitously located in the cortex and basal ganglia.[27,44] Cotton wool plaques are particularly important not only because of their distribution in the striatum and cortex but also because they are mildly stained with thioflavin S,[45] in contrast to conventional Aβ plaques seen in SAD or normal aging. Cotton wool plaques should be studied more extensively to explain their etiologic mechanism and how they might contribute to the different patterns of PiB retention among FAD,

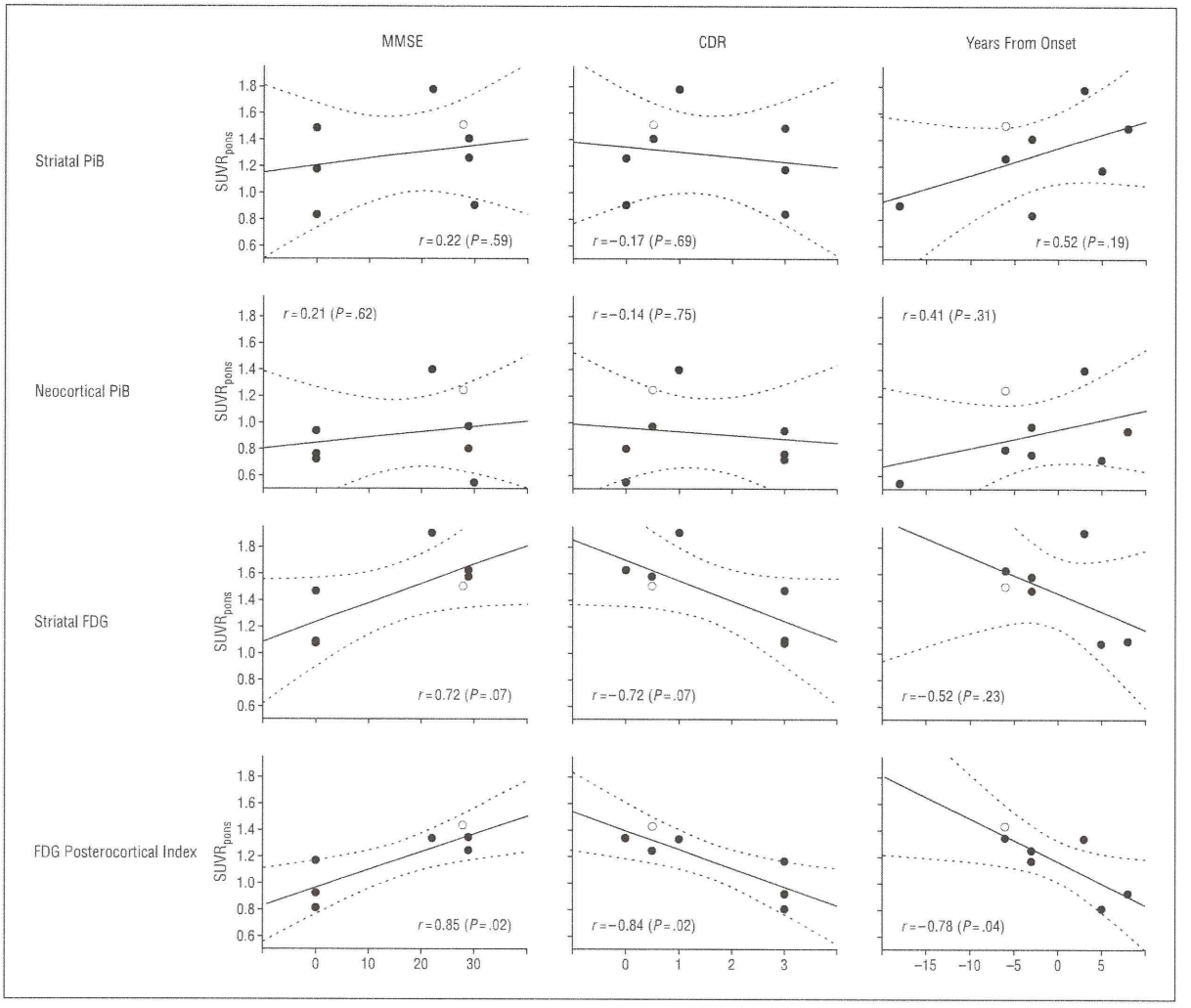

Figure 2. Correlational analysis. Pearson product moment correlation linear correlation analysis shows lack of association between striatal or neocortical Pittsburgh Compound B (PiB) retention and disease severity data or years from onset for the respective pedigrees. Conversely, there are strong correlations between the same variables and fluorodeoxyglucose F 18 (FDG) posterocortical uptake. CDR indicates Clinical Dementia Rating; MMSE, Mini-Mental State Examination; and SUVR, standardized uptake value ratio.

SAD, and normal aging. Longitudinal studies combined with postmortem assessment of Aβ are needed to elucidate this point.

Although PiB investigations (in accord with previous studies[20,21]) showed higher Aβ burden in the striata of all of the mutation carriers studied herein, there was no clear pattern of FDG hypometabolism, neither the typical temporoparietal hypometabolism observed in SAD[46] nor the more restricted temporoparietal hypometabolism reported in asymptomatic at-risk subjects with known *APP* or chromosome 14–linked mutations[47,48] and in subjects with a strong family history of AD.[49] Despite their having generally lower FDG uptake than HCs, most mutation carriers did not show significant regional differences vs HCs or subjects with probable SAD. The reason may be the variance of FDG uptake among HCs and subjects with probable SAD, a variance that precluded achieving higher *z* scores among the mutation carriers. The 2 subjects with extremely low FDG uptake (the $PSEN1_f$ and $PSEN1_g$ mutation carriers) also have the most severe brain atrophy and the most severe cognitive impairment. The third subject with atrophy and marked cognitive impairment (the $PSEN1_f$ mutation carrier) showed an asymmetric pattern of FDG uptake. In FAD as in SAD, PiB seems to be a more sensitive and accurate biomarker than FDG for early detection of disease.[50] This might be because Aβ deposition starts approximately 10 years before any cognitive or memory decline is noted[29] and much earlier than the synaptic and neuronal loss that is reflected in regional glucose hypometabolism. Conversely, FDG uptake correlates with MMSE score and (as in SAD) might prove to be a better marker of disease progression than PiB.[51] Evaluation of more familial mutation cases with PiB and longitudinal follow-up are warranted to establish the usefulness of PiB as an early and reliable method of detecting Aβ deposition, while also providing insights on the progression of Aβ deposition and assessing its prognostic accuracy. An international consortium, the Dominantly Inherited Alzheimer Network (http://www.dian-info.org/), has been organized to

comprehensively assess the origin of AD through FAD and to evaluate the usefulness of different biomarkers such as amyloid imaging. This kind of multidisciplinary approach should define the role of amyloid imaging in the evaluation of asymptomatic mutation carriers at risk of developing FAD.

In conclusion, although Aβ deposition (as in SAD) seems to precede the clinical manifestation of dementia, the pattern of Aβ deposition in FAD is not related to disease severity and (irrespective of mutation type) differs from that observed in SAD. When disease-specific therapies aimed at preventing or slowing AD progression become available, amyloid imaging studies will have an important role in the identification of Aβ deposits in at-risk mutation carriers before the development of symptoms.

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Author Affiliations: Department of Nuclear Medicine, Centre for Positron Emission Tomography, Austin Health, Heidelberg (Drs Villemagne, Mulligan, O'Keefe, and Rowe and Mr Jones), The Mental Health Research Institute, The University of Melbourne, Melbourne (Drs Villemagne and Masters), and Prince of Wales Medical Research Institute, Randwick, and The University of New South Wales, Sydney (Dr Brooks), Australia; and Neuroscience, Gerontology, and Neurology, Osaka City University Medical School, Osaka (Drs Ataka, Miki, Shimada, and Mori), Molecular Neurology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto (Drs Mizuno, Kondo, and Nakagawa), and Molecular Imaging Research Program, RIKEN, Kobe (Dr Wada and Watanabe), Japan.
Correspondence: Victor L. Villemagne, MD, Department of Nuclear Medicine, Centre for Positron Emission Tomography, Austin Health, 145 Studley Rd, Heidelberg, Victoria, Australia 3084 (villemagne@petnm.unimelb.edu.au).
Author Contributions: Drs Villemagne, Mori, and Rowe had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Villemagne, Rowe, and Mori. *Acquisition of data:* Villemagne, Ataka, Mizuno, Brooks, Wada, Kondo, Jones, Watanabe, Mulligan, Nakagawa, Miki, Shimada, O'Keefe, Mori, and Rowe. *Analysis and interpretation of data:* Villemagne, Ataka, Masters, Mori, and Rowe. *Drafting of the manuscript:* Villemagne, Mori, and Rowe. *Critical revision of the manuscript for important intellectual content:* Villemagne, Masters, Mori, and Rowe. *Statistical analysis:* Villemagne. *Study supervision:* Villemagne, Mori, and Rowe.
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認知症

アルツハイマー病の分子病態入門

—実地医家に必要な知識—

山川義宏・安宅鈴香・森　啓*

大阪市立大学医学部老年科神経内科・*同　脳神経科学/やまかわ・よしひろ　あたか・すずか　もり・ひろし

はじめに●

認知症の原因疾患として主にアルツハイマー病 Alzheimer disease（AD），前頭側頭型認知症，脳血管性認知症があげられ，日本ではかつて脳血管性認知症が最も多かったが，1990年代に入ってからはADが多くなった．2000年のわが国の推定認知症有病率は7.2%であり，ADはその約40%を占める．一方でAD病因論としてアミロイドβ蛋白 amyloid beta protein（Aβ）による老人斑の形成およびリン酸化タウによる神経原線維変化が認められ，不溶性Aβの沈着が神経細胞死につながるとするアミロイドカスケード仮説が提唱されてきたが，最近ではAβのオリゴマーの段階での神経毒性が判明し，オリゴマーこそ病因の主体であるとするオリゴマー仮説が有力視されつつある．

ADの病理●

アミロイド前駆体蛋白 amyloid precursor protein（APP）がβおよびγセクレターゼによって蛋白加水分解を受け，Aβが切り出される（図1）．灰白質のうち神経細胞やグリア細胞の細胞体以外の部分であるニューロピルと呼ばれる細胞外組織周辺にAβが沈着，異常凝集し，これに伴い神経突起やグリア細胞の変性が起こり，老人斑 senile plaque（SP）が形成される．SPは最初，新皮質，特に前頭・側頭葉の下面に，次いで一次運動感覚野を除く新皮質に広がってゆく．記憶と関係の深い海馬には初期にはSPは認められない．一方でSPの形成からしばらく遅れて嗅内野，海馬，視床を中心に，神経細胞内における神経原線維変化 neurofibrillary tangle（NFT）が認められるようになり，前頭・側頭・後頭連合野を含む皮質，脳幹へ広がってゆく．NFTは2本の線維が捩れ合わさったような構造 paired helical filaments（PHF）の集積物であり，高度にリン酸化されたタウからなる．Aβの凝集とNFTとの関係はまだ明確ではないが，SP，神経原線維変化に伴い，神経細胞数の減少が認められるようになり，グリオーシス，大脳白質病変などの二次的

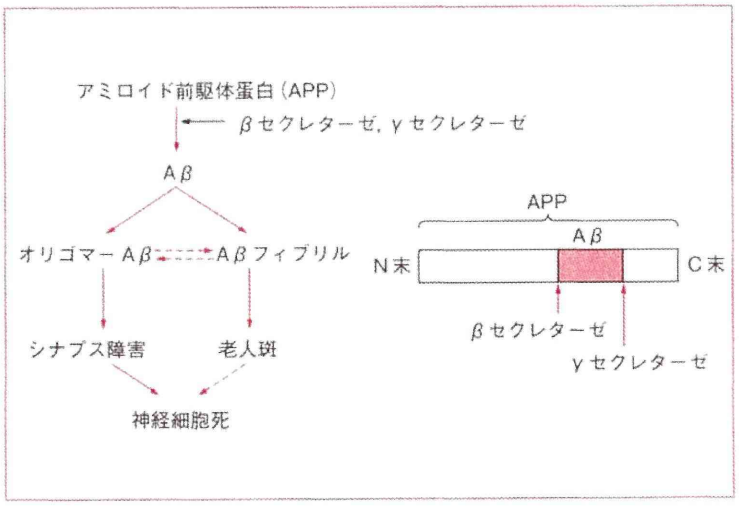

図1　アミロイドカスケード仮説およびオリゴマー仮説

図で老人斑が神経細胞死につながるとする流れがアミロイドカスケード仮説．オリゴマーAβによるシナプス障害が神経細胞死につながるとする流れがオリゴマー仮説．オリゴマーAβのすべてがAβフィブリルを形成するわけではない．矢印は仮想反応を含む．

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- ADではSPの形成から遅れてNFTが現れ，初期には海馬にはSPが認められない．
- ADではコリン系，ドパミン系，セロトニン系と広く神経細胞の減少が認められる．
- オリゴマーAβの神経毒性に注目したオリゴマー仮説が有力となってきている．

変化を伴いながら認知機能が低下してゆく．SPおよびNFTの脳での広がりかたに関し，ブラークのステージ分類がある．ステージI，IIは認知症レベルではなく，ステージIII，IVは初期のAD，あるいはADの可能性のある段階，ステージV，VIは確実なADとされる．SP，NFT形成あるいは単純萎縮を介し，最終的に起こる神経細胞脱落の分布を6層構造でみるとII，III層で最も強い．領域別でみると海馬，下側頭回，内・外側後頭側頭回で最も強い．一方で皮質下でも神経細胞脱落を起こしやすい神経核があり，特にアセチルコリン作動性のマイネルト核では約30%にまで神経細胞が減少することに注目したコリン仮説は学説としては今や下火となっている．他，ドパミン作動性の青斑核(19～33%への減少)，セロトニン作動性の縫線核(64%への減少)などがみられる[1]．

オリゴマー仮説

NFTと神経細胞脱落の分布領域はほぼ一致しており，NFTと神経細胞死の関連性は密接とされる．一方でAβ単体(モノマー)は可溶性であり，細胞外液中に溶解している状態では神経細胞に対して特別な毒性を発揮しない．SPにみられるのはAβ単体が重合・凝集し，不溶化してフィブリル(線維)となって沈着したものであり，これが神経毒性をもつものと考えられてきた．しかしオリゴマーAβを形成した段階で，まだ可溶性を保ったオリゴマーAβがシナプス後膜に結合すると細胞死を引き起こし，特に海馬シナプスにおける長期増強long-term potentiation(LTP)を強く抑制することが判明し，また家族性のADのある一家系にみられたAPPの変異体からはフィブリルやSPが形成されず，オリゴマーAβのみ形成されたことが強く示唆されたことからオリゴマーAβの神経毒性に注目したオリゴマー仮説が有力となってきている[2]．

画像診断

ADではCT，MRIにて海馬を含めた側頭葉前半部と内側部に萎縮が目立ち，頭頂後頭葉にも萎縮が及ぶ．SPECTでは頭頂・側頭葉の連合野皮質で血流低下がまずみられ，進行に伴い前頭葉の連合野皮質でも血流低下がみられるようになる．FDG-PETでもまず頭頂・側頭葉の連合野皮質で糖代謝の低下がみられ，前頭葉の連合野皮質での糖代謝の低下とつづく．病理学的変化が起こりにくい一次運動感覚野はSPECTやFDG-PET所見でも最後まで血流，糖代謝が保たれる．ADではmild cognitive impairment(MCI)と呼ばれる軽度認知機能低下を呈する段階ですでに後部帯状回や楔前部での血流低下・糖代謝の低下が認められる．後部帯状回や楔前部はNFTが初期より出現する嗅内野，海馬と密接な連絡線維をもつ．一方で海馬を含め，側頭葉内側部の血流低下や糖代謝の低下は初期には認められない．

図2にPIB-PETの典型的画像を示した．若年健常者では皮質にPIB集積を認めず，白質の非特異的集積が主体．健常高齢者では加齢に伴い，わずかに皮質にPIB集積を認める．健常高齢者のPIBシグナルがびまん性老人斑に起因すると結論するには，なお慎重な検証が必要である．ADでは明らかに皮質とくに楔前部，後頭帯状回，前頭葉，頭頂葉，外側側頭葉優位にPIBの集積がみられる．MCIはADほど著明ではないが，ADと同様の分布でPIB集積の上昇がみられる症例群がある．逆にPIB集積の低いMCI群はADへの移行率が低いことが示されつつある．PIBの意義についての結論は今後の詳細な分析を待たなければならないが，現時点で，その実際的な有用

- ADではMCIの段階ですでに後部帯状回や楔前部で血流低下・糖代謝の低下が認められる.
- 進行に伴い,前頭葉の連合野皮質でも血流低下・糖代謝の低下がみられるようになる.
- MCIにはAD同様に高いPIB集積を示す症例群と,PIB集積の低い症例群とが存在する.

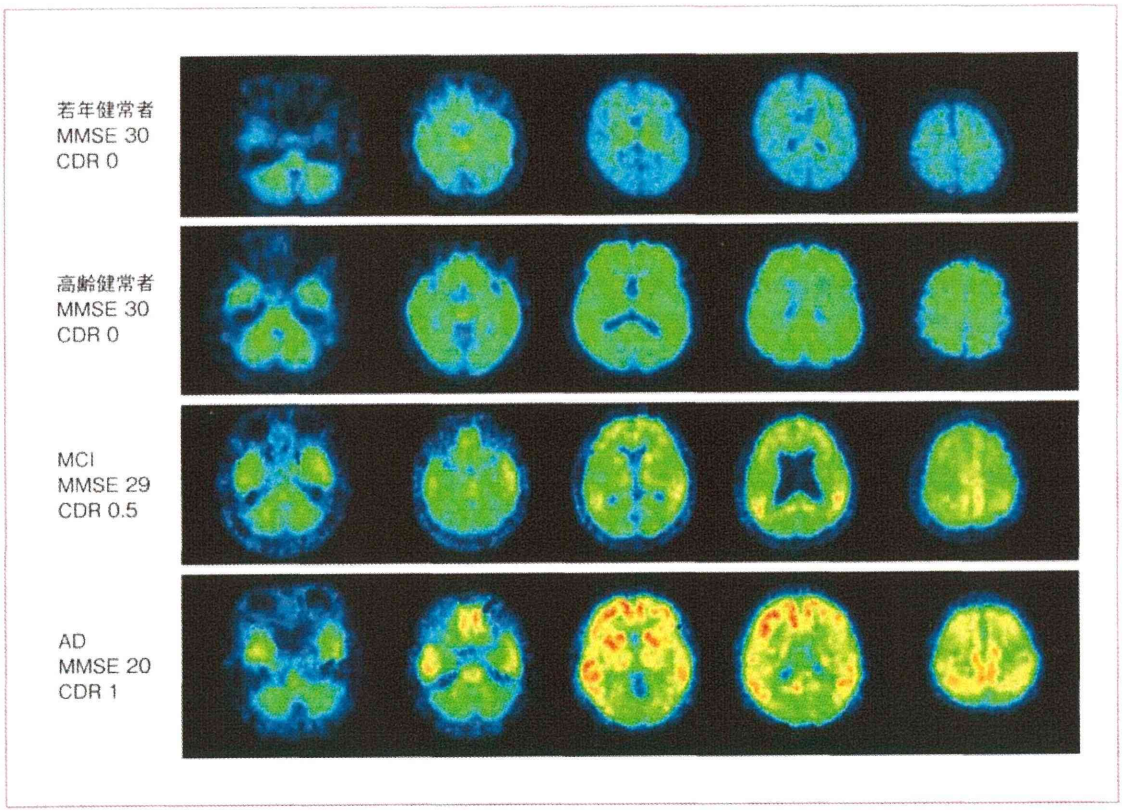

図2 PIB-PET画像

最上段は若年健常者,2段目が高齢健常者,3段目がMCI,4段目がAlzheimer病の患者のPIB-PET画像.各患者のMini-Mental State Examination(MMSE)とClinical Dementia Rating(CDR)の点数を付記した.

性は評価に堪えるレベルであろうと考えている.

予防・治療

本項ではADの病理・病態の正しい理解に裏打ちされた内容が重要である.病因として原因分子であるアミロイドを生成する基質(APP)および酵素(presenilin-1, presenilin-2)の阻害薬および消去法が検討されている.現在β-site APP cleaving enzyme 1(BACE1)阻害薬をはじめとするβセクレターゼ阻害薬[3],γセクレターゼ阻害薬によりAβの産生を抑制する方法やAβワクチン療法などが現在研究開発されている.Aβワクチン療法の作用機序は大きく受動免疫,能動免疫に分けられ,受動免疫によるものにAβ抗体,能動免疫によるものに粘膜免疫ワクチン(AAV/Aβ経口ワクチン,SeV/Aβ経鼻ワクチン),Aβcyclic DNAワクチン,ペプチド経鼻ワクチンなどがあり,現在も研究がなされている[4].この他

- ADの治療ではセクレターゼ阻害薬，Aβワクチン療法などが現在研究開発されている．
- ADの予防法として生活習慣病への対策，運動療法などが最近注目されつつある．
- ADでは一般には一次運動野が最後まで保たれるが，運動障害を顕著に呈する例もある．

ADの危険因子として近年注目を集めるようになった生活習慣病(高脂血症，高血圧，糖尿病)および運動療法が新しい視点としてのAD予防法となる可能性が検討されはじめていることを付記しておきたい．

ADにおける運動障害に関する議論は多くない．ただ，presenilin-1変異にみる家族性アルツハイマー病に代表されるように痙性対麻痺，歩行障害が顕著な臨床像を呈する報告もあり，該当症例を感覚系と運動系の単なる個別合併症と考えるより，病態の進行に連鎖した病因論としての視点に立った検討が必要である可能性があり，今後の重要な研究課題として捉えたい．

おわりに

オリゴマー仮説のさらなる検証，PET studyを含めた画像診断におけるさらなる知見，新しい治療法の研究開発に今後の期待がかかる．ADの分子生物学的側面に対する正しい理解こそが正しい診断と治療に直結するものと思われ，本項がその一助となれば幸いである．

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