博士学位論文

IMP 脳血流 SPECT における
後頭葉血流低下に着目した MCI with Lewy Bodies と
MCI due to Alzheimer's Disease の鑑別能

近畿大学大学院
医学研究科医学系専攻

仲田　崇

Doctoral Dissertation

Differential diagnosis of MCI with Lewy bodies and MCI due to Alzheimer's disease by visual assessment of occipital hypoperfusion on SPECT images

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Differential diagnosis of MCI with Lewy bodies and MCI due to Alzheimer's disease by visual assessment of occipital hypoperfusion on SPECT images

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Type of manuscript: Original article

Abstract

Purpose: Predicting progression of mild cognitive impairment (MCI) to Alzheimer's disease (AD) or dementia with Lewy bodies (DLB) is important. We evaluated morphological and functional differences between MCI with Lewy bodies (MCI-LB) and MCI due to AD (MCI-AD), and a method for differentiating between these conditions using brain MRI and brain perfusion SPECT.

Methods: A continuous series of 101 subjects, who had visited our memory clinic and met the definition of MCI, were enrolled retrospectively. They were consisted of 60 MCI-LB and 41 MCI-AD subjects. Relative cerebral blood flow (rCBF) on SPECT images and relative brain atrophy on MRI images were evaluated. We performed voxel-based analysis and visually inspected brain perfusion SPECT images for regional brain atrophy, occipital hypoperfusion and the cingulate island sign (CIS), for differential diagnosis of MCI-LB and MCI-AD.

Results: MRI showed no significant differences in regional atrophy between the MCI-LB and MCI-AD groups. In MCI-LB subjects, occipital rCBF was significantly decreased compared with MCI-AD subjects ($p < 0.01$, family wise error [FWE]-corrected). Visual inspection of occipital hypoperfusion had sensitivity, specificity, and accuracy values of 100%, 73.2% and 89.1%, respectively, for differentiating MCI-LB and MCI-AD. Occipital hypoperfusion was offered higher diagnostic utility than the CIS.

Conclusion: The occipital lobe was the region with significantly decreased rCBF in MCI-LB compared with MCI-AD subjects. Occipital hypoperfusion on brain perfusion SPECT may be a more useful imaging biomarker than the CIS for visually differentiating MCI-LB and MCI-AD.

Keywords

Mild cognitive impairment with Lewy bodies (MCI-LB), Mild cognitive impairment due to Alzheimer's

disease (MCI-AD), Single photon emission computed tomography (SPECT), Occipital hypoperfusion, Cingulate island sign (CIS)

Introduction

Mild cognitive impairment (MCI) [1] is not just an intermediate stage in the process of reaching dementia, MCI may convert to dementia or return to normal in the natural course. In general, it is a mistake that MCI tends to be simply evaluated using a simple cognitive function scale, such as the Mini–Mental State Examination (MMSE) or Clinical Dementia Rating scale (CDR). The key points for MCI diagnosis were never the score for MMSE tests, but the presence or absence of cognitive decline and the acquisition of medical history from patients and families were more important than cognitive function tests. Clinically, MCI is associated with a variety of background pathologies and is not considered only as a precursor of dementia. It has been reported that 5% – 15% people with MCI progress to dementia, while 16% – 41% revert to normal [2-5]. The previous symptom-modifying medications such as donepezil had no effect on the cognitive function of MCI subjects to prevent progression from MCI to dementia [6, 7], but the use of non-drug therapy for early intervention (i.e., physical exercise and cognitive training, reducing the risks of lifestyle-related diseases, review of daily diet and activity habits, and participation in social activity) [8-15] may be considered to reduce the burden on caregivers by delaying the emergence of behavioral and psychological symptoms of dementia (BPSD) and lifestyle disorders from an early dementia stage. Early detection and diagnosis at the MCI stage and non-drug therapy are considered important. As the pathology of MCI is complex, neuroimaging in the MCI stage is an important component of dementia care. Imaging studies can be used to identify the cause of MCI, and to predict the type of dementia that it may progress to in the future. Neuroimaging can help prevent the onset and progression of dementia by aiding early diagnosis, treatment, and intervention.

MCI that progresses to AD is called MCI due to AD (MCI-AD), while MCI that progresses to Lewy body disease (LBD) is called MCI with Lewy bodies (MCI-LB). Dementia with Lewy bodies (DLB), similar to Parkinson's disease (PD), is an α-synucleinopathy in which Lewy bodies accumulate mainly in α-synuclein. Recently, DLB and PD have been collectively referred to as LBD. Symptoms of DLB, such as

memory impairment and visual hallucinations, are relatively responsive to donepezil, which is a conventional anti-dementia drug [16]. Recently, amyloid positron emission tomography (PET) imaging techniques have made remarkable progress. Clinical trials of AD-modifying therapies targeting amyloid β (Aβ), such as the anti-Aβ protofibril monoclonal antibodies lecanemab [17] and aducanumab [18], have been conducted; these therapies will be applied in early dementia cases in the near future.

Since the aetiologies of MCI are diverse, differential diagnosis by neuroimaging is very important for preventing onset, as well as reducing symptoms and the burden on caregivers. In particular, differential diagnosis of MCI-LB and MCI-AD using neuroimaging is clinically important, although differential diagnosis at MCI stage is often difficult.

Many papers on neuroimaging diagnosis based on their respective MRI [19-23] and [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET) [24, 25] have been reported in LBD and AD at the dementia stage. FDG-PET imaging at the MCI stage has recently been reported by differential diagnosis between MCI-LB and MCI-AD [26-28]. The previous reports were found on differential diagnosis of MCI-LB and MCI-AD using [^{123}I]-metaiodobenzylguanidine (MIBG) myocardial scintigraphy and/or dopamine transporter single photon emission computed tomography (DAT-SPECT) [29, 30]. However, no report has been found to attempt differential diagnosis between MCI-LB and MCI-AD using brain perfusion SPECT imaging, this imaging technique at MCI stage has not yet been established in clinical practice. We investigated morphological and functional imaging differences between MCI-AD and MCI-LB; the aim was to establish a useful method for differentiating between these conditions. In particular, we evaluated the utility of visual inspection of regional hypoperfusion in brain perfusion SPECT images for differentiating between MCI-LB and MCI-AD.

Subjects and Methods

This study was approved by the ethics committee of Hyogo Brain and Heart Center (now called Hyogo Prefectural Harima-Himeji General Medical Center) and the requirement to obtain written informed consent was waived because this was a retrospective study.

Subjects

In this study, MCI was diagnosed in subjects who satisfied all of the following conditions: (i) aged > 50 years, (ii) memory impairment (amnestic MCI) as the main symptom, (iii) MMSE score of 24 – 27 at least twice or more between January 2017 and December 2021, and (iv) no problems in daily life and social activity (equivalent to a CDR score of 0.5) reported during the medical interview from patients and families [1].

MCI is a transitional state, it was necessary to discuss the conversion criteria of MCI to dementia. In particular, the conversion criteria of MCI were controversial. In this study, the criteria were initially set along the actual clinical scene and proceeded with the discussion. However, setting the conversion criteria of MCI was very difficult to get consensus in our research group alone.

The criterion for conversion from MCI to dementia in this study was a reduction in the MMSE score from one indicative of MCI to ≤ 23 points with problems in daily life and social activity after the second visit. Patients with an MMSE score indicative of MCI that improved to ≥ 24 with no problems in daily life and social activity after the second visit were excluded.

In this study, we focused on the research criteria for the diagnosis of prodromal DLB which has not emphasized dementia conversion. We applied our MCI subjects to the research criteria for the diagnosis of prodromal DLB, our MCI-LB subjects were diagnosed as the subjects with MCI-LB subtype on the basis of one or more core symptoms in clinical features (e.g., cognitive fluctuation, visual hallucinations, visual/visuospatial cognitive impairment and rapid eye movement behavior disorder [RBD]) and the proposed biomarkers and/or potential biomarkers (e.g., DAT-SPECT and brain perfusion SPECT). [31] We

believed that our MCI-LB subjects met the diagnostic criteria for the MCI subtype in prodromal DLB in this study. On the other hand, MCI-AD was diagnosed as well as probable AD according to National Institute on Aging-Alzheimer's Association workgroups (NIA-AA) guidelines [32].

MCI-LB and MCI-AD were diagnosed as the transition from MCI to probable DLB and probable AD, respectively. Regarding background pathology, relative cerebral blood flow (rCBF) on SPECT images and relative brain atrophy on MRI images were evaluated in MCI subjects. When DAT-SPECT was positive or clinical findings met in DLB criteria without DAT-SPECT, our MCI-LB was diagnosed as MCI-LB subtype on the basis of research criteria for the diagnosis of prodromal DLB [31]. Because it is clinically difficult to distinguish between DLB and Parkinson's disease dementia (PDD) in early disease stages, patients with both entities were eligible for the current study. While DAT-SPECT was negative or clinical features met in AD criteria without DAT-SPECT, MCI-AD was diagnosed as well as probable AD according to NIA-AA guidelines [32]. Following the procedure described above, MCI-LB and MCI-AD were diagnosed respectively.

Cases with comorbidities such as cerebrovascular diseases, chronic subdural hematoma or idiopathic normal pressure hydrocephalus were excluded, along with those having insufficient data and ambiguous cases. The characteristics of the 101 MCI subjects included in this study are shown in Table 1.

Brain perfusion SPECT and MRI

Details of the brain perfusion SPECT procedure are provided elsewhere [33]. In brief, brain perfusion SPECT scans were initiated with subjects in the resting state (with the eyes closed wearing eye mask) 15 min after an injection of 111 MBq of N-isopropyl-p-[^{123}I]-iodoamphetamine. All SPECT scans were performed using a rotating dual-headed gamma camera (E-CAM; Siemens, Erlangen, Germany) and a low-to-medium energy general purpose collimator. SPECT images were obtained with a 128 × 128 matrix and 12 rotations (2.5 rotations/min). For SPECT image reconstruction, a Butterworth filter (cut-off frequency,

0.58 cycles/cm; order, 8) was used. Attenuation correction was performed using Chang's method (μ = 0.09 /cm) and scatter correction was performed with a triple energy window.

MRI was performed using a 3T Achieva or 1.5T Ingenia scanner (Philips, Best, Netherlands). The scanning–protocol included sagittal T1-weighted three-dimensional whole-brain images (Achieva: slice thickness, 1.2 mm; slices, n = 140; matrix size, 256 × 256; field of view, 25.6 × 25.6 cm; echo time, 3.11 ms; repetition time, 6.7 ms; flip angle, 8°; Ingenia: slice thickness, 1.2 mm; slices, n = 140; matrix size, 192 × 192; field of view, 24.0 × 24.0 cm; echo time, 4.0 ms; repetition time, 8.6 ms; flip angle, 8°). A 3T Achieva or 1.5T Ingenia scanner was performed under each condition, total scan duration time 3 min 30sec or 3 min 47 sec, and acceleration factor 2 each other.

To obtain rCBF values, the voxel counts for each SPECT image were normalized by dividing them by the cerebellar counts [33] measured with our homemade cerebellar voxels of interest (VOIs), because global cerebral blood flow is often decreased in DLB and normalization according to the global counts may lead to underestimation of rCBF values [34].

[^{123}I] FP-CIT SPECT (DAT-SPECT)

Functional imaging methods widely used for diagnosing LBD include ^{123}I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropan (FP-CIT) with DAT-SPECT [35, 36]. To acquire images in this study, each subject received an average dose of 167 MBq [^{123}I] FP-CIT (DaTSCAN®, Nihon Medi-Physics Co., Ltd., Tokyo, Japan), intravenously as a slow bolus injection. The image acquisitions started 3 h after the tracer injection. As stated above, the SPECT scans were performed using a rotating dual-headed gamma camera (E-CAM) with a low-to-medium energy general purpose collimator. [^{123}I] FP-CIT SPECT images were obtained with a 128 × 128 matrix, 7 min/rotation × 4 rotations. The median total scan time was 28.5 min. The projection data were reconstructed using filtered back projection or an ordered subset expectation-maximization method. Images were filtered with a Butterworth filter (cutoff frequency 0.6 cycle/cm, order

of 10). Attenuation correction was performed using Chang's method ($\mu = 0.12$ /cm) and scatter correction was performed with a triple energy window.

Data analysis

We have described voxel-based analysis and VOI analysis separately and described each statistical method and thresholds in detail. First, an exploratory voxel-based study was conducted to identify areas with significant differences in grey matter (GM) and rCBF between the MCI-LB and MCI-AD groups; we focused on such areas when evaluating the diagnostic utility of visual inspection. Voxel-based analysis was performed using Statistical Parametric Mapping 12 (SPM12) software (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/), for comparison of the GM volume and rCBF between the MCI-LB and MCI-AD groups. Each SPECT image was coregistered to the corresponding MR image, and the MR image was then segmented into GM, white matter, and cerebrospinal fluid. The GM images were then spatially normalized to the template using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) technique [37], and normalized parameters were applied to the coregistered SPECT image. The SPECT image was then spatially normalized to Montreal Neurological Institute space. All images were smoothed using a 12-mm Gaussian filter. Next, SPM12 was used to perform a voxel-wise two-sample *t*-test comparing the GM or CBF images between the two groups. Significance was set at $p < 0.001$ (uncorrected) for comparison of GM volume or $p < 0.01$ (family wise error [FWE]-corrected) for comparison of rCBF and the voxel extent threshold was set at 300. Although the default setting for SPM12 was $p < 0.05$ (FWE-corrected), we set $p < 0.01$ (FWE-corrected) because we believed that it was possible to get a significant result by setting the strict threshold of p-value: $p < 0.01$ (FWE-corrected) in CBF analysis due to a large number of subjects in this study.

On the basis of the results of the voxel-based analysis, VOIs were defined in areas where significant differences were seen, and rCBF values for these VOIs were calculated for each subject. We performed

receiver operating characteristic (ROC) analysis to evaluate diagnostic performance in the MCI-AD and MCI-LB groups.

Regardless of the results of the exploratory analysis, we measured the hippocampal volume of each subject using our hippocampal VOI [38] because the hippocampal volume in AD patients is significantly smaller than that in DLB patients at the dementia stage [39]. A two-sample *t*-test was used to compare hippocampal volume between in the MCI-LB and MCI-AD groups and occipital rCBF between in the MCI-LB and MCI-AD groups.

Visual assessment for differentiation between MCI-LB and MCI-AD patients

The visual inspection focused on the occipital hypoperfusion cingulate island sign (CIS) [40, 41]. Surface maps and Z-scores for individual SPECT images were obtained using 3D-SSP software [42]. Then, transaxial sections of brain perfusion SPECT images, surface maps and Z-score images normalized by cerebellar counts [33] were visually assessed to diagnose MCI-LB or MCI-AD. The CIS was evaluated in the posterior or midcingulate gyrus rather than the relatively well-preserved surrounding areas [34, 43, 44].

The CIS was defined as positive in cases showing preserved mid and/or posterior cingulate along with decreased occipital CBF. Despite the island-like appearance of preserved mid and/or posterior cingulate gyrus CBF, cases without decreased occipital CBF were regarded as CIS negative.

On each SPECT image, occipital hypoperfusion and CIS were classified as positive or negative. On the basis of the visual inspection, MCI-LB was diagnosed if there was hypoperfusion in the occipital lobe, the CIS was present, or both. Diagnostic sensitivity, specificity and accuracy were calculated for each condition. Visual inspection was performed by two doctors: one is an expert neuroradiologist, who has 35 years of experience, and the other is a neurologist, who specializes in dementia practice with 20 years of experience separately and if there are discrepancies, they were resolved by discussion. Each doctor read original transaxial and sagittal SPECT images and Surface map and Z-score map demonstrated in 3D-SSP

software on the monitor without looking at the subject's clinical information nor other images (MRI and DAT images). The findings of occipital hypoperfusion and CIS were visually evaluated.

Results

During the period between January 2017 and December 2021, 2,721 subjects visited our outpatient clinic and underwent MRI, brain perfusion SPECT and, in some cases, DAT-SPECT. A flowchart of subject inclusion and exclusion was shown in Fig. 1. Of these 2,721 subjects, 913 were clinically diagnosed with MCI on the basis of the above-described criteria, 812 of whom were subsequently excluded. One PDD patient was diagnosed on the basis of the '1-year-rule' [45]. Finally, 101 subjects with MCI were investigated in this study. Sixty subjects with MCI were diagnosed as MCI-LB on the basis of the research criteria for the diagnosis of prodromal DLB [31], of whom four and fifty-six met the criteria for possible and probable DLB respectively, 41 subjects with MCI ware diagnosed as MCI-AD on the basis of the NIA-AA diagnostic guidelines [32].

All MCI subjects were planned to be tracked by the transition from MCI to dementia (probable DLB and probable AD) and performed by DAT scan imaging to differentiate between MCI-LB and MCI-AD. DAT-SPECT was carried out in 36 subjects with MCI due to rejection of imaging tests, physical problems and mental burden of patients and families, or financial problems. Twenty-seven subjects with MCI-LB were positive for DAT-SPECT. In this study, MIBG myocardial scintigraphy was not performed for MCI-LB subjects.

The characteristics of 101 subjects with MCI-LB and MCI-AD summarized in Table 1. There was no difference in age and MMSE score between the subjects with MCI-LB and MCI-AD. The clinical symptoms in subjects with MCI-LB and MCI-AD listed in Table 2. In subjects with MCI-AD, cognitive fluctuations, visual hallucinations and RBD were not appeared. Parkinsonism and visual/visuospatial

cognitive impairment were more common in the MCI-LB subjects than in the MCI-AD subjects. Our subjects with MCI-LB, who were almost matched to the subjects with MCI-LB subtype of prodromal DLB, were diagnosed as MCI-LB on the basis of the research criteria for the diagnosis of prodromal DLB.

With voxel-based analysis, there was no significant difference in GM volume including hippocampal volume or occipital volume between the MCI-LB and MCI-AD groups (threshold setting: $p < 0.001$, uncorrected), which also showed no occipital atrophy. In MCI-LB group, the bilateral occipital rCBF was significantly lower than that in MCI-AD group ($p < 0.01$, FWE-corrected) (Fig. 2, Table 3). There was no significant group difference of rCBF in the medial temporal lobe or cingulate cortices. With VOIs analysis, there were no significant hippocampal volume differences between in MCI-LB (5.79 ± 0.83 cm^3) and MCI-AD (6.06 ± 0.90 cm^3) by two-sample *t*-test ($p = 0.131$). In MCI-LB group, the occipital rCBF in MCI-LB group (mean: 0.850 ± 0.086) was significantly lower than that in MCI-AD group (mean: 0.977 ± 0.096) by two-sample *t*-test ($p < 0.05$).

The ROC curves for differentiating MCI-LB and MCI-AD on the basis of the occipital rCBF are shown in Fig. 3. A threshold of occipital rCBF 0.922 had a sensitivity of 86.7% and specificity of 70.7%, and the highest accuracy (area under the curve) of 85.9%.

Four patterns were distinguished through visual evaluation of the SPECT images: (a) occipital hypoperfusion (+) and CIS (+) (typical MCI-LB findings), (b) occipital hypoperfusion (+) and CIS (–), (c) occipital hypoperfusion (–) and CIS (+), and (d) occipital hypoperfusion (–) and CIS (–) (typical MCI-AD findings). The transaxial sections, surface maps and Z-scores obtained by 3D-SSP are shown in Fig. 4 for each pattern. Of the 101 patients, 43 were classified as pattern (a), 28 as pattern (b), 3 as pattern (c) and 27 as pattern (d).

As shown in Table 4, for differential diagnosis of MCI-LB and MCI-AD, the sensitivity, specificity, and diagnostic accuracy of occipital hypoperfusion were 100%, 73.2% and 89.1%, respectively; the respective values for the CIS were 63.3%, 80.5%, and 70.3%, and those for occipital hypoperfusion and

the CIS combined were 100%, 65.9%, and 86.1%. These results indicated that occipital hypoperfusion is useful for distinguishing between MCI-LB and MCI-AD.

Discussion

In this study, occipital hypoperfusion showed utility for predicting MCI-LB, which was differentiated from MCI-AD by visual inspection of brain perfusion SPECT images.

Previous studies differentiating between MCI-LB and MCI-AD using neuroimaging

Many studies of neuroimaging on differentiating between LBD and AD have been conducted in the MCI and dementia stage. Recently, several reports have been concerned with the differentiation between MCI-LB and MCI-AD. Brain FDG-PET was more useful than brain perfusion SPECT for differential diagnosis in the MCI stage [25]. The FDG-PET-derived CIS ratio is more valuable than the perfusion SPECT-derived one for differential diagnosis in patients with MCI [28]. However, the results have been still inconsistent. Massa et al. evaluated the CIS and glucose hypometabolism in the posterior cingulate gyrus, precuneus, and occipital lobe using FDG-PET and voxel-based analysis, and reported that the imaging findings were able to visually differentiate between MCI-LB and MCI-AD with high accuracy (76.8 ± 5.0%) [26]. Using FDG-PET, Kantarci et al. revealed that higher medial temporal metabolism and CIS ratios, and lower substantia nigra metabolism, could distinguish prodromal DLB from prodromal AD (CIS ratio: specificity, 90%; sensitivity, 59%; medial temporal to substantia nigra ratio: sensitivity, 94%; specificity 83%). FDG-PET is a potential biomarker for the prodromal stage of DLB [46]. Although FDG-PET imaging is superior for prognostic predictions of subjects with MCI, brain perfusion imaging is also useful [47]. The CIScore can discriminate DLB from AD at dementia stage~~,~~ but the CIScore is less useful for identifying MCI [48]. This may be due to the hypo-sensitivity of SPECT relative to FDG-PET especially

at the early stage of DLB patients. Also, the CIS may be found in the middle or posterior cingulate gyrus.

Diffuse atrophy, including of the insula, was previously demonstrated in DLB dementia patients but no brain atrophy was observed at the same site in prodromal DLB cases; the bilateral insula might be a key region in prodromal-stage DLB meriting voxel-based morphometry analysis using SPM8 plus DARTEL [49]. Comparison of prodromal DLB and prodromal AD cases using FreeSurfer indicated right anterior insula thinning and bilateral parietal lobe thinning, along with left parahippocampal gyri thinning in the latter and former groups, respectively [50]. Previous investigation was reported the thinning of the cortex in DLB was recognized at dementia stage. In this study, we believe that the cortex thinning and hippocampal atrophy was not yet recognized at early stage (i.e., MCI stage).

In another study, the rCBF in MCI-LB subjects was similar to that of those with DLB, but the rCBF in MCI-LB subjects was reduced in posterior parietal and occipital regions (although it was relatively well-conserved in the posterior cingulate gyrus, as revealed by arterial spin labelling [ASL] MRI) [51]. Finally, perfusion MRI using ASL revealed reduced rCBF in the right parietal and right inferior frontal lobes, as well as in the insular region, in a stable MCI group, whereas a group that had progressed from MCI-AD to AD showed decreased rCBF in the bilateral temporal parietal region [52].

The studies described above had relatively small sample sizes. Occipital hypoperfusion was revealed by brain perfusion SPECT and ASL imaging in subjects with MCI-LB, and the CIS (shown by FDG-PET) and atrophy in the medial temporal lobe, hippocampal and insula (revealed by MRI) were also reported. In our MCI-LB subjects, the decrease in occipital CBF shown by brain perfusion SPECT, but not the results regarding the CIS.

Differentiation between MCI-LB and MCI-AD on the basis of visual assessment of brain perfusion SPECT images

The sample size (n = 101) of this study was larger compared with previous studies. We observed

decreased occipital CBF in subjects with MCI-LB; the sensitivity of that analysis was 100%. The findings of occipital hypoperfusion at MCI-LB stage in the brain perfusion SPECT study were consistent with that at the dementia stage of LBD patients. At the MCI stage, only occipital CBF was significantly decreased in MCI-LB. As shown in Table 4, visual inspection of occipital CBF images showed 100% sensitivity and 89.1% accuracy for differentiating between MCI-LB and MCI-AD. In our MCI-LB group, voxel-based analysis clearly showed altered occipital CBF, but the CIS was not apparent. Considering the high diagnostic performance, we believed that it was plausible to carry out the differentiation of these pathologic conditions using brain perfusion SPECT.

In a brain FDG-PET study, glucose metabolism in the midcingulate gyrus, which corresponds to the CIS, was reported to be higher in DLB than AD patients [44]. The use of perfusion SPECT instead of FDG-PET in our study may explain the absence of the CIS at the MCI stage. Brain perfusion SPECT in a previous study revealed lower medial temporal lobe flow in AD compared with DLB patients at dementia stage [53], whereas we found no differences between these two groups. Even MRI failed to detect hippocampal atrophy in the MCI stage, such that it may be difficult to differentiate between MCI-AD and MCI-LB on the basis of that parameter. Visual evaluation of the subtle changes revealed by 3D-SSP surface maps is useful [42]. Therefore, we considered visual assessment of rCBF with reference to the cerebellar CBF to be important at the MCI stage (Fig. 4). This study has some important implications regarding the differential diagnosis of MCI-LB and MCI-AD. Although the importance of the CIS for the diagnosis of DLB has been emphasized previously, it appears that occipital hypoperfusion on brain perfusion SPECT may be more useful for distinguishing MCI-LB from MCI-AD. We believe that visual inspection of the brain perfusion SPECT images of patients in the early stages of dementia can help elucidate the pathology of MCI, thus facilitating early intervention and reducing the caregiver burden.

Limitations

There were some limitations to this study. First, we were only able to track a few subjects converting from MCI to dementia, and MCI was diagnosed in many cases on the basis of the MMSE score at the first visit. In this study, we focused on the research criteria for the diagnosis of prodromal DLB [31] which has not emphasized dementia conversion. We applied our MCI subjects to the research criteria for the diagnosis of prodromal DLB. MCI is a transitional state, it was necessary to discuss the conversion criteria of MCI to dementia. In particular, the conversion criteria of MCI were controversial. In this study, the criteria were initially set along the actual clinical scene and proceeded with the discussion. However, setting the conversion criteria of MCI was very difficult to get consensus in our research group alone. Also, in a few cases LBD was confirmed on the basis of the morphology of the striatum, specific binding ratio, and asymmetry index, as revealed by DAT imaging [35, 36, 54]. All of the brain perfusion SPECT images were visually evaluated for the CIS and occipital CBF reduction by a neuroradiologist and neurologist who were both proficient and experienced, and who reached a consensus through discussion. While reduced occipital CBF can be determined by both visual inspection and quantitatively measuring the CBF decline, CIS could only be determined by visual inspection due to the difficulty in quantitatively demonstrating apparent contrasts with the precuneus and surrounding regions in the middle and/or posterior cingulate CBF.

Conclusion

MCI-AD and MCI-LB could not be distinguished in the basis of findings such as hippocampal atrophy on MRI, although significantly decreased rCBF in the occipital lobe with brain perfusion SPECT was noted in MCI-LB compared with MCI-AD subjects. In the MCI stage, this latter finding on brain perfusion SPECT images could be an important imaging biomarker for differentiation between MCI-LB and MCI-AD. This study proved the utility of visual inspection of brain perfusion SPECT images for differentiating

MCI-LB and MCI-AD. The findings could aid early diagnosis and therapeutic intervention for patients exhibiting signs of dementia.

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Figure legends

Fig. 1. Flowchart of subject inclusion and exclusion.

Mild cognitive impairment (MCI) subjects (n = 101) were diagnosed as MCI-LB and MCI-AD according to each research criteria for diagnosis of prodromal dementia with Lewy bodies (DLB) and National Institute on Aging-Alzheimer's Association workgroups (NIA-AA) diagnostic guidelines.

Fig. 2. Hypoperfusion area of MCI-LB subjects compare to MCI-AD subjects.

Brain areas where relative cerebral blood flow (rCBF) in brain perfusion SPECT was significantly decreased in mild cognitive impairment with Lewy bodies (MCI-LB) compared with MCI due to AD (MCI-AD) subjects ($p < 0.01$, family wise error-corrected).

Fig. 3. Receiver operating characteristic (ROC) curves of occipital rCBF for differentiating MCI-LB and MCI-AD.

An rCBF of 0.922 had a sensitivity of 86.7% and specificity of 70.7%, and the highest accuracy (area under the curve) of 85.9%.

Fig. 4. Representative cases of occipital perfusion and CIS patterns.

Four patterns were distinguished through visual evaluation of the single photon emission computed tomography (SPECT) images: (a) occipital hypoperfusion (+) and CIS (+) (typical MCI-LB findings), (b) occipital hypoperfusion (+) and CIS (–), (c) occipital hypoperfusion (–) and CIS (+), and (d) occipital hypoperfusion (–) and CIS (–) (typical MCI-AD findings). Transaxial sections of brain perfusion SPECT images, surface maps and Z-score images [CBL; regional CBF normalized by cerebellar CBF] obtained using 3D-SSP software were shown. Each profile of subjects was pattern (a) 79 yo, Female, MMSE 25; (b)

79 yo, Male, MMSE 24; (c) 82 yo, Female, MMSE 26; and (d) 70 yo, Female, MMSE 25.

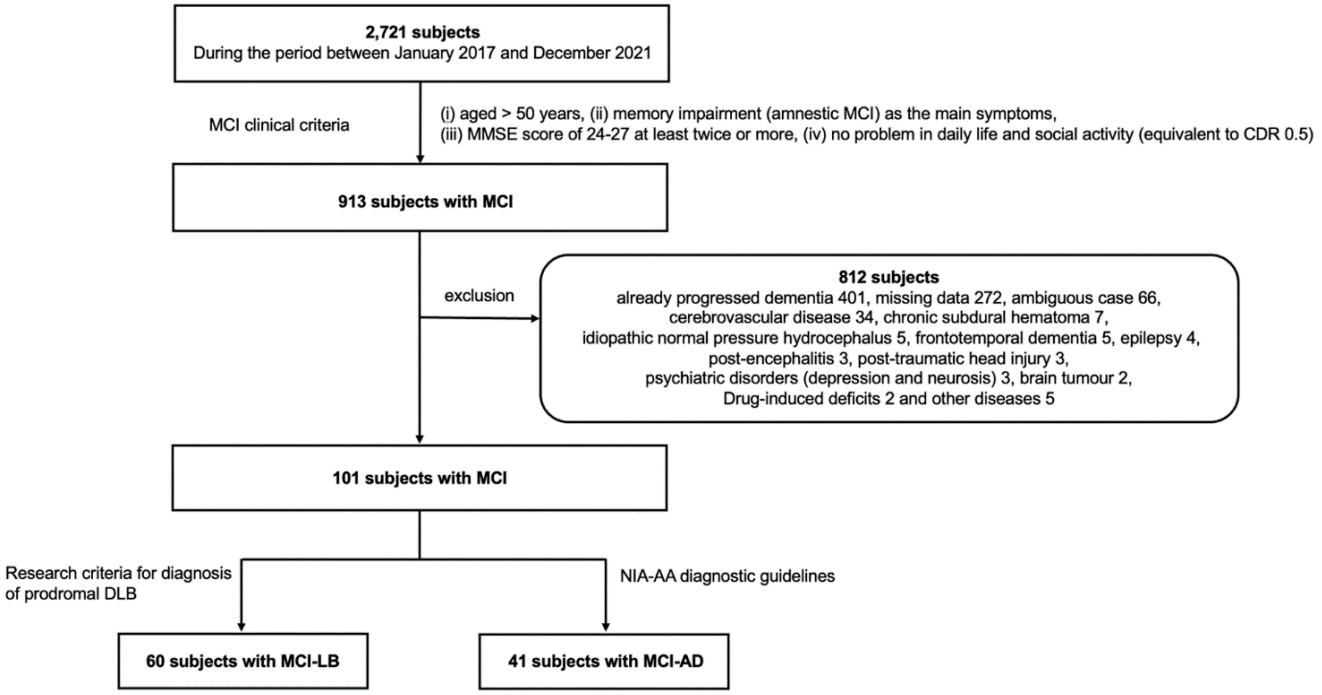

2,721 subjects
During the period between January 2017 and December 2021
MCI clinical criteria
(i) aged > 50 years, (ii) memory impairment (amnestic MCI) as the main symptoms,
(iii) MMSE score of 24-27 at least twice or more, (iv) no problem in daily life and social activity (equivalent to CDR 0.5)
913 subjects with MCI
exclusion
812 subjects
already progressed dementia 401, missing data 272, ambiguous case 66,
cerebrovascular disease 34, chronic subdural hematoma 7,
idiopathic normal pressure hydrocephalus 5, frontotemporal dementia 5, epilepsy 4,
post-encephalitis 3, post-traumatic head injury 3,
psychiatric disorders (depression and neurosis) 3, brain tumour 2,
Drug-induced deficits 2 and other diseases 5
101 subjects with MCI
Research criteria for diagnosis of prodromal DLB
NIA-AA diagnostic guidelines
60 subjects with MCI-LB
41 subjects with MCI-AD

Fig.1

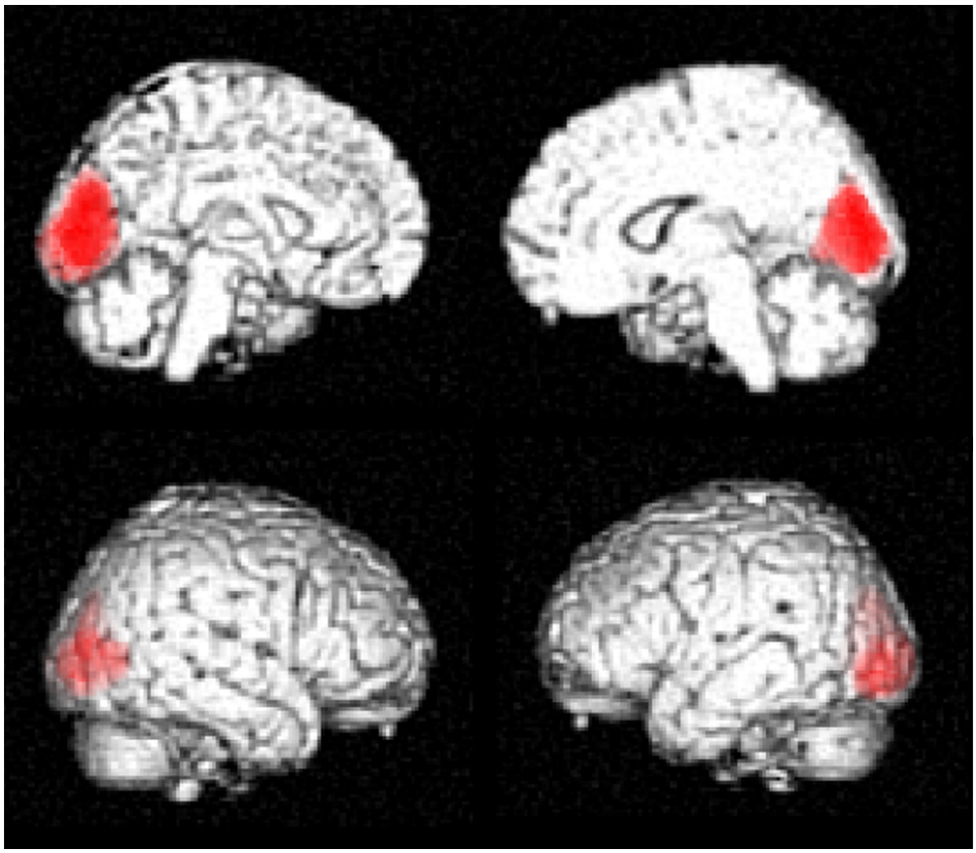
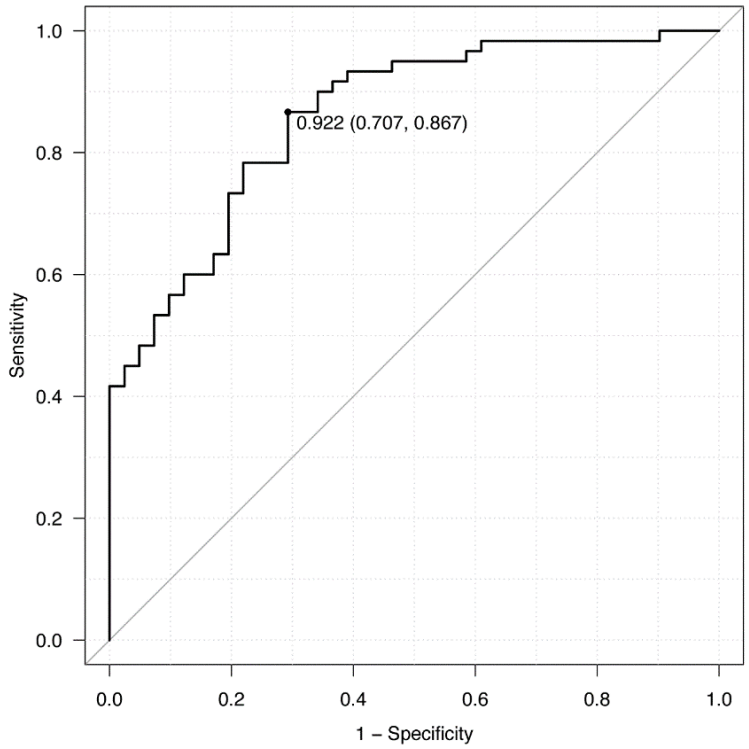


Fig.2


1.0
0.8
0.6
0.4
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Sensitivity
0.922 (0.707, 0.867)
0.0
0.2
0.4
0.6
0.8
1.0
1 – Specificity

Fig.3

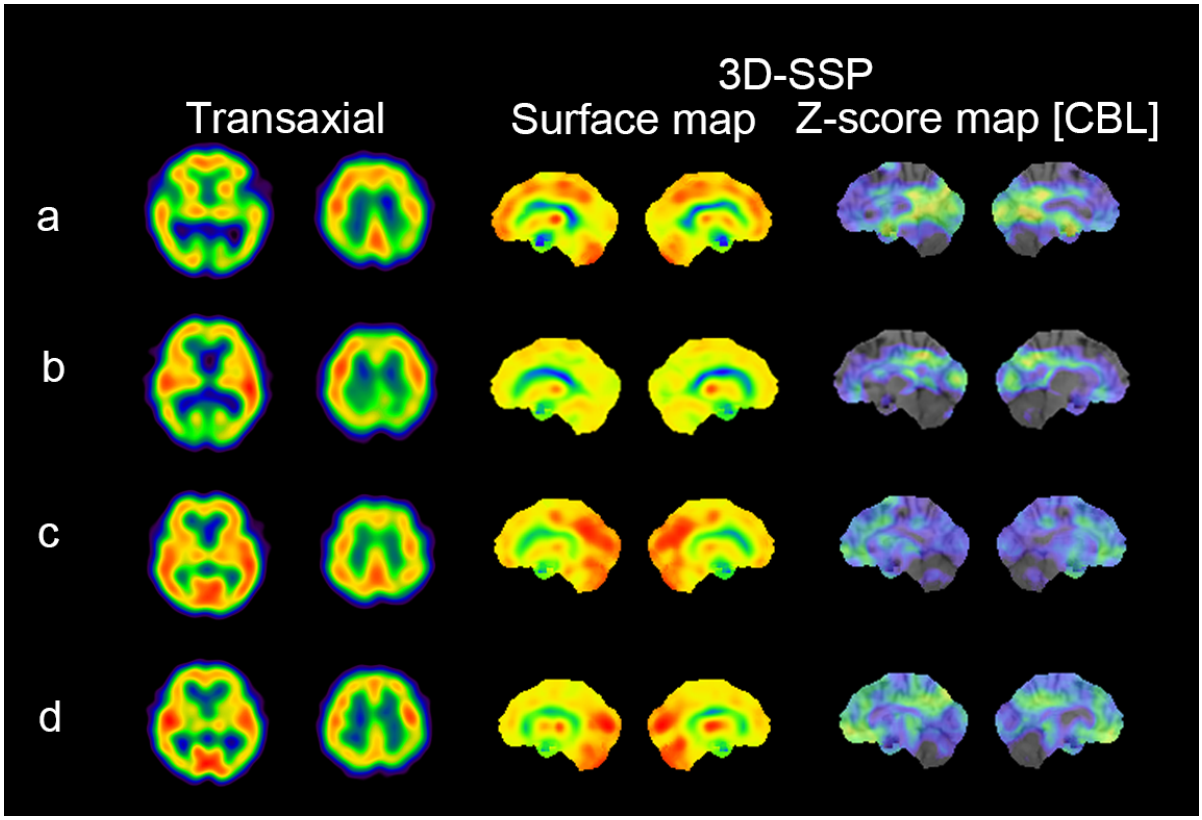
3D-SSP
Transaxial
Surface map
Z-score map [CBL]
a
b
c
d

Fig.4

Table 1. Characteristics of 101 MCI subjects

	MCI (n = 101)	MCI-LB (n = 60)	MCI-AD (n = 41)
Female / male	75 / 26	43 / 17	32 / 9
Mean age, years (mean: F 77.1 yo, M 76.0 yo)	76.9 ± 6.7	76.8 ± 7.3	76.9 ± 5.8
Age range	57 – 91	57 – 91	62 – 87
Mean MMSE score at first visit (mean: F 25.2, M 25.1)	25.2 ± 1.1	25.3 ± 1.1	25.0 ± 1.0
MMSE range	24 – 27	24 – 27	24 – 27

MCI: mild cognitive impairment, n: number of subjects, F: female, M: male, MMSE: Mini-Mental State Examination, LB: Lewy bodies, AD: Alzheimer's disease, MCI-LB: MCI due to LBD, MCI-AD: MCI due to AD; yo: years old

Table 2. Clinical symptoms in subjects with MCI-LB and MCI-AD

	MCI (n = 101)	MCI-LB (n = 60)	MCI-AD (n = 41)
Cognitive fluctuations	10	10	0
Visual hallucinations	10	10	0
Parkinsonism	54	43	11
RBD	6	6	0
Depression	3	2	1
Visual/visuospatial cognitive impairment	60	42	18

MCI: mild cognitive impairment, n: number of subjects, MCI-LB: mild cognitive impairment with Lewy bodies, MCI-AD: mild cognitive impairment due to Alzheimer's disease, RBD: rapid eye movement sleep behavior disorder

Table 3. Hypoperfusion regions in subjects with MCI-LB compared with those in subjects with MCI-AD based on SPECT images

Comparison	Brain region	Brodmann area	Talairach coordinates				Cluster dimension	t value
			Side	x	y	z		
CBF	Visual association cortex (V2)	18	R	2	−79	15	7943	7.44
	Visual association cortex (V2)	18	L	−10	−90	5		7.14
	Visual association cortex (V2)	18	L	−30	−82	−2		6.48

Family Wise Error (FWE) corrected at $p < 0.01$.

CBF: cerebral blood flow, MCI: mild cognitive impairment, MCI-LB: MCI with Lewy bodies, MCI-AD: MCI due to Alzheimer's disease, SPECT: single photon emission computed tomography

Table 4. Statistics for Differential Diagnosis between MCI-LB and MCI-AD by visual assessment of perfusion SPECT images

Perfusion Image	Sensitivity (%)	Specificity (%)	Accuracy (%)
(a) Occipital CBF hypoperfusion	100	73.2	89.1
(b) positive CIS	83.0	80.5	70.3
(a) or (b)	100	85.9	86.1

MCI: mild cognitive impairment, LB: Lewy bodies, AD: Alzheimer's disease, MCI-LB: MCI with LB, MCI-AD: MCI due to AD, CBF: cerebral blood flow, CIS: cingulate island sign, SPECT: single photon emission computed tomography

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