The evaluation of brain perfusion SPECT using an easy Z-score imaging system in the mild cognitive impairment subjects with brain amyloid-β deposition.

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Running title: eZIS analysis in MCI subjects with brain amyloid-β deposition

Abstract

Objective The analysis of ^{99}mTc-ECD single-photon emission computed tomography (SPECT) images using the easy Z-score imaging system **(**eZIS) program is useful for the diagnosis of early AD in daily medical practice. However, it remains unclear whether eZIS analysis can identify the amnestic mild cognitive impairment (MCI) subjects with brain amyloid-β deposition. The aim of this study was to evaluate the usefulness of an eZIS analysis for predicting amnestic MCI subjects with brain amyloid β deposition.

Patients and Methods Twenty-three subjects with MCI (10 men and 13 women, mean age; 74.2 years) underwent brain perfusion SPECT and PiB-PET. MCI subjects were classified into PiB-positive and PiB-negative subgroups. SPECT data was analyzed using the Specific Volume of interest Analysis of the eZIS program. Three indicators (severity, extent, and ratio) were calculated automatically and compared between the two subgroups.

Results Five of 12 (41.7%) subjects in the PiB-positive subgroup and three of 11 (27.3%) subjects in the PiB-negative subgroup showed the abnormal value for each indicator. The frequency of subjects with abnormal ratio values was significantly higher in the PiB-positive subgroup compared to the PiB-negative subgroup ($p = 0.02$), whereas that subjects with abnormal values in severity and extent did not differ among the two subgroups. In particular, all subjects in the PiB-negative subgroup showed normal ratio values. Moreover, the subjects with abnormal values on two indicators, including ratio, or on all three indicators, showed PiB-positive.

Conclusion The analysis of brain perfusion SPECT using an eZIS program cannot identify the amnestic MCI subjects with brain amyloid-β deposition. However,

abnormal three indicators or normal ratio values may be helpful SPECT findings for predicting the results of PiB-PET in the amnestic MCI subjects.

Keywords: amyloid PET imaging; brain perfusion SPECT; easy Z-score analysis; mild cognitive impairment

1. Introduction

Alzheimer's disease (AD) is a major cause of dementia in elderly subjects over the age of 65 years. Diagnosis of AD in earlier stages is important for providing the greatest efficacy of cholinesterase inhibitors and disease-modifying drugs [1, 2]. The diagnosis of mild AD and mild cognitive impairment (MCI) due to AD is, however, often difficult using clinical criteria. Amnestic MCI subjects have a significantly higher likelihood of progressing to probable AD, with a conversion rate of 10-15% per year [3]. Therefore, the development of biological and neuroimaging markers for MCI due to AD pathophysiology is an important issue both clinically and with regards to future research. Structural and functional imaging techniques are useful for predicting future conversions from MCI to AD [4, 5]. Particularly, ^{11}C-Pittsburgh Compound B positron emission tomography (PiB-PET) is a useful tool for identifying subjects who are at risk of developing AD [6, 7]. However, PiB-PET is not practical due to the limited availability of PET. In Japan, magnetic resonance imaging (MRI) and brain perfusion single-photon emission computed tomography (SPECT) are mainly used for the imaging diagnosis of dementia in daily medical practice. Brain perfusion SPECT imaging provides an indirect marker of neuronal function and can show significantly decreased regional cerebral blood flow (rCBF) in the posterior cingulate cortex and parietotemporal lobe in the earlier stages of AD [8, 9]. Moreover, statistical analysis techniques for SPECT images, such as three-dimensional stereotactic parametric mapping (3D-SSP), eZIS, and statistical parametric mapping (SPM) have been developed to increase the sensitivity and accuracy of the diagnosis of AD compared

with simple visual interpretation [10-12]. In the eZIS program, Specific Volume of interest Analysis (SVA) and indicators characterizing rCBF decreases in very mild AD are useful for discriminating between healthy controls and AD patients. To our knowledge, few studies have performed both the analysis of ^{99}mTc-ECD SPECT images using the eZIS program and amyloid imaging in the amnestic MCI subjects [13, 14]. Here, we firstly compared the indicators of eZIS analysis between PiB-positive and PiB-negative MCI subjects. Our findings provide important information toward the diagnostic role of eZIS analysis in MCI subjects. The aim of this study was to evaluate the usefulness of eZIS analysis for predicting amnestic MCI subjects with brain amyloid-β deposition.

2. Materials and Methods

2.1. Subjects

Twenty-three subjects with MCI (10 men and 13 women) with a mean age of 74.2 years, an ischemic score of four or lower on the Hachinski's scale, and at least a sixth-grade education level were included in the study. All subjects underwent a clinical examination that included physical, neurologic, and neuropsychologic evaluation, brain perfusion SPECT, and PiB PET. The diagnosis of amnestic MCI was made according to previous studies as follows [15]: 1) subjective memory complaints and objective memory impairment; 2) a score of 24-30 on the Mini-Mental State Examination (MMSE); 3) impairment of education-adjusted score in delayed recall of logical memory on the Wechsler's Memory Scale Revised (WMS-R II; for 0–7 years of education, 2 or lower; for 8–15 years, 4 or lower; for 16 years or more, 8 or lower); 4) a score of 0.5 on the Clinical Dementia Rating; 5) absence of significant impairment in

cognitive function or activities of daily living. We excluded subjects with a history of stroke, other neurologic and psychiatric disorders (e.g., major depression, psychosis), severe head trauma, alcoholism, severe cardiac disease, arrhythmia, hepatic failure, and recent changes in medication. Information regarding age, sex, and education level was collected, and cognitive function was assessed by the MMSE and Alzheimer's Disease Assessment Scale-cognitive component- Japanese version (ADAS-Jcog). Each subject signed an informed consent form before inclusion, and this study was approved by the local ethics committee at Oita University Hospital.

2.2. Positron Emission Tomography Scans

Static ^{11}C-PiB PET images were acquired using the Siemens Biograph mCT40 (Siemens Medical Solutions, Inc., Knoxville TN, USA) in three-dimensional scanning mode. The reagent was supplied by the PET center of our hospital. X-ray computed tomography for attenuation correction was performed before PET imaging. Each patient was injected intravenously with a bolus of ^{11}C-PiB (555 ± 185 MBq) followed by a saline flush. Starting at 50 min post-injection, PET scans were performed for 20 min, providing 110 slices of 1.5-mm thickness covering the entire brain. The spatial resolution 1 cm away from the center of the PET was 6.0 mm transversely and 5.7 mm axially. All imaging data were reconstructed into a 256 × 256 matrix and a 3x magnification with an ordered subset expectation maximization + point spread function + time of flight protocol. This included six iterations and 21 subsets using a 2 mm Gaussian filter (the reconstructed images had 1.06-mm pixels). PiB-PET scans were spatially normalized to a customized PiB-PET template in the Montreal Neurological Institute reference space using Statistical Parametric Mapping 8 (Wellcome Trust Centre

for Neuroimaging, London, UK). The region of interest (ROI) analysis was performed using FreeSurfer (http://surfer.nmr.mgh.harvard.edu), which is an automated tool for reconstructing the brain's cortical surface from structural MRI data [16]. Moreover, ROIs in the frontal lobes, parietotemporal lobes, and posterior cingulate gyrus were extracted using MarsBaR; ROI values were averaged across both hemispheres. PiB uptake was assessed based on a standardized uptake value ratio (SUVR), which was calculated by dividing ^{11}C-PiB retention from a specific ROI by the ROI value in the cerebellar hemispheres. Mean cortical SUVR was expressed as the average SUVR of the mean of the frontal lobes, parietotemporal lobes, and posterior cingulate regions. An SUVR cutoff of 1.4 was used to classify the subjects into either the PiB-positive or PiB-negative subgroups.

2.3. SPECT image analysis using eZIS program

Brain ^{99}mTc-ECD SPECT was performed according to previous studies [17]. After intravenous injection of ^{99}mTc ethylcysteinate dimer (600 MBq, FUJIFILM RI Pharma Co., Ltd., Japan), its passage from the heart to the brain was monitored using a rectangular large-field gamma camera (E. Cam Signature, Toshiba Medical, Japan). The Patlak plot method was used on a ^{99}mTc ethylcysteinate dimer cerebral blood perfusion SPECT to measure mean global CBF [18]. SPECT images were anatomically standardized with an original ^{99}mTc-ECD template using the eZIS program. A Z-score map for each SPECT image was extracted from the comparison with the mean and standard deviation (SD) of the SPECT images of age-matched normal controls that had been incorporated into the eZIS program to function as a normal control database. A voxel-by-voxel Z-score analysis was performed after voxel normalization to global

means or cerebellar values; Z-score = [control mean] – [individual value]/ (control SD). In the eZIS program, a specific region showing decreased rCBF in very early AD determined by SPM analysis was incorporated into an automated analysis of Z-score values as a volume of interest (VOI). A specific VOI was determined by group comparison of ^{99m}Tc-ECD SPECT images between very early AD patients and age-matched healthy volunteers. This could be set on the posterior cingulate gyrus, precuneus, and parietal association cortex in the eZIS program. Three indicators discriminating between patients with very early AD and healthy controls were calculated automatically according to previous reports [11, 14]. The severity of significantly decreased rCBF in a specific brain region in very early AD was obtained from the averaged positive Z-score in the VOI. The extent was obtained from the percentage rate of the coordinates with a Z value over the threshold value of 2 in the VOI. The ratio of the extent of a region showing significant rCBF reduction in the VOI to the extent of a region showing significant rCBF reduction in the whole brain was obtained—that is, the percentage rate of the coordinates with a Z value exceeding the threshold value of 2. This ratio indicates the specificity of the rCBF reduction in the VOI compared with that of the whole brain. Cutoff values for discrimination between groups were 1.19, 14.2%, and 2.22 for severity, extent, and ratio, respectively.

2.4. Statistical analysis

Comparisons between PiB-positive and PiB-negative subgroups were performed using the χ^2 test for sex distribution and the frequency of patients with abnormal values in the three indicators of the eZIS analysis. The Mann-Whitney U-test was performed for age at examination, education level, MMSE and ADAS scores, and

mean global CBF as well as the values of three indicators and mean SUVR values. Comparisons of the mean SUVR values among MCI with normal indicators, MCI with two abnormal indicators, and MCI with three abnormal indicators were made using the Kruskal-Wallis test. Correlations between mean SUVR values and the three indicators were evaluated by Spearman's rank correlation coefficients. A p value of less than 0.05 was considered statistically significant.

3. Results

3.1. Patients characteristics

Table 1 summarizes the clinical and demographic characteristics of the PiB-positive and PiB-negative subjects. The two subgroups did not differ significantly in age at examination, sex distribution, MMSE and ADAS-Jcog scores, or mean global CBF. The education level in the PiB-positive MCI subgroup was higher than in the PiB-negative MCI subgroup. The mean SUVR value in the PiB-positive subgroup was significantly higher than in the PiB-negative subgroup (Mann-Whitney U-test: p= < 0.0001).

3.2. Three indicators of the eZIS analysis

Figure 1 and Table 2 show the comparisons of the three indicators of eZIS analysis between the two subgroups. The frequency of subjects with an abnormal ratio was significantly higher in the PiB-positive subgroup compared with the PiB-negative subgroup (Table 2. $p = 0.02$). The frequencies of subjects with an abnormal severity and extent, however, did not differ between the two subgroups (Table 2. Severity, $p = 0.47$; extent, $p = 0.90$). The PiB-positive subgroup showed 1.14 ± 0.56 for severity, 11.18 ±

17.01 for extent, and 2.06 ± 2.28 for ratio, whereas the PiB-negative subgroup showed 1.06 ± 0.37 for severity, 8.15 ± 8.66 for extent, and 0.93 ± 0.66 for ratio. Moreover, there were no subjects with an abnormal ratio in the PiB-negative subgroup (Fig. 1C). There were no significant differences in these indicators between the two subgroups (Fig 1. Severity, p = 0.98; extent, p = 0.93; ratio, p = 0.54). Table 3 shows the comparison of the number of abnormal indicators between the two subgroups. Two of the three indicators were over the cut-off value in two subjects in the PiB-positive subgroup and three subjects in the PiB-negative subgroup. The two subjects in the PiB-positive subgroup had abnormal values for severity and ratio, whereas the three subjects in the PiB-negative subgroup had abnormal values for severity and extent. The three subjects who had all three indicators over the cut-off value were in the PiB-positive subgroup.

3.3. Mean SUVR and three indicators of the eZIS analysis

Mean SUVR did not correlate with any of the three indicators (severity, p = 0.86; extent, p = 0.81; ratio, p = 0.47) and tended to be higher in MCI subjects with three abnormal indicators (1.93 ± 0.46) than in MCI subjects with three normal indicators (1.37 ± 0.66) and two abnormal indicators (1.35 ± 0.55), but the difference was not statistically significant (Figure 2. p = 0.38).

Discussion

The present study examined the usefulness of eZIS analysis for predicting amnestic MCI subjects with brain amyloid-β deposition. Our results showed an abnormal value for each indicator in five of 12 (41.7%) subjects in the PiB-positive

subgroup and three of 11 (27.3%) subjects in the PiB-negative subgroup. The frequency of subjects with abnormal ratio values was significantly higher in the PiB-positive subgroup than that in the PiB-negative subgroup. Particularly, all subjects in the PiB-negative subgroup showed normal ratio values. Moreover, amnestic MCI subjects with abnormal values for two indicators, including ratio, or with three abnormal indicators showed PiB-positive. These results suggest that the normal ratio values or all three indicators may be helpful SPECT findings for predicting the results of PiB-PET in the amnestic MCI subjects. Our supplementary analysis, however, showed that there was no significant difference in the values of three indicators between the PiB-positive and PiB-negative subgroups. These negative findings may be due to the relatively small sample size.

The most interesting finding of our study was the usefulness of abnormal ratio values for discriminating between PiB-positive and PiB-negative MCI subjects. Previous studies have not compared each indicator between PiB-positive and PiB-negative MCI subjects [14]. Our results firstly suggest that a normal ratio value may reflect MCI without amyloid pathology. The ratio indicates the specificity of rCBF reduction in the VOI compared with the whole brain, and may be useful for differentiating AD from other neuropsychiatric diseases manifesting dementia. Previous SPECT studies using SVA, however, have suggested that the extent was more rational than the severity and ratio for the discrimination between AD patients and healthy controls. This discrepancy may be attributed to the difference in subjects or diagnostic methods. The results of previous studies were derived from the SPECT data of AD patients who were clinically diagnosed, whereas our study included amnestic MCI subjects with or without AD pathology who were confirmed by amyloid PET imaging.

Therefore, our results suggest that eZIS analysis in MCI subjects due to AD may frequently show abnormality in three indicators including ratio, whereas those without AD pathophysiology may have normal ratio values.

The eZIS program, which is a computer-assisted analysis technique, is used for the diagnosis of early AD in daily medical practice by multiple institutions, which do so by sharing a normal database of SPECT images across different institutions [11, 19]. In this program, a specific VOI for very early AD is incorporated to evaluate tracer uptake in the posterior cingulate gyrus, precuneus, and parietal association cortex [20]. Moreover, Matsuda et al. developed the SVA with three indicators: severity, extent, and ratio, for characterizing rCBF decreases in very mild AD [11, 14]. These indicators are calculated automatically by regional Z-scores; accuracies for discrimination between healthy controls and patients AD were 85%, 86%, and 80% for severity, extent, and ratio, respectively, with an optimal cutoff value. In the present study, all MCI subjects with three abnormal indicators were included in the PiB-positive subgroup. Moreover, mean SUVR in MCI subjects with three abnormal indicators tended to be higher than in MCI subjects with three normal indicators or two abnormal indicators. Similarly, a previous study using eZIS analysis of SPECT images and PiB-PET in AD and MCI subjects reported that the ratios of amyloid positive patients and SUVR were both higher in the patients with three abnormal indicators compared to those with 0–2 abnormal indicators [14]. In the present study, mean SUVR did not correlate with any of the three indicators of eZIS analysis. PiB-PET is established method of detecting amyloid pathology in the brain, Whereas FDG-PET and brain perfusion SPECT reflect the neuronal dysfunction. Previous PiB- and FDG-PET studies in MCI subjects showed that PiB distribution volume ratio were not correlated with FDG SUVR [23, 24]. These

findings are supported by hypothetical biomarker model suggesting that the formation of senile plaques precedes the metabolic changes and reaches a relative plateau by the time clinical symptoms develop [25].

However, our study also identified a problem of eZIS analysis, in that not all PiB-positive subjects showed abnormal indicators and some PiB-negative subjects showed abnormal indicators. Previous studies have also reported discrepancies between the results of PiB-PET and SPECT findings [13, 14]. In one study, the results showed that two of the eight (25%) MCI subjects with AD pattern on both MRI and SPECT were PiB-negative, and three of seven (43%) MCI subjects with no AD pattern on either MRI or SPECT were PiB-positive [13]. The one potential explanation is that the PiB-positive MCI subgroup might include mixed AD, such as the coexistence of AD pathology with cerebrovascular disease or dementia with Lewy bodies. On the other hand, the PiB-negative MCI subgroup might include the suspected non-AD pathology such as argyrophilic grain disease or primary age-related tauopathy, which can show the evidence of AD-like neurodegeneration without evidence of amyloid deposition [13, 21, 22]. Therefore, not all PiB-positive subjects might show decreased rCBF in the characteristic regions of AD, and some of PiB-negative subjects might show SPECT findings similar to AD pattern.

The present study has several limitations. First, we did not use ^{18}F-FDG PET, only brain perfusion SPECT, in the present study. ^{18}F-FDG PET is also useful for the prediction of conversion from MCI to AD, and is generally superior to SPECT in sensitivity and spatial resolution [26, 27]. ^{18}F-FDG PET for diagnosis of dementia, however, is not accepted for reimbursement by the health insurance system in Japan. On

the other hand, brain perfusion SPECT imaging is widely used for the diagnosis of AD in daily medical practice. Some previous studies have shown similar diagnostic accuracies between ^{18}F-FDG PET and SPECT for mild to moderate AD [28]. A second limitation was that diagnosis of MCI in all subjects was based solely on clinical findings without pathologic confirmation. Our results must be considered preliminary because of the small number of patients and further studies with larger samples, are needed to confirm our results.

In conclusion, the analysis of brain perfusion SPECT using an eZIS program cannot identify the amnestic MCI subjects with brain amyloid-β deposition. However, amnestic MCI subjects with the normal ratio values showed PiB-negative and those with abnormal values in two indicators including ratio, or all three indicators, may have a high probability of amyloid pathology in the brain. Therefore, three indicators of eZIS analysis may be helpful SPECT findings for predicting the results of PiB-PET in the amnestic MCI subjects.

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

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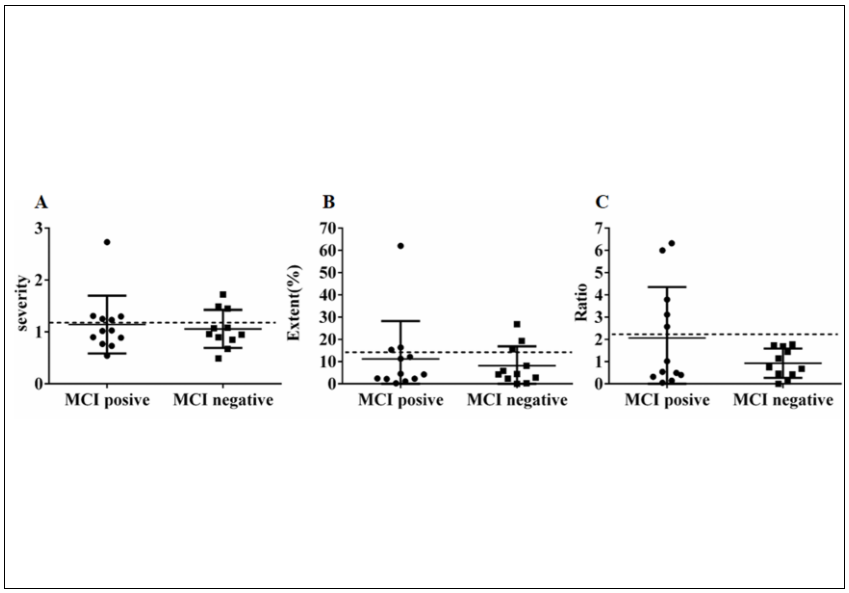
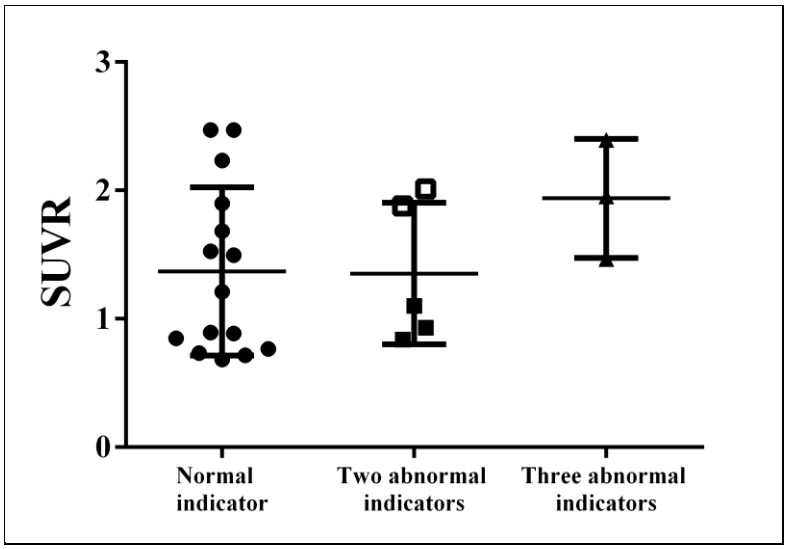
Figure 1. The comparison of three indicators of eZIS analysis between the two subgroups.



The indicators of severity (A), extent (B), and ratio (C) did not differ between the two subgroups (severity; $p = 0.98$, extent; $p = 0.93$, ratio; $p = 0.54$, respectively). A dotted line shows the cutoff values.

Figure 2. The comparison of mean SUVR among the normal indicator, two abnormal indicators, and three anormal indicators subgroups.



Mean SUVR tended to be higher in MCI subjects with three abnormal indicators (1.93 ± 0.46) than in MCI subjects with three normal indicators (1.37 ± 0.66) and two abnormal indicators (1.35 ± 0.55). Normal indicator (●), Two abnormal indicators (■; normal ratio value, □; abnormal ratio value), Three normal indicators (▲).

Table 1. Clinical and demographic characteristics of PiB-positive and PiB-negative MCI subjects.

Characteristics	PiB-positive MCI	PiB-negative MCI	*p*-value
Sex (M:F)	4 : 8	6 : 5	0.30
Age (years)	74.0 ± 5.5	74.4 ± 10.8	0.58
Education (years)	11.2 ± 1.6	12.6 ± 1.2	0.04
MMSE	25.7 ± 1.8	25.4 ± 2.5	0.76
ADAS-Jcog	9.9 ± 2.5	9.3 ± 6.1	0.44
mean CBF	39.7 ± 2.7	38.8 ± 4.0	0.46
mean SUVR	1.96 ± 0.37	0.87 ± 0.2	< 0.0001

Data are shown as mean ± SD, MMSE: Mini-Mental State Examination, ADAS-Jcog: Alzheimer's Disease Assessment Scale-cognitive component- Japanese version, SUVR: standardized uptake value ratio of PiB, CBF: cerebral blood flow.

The χ^2 test for sex distribution and the Mann-Whitney U-test for age at examination, MMSE, ADAS-Jcog, mean SUVR values, and mean CBF were used to compare the characteristics of the two study subgroups. A *p*-value of less than 0.05 was considered statistically significant.

Table 2. Comparison of the distribution of subjects with abnormal values for each indicator between PiB-positive and PiB-negative MCI subjects.

Indicators	Number of patients with abnormal values		*p*
	PiB-positive MCI (n=12)	PiB-negative MCI (n=11)	
Severity	5 (41.7%)	3 (27.3%)	0.47
Extent	3 (25.0%)	3 (27.3%)	0.90
Ratio	5 (41.7%)	0 (0%)	0.02

The χ^2 test for distribution of subjects with abnormal values for each indicator was used to compare the characteristics of the two subgroups. A *p*-value of less than 0.05 was considered statistically significant.

Table 3. Comparison of number of subjects with abnormal indicators between PiB-positive and PiB-negative MCI subjects.

Indicators	Number of subjects with abnormal values	
	PiB-positive MCI (n=12)	PiB-negative MCI (n=11)
One indicator	0	0
Two indicators	2	3
Three indicators	3	0