Association between Cerebral Amyloid Deposition and Clinical Factors Including Cognitive Function in Geriatric Depression: Pilot Study Using Amyloid Positron Emission Tomography

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The purpose of this study was to explore the relationship between cerebral amyloid deposition and overall clinical factors including cognitive functions in geriatric depression by using 18F-florbetaben positron emission tomography. Thirteen subjects aged over 60 years who had a history of major depressive disorder and also had subjective memory complaint were included. Of all subjects, 3 subjects judged as amyloid positive, and the others judged as amyloid negative. Their memory, visuospatial functions and attention abilities were negatively correlated with amyloid deposition in specific brain regions, but their language and recognition abilities were not correlated with any region. The amyloid deposition of the whole brain region was significantly negatively correlated with immediate memory.

KEY WORDS: Amyloid positron emission tomography; Geriatric depression; Alzheimer disease; Subjective memory complaint.

INTRODUCTION

Patients with geriatric depression (GD) often have subjective memory complaint (SMC), and patients in early stage of Alzheimer diseases (AD) also not seldom have depressive symptoms. 1-4 There are many hypotheses about the correlation between GD and AD, but none of them can explain the causal relationship correctly. However, several recent studies have indicated that depression is associated with developing AD. 5-8 Two meta-analyses reported that a history of depression increased the risk of developing AD, with the risk being approximately two times greater than that of the control group. 6,8 The mechanisms linking depression and the risk of AD are unknown, but may involve abnormalities in multiple biological cascades, including the metabolism of β-amyloid (Aβ) peptide in the brain. 9,10 The recent development of high-affinity positron emission tomography (PET) imaging ligands for Aβ now permits the evaluation of the neuropathologic link among depression, cognitive impairment, and AD in vivo. 11 However, there are few studies that have examined cerebral Aβ levels in GD until now.

Given this background, in this study, we aimed to explore the relationship between cerebral amyloid deposition in each brain region and the overall clinical factors including cognitive functions in GD by using amyloid PET.

METHODS

Participants
We studied a total of 13 subjects aged over 60 who had a history of major depressive disorder based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). 12 They also had SMC, but had not been diagnosed with dementia yet. The exclusion criteria were a history of psychotic disorder including schizophrenia, other current clinically relevant neurologic illnesses, a history of apparent brain injury, or ever having undergone interventional treatments, including transcranial magnetic stimulation and electroconvulsive therapy.

All participants received clinical, psychological assessments, and were checked with 18F-florbetaben (AV-1) PET at the same time. We assessed the cognitive functions...
by the mini mental state examination (MMSE), Clinical
Dementia Rating (CDR), and Repeatable Battery for
the Assessment of Neuropsychological Status (RBANS).\textsuperscript{13)}

The depressive symptom severity was evaluated based on
the Hamilton Rating Scale for Depression (HAM-D). All
participants were allowed to continue taking psychotropic
drugs, but changes in medication were prohibited during
the study period.

The protocol of this study was approved by the institutional
review board at Yeungnam University Hospital in
Daegu, Korea (YUMC 2015-07-028-002).

Scanning and Imaging Procedure

All of the subjects received a single intravenous bolus
of approximately 296 MBq (8 mCi) of \textsuperscript{18}F-florbetaben.
The PET scanner used was a Discovery 710 PET/CT
system (GE Healthcare, Waukesha, WI, USA) in three-
dimensional acquisition mode. A continuous 20 minutes
(min) brain PET data scan was acquired 90-min post in-
jection and was reconstructed using 4 frames of 5-min
each. Each subject also had an magnetic resonance imaging
scan session, including a T1-weighted scan, which
was employed for spatial normalization during voxel-
based analysis.

Image Analysis

For the quantitative analysis of the \textsuperscript{18}F-florbetaben PET
images, we used the method of a previous study.\textsuperscript{14)} A re-
gion-of-interest (ROI) analysis was performed on the in-
dividual PET images, which were spatially normalized to
the Montreal Neurological Institute (MNI) atlas space us-
ing Statistical Parametric Mapping 2.0 (SPM2; Wellcome
Department of Imaging Neuroscience, Institute of
Neurology, University College London). The mean
cortical ROI templates contained 10 regions (frontal, tempo-
ral, occipital, parietal regions, basal ganglia [BG], cing-
ulum, hippocampus, insula, amygdala and central region),
as defined by the Automated Anatomic Labeling.\textsuperscript{15)} Mean
cortical and whole cerebellar ROI templates were applied
to all PET scans to calculate the mean regional cere-
bral-to-cerebellar standard uptake values (SUVRs).\textsuperscript{16)} The
average of these regions was evaluated as a measure of the
global mean cortical \textsuperscript{18}F-florbetaben binding. A\textbeta-positive
(A\textbeta+) and A\textbeta-negative (A\textbeta−) \textsuperscript{18}F-florbetaben PET sta-
tuses were defined according to the threshold of ≥1.10, a
criterion derived from the Alzheimer’s Disease Neuro-
imaging Initiative (ADNI) database.\textsuperscript{16)}

Statistical Analyses

The demographic and clinical characteristics between the A\textbeta+ and A\textbeta− groups were compared by the Mann-
Whitney \textit{U}-test. The categorical data were analyzed using
Fisher’s exact test. The associations between the cerebral
SUVRs and cognitive functions were evaluated using
Pearson correlation coefficients. Significant correlations
were validated using Spearman’s rank correlations co-
eficients (Spearman’s rho).

Statistical analyses were performed with the IBM SPSS
Statistics ver. 22.0 statistical package (IBM Co., Armonk,
NY, USA), and \textit{p} values < 0.05 were considered significant.

\textbf{Table 1. Demographic and clinical characteristics of all subjects}

| Subject | Age (yr) | Sex | Education (yr) | FHx_Dep | FHx_Dem | Psychotic features | Anxious distress | HAM-D | MMSE | CDR | RBANS |
|---------|---------|-----|---------------|---------|---------|-------------------|-----------------|-------|------|-----|-------|
| A*      | 65      | Male| 18            | +       | +       | +                 | 37              | 24    | 0.5  | 112 |       |
| B*      | 72      | Male| 12            | +       | +       | +                 | 12              | 22    | 1    | 81  |       |
| C*      | 76      | Female| 0              | +       | +       | +                 | 15              | 27    | 0    | 116 |       |
| D       | 70      | Female| 0.5           | −       | +       | +                 | 8               | 21    | 0.5  | 102 |       |
| E       | 70      | Male| 16            | −       | −       | +                 | 10              | 27    | 0.5  | 158 |       |
| F       | 68      | Female| 9             | −       | −       | −                 | 13              | 29    | 0.5  | 157 |       |
| G       | 74      | Female| 7             | −       | −       | −                 | 24              | 18    | 1    | 79  |       |
| H       | 69      | Female| 14            | −       | −       | −                 | 19              | 25    | 0    | 169 |       |
| I       | 76      | Female| 11            | +       | −       | −                 | 28              | 23    | 1    | 141 |       |
| J       | 72      | Male| 12            | −       | −       | −                 | 24              | 27    | 0.5  | 145 |       |
| K       | 70      | Female| 6             | −       | −       | −                 | 10              | 23    | 0.5  | 93  |       |
| L       | 80      | Male| 6             | −       | +       | −                 | 7               | 24    | 0.5  | 133 |       |
| M       | 74      | Male| 12            | −       | −       | +                 | 15              | 22    | 1    | 133 |       |

\textit{FHx}, first degree family history; \textit{Dep}, depression; \textit{Dem}, dementia; HAM-D, total score of Hamilton Rating Scale for Depression; MMSE, total score of mini mental state examination; CDR, Clinical Dementia Rating score; RBANS, total score of Repeatable Battery for the Assessment of Neuropsychological Status; SD, standard deviation.

*Subjects A, B, C were A\textbeta positive, the other subjects were A\textbeta negative.
RESULTS

The demographic data and other clinical information are summarized in Table 1. The sample included 13 subjects (mean age [SD]=72 [3.98] years) including 7 females and 6 males. Ten subjects were judged as Aβ− and 3 subjects as Aβ+. The sex, age, education level, depressive symptom severity and cognitive functions did not differ between the Aβ− and Aβ+ groups. However, a first degree family history of AD was more prevalent in the Aβ+ group (p=0.038) and anxious distress specifier based on DSM-5[12] was more prevalent in the Aβ+ group (p=0.033).

In the results of the correlation analysis (Table 2), immediate memory abilities are correlated negatively with amyloid deposition in following brain regions, right insula (r=−0.657, p=0.01), right hippocampus (r=−0.603, p=0.03), right amygdale (r=−0.630, p=0.02), both BG (r=−0.702, p=0.01 in left; r=−0.733, p=0.00 in right), and whole brain region (r=−0.574, p=0.04) respectively. Word recall abilities of delayed memory are correlated negatively with amyloid deposition in left central region (r=−0.626, p=0.02) and left insula (r=−0.612, p=0.03). Story recall abilities of delayed memory are correlated negatively with amyloid deposition in right insula (r=−0.617, p=0.02), both BG (r=−0.586, p=0.04 in left; r=−0.678, p=0.01 in right) and right temporal region (r=−0.567, p=0.04). Attention abilities are correlated negatively with amyloid deposition in right central region (r=−0.590, p=0.03), both lateral frontal region (r=−0.584, p=0.04 in left; r=−0.600, p=0.03 in right), and right parietal region (r=−0.564, p=0.04). And such correlations also are observed in between visuospatial function and both insula (r=−0.600, p=0.03 in left; r=−0.657, p=0.01 in right).

On the other hand, the language functions, including naming and fluency, and recognition functions were not associated with any regional SAVURs.

Table 2. Correlation between amyloid deposition and cognitive functions in each brain region

| Cognitive function domains | Immediate memory | Visuospatial function | Language _naming | Language _fluency | Attention | Delayed memory _word recall | Delayed memory _recognition | Delayed memory _story recall |
|----------------------------|------------------|----------------------|------------------|------------------|----------|-----------------------------|----------------------------|----------------------------|
| Central_L                  | Correlation coefficient | −0.52 | −0.30 | −0.43 | −0.39 | −0.52 | −0.626* | −0.35 | −0.38 |
| Sig. (2-tailed)            | 0.07             | 0.32 | 0.14 | 0.19 | 0.07 | 0.02 | 0.25 | 0.2 |
| Central_R                  | Correlation coefficient | −0.47 | −0.14 | −0.34 | −0.45 | −0.590* | −0.43 | −0.20 | −0.28 |
| Sig. (2-tailed)            | 0.11             | 0.65 | 0.25 | 0.13 | 0.03 | 0.14 | 0.50 | 0.35 |
| Lat_frontal L             | Correlation coefficient | −0.30 | −0.11 | −0.13 | −0.36 | −0.584* | −0.27 | −0.01 | −0.10 |
| Sig. (2-tailed)            | 0.32             | 0.71 | 0.68 | 0.23 | 0.04 | 0.96 | 0.75 | 0.75 |
| Lat_frontal R             | Correlation coefficient | −0.28 | −0.01 | −0.07 | −0.49 | −0.600* | −0.28 | 0.04 | −0.15 |
| Sig. (2-tailed)            | 0.35             | 0.98 | 0.81 | 0.09 | 0.03 | 0.36 | 0.91 | 0.63 |
| Insula_L                   | Correlation coefficient | −0.53 | −0.600* | −0.35 | −0.20 | −0.33 | −0.612* | −0.32 | −0.48 |
| Sig. (2-tailed)            | 0.06             | 0.03 | 0.25 | 0.05 | 0.28 | 0.03 | 0.28 | 0.1 |
| Insula_R                   | Correlation coefficient | −0.657* | −0.657* | −0.46 | −0.03 | −0.31 | −0.49 | −0.43 | −0.617* |
| Sig. (2-tailed)            | 0.01             | 0.01 | 0.11 | 0.91 | 0.3 | 0.09 | 0.15 | 0.02 |
| Hippocampus_R             | Correlation coefficient | −0.603* | −0.37 | −0.52 | 0.08 | −0.07 | −0.35 | 0.17 | −0.48 |
| Sig. (2-tailed)            | 0.03             | 0.21 | 0.07 | 0.81 | 0.82 | 0.25 | 0.57 | 0.09 |
| Amygdala_L                 | Correlation coefficient | −0.48 | −0.01 | −0.01 | −0.37 | −0.23 | −0.40 | −0.25 | −0.568* |
| Sig. (2-tailed)            | 0.09             | 0.98 | 0.96 | 0.21 | 0.44 | 0.17 | 0.42 | 0.04 |
| Amygdala_R                 | Correlation coefficient | −0.630* | −0.18 | −0.49 | −0.25 | −0.54 | −0.38 | −0.556* |
| Sig. (2-tailed)            | 0.02             | 0.96 | 0.55 | 0.09 | 0.42 | 0.06 | 0.19 | 0.05 |
| Parietal_R                 | Correlation coefficient | −0.40 | −0.13 | −0.26 | −0.34 | −0.564* | −0.27 | −0.09 | −0.20 |
| Sig. (2-tailed)            | 0.18             | 0.64 | 0.39 | 0.26 | 0.04 | 0.37 | 0.77 | 0.52 |
| BG_L                       | Correlation coefficient | −0.702* | −0.33 | −0.43 | −0.08 | −0.33 | −0.37 | −0.20 | −0.586* |
| Sig. (2-tailed)            | 0.01             | 0.27 | 0.14 | 0.8 | 0.27 | 0.21 | 0.51 | 0.04 |
| BG_R                       | Correlation coefficient | −0.733* | −0.34 | −0.44 | −0.18 | −0.27 | −0.47 | −0.35 | −0.678* |
| Sig. (2-tailed)            | 0.00             | 0.25 | 0.13 | 0.56 | 0.37 | 0.10 | 0.24 | 0.01 |
| Temporal_R                | Correlation coefficient | −0.55 | −0.46 | −0.36 | −0.09 | −0.27 | −0.48 | −0.31 | −0.567* |
| Sig. (2-tailed)            | 0.05             | 0.12 | 0.22 | 0.77 | 0.38 | 0.10 | 0.30 | 0.04 |
| Whole brain region         | Correlation coefficient | −0.574* | −0.16 | −0.36 | −0.21 | −0.37 | −0.35 | −0.19 | −0.47 |
| Sig. (2-tailed)            | 0.04             | 0.59 | 0.23 | 0.48 | 0.22 | 0.26 | 0.54 | 0.11 |

BG: basal ganglia; L: left; R: right; Sig.: significance. Significant correlations are given in bold. *Correlation is significant at the 0.05 level (2-tailed). †Correlation is significant at the 0.01 level (2-tailed). Central region included precentral gyrus, postcentral gyrus and Rolandic operculum.
DISCUSSION

In this study, we provide pilot data of amyloid PET in a sample of patients with GD and also with SMC. Most of the previous studies using amyloid PET focused on cerebral Aβ in subjects with minor cognitive impairment (MCI)\(^1\) or AD progression. However, there have been few studies which targeted subjects with GD.\(^5,18,19\)

Although we targeted subjects with GD, not AD, 3 subjects were assigned to the Aβ + group. This implies that some of the GD subjects have significant accumulation of cerebral amyloid. However, the depressive symptoms or cognitive impairment of the Aβ + subjects were not significantly different from those of the subjects with Aβ −. This is because, in addition to the small sample size, all subjects had received a diagnosis of major depression, but its current severity varied. Therefore, the results of the cognitive function tests also varied, seemingly because they were affected by the current depressive symptoms. Most research on cognitive functions in patients with depression had found that depressed subjects tend to have worse performance.\(^20,21\) In one meta-analysis, there were significant associations between depression severity and some cognitive areas, including episodic memory, executive function and processing speed.\(^22\) These complex interactions between depressive symptoms and cognitive impairment often make it difficult for the clinician to make an accurate diagnosis. However, it is important not to underestimate the possible role of cognitive impairment in GD.

All of the subjects in the Aβ + group had been diagnosed with the anxious distress specifier, while only 1 subject in the Aβ − group was so diagnosed. In the present study, the sample size is too small to show statistical significance, but there was a link with recent studies in which anxiety and irritability were significantly associated with greater amyloid deposition,\(^23\) or the occurrence of dementia.\(^24\) In addition, a first degree family history of AD was more prevalent in the Aβ + group in this study. In similar previous studies, significant positive correlations were found in amyloid PET and FDG PET when there is a family history of AD.\(^25\) Larger studies are needed for the purpose of replication.

In the results of the correlation analysis, memory, visuospatial functions and attention abilities were negatively correlated with amyloid deposition in specific brain regions. On the other hand, the language abilities, including naming and fluency, and recognition abilities were not associated with any regional SUVRs. Previous studies reported that the degree of episodic memory most accurately predicts future cognitive deterioration.\(^26\) Moreover, language abilities are known to be a non-useful method of predicting the progression to AD.\(^27\) The brain regions that showed significant associations in this study, including the insula,\(^27\) hippocampus,\(^28\) amygdale,\(^29\) and BG,\(^30\) are known to be related to specific cognitive functions which are usually found in AD or MCI.

While the results of this study are preliminary, they suggest that amyloid deposition in patients with GD is correlated with certain cognitive domains, which are known to be found in early dementia. Future large prospective studies will be able to address the relationship between the amyloid burdens as measured by amyloid PET and clinical factors including depression that may contribute to the manifestation of cognitive impairment and development of AD.

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