Research Article

Brain perfusion SPECT using an easy Z-score imaging system predicts progression to neurodegenerative dementia in REM sleep behavior disorder

Kyoko Numahata, MD[a], Tomoyuki Miyamoto, MD, PhD[a], Yasuhisa Akaiwa, MD, PhD[a], Masayuki Miyamoto, MD, PhD[b]

[a] Department of Neurology, Dokkyo Medical University Saitama Medical Center, Saitama, Japan

[b] Center of Sleep Medicine, Dokkyo Medical University, Tochigi, Japan

Short title: Brain perfusion SPECT predicts progression to neurodegenerative dementia in IRBD

Corresponding Autor:
Tomoyuki Miyamoto, MD. PhD
Department of Neurology
Dokkyo Medical University Saitama Medical Center
2-1-50 Minamikoshigaya,
Koshigaya, Saitama, 343-8555, Japan
Tel: +81-48-965-1243
E-mail: miyatomo@dokkyomed.ac.jp

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Abstract

Introduction: Longitudinal studies have reported that patients with idiopathic rapid eye movement sleep behavior disorder (IRBD) have an increased risk of developing synucleinopathies, such as Parkinson's disease and dementia with Lewy bodies. Clinical trials of disease-modifying therapies for IRBD patients require suitable biomarkers that can predict the short-term onset of neurodegenerative dementia.

Methods: We retrospectively examined if 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) can predict the short-term development of neurodegenerative dementia in 30 patients with IRBD.

Results: Ten patients (33.3%) who exceeded the thresholds for three indicators (severity, extent, and ratio) were included in an SVA-positive group, while 20 (66.7%) were included in an SVA-negative group. Nine (30.0%) IRBD patients had phenoconversion, of which eight had dementia with Lewy bodies and one had Parkinson's disease with dementia. In Kaplan-Meier analysis, patients in the SVA-positive group converted to neurodegenerative dementia in a significantly shorter period of time compared to patients in the SVA-negative group.

Conclusions: These data suggest that SVA-positive IRBD patients have an increased short-term risk of developing neurodegenerative dementia.

Introduction

Patients with rapid eye movement (REM) sleep behavior disorder (RBD) exhibit abnormal violent behavior associated with dreams during REM sleep. In these patients, polysomnography indicates the presence of REM sleep without muscle tone loss [1]. RBD may be prodromal to neurodegenerative diseases, such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy. In a meta-analysis of longitudinal studies, the estimated risk of RBD patients developing a neurodegenerative disease was 33.5% at 3 years, 82.4% at 10.5 years, and 96.6% at 14 years [2]. RBD has been shown to predict the progression to neurodegenerative disease using cerebral perfusion scintigraphy, dopamine transporter imaging, positron emission tomography (PET), and transcranial ultrasound [3,4].

Previous cross-sectional studies assessing regional cerebral perfusion in patients with idiopathic RBD (IRBD) have reported abnormal perfusion on ^{99m}Tc-ethylene cysteinate dimer (ECD) and ^{123}I-iodoamphetamine single-photon emission computed tomography (SPECT) [5,6,7,8]. Longitudinal studies have investigated the changes in perfusion in IRBD patients [9,10,11]. IRBD patients showing increased perfusion in the hippocampus on ^{99m}Tc-ECD SPECT have a high risk of phenoconversion to PD or DLB [10]. A model with an age- and PD-related covariance pattern at the time of imaging was shown to be a predictor of phenoconversion during follow-up in IRBD patients who underwent ^{99m}Tc-ECD SPECT [11]. Thus, recent studies have demonstrated that specific areas of abnormal blood flow can be used to predict disease progression in IRBD patients.

In clinical practice in Japan, easy Z-score imaging (eZIS) analysis is used to show 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 diagnosing AD at the mild cognitive impairment stage [12].

In the present study, we used ^{99m}Tc-ECD SPECT eZIS analysis for the early diagnosis of dementia in IRBD patients, and conducted a retrospective longitudinal study on its ability to predict progression to neurodegenerative dementia.

Materials and Methods

This study included 30 consecutive IRBD patients who underwent ^{99m}Tc-ECD SPECT at our hospital from November 2011 to February 2018. We retrospectively investigated the results of eZIS by SPECT in IRBD patients and longitudinally evaluated progression to neurodegenerative dementia, such as DLB or PD with dementia. The diagnosis of IRBD was based on the International Classification of Sleep Disorders, Second Edition [1]. In addition, ^{99m}Tc-ECD SPECT was performed on 19 DLB patients as disease controls, and the data were compared (Table 1). DLB was diagnosed on the basis of the 2017 diagnostic criteria (4th edition) [13], probable DLB was diagnosed using ^{123}I-metaiodobenzylguanidine myocardial scintigraphy, and dementia was diagnosed using the Diagnostic and Statistical Manual of Mental Disorders (5th edition) criteria [14]. 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 [15]. All IRBD and DLB cases showed delayed heart-to-mediastinum ratios (Table 1). In the DLB cases, clinically probable RBD required an informant report of a history of recurrent episodes of dream-enactive behavior during sleep with movements that appeared to match dream content. The diagnosis of parkinsonism was based on neurologic examination by a neurologist.

SPECT eZIS

Brain ^{99m}Tc-ECD SPECT was performed according to previously reported methods [12,16]. After intravenous injection of 400 MBq of ^{99m}Tc-ECD (Fujifilm Toyama Chemical Co., Ltd., Tokyo, Japan), ^{99m}Tc-ECD levels were measured using a gamma camera (GCA-9300; Toshiba, Inc., Tokyo, Japan) and the Patlak plot method. Cardiac-to-brain effects were assessed to measure mean global cerebral blood flow of ECD using perfusion SPECT and monitored with rectangular gamma rays. SPECT images were generated using the anatomically standardized eZIS program with the original ^{99m}Tc-ECD template (Fig. l). Briefly, 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, and transforms individual cerebral blood flow SPECT images into standard brain images. A Z-score map of each SPECT image was extracted from a 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 a database of 60–69-year-old subjects, a database of >70-year-old subjects, and a database of >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 identified automatically using three indicators, i.e., severity, extent, and ratio [12,16]. In eZIS-specific VOI analysis (SVA), severity was used to indicate reduced mean local cerebral perfusion flow at a Z-score > 0 in very early AD; extent was the Z-score generated from the percentage of positive Z-score > 2 coordinates averaged by the VOI; the ratio, which exceeds a score of 2, was the index showing a significant decrease in local cerebral blood flow in a VOI within the range where local cerebral blood flow in the entire brain was significantly decreased. A decrease in regional cerebral perfusion flow in a VOI was evaluated in comparison 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 receiver operating characteristic analysis [12]. AD or DLB patients were used to examine the distribution of cerebral perfusion in the SVA region (Fig. 1A).

The CIScore is the same evaluation method as that used for the cingulate island sign (CIS), in which glucose metabolism is decreased in the posterior cingulate gyrus of patients with AD on fluorodeoxyglucose-PET, but metabolism is maintained in the posterior cingulate gyrus of patients with DLB [13]. The CIScore is calculated by dividing the sum of the Z-scores of the hypoperfusion region centered on the posterior cingulate gyrus, excluding SVA of DLB patients, by the sum of the Z-scores of the hypoperfusion region in SVA of DLB patients [16,17] (Fig. 1B). In this study, three indicators of SVA (i.e., severity, extent, and ratio) and the CIScore were evaluated in patients with IRBD and DLB (Table 2).

Statistical analysis

Descriptive demographic, clinical, and ^{99m}Tc-ECD-SPECT data are given as the mean, standard deviation, number, and percentage (Table 1). Comparisons between groups were conducted

using Fisher's exact test and the Mann-Whitney U test. Between October and November 2021 (the end of the current study), the patients' medical records were reviewed. If a diagnosis (DLB or PD with dementia) was found in the charts, the initial date of diagnosis was used as the date of onset of the condition.

To compare ^{99m}Tc-ECD-SPECT between groups, IRBD subjects who exceeded the thresholds for severity, extent, and ratio were included in the SVA-positive group, with the remaining patients included in the SVA-negative group, and used for statistical comparisons [12]. Plots of the estimated proportion of subjects who developed clinically defined neurodegenerative dementia (DLB or PD with dementia) over time were generated by the Kaplan-Meier method and compared by the log-rank test (Fig. 2).

All statistical analyses were performed using Prism (version 7 for Mac OS X; GraphPad Software, Inc., San Diego, CA, USA), SPSS (version 28.0; IBM Corp., Armonk, NY, USA), and R (version 4.0.1; freely available at https://www.R-project.org).

Results

SVA of DLB patients showed that the threshold was exceeded in 16 cases for severity (88.9%), 14 cases for extent (77.8%), and 14 cases for ratio (77.8%). In IRBD patients, the threshold was exceeded in 13 cases (43.3%) for severity, 11 cases (38.7%) for extent, and 18 cases (60.0%) for ratio. When IRBD and DLB patients were compared, there was a significant difference in severity ($p < 0.007$), while there was no significant difference in extent ($p = 0.187$) or ratio ($p = 0.070$). Mean cerebral blood flow of the whole brain was significantly lower in DLB patients compared to IRBD patients (Table 2).

Ten patients (33.3%) with IRBD were included in the SVA-positive group, while 20 patients (66.7%) were included in the SVA-negative group. The presence or absence of

transition from IRBD to neurodegenerative dementia was examined using a Kaplan-Meier curve (Fig. 2). The SVA-positive group converted to neurodegenerative dementia in a significantly shorter period of time than the SVA-negative group (log-rank test, $p < 0.005$). The estimated 3-year risk of developing neurodegenerative dementia was 21.2%, the estimated 5-year risk was 34.4%, and the estimated 7-year risk was 61.0% in the SVA-positive group.

When adjusted for age, Cox proportional-hazards analysis showed that SVA-positive status (hazard ratio 8.46; 95% confidence interval 2.29–71.26; $p < 0.004$) (hazard ratio 7.46; 95% confidence interval 1.56–35.7; $p < 0.012$) predicted progression to neurodegenerative dementia.

Of the 30 IRBD patients, nine (30.0%) progressed to dementia over an average observation period of 6.4 ± 2.8 years: eight to DLB (88.9%) and one to PD with dementia (11.1%).

Spearman's rank correlation coefficient analysis showed a significant positive correlation between age and the CIScore in patients with DLB ($r = 0.616$, $p = 0.005$). No significant correlation was found between age and the CIScore in IRBD patients ($r = -0.1058$, $p = 0.58$).

Discussion and Conclusion

In this study, in patients with IRBD exceeding the thresholds for the reduction of cerebral perfusion in eZIS-SVA, the conversion rate to neurodegenerative dementia was 30.0% over an average duration of 6.4 years. IRBD patients had a low CIScore and, unlike AD patients, they exhibited a CIScore similar to DLB patients. These data suggest that SVA abnormalities in IRBD patients may reveal cerebral perfusion anomalies at a very early stage of neurodegenerative dementia.

Mild cognitive impairment, the pre-stage of dementia, is attracting attention as a prodromal sign of AD or DLB, and RBD is a risk factor for mild cognitive impairment as well as synucleinopathy [18,19]. Mild cognitive impairment is found in 50% of IRBD patients and 73%

of PD patients with RBD, while it is found in only 11% of PD patients without RBD [18]. Most types of dementia progress to DLB or PD with dementia in patients with IRBD [4]. In a ^{123}I-iodoamphetamine SPECT study of mild cognitive impairment evaluating cerebral perfusion in the posterior cingulate gyrus, precuneus, temporal and parietal cortices, frontal cortex, and visual cortex, an AD pattern was observed in 47.8% of patients, a DLB pattern was found in 18.7%, and the combined frequency of patients with the AD or DLB pattern was 66.5% [20]. In an ^{11}C-Pittsburgh compound B (PiB)-PET study, the conversion rate to AD was high in the PiB-positive group, whereas PiB-negative converters were thought to have some form of dementia other than AD [21]. eZIS analysis of PiB-positive and PiB-negative cases revealed the high possibility of β-amyloid (Aβ) lesions in cases showing abnormal values for severity, extent, and ratio [22, 23]. In a recent study applying eZIS-SPECT to Aβ-positive AD patients, reduced cerebral blood flow in the posterior cingulate cortex, precuneus, and parietal lobe was suggested to be more pronounced in early-onset AD than in late-onset AD [24].

The pathological findings of Lewy body-related diseases, such as DLB and PD, are characterized by the deposition of α-synuclein, but may include mixed AD pathology [25,26,27,28]. Aβ deposits were observed in 75 (68.2%) of 110 PD patients at necropsy and were associated with Braak stages 1 and 2 in the clinical prodromal stage [25]. AD pathology was observed in 164 (77%) of 213 autopsy cases of Lewy body-related disease, of which 26% were mild, 21% were moderate, and 30% were severe [29]. The pathological findings of patients with mild cognitive impairment in the pre-dementia stage showed that there is increased PiB binding to soluble Aβ42 and insoluble Aβ aggregates in the precuneus [30]. Additionally, there is an increase in the number of neurofibrillary tangles in the amygdala, entorhinal cortex, and inferior parietal cortex of patients with mild cognitive impairment compared to controls [31].

Areas with high neural activity are thought to be prone to Aβ deposition and include the precuneus, posterior cingulate gyrus, medial prefrontal cortex, medial/lateral parietal lobe, inferior parietal lobe, hippocampal formation, and posterior cerebral canal [32,33]. Functional connectivity disturbances in the default mode network are a useful biomarker of early AD [34,35], and the default mode network is the region most vulnerable to Aβ deposition [36,37]. In a recent study, the cuneus/precuneus was shown to be the hub of a large functional network subserving cognitive function in patients with IRBD [38]. The disease-specific region of eZIS is also a part of the default mode network and is consistent with the site of decreased cerebral perfusion on SPECT. Therefore, Aβ deposits, i.e., complications of AD pathology, are suspected if the eZIS index exceeds the SVA threshold. In the present study, the eZIS-SVA results in patients with IRBD also suggested that the pathological background of AD coexists with Lewy body pathology in cases who progress from IRBD to neurodegenerative dementia, such as DLB with AD pathology or PD with dementia [39]. Conversely, suspected non-AD pathophysiology shows a milder reduction of regional cerebral blood flow in the posterior cingulate cortex, precuneus, and parietal lobe as compared to AD, and it may be difficult to distinguish between non-AD pathophysiology and AD using the degree of cerebral blood flow decrease in these regions [40]. These data suggest that the decrease in cerebral blood flow in these areas may be regarded as an abnormality common to the early pathological stages of neurodegenerative dementia, not limited to Aβ pathology, and further investigation is required.

Furthermore, the CIS has been adopted as a supporting biomarker for the 2017 DLB diagnostic criteria. The CIScore can distinguish DLB from AD with a sensitivity of 92.3% and specificity of 76.9% for a CIScore < 0.281; DLB is likely with a CIScore < 0.281 [16]. CIS can also be evaluated by ^{99m}Tc-ECD SPECT, but PET has a better spatial resolution. However, a

common problem in this evaluation is the relationship with age [41,42,43], and age needs to be taken into consideration when interpreting the CIScore.

A limitation of the present study was that the results were obtained from a single facility, and further large-scale prospective studies are needed to confirm our findings. In addition, it is necessary to obtain pathological confirmation for the transition to neurodegenerative dementia. Further, the DLB group had the core feature of RBD, so it is necessary to consider whether eZIS-SVA can be used to characterize the clinical phenotypes of DLB patients with or without RBD.

The significantly lower mean cerebral blood flow values of the whole brain in DLB patients compared to IRBD patients suggest that extensive cortical and subcortical progression in IRBD patients may result in the development of a clinical form of probable DLB. A characteristic pattern of occipital and parietal hypoperfusion has been demonstrated in DLB [44]. Generalized low uptake on SPECT/PET perfusion/metabolism scanning with reduced occipital activity is one of the supportive biomarkers for DLB [13]. Occipital hypometabolism or hypoperfusion has not been studied in detail at the pre-dementia stage and it remains to be determined whether any imaging abnormalities are indicative of prodromal DLB [45]. Future work should focus on longitudinal perfusion studies to develop and validate diagnostic criteria for prodromal DLB.

In conclusion, this study confirmed that patients with IRBD abnormalities in eZIS-SVA were more likely to develop neurodegenerative dementia over the short term. In the future, eZIS will be useful as one of the evaluation methods for case selection during clinical trials of disease-modifying drugs.

Statement of Ethics

This study protocol was reviewed and approved by the Ethics Review Committee of Dokkyo Medical University Saitama Medical Center (approval number 1821). This study was performed in accordance with the Declaration of Helsinki. Written or verbal informed consent was obtained from each subject. All subjects were informed about the research project and a procedure was established for them to opt out of the study if they did not wish to participate in it.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

T.M. contributed to study conception. T.M., K.N., Y.A., and M.M. analyzed and interpreted the patient data. K.N. and T.M. wrote the first draft of the manuscript and created the graphs. M.M., N.K., Y.A., and T.M. made significant revisions to the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Figure legends

Fig. 1.

A: Automated voxel-by-voxel Z-score analysis by comparison of brain perfusion single-photon emission computed tomography (SPECT) images of a 75-year-old man with probable dementia with Lewy bodies and a Mini-Mental State Examination score of 19. The mean and standard deviation of SPECT images of healthy volunteers after normalization to global mean cerebral blood flow values are shown. Color-scaled Z-score maps (range: 2.0–6.0), with an extent threshold of 300 voxels, are displayed by overlaying on trans-axial sections and surface rendering of the spatially normalized magnetic resonance imaging template. Red lines enclose a volume-of-interest (VOI) with the most significant decrease in regional cerebral blood flow in very early Alzheimer's disease compared to healthy volunteers by Statistical Parametric Mapping 2 analysis. Severity, extent, and ratio were 1.79, 36.01%, and 6.04, respectively. VOI-1: occipital, enclosed with a light blue line; VOI-2: occipital cingulate gyrus, enclosed with a red line.

B: The cingulate island sign score (CIScore) is 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).

Fig. 2.

Progression of the onset of dementia in patients with idiopathic rapid eye movement sleep behavior disorder (Kaplan-Meier analysis).

SVA, specific volume of interest analysis.