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Original

An Easy Z-score Imaging System for Discrimination Between Alzheimer's Disease and Dementia with Lewy Bodies Using Brain Perfusion SPECT

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Summary

Objective: We retrospectively examined whether easy Z-score imaging system (eZIS)-specific volume of interest analysis (SVA) using brain perfusion single photon emission computed tomography (SPECT) imaging or the cingulate island sign score (CIScore) could distinguish between Alzheimer's disease (AD) and dementia with Lewy bodies (DLB).

Methods: This study included 22 AD and 22 DLB patients who underwent ^{99m}Tc-ECD SPECT at Dokkyo Medical University Saitama Medical Center from November 2011 to February 2023.

Results: The SVA of AD and DLB patients showed that the threshold was exceeded in 77.3% for severity, 72.7% for extent, and 63.6% for ratio in AD, and in 86.4% for severity, 77.3% for extent, and 72.7% for ratio in DLB, with no significant difference between the two patient groups. The CIScore threshold of 0.281 allowed DLB to be discriminated from AD with an accuracy, sensitivity, and specificity of 63.6%, 77.2%, and 50.0%, respectively. The mean CIScore was significantly lower in DLB patients than in AD patients ($p = 0.028$, Mann-Whitney U test). A significant positive correlation was found between the CIScore and age of AD and DLB patients by Spearman's rank correlation coefficient analysis.

Conclusion: SVA is useful for the diagnosis of dementia with AD and DLB. CIScore is an adjunctive assessment method to distinguish between AD and DLB. Although CIScore can distinguish AD and DLB, it was strongly affected by age.

Key Words: Alzheimer's disease, cingulate island sign, dementia with Lewy bodies, easy Z-score imaging system

Introduction

Cerebral perfusion scintigraphy with single photon emission computed tomography (SPECT) is used for the very early diagnosis of Alzheimer's disease (AD). In early AD, perfusion is decreased in the posterior

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cingulate gyrus and precuneus[1,2]. In Japan, easy Z-score imaging (eZIS) analysis is used in clinical practice to demonstrate a decrease in cerebral perfusion with SPECT in the posterior cingulate gyrus, precuneus, and inferior parietal lobe, which are areas of particular interest in early AD, using three indicators, i.e., severity, extent, and ratio. This system is useful for the diagnosis of AD at the stage of mild cognitive impairment (MCI)[3].

Early AD and early dementia with Lewy bodies (DLB) are often difficult to distinguish clinically. Cerebral blood flow SPECT shows decreased blood flow from the posterior cingulate gyrus to the precuneus in AD, and decreased occipital lobe blood flow with preserved blood flow in the posterior cingulate gyrus in DLB. The CIScore is based on the same evaluation method as the cingulate island sign (CIS), in which glucose metabolism is decreased in the posterior cingulate gyrus of patients with AD on fluorodeoxyglucose-PET. By contrast, metabolism in the posterior cingulate gyrus is maintained in DLB patients[4-7].

In this study, three indicators of SVA (severity, extent, and ratio) and CIScore were assessed in patients with AD and DLB to determine whether it is possible to distinguish between the two diseases at an early stage.

Materials and Methods

The study included 44 patients with 22 probable AD patients and 22 probable DLB patients who underwent ^{99m}Tc-ECD SPECT at Dokkyo Medical University Saitama Medical Center from November 2011 to February 2023. We retrospectively investigated the results of eZIS by SPECT. DLB was diagnosed according to the 2017 diagnostic criteria (4th edition)[4], whereas probable DLB was diagnosed using ^{123}I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy. In the ^{123}I-MIBG myocardial scintigraphy images, the lower limit of the heart-to-mediastinum ratio for early and delayed images was set to 2.2 according to the database of the Standardization Working Group of the Japanese Society of Nuclear Medicine[8]. AD was diagnosed according to the DSM-5 criteria[9].

SPECT eZIS

Brain ^{99m}Tc-ECD SPECT was performed using a similar protocol to previous studies[2,3,5,6]. After intravenous injection of 400 or 600 MBq ^{99m}Tc-ECD (Fujifilm RI Pharma Co., Ltd., Tokyo, Japan), the ^{99m}Tc-ethyl cysteine levels were measured using a gamma camera (GCA-9300; Toshiba Medical, Japan or Symbia Evo Excel; Siemens, Germany) with the Patlak plot method. Cardiac-to-brain effects were evaluated to measure the mean global cerebral blood flow of ECD using perfusion SPECT monitored with rectangular gamma rays[10].

SPECT images were generated using the anatomically standardized eZIS program with the original ^{99m}Tc-ECD template (Fig. 1). eZIS is a processing method based on statistical parametric mapping, which corrects size by linear transformation and anatomically corrects curved surfaces by non-linear transformation. In addition, it transforms individual cerebral blood flow SPECT images into standard brain images. A Z-score map of each SPECT image was extracted by comparison of an age-matched normal control database using mean and standard deviation, and incorporated into eZIS to generate a SPECT image. After inter-institutional corrections, spatially normalized ^{99m}Tc-ECD SPECT images from each patient were compared with normal images from databases of 60-69-year-old, > 70-year-old, and > 80-year-old subjects using voxel-by-voxel Z-score analysis after pixel normalization to the global mean values: Z-score = (control mean − individual value) / control standard deviation.

In eZIS analysis, specific regions showing decreased local cerebral blood flow in very early AD patients were determined by the following method. The value obtained by incorporating the statistical parametric mapping analysis into the automatic analysis of the Z-score was measured as the volume of interest (VOI). The eZIS program was used to compare the precuneus, posterior cingulate gyrus, and parietal association cortex areas in age-matched healthy volunteers with specific VOIs in patients with very early AD on ^{99m}Tc-ECD SPECT images. Very early AD patients and healthy controls were automatically identified on the basis of three indicators, i.e., severity, extent, and ratio[2,3,11]. In eZIS-SVA, severity is an index of the reduced mean local cerebral perfusion flow at a Z-score > 0 in very early AD; extent is a Z-score generated from the percentage of coordinates with positive Z-score > 2 averaged by VOI; and the ratio, which exceeds a score of

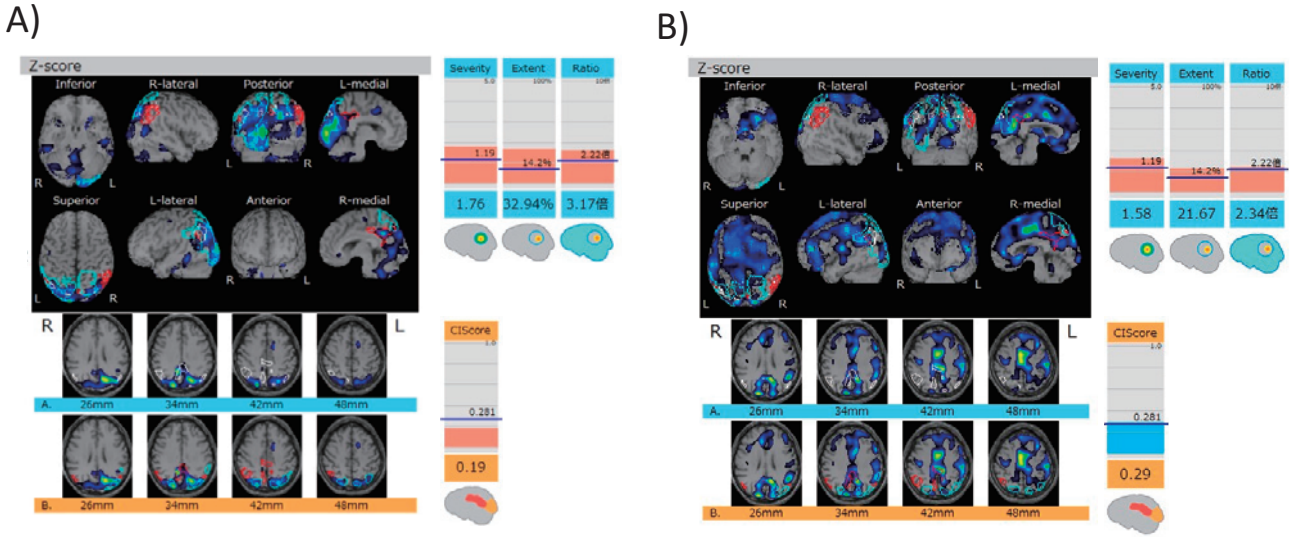

Figure 1

A: Upper panel: Automated voxel-by-voxel Z-score analysis by comparison of brain perfusion SPECT images of an 86-year-old man with probable DLB and an Mini-Mental State Examination (MMSE) score of 20 with the mean and SD of SPECT images of healthy volunteers after normalization to global mean cerebral blood flow values. Color-scaled Z-score maps ranging from 2.0 to 6.0 with an extent threshold of 300 voxels are displayed by overlaying on trans-axial sections and surface-rendering of the spatially normalized MRI template. Red lines enclose a volume of interest (VOI) with the most significant decline in regional cerebral blood flow in very early Alzheimer's disease (AD) obtained by comparison with a group of healthy volunteers by SPM2. The severity, extent, and ratio are 1.76, 32.94%, and 3.17, respectively. Lower panel: CIScore of 0.19 was obtained by dividing the total Z-score on the low blood flow side in VOI-2 (occipital cingulate gyrus, enclosed with a red line) by the total Z-score on the low blood flow side in VOI-1 (occipital, enclosed with a light blue line).
B: A 44-year-old man with AD and an MMSE score of 26 with the severity, extent, ratio, and CIScore of 1.58, 21.67%, 2.34, and 0.29, respectively.

2, is an index showing a significant decrease in local cerebral blood flow in a VOI within the range where the local cerebral blood flow in the entire brain is significantly decreased. A decrease in regional cerebral perfusion flow in a VOI was compared with that in the whole brain. The cut-off values for discrimination between the severity, extent, and ratio groups were set to > 1.19, > 14.2, and > 2.22, respectively, using the threshold values obtained from the receiver operating characteristic analysis[3].

The CIScore is calculated by dividing the sum of the Z-scores of the hypoperfused region centered on the posterior cingulate gyrus excluding SVA by the sum of the Z-scores of the hypoperfused region in the SVA of DLB patients[5-7].

In this study, patients with AD and DLB, a type of dementia, were assessed using three SVA indicators (severity, extent, and ratio) and the CIScore to investigate the distribution of cerebral perfusion in the SVA region and to compare the characteristics of AD and DLB.

In accordance with the Declaration of Helsinki, informed consent was exempted because this was a retrospective medical record survey.

Statistical Analysis

Descriptive demographic, clinical, and ^{99m}Tc-ECD-SPECT data are presented as mean, standard deviation, number, and percentage (Table 1 and 2). The groups were compared using Fisher's exact test and Mann-Whitney U test, as appropriate. The patients' medical records were reviewed. If a diagnosis (AD or DLB) was found in the records, the initial date of diagnosis was used as the date of onset of the condition.

Statistical analyses were performed with GraphPad Software Prism 9 for Mac OS (GraphPad Software, Inc., San Diego, CA) and SPSS statistical software (version 28.0; SPSS, Inc., Chicago, IL).

Table 1 Demographic data

	DLB (n = 22)	AD (n = 22)	*p* value
Male/Female (male, %)	15/7 (68.2)	10/12 (45.5)	0.223
Age at ECD-SPECT, years	75.3 ± 5.5	70.9 ± 10.9	0.136
Disease duration at ECD-SPECT, years	1.4 ± 1.2	1.4 ± 1.2	0.897
MMSE	21.4 ± 6.2*	21.7 ± 3.8	0.678
H/M early	1.52 ± 0.22	NA	NA
H/M delayed	1.30 ± 0.17	NA	NA
H/M early < 2.2*	20 (90.9)	NA	NA
H/M delayed < 2.2*	22 (100)	NA	NA

DLB, dementia with Lewy bodies; AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; H/M, heart-to-mediastinum ratio in ^{123}I-MIBG; NA, not applicable. *The lower limit of the heart-to-mediastinum ratio for early and delayed images in ^{123}I-metaiodobenzylguanidine myocardial scintigraphy was set to 2.2 according to the database of the Standardization Working Group of the Japanese Society of Nuclear Medicine [8]. *, n = 21.

Table 2 ^{99m}Tc-ECD SPECT images and SVA data

	DLB (n = 22)	AD (n = 22)	*p* value
mCBF, mL/100 g/min	38.2 ± 3.0	39.7 ± 2.7	0.1807
Severity	1.69 ± 0.56	1.59 ± 0.63	0.573
Extent	31.34 ± 21.12	27.09 ± 21.15	0.453
Ratio	3.31 ± 1.64	2.79 ± 1.84	0.372
Severity > 1.19	19 (86.4)	17 (77.3)	0.6981
Extent > 14.2	17 (77.3)	16 (72.7)	> 0.9999
Ratio > 2.22	16 (72.7)	14 (63.6)	0.3102
Abnormalities in three indicators	17 (77.3)	14 (63.6)	0.3102
CIScore* (entire)	0.24 ± 0.08	0.32 ± 0.14	0.0280
< 0.281	17 (77.3)	11 (50.0)	0.1159
CIScore* (aged < 79 years, n = 16)	0.21 ± 0.06	0.29 ± 0.12	0.024
< 0.281	13 (81.3)	9 (40.9)	0.1134

SVA, eZIS-specific VOI analysis; DLB, dementia with Lewy bodies; AD, Alzheimer's disease; mCBF, mean cerebral blood flow in bilateral cerebral hemispheres; CIScore, cingulate island sign score. * CIScore involves the same evaluation method as for the cingulate island sign.

Results

There were no significant differences in age, disease duration, and Mini-Mental State Examination (MMSE) score between AD and DLB patients. In ^{123}I-MIBG myocardial scintigraphy, the early and delayed heart-to-mediastinum ratios showed decreased uptake in all DLB patients (Table 1).

The SVA of AD and DLB patients showed that the threshold was exceeded in 17 patients for severity (77.3%), 16 patients for extent (72.7%), and 14 patients for ratio (63.6%) in AD, and in 19 patients (86.4%) for severity, 17 patients (77.3%) for extent, and 16 patients for ratio (72.7%) in DLB, with no significant differences between the two patient groups (Table 2).

The mean CIScore was significantly lower in DLB patients than in AD patients (0.236 ± 0.08 and 0.323 ± 0.142, respectively; Mann-Whitney U test p = 0.0280). The CIScore threshold of 0.281 allowed DLB to be discriminated from AD with an accuracy, sensitivity, and specificity of 63.6%, 77.2%, and 50.0%, respectively (Table 3).

The Spearman's rank correlation coefficient analysis showed a significant positive correlation between the CIScore and age in AD and DLB patients (p = 0.02 and p = 0.02, respectively; Table 4). A decreased CIScore was observed in DLB patients aged < 79 and ≥ 79 years, whereas the CIScore in patients aged < 79

Table 3 Diagnostic ability of CIScore threshold of 0.281

	DLB TP	DLB FN	AD FP	AD TN
Number	17	5	11	11
Age	75.1 ± 5.7	79.2 ± 4.9	68.9 ± 9.4	72.9 ± 12.3
Sex (M:F)	13:4	2:3	4:7	6:5
MMSE	21.1 ± 6.6	22.8 ± 4.5	21.8 ± 4.0	21.5 ± 3.9
Disease duration (years)	1.6 ± 1.3	0.8 ± 0.6	1.5 ± 0.7	1.2 ± 1.6

CIScore, cingulate island sign score; AD, Alzheimer's disease; DLB, dementia with Lewy body; FN, false negative based on CIScore; FP, false positive based on CIScore; MMSE, Mini-Mental State Examination; TN, true negative based on CIScore; TP, true positive based on CIScore.

Table 4 Correlation between age and CIScore*

	n	Spearman's r	*p* value
DLB	22	0.49	0.02
AD	22	0.50	0.02
DLB and AD	44	0.37	0.01

CIScore, cingulate island sign score; AD, Alzheimer's disease; DLB, dementia with Lewy bodies. *CIScore involves the same evaluation method as for the cingulate island sign.

years was significantly higher in AD patients than in DLB patients. The area under the curve (AUC) values of the CIScore were 0.6921 and 0.7383 for patients aged ≥ 79 and < 79 years, respectively. The AUC value was larger for patients aged < 79 years than those aged ≥ 79 years (Fig. 2).

Discussion

In this study, SVA of the precuneus, inferior parietal lobe, and posterior cingulate gyrus exceeded the threshold of cerebral perfusion reduction by eZIS in patients with AD and DLB. Conversely, DLB patients had a lower CIScore than AD patients.

MCI, the pre-symptomatic stage of dementia, is attracting attention as a prodromal sign of AD and DLB. In an ^{123}I-IMP SPECT study of MCI, cerebral perfusion was evaluated in the posterior cingulate gyrus, precuneus, temporal/parietal cortex, frontal cortex, and visual cortex[12]. An AD pattern was observed in 47.8% and a DLB pattern was found in 18.7% of patients. In total, 66.5% of patients had an AD or DLB pattern[12]. In an ^{11}C-Pittsburgh compound B (PiB)-PET study, the conversion rate to dementia was high in the PiB-positive group[13], and eZIS analysis was performed on PiB-positive and PiB-negative cases. There was a high possibility that β-amyloid (Aβ) lesions were present in cases showing abnormal values for severity, extent, and ratio[14]. Analysis of the pathological correlation of PiB uptake with PET in patients who were pre-diagnosed with DLB or probable DLB at autopsy showed that low PiB uptake accurately identified DLB patients and patients with AD or mixed lesions of DLB and AD[15,16]. Hayashi et al.[17] reported that applying eZIS-SPECT to amyloid-positive AD patients demonstrates more pronounced reduction in cerebral blood flow in the posterior cingulate cortex, precuneus, and parietal lobe in the early-onset type rather than the late-onset type of disease. These studies suggest that pathophysiological abnormalities of the posterior cingulate cortex, precuneus, and parietal lobes are more pronounced in the early-onset type than in the late-onset type disease. This study only included patients with late-onset AD, which was thought to be a result of the small proportion of three-indicator abnormalities. Future studies should examine young-onset and late-onset AD separately.

Furthermore, the CIS has been adopted as a supporting biomarker in the 2017 DLB diagnostic criteria. CIS can also be evaluated by ^{99m}Tc-ECD or ^{123}I-IMP SPECT, but PET has better spatial resolution[4]. The CIScore on ^{99m}Tc-ECD-SPECT can distinguish DLB from AD with a sensitivity of 92.3% and specificity of 76.9% for CIScore < 0.281[5]. On the other hand, Honda et al.[18] found a sensitivity of 93% and a specificity of 48% when the cut-off CIScore was set at 0.27. Ishibashi et al.[19] performed ROC analysis and showed that a CIScore threshold of 0.255 allowed DLB to be discriminated from AD with an accuracy, sensitivity, and

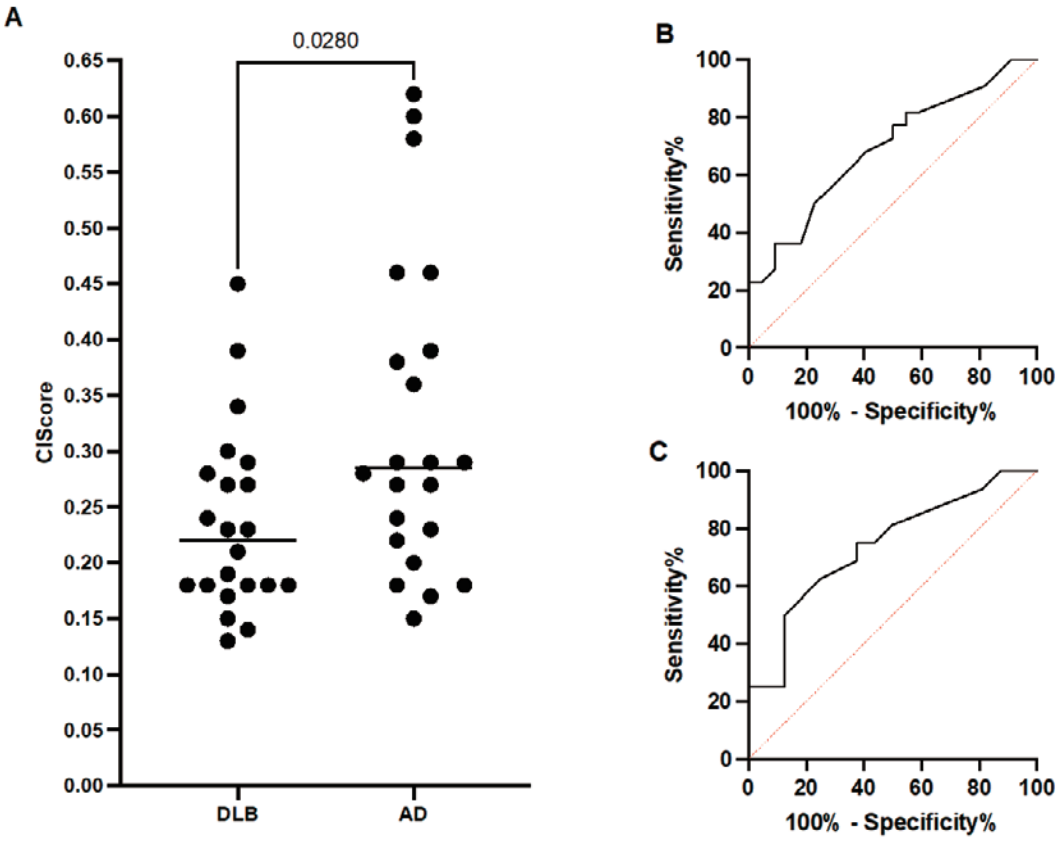

Figure 2

A. CIScore for AD and DLB patients.
B. ROC curve for AD and DLB patients.
C. ROC curve for AD and DLB patients aged < 79 years.
AD, Alzheimer's disease; CIScore, cingulate island sign score; DLB, dementia with Lewy bodies; ROC, receiver operating characteristic.

specificity of 67.0%, 60.5%, and 71.4%, respectively. The cut-off values reported in previous reports should also be changed in the current survey to set and interpret the appropriate values for each hospital.

The CIS on ^{123}I-IMP SPECT is associated with medial temporal lobe atrophy and neurofibrillary tangles. The CIS becomes obscured with increase in neurofibrillary tangles. An examination of other indicators on ^{123}I-IMP SPECT showed that a low CIS ratio was associated with a poor prognosis in dementia, and that CIS disappeared with DLB progression. It is speculated that this is due to the increase in neurofibrillary tangles[20,21]. Similarly, the CIScore on ^{99m}Tc-ECD-SPECT was not related to the cerebrospinal fluid (CSF) biomarkers (Aβ1-42/Aβ1-40, p-tau, and t-tau) in DLB or Parkinson's disease (PD). High CSF tau levels were related to clinical disease severity and hippocampal atrophy[22].

A common problem with the use of CIScore is its relationship with age. Most patients with DLB also demonstrate AD pathology, including cortical amyloid plaques and neurofibrillary tangles[16]. The diagnostic accuracy of the CIScore may be low as it often shows an increase in elderly DLB patients, in whom the pathologically common form is most prevalent[7]. In a study based on PET scans, the CIS ratio on FDG-PET is not associated with fibrillar β-amyloid deposition but indicates lower Braak NFT stage in patients with DLB[23]. In our study, CIScore was positively correlated with age in DLB and AD patients. The prevalence of AD is 10-30% in patients aged ≥ 65 years, and neurofibrillary tangles are strongly associated with dementia at 75 years of age[24]. Neurofibrillary tangles are a common finding in AD, but are also characteristic of brain aging, with the appearance of AD pathology during physiological brain aging[25]. Therefore, the differ-

ence in the CIScore between AD and DLB decreases with age. The relationship between age and CIScore was previously examined in two groups aged ≤ 78 and > 78 years. The discrimination ability of the ROC curve analysis was higher in the group aged ≤ 78 years[19]. There was a correlation between age-specific sensitivity and specificity in the group aged ≤ 78 years[26]. Similar trends were found in our results as in the previous two studies. A limitation of the use of CIScore is that age needs to be taken into consideration during interpretation.

A limitation of the present study was that the data were collected from a single facility. Further studies with larger sample sizes are needed to confirm our findings. In addition, it is necessary to provide pathological confirmation of neurodegenerative dementia. We did not evaluate the AD biomarkers in our study. As a result, it was not possible to accurately assess cognitive impairment and pathological abnormalities in AD based on the National Institute for Aging-Alzheimer Association (NIA-AA) guidelines, which is a novel AD staging system based on biomarkers[27].

In recent years, research on disease-modifying therapy for AD has been progressing by targeting processes involved in the development of Aβ, oligomerization, and neurofibrillary tangles[28]. The development of disease-modifying agents targeting α-synuclein for Parkinson's disease is also underway[29]. Considering that Aβ pathology is common in patients with probable DLB[16], disease-modifying therapy for AD may also be effective. In the future, it is expected that eZIS will be useful as an evaluation method for case selection in clinical trials of highly accurate disease-modifying drugs.

Conclusion

The current study confirmed the potential for SVA of eZIS and CIScore to distinguish between AD and DLB. It is expected that detecting such abnormalities will identify the type of AD and DLB, and aid in the selection of suitable cases for disease-modifying therapy. Large-scale prospective studies are needed to verify our findings.

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