VIII. 4. Amyloid Imaging in MCI and Alzheimer’s Disease with BF-227, a New PET Tracer: Comparison to FDG-PET

Furukawa K.1, Okamura N.2, Tashiro M.3, Waragai M.1, Furumoto S.2, Iwata R.4, Yanai K.2, Kudo Y.5, and Arai H.1

1Department of Geriatrics and Gerontology, Division of Brain Sciences, Institute of Development, Aging and Cancer, Tohoku University
2Department of Pharmacology, Tohoku University Graduate School of Medicine
3Division of Cyclotron Nuclear Medicine, Cyclotron and Radioisotope Center
4Division of Radiopharmaceutical Chemistry, Cyclotron and Radioisotope Center
5Department of NeuroImaging Research, Innovation New Biomedical Engineering Center

Introduction

In recent years several laboratories, including ours, have succeeded in visualizing Ab deposition in living patients’ brains with AD using PET probes1,2). Ronald Petersen addressed the concept of mild cognitive impairment (MCI), which is an intermediate state between normal aging and AD3). Regional cerebral glucose metabolism (rCMRglu) has been investigated by several investigators4) using 2-[18F]fluoro-deoxy-D-glucose (FDG) and PET in AD. We used [11C]BF-227-PET as well as FDG-PET on the same subjects (AN, MCI, and AD) and carefully analyzed and compared the results with these two kinds of PET.

Method

The diagnosis for MCI and probable AD followed the MCI clinical criteria presented by “Petersen et al.”3) and “the National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer’s Disease and Related Disorders Association”5), respectively. 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 for [11C]BF-227 was described precisely before1). [11C]BF-227 and its N-desmethylated derivative (a precursor of [11C]BF-227) were custom-synthesized
by Tanabe R&D Service Co. After intravenous injection of 211-366 mBq of $[^{11}\text{C}]\text{BF}-227$, dynamic PET images were obtained for 60 min with each subject’s eyes closed. Standardized uptake value (SUV) images of $[^{11}\text{C}]\text{BF}-227$ were obtained by normalizing tissue radioactivity concentration by injected dose and body weight. The FDG-PET procedure was described previously\textsuperscript{6}. Subjects were scanned in a quiet and dimly-lit room with their eyes closed after at least four hours of food restriction. The emission data were corrected for tissue attenuation using the transmission data. Regions of interest (ROIs) were placed on individual axial magnetic resonance (MR) images. Because there were neither senile plaques nor glucose hypometabolism in the cerebellum of AD, ratios of regional SUV to cerebellar SUV (SUVR) were calculated as an index of $[^{11}\text{C}]\text{BF}-227$ retention and CMRglu.

Results

BF-227 retention in MCI

First, we analyzed PET images with $[^{11}\text{C}]\text{BF}-227$ among the three groups (AN, MCI, and AD), and representative brain PET images are shown in Fig. 1. As indicated in the figure, some MCI subjects showed strong retention of $[^{11}\text{C}]\text{BF}-227$, but other MCI subjects did not. Most AD cases, however, indicated strong accumulation of $[^{11}\text{C}]\text{BF}-227$ especially in frontal, temporal and parietal cortices. If the retention pattern of $[^{11}\text{C}]\text{BF}-227$ is compared to that of PIB, the accumulation of $[^{11}\text{C}]\text{BF}-227$ in the frontal lobe looks much weaker than that of PIB.

Figure 2 shows the mean neocortical and regional SUVRs of $[^{11}\text{C}]\text{BF}-227$ for the three groups. Both the mean neocortical SUVRs for MCI and AD are significantly higher than that for AN. As we previously reported\textsuperscript{1}, significantly higher SUVRs were observed in most cerebral regions in AD compared to AN except for the medial temporal lobe. A significantly lower SUVR in MCI was observed in the parietal cortex compared to AD. In the other neocortical regions, MCI subjects showed a tendency towards milder retention of $[^{11}\text{C}]\text{BF}-227$ than that in AD.

Cerebral glucose metabolism in AN, MCI and AD

A significant reduction of neocortical SUVR was observed in both MCI and AD patients compared to AN in FDG-PET (Table 1, Fig. 3). Neocortical SUVR of FDG-PET for each subject was plotted against neocortical SUVR of BF-227-PET (Fig. 4A). ROC
analysis was performed for the lateral temporal SUVR of BF-227 and posterior cingulate SUVR of FDG (Fig. 4B). The AUC for BF-227 (0.994) is much higher than that for FDG (0.839).

Discussion

It was presented that FDDNP can detect a high signal in MCI by binding not only for amyloid plaques but also tau neurofibrillary tangles\(^7\), and the retention level for MCI is between AN and AD. On the other hand, several groups reported that about a half of the MCI subjects showed PIB uptake in the AD range, and other MCI subjects indicated retention levels lower than the AD range\(^8\). The present study also revealed higher retention of BF-227 in 60-70% of MCI subjects and in almost all the AD patients. Therefore, the amyloid PET technique is considered to be a highly useful and strong method for early detection of AD patients in the MCI stage.

FDG-PET has been used in investigations for MCI, and low rCMRglu in the temporo-parietal and medial frontal cortices and hippocampus was reported as the most prominent predictor of subsequent cognitive decline\(^9\). Our results indicate, however, that amyloid retention detected by BF-227 is more sensitive and specific than FDG-PET for AD diagnosis. Therefore it is reasonable that amyloid PET is more sensitive than FDG-PET for detecting MCI, which is regarded as a prodromal state of dementia or early AD.

References

Table 1. Demographic details of the subjects in this study. AN aged normal, MCI mild cognitive impairment, AD Alzheimer’s disease. MMSE scores are significantly different between "AN and MCI", "AN and AD", and "MCI and AD".

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Gender</th>
<th>Age</th>
<th>MMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AN</td>
<td>12</td>
<td>M/F=7/5</td>
<td>66.3 ± 3.3</td>
<td>29.9 ± 0.3</td>
</tr>
<tr>
<td>MCI</td>
<td>16</td>
<td>M/F=8/8</td>
<td>73.3 ± 3.8</td>
<td>25.5 ± 2.6</td>
</tr>
<tr>
<td>AD</td>
<td>15</td>
<td>M/F=5/10</td>
<td>72.5 ± 8.9</td>
<td>19.6 ± 3.7</td>
</tr>
</tbody>
</table>

Table 2. Box plots of SUVR values with BF-227 PET for AN, MCI and AD. Each dot indicates the mean SUVR from "the mean neocortex" and "the eight regions", that is, frontal, temporal, parietal, occipital, anterior cingulate, posterior cingulated, striatum and medial temporal cortex. Box indicates interquartile range. Vertical bars indicate minimum aximum range.

<table>
<thead>
<tr>
<th></th>
<th>Mean neocortex</th>
<th>Frontal</th>
<th>Lateral temporal</th>
<th>Parietal</th>
<th>Occipital</th>
<th>Anterior cingulate</th>
<th>Posterior cingulate</th>
<th>Striatum</th>
<th>Medial temporal</th>
</tr>
</thead>
<tbody>
<tr>
<td>AN</td>
<td>1.05 ± 0.04</td>
<td>1.00 ± 0.06</td>
<td>1.03 ± 0.04</td>
<td>1.06 ± 0.05</td>
<td>1.03 ± 0.05</td>
<td>1.04 ± 0.03</td>
<td>1.11 ± 0.07</td>
<td>1.34 ± 0.06</td>
<td>1.16 ± 0.05</td>
</tr>
<tr>
<td>MCI</td>
<td>1.16 ± 0.10*</td>
<td>1.10 ± 0.15*</td>
<td>1.17 ± 0.10*</td>
<td>1.19 ± 0.10*</td>
<td>1.16 ± 0.08*</td>
<td>1.15 ± 0.11*</td>
<td>1.20 ± 0.11</td>
<td>1.41 ± 0.11</td>
<td>1.18 ± 0.10</td>
</tr>
<tr>
<td>AD</td>
<td>1.22 ± 0.06*</td>
<td>1.13 ± 0.09*</td>
<td>1.24 ± 0.09*</td>
<td>1.25 ± 0.06*</td>
<td>1.19 ± 0.06*</td>
<td>1.16 ± 0.08*</td>
<td>1.25 ± 0.06*</td>
<td>1.47 ± 0.03*</td>
<td>1.19 ± 0.06</td>
</tr>
<tr>
<td>BF-227</td>
<td>1.18 ± 0.10</td>
<td>1.10 ± 0.11</td>
<td>1.15 ± 0.09</td>
<td>1.24 ± 0.12</td>
<td>1.10 ± 0.10</td>
<td>1.39 ± 0.13</td>
<td>1.20 ± 0.13</td>
<td>0.00 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>FDG</td>
<td>1.10 ± 0.08*</td>
<td>1.05 ± 0.06</td>
<td>1.03 ± 0.07</td>
<td>1.08 ± 0.08</td>
<td>1.23 ± 0.14</td>
<td>0.99 ± 0.08</td>
<td>1.24 ± 0.09</td>
<td>1.27 ± 0.13</td>
<td>0.82 ± 0.08*</td>
</tr>
<tr>
<td>AD</td>
<td>1.06 ± 0.08*</td>
<td>1.05 ± 0.14</td>
<td>0.98 ± 0.11*</td>
<td>1.01 ± 0.09*</td>
<td>1.25 ± 0.15</td>
<td>1.00 ± 0.12</td>
<td>1.20 ± 0.13</td>
<td>1.31 ± 0.11</td>
<td>0.81 ± 0.07*</td>
</tr>
</tbody>
</table>

Figure 1. Representative axial brain PET images with [11C]BF-227.
Figure 2. Box plots of SUVR values with $[^{11}C]BF-227$ PET for AN, MCI and AD.
Figure 3. Box plots of SUVR values with FDG-PET for AN, MCI and AD.

Figure 4. (A) Relationship between neocortical SUVRs in FDG-PET and BF-227-PET. White, gray and black dots indicate AN, MCI and AD, respectively. (B) Receiver operating characteristic (ROC) curves of BF-227 and FDG-PET. BF-227-PET SUVR in the lateral temporal cortex and FDG-PET SUVR in the posterior cingulate cortex for differentiation between AD and AN.