Research Article

Utility of Easy *Z*-Score Imaging System-Assisted SPECT in Detecting Onset Age-Dependent Decreases in Cerebral Blood Flow in the Posterior Cingulate Cortex, Precuneus, and Parietal Lobe in Alzheimer's Disease with Amyloid Accumulation

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Abstract

Background: Easy *Z*-score imaging system (eZIS)-assisted SPECT accurately detects decreases in cerebral blood flow in the posterior cingulate cortex (PCC), precuneus, and parietal lobe, the cerebral regions deeply implicated in Alzheimer's disease (AD). Several studies suggested onset age-dependent decreases in cerebral blood flow in these regions in AD, but these studies did not screen for amyloid accumulation, suggesting inclusion of non-AD patients in their subjects. ***Objective:*** By applying eZIS-SPECT to patients with amyloid deposition, it was the aim of this study to clarify onset age-dependent decreases in cerebral blood flow in the regions critical to AD. ***Methods:*** We retrospectively analyzed eZIS-SPECT data on 34 AD patients with amyloid retention confirmed by ^{11}C-Pittsburgh compound B-PET. The subjects were divided into an early-onset group (*n* = 16) and a late-onset group (*n* = 18). The three indicators of the eZIS that had discriminated between AD patients and normal controls in previous studies were compared between the two groups. ***Results:*** The mean values for the respective indicators were significantly higher in the early-onset group than in the late-onset group. Also, the proportion of patients with abnormalities in all indicators was significantly higher in the

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early-onset group (93.8%) than in the late-onset group (50.0%). ***Conclusions:*** The present study, applying eZIS-SPECT to amyloid-positive AD patients, suggests that reduced cerebral blood flow in the PCC, precuneus, and parietal lobe is more pronounced in the early-onset type than in the late-onset type of the disease.

Introduction

Alzheimer's disease (AD) is the most common progressive neurodegenerative disease that causes dementia [1]. The posterior cingulate cortex (PCC), precuneus, and parietal lobe are considered to be deeply implicated in the pathophysiology of AD, since these regions show reduced glucose metabolism [2] and regional cerebral blood flow (rCBF) [3] from an early stage of the disease. Meanwhile, the importance of amyloid deposition in the pathophysiology of AD is increasingly recognized, as reflected by the inclusion of this index in the diagnostic criteria for the disease [4]. ^{11}C-Pittsburgh compound B (PiB) is a biomarker for amyloid accumulation, and the most reliable tracer for amyloid positron emission tomography (PET) [5]. Previous studies using amyloid PET [6, 7] showed that approximately 20–40% of patients with probable AD based on the clinical diagnostic criteria were amyloid negative, indicating the usefulness of this imaging method to discriminate between AD and non-AD.

Single-photon emission computed tomography (SPECT) is an imaging technique that is widely used in diagnosing dementia including AD [3, 8]. However, it has some difficulty in visually detecting a reduction of cerebral blood flow in the regions mentioned before, since they are inherently high in cerebral blood flow [9]. The easy *Z*-score imaging system (eZIS) (FUJIFILM RI Pharma, Co., Ltd., Tokyo, Japan) objectively evaluates the degree of reduction in rCBF in the PCC, precuneus, and parietal lobe, and automatically calculates three indicators that discriminate between AD patients and normal controls [10]. Because of these advantages, eZIS-SPECT is increasingly used for the diagnosis of AD [11, 12].

Previous studies using SPECT suggested onset age-dependent decreases in rCBF in AD [8, 13]. However, in none of these studies, amyloid PET was conducted, suggesting inclusion of substantial numbers of non-AD patients in their subjects. Therefore, the present study using eZIS-SPECT examined whether the degree of reduction in rCBF in the PCC, precuneus, and parietal lobe differs depending on the age at onset in AD with PiB positivity.

Subjects and Methods

Subjects

In this retrospective study, we firstly checked all patients with dementia who underwent PiB-PET at Yamagata University Hospital between September 2013 and March 2018. All of these patients had undergone magnetic resonance imaging (MRI) and eZIS-SPECT prior to PiB-PET. There were 68 patients with PiB retention and fulfilling the diagnostic criteria for probable AD dementia with amnestic presentation by the National Institute on Aging-Alzheimer's Association [4]. Next, we excluded patients who were taking antidementia drugs and who had a history of psychiatric disorders, severe physical illness, a Mini-Mental State Examination (MMSE) score <15, and presence of cerebrovascular lesions and extensive white matter abnormalities. Thirty-four patients remained, and they constituted the subjects of this study.

The mean age (±SD) was 69.4 ± 9.0 years, and the sex ratio (male:female) was balanced (15:19). The subjects were divided into an early-onset group with an onset age of <65 years (*n* = 16) and a late-onset group with an onset age of ≥65 years (*n* = 18).

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Table 1. Demographic and clinical data for the early-onset and late-onset groups

	Early-onset group (*n* = 16)	Late-onset group (*n* = 18)	*p* value
Age, years	61.2 (5.1)	76.7 (4.1)	0.000
Sex (male/female)	8/8	7/11	0.515
Educational history, years	12.1 (1.8)	12.4 (1.6)	0.654
Disease duration, years	3.3 (1.6)	3.3 (2.6)	0.974
MMSE score (max. 30)	23.1 (3.3)	21.3 (4.4)	0.204
mcSUVR	1.65 (0.15)	1.62 (0.18)	0.732

Values are presented as mean (SD) or *n*. Differences between groups were assessed using Student's *t* test (age, educational history, disease duration, and MMSE score) and Fisher's exact test (sex ratio). MMSE, Mini-Mental State Examination; mcSUVR, mean cortical standardized uptake value ratio.

eZIS-SPECT

Firstly, the patients received an intravenous injection of 600 MBq of ^{99m}Tc-ethylcysteinate dimer (FUJIFILM Toyama Chemical, Co., Ltd., Tokyo, Japan). After 6 min 50 s, SPECT data were obtained in a 128 × 128 matrix on a Symbia T2 (Siemens Healthcare, Erlangen, Germany) mounted with low-energy, high-resolution collimators. Images were reconstructed by the filtered back-projection method with combined Chang attenuation and scatter correction. Statistical imaging analysis was performed with the eZIS software (FUJIFILM Toyama Chemical). *Z*-scores were calculated using the statistical parametric mapping 8 and the eZIS program. After anatomical standardization, a *Z*-score map for each SPECT image was drawn while referring to the mean and SD of age-matched normal controls already built into the eZIS program. After voxel normalization to global means or cerebellar values, a voxel-by-voxel *Z*-score was calculated and evaluated as follows: *Z*-score = ([control mean] – [individual value])/(control SD), and a *Z*-score of >2 SDs was considered to indicate a reduction in rCBF.

A specific volume of interest (VOI) was set on the PCC, precuneus, and parietal lobe in the eZIS program. The three indicators that had discriminated between AD patients and normal controls in previous studies [10–12] were automatically calculated. The severity of the decrease in rCBF was obtained from the averaged *Z*-score in the VOI. The extent of significantly decreased rCBF was obtained from the rate of voxels with a *Z*-score >2 in the VOI. The ratio of the extent of significantly decreased rCBF in the VOI to that in the whole brain was also calculated. This ratio indicates the specificity of rCBF reduction in a VOI compared with that in the whole brain. Cutoff values for likely AD were >1.19 for the severity, >14.2% for the extent, and >2.22 for the ratio [10]. Previous studies demonstrated that patients with abnormalities in all indicators exhibited PiB retention by PiB-PET [11, 12].

PiB-PET

PiB-PET scans were performed using a PET/CT scanner (Biograph mCT; Siemens Healthineers, Tokyo, Japan) in 3D scanning mode. PiB was injected intravenously at a dose of 555 ± 185 MBq, immediately followed by a 70-min dynamic acquisition. PET images acquired 50–70 min after injection (300 s × 4 frames) were used. The images were analyzed with the PMOD software (version 3.409; PMOD Technologies Ltd., Zurich, Switzerland). The mean cortical standardized uptake value (mcSUV) was calculated for all brain regions examined. The mcSUV ratio (mcSUVR) was generated by normalizing the mcSUV to the cerebellar cortex SUV. Subjects with an mcSUVR >1.4 were classified as PiB positive [14].

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Table 2. Three indicators of the eZIS in the early-onset and late-onset groups

	Early-onset group (*n* = 16)	Late-onset group (*n* = 18)	*p* value
Severity	2.50 (0.84)	1.42 (0.49)	0.000
Extent	52.3 (22.3)	20.4 (15.6)	0.000
Ratio	4.05 (1.57)	2.68 (1.96)	0.033
Abnormalities in all indicators	15/16 (93.8)	9/18 (50.0)	0.008

Values are presented as mean (SD) or *n* (%). Differences between groups were assessed using Student's *t* test (severity, extent, and ratio) and Fisher's exact test (rate of patients with abnormalities in all indicators). eZIS, easy *Z*-score imaging system.

Statistical Analysis

Student's *t* test was used to compare demographic data except the sex ratio, clinical data, and three indicators of the eZIS of the subjects between the early-onset and the late-onset group. Fisher's exact test was used to compare the sex ratio and the rate of patients with abnormalities in all indicators of the eZIS between the two groups. Statistical analyses were performed using the SPSS software (version 25), and a *p* value <0.05 was considered statistically significant.

Results

Table 1 shows the demographic and clinical data for the early-onset and late-onset groups. No significant differences were found regarding sex ratio, educational history, disease duration, MMSE score, or mcSUVR value between the two groups.

Table 2 shows the three indicators of the eZIS in the early-onset and late-onset groups. The mean values of severity, extent, and ratio were significantly higher in the early-onset group than in the late-onset group (*p* = 0.000, *p* = 0.000, and *p* = 0.033, respectively). The proportion of patients with abnormalities in all indicators was significantly (*p* = 0.008) higher in the early-onset group (93.8%) than in the late-onset group (50.0%).

Discussion

In contrast to previous SPECT studies on AD [8, 13], the present study included confirmation of amyloid accumulation using PiB-PET in its protocol. Therefore, it is unlikely that our patients included those with non-AD such as argyrophilic grain dementia and senile dementia of the neurofibrillary tangle type, which exhibit similar clinical symptoms and hippocampal atrophy to AD [15, 16].

By applying eZIS-SPECT to these amyloid-positive AD patients, the present study clarified onset age-dependent decreases in rCBF in the PCC, precuneus, and parietal lobe; the degree of reduction in these cerebral regions was significantly higher in the early-onset group than in the late-onset group. Recently, several neuroimaging studies have compared early-onset and late-onset AD with positivity for AD biomarkers. MRI studies have demonstrated that cerebral atrophy of the early-onset type was predominant in temporoparietal regions, especially the PCC, whereas that of the late-onset type was predominant in medial temporal regions [17, 18].

In studies using fluorodeoxyglucose PET, the early-onset type showed hypometabolism in the precuneus and parietal lobe, more than the late-onset type did [18, 19]. Furthermore, a neuro-pathological study revealed that the neurofibrillary tangle densities in the association cortices including the parietal cortex were higher in the early-onset type than in the late-onset type [20]. These studies suggest that pathophysiological abnormalities of the PCC, precuneus, and parietal lobes are more pronounced in the early-onset type than in the late-onset type. Therefore, our results complement these morphological, metabolic, and neuropathological findings.

From a clinical perspective, the present study suggests that eZIS-SPECT has high diagnostic utility for early-onset AD. On the other hand, it is recommended that this imaging method be applied to the diagnosis of late-onset AD with caution, probably in combination with morphological imaging such as MRI [21].

There are several limitations to this study. First, the sample size was small. Second, this study was performed retrospectively at one medical institution only, and the possibility of an unintended bias in patient selection cannot be ruled out entirely. Therefore, our results should be replicated in prospective studies with a larger number of subjects recruited from multiple facilities. Third, neuropathological confirmation was not performed.

In conclusion, the present study applying eZIS-SPECT to amyloid-positive AD suggests that the reduction in cerebral blood flow in the PCC, precuneus, and parietal lobe is more pronounced in the early-onset type than in the late-onset type of the disease.

Acknowledgements

Statement of Ethics

The present study was approved by the Ethics Committees of Yamagata University School of Medicine and complied with the rules for human experimentation stated in the World Medical Association Declaration of Helsinki. All patients or their families provided written informed consent for participation.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

H.H. conceptualized the study, performed the neuropsychological assessment, analyzed the patient data, and drafted the manuscript; R.K., S.K., and D.M. performed the neuropsychological assessment and revised the manuscript; K.O. encouraged the study and revised the manuscript. All authors read and approved the final version of this manuscript.

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