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Early differential diagnosis between Alzheimer's disease and dementia with Lewy bodies: Comparison between ^{18}F-FDG PET and ^{123}I-IMP SPECT

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ABSTRACT

Both ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) and ^{123}I-iodoamphetamine (IMP) single-photon emission computed tomography (SPECT) have been used for the differential diagnosis of Alzheimer's disease (AD) and dementia with Lewy bodies (DLB). Less information is available, however, regarding the differential diagnosis of mild cognitive impairment (MCI) due to AD and MCI due to DLB. We examined nine AD patients (AD group), nine DLB patients (DLB group), eight MCI due to AD patients (MCI-AD group), and nine MCI due to DLB patients (MCI-DLB group) with FDG PET and IMP SPECT using a well-characterized normal database and a stereotactic extraction estimation method. In the AD and DLB groups, receiver operating characteristic (ROC) analysis in the occipital regions showed significant accuracy of both FDG PET and IMP SPECT for the differential diagnosis. In the MCI-AD and MCI-DLB groups, ROC analysis showed significant accuracy of only FDG PET for the differential diagnosis. Both FDG PET and IMP SPECT would be useful for the differential diagnosis between AD and DLB. For the differential diagnosis of MCI-AD versus MCI-DLB, FDG PET would be more useful than IMP SPECT.

1. Introduction

Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia after Alzheimer's disease (AD). DLB is clinically characterized by progressive dementia, which is frequently accompanied by parkinsonism and visual hallucinations (McKeith et al., 2005). In addition, DLB patients often exhibit various clinical symptoms, including autonomic dysfunction, rapid eye movement sleep behavior disorder (RBD), depression, delusions, and hallucinations in other modalities, all of which are included in the clinical criteria of the Third Consortium on DLB (CDLB) (McKeith et al., 2005). Because some of the clinical symptoms in DLB patients antedate the onset of dementia by years or even decades, the existence of these symptoms suggests an early phase or a prodromal phase of DLB (Boeve, 2010; Fujishiro et al., 2010; Ferman et al., 2011; Chiba et al., 2012; Fujishiro et al., 2013a, 2013b; Donaghy et al., 2014). Early differential diagnosis of DLB from AD is important because several treatments with disease-modifying or neuroprotective potential in DLB are under investigation.

Both cerebral hypometabolism (CHM) as measured by ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) and cerebral hypoperfusion (CHP) as measured by ^{123}I-iodoamphetamine (IMP) single-photon emission computed tomography (SPECT) have been used to differentiate AD from DLB (Ishii et al., 1998; Higuchi et al., 2000; Minoshima et al., 2001; Mosconi et al., 2008; Lim et al., 2009; Inui et al., 2014). In particular, CHM and CHP in the occipital lobe support the clinical differential diagnosis of DLB (Davison and O'Brien, 2014). However, there is little information regarding differential diagnosis by FDG PET and IMP

Abbreviations: AD, Alzheimer's disease; DLB, dementia with Lewy bodies; MCI, mild cognitive impairment; ^{18}F-FDG PET, ^{18}F-fluorodeoxyglucose positron emission tomography; ^{123}I-IMP SPECT, ^{123}I-iodoamphetamine single-photon emission computed tomography; CHM, cerebral hypometabolism; CHP, cerebral hypoperfusion; RBD, rapid eye movement sleep behavior disorder; MMSE, Mini-Mental State Examination; MTA, medial temporal lobe atrophy; PVH, periventricular hyperintensity; DSWMH, deep and subcortical white matter hyperintensity; ROC, receiver operating characteristic; AUC, area under the curve

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SPECT between mild cognitive impairment (MCI) due to AD and MCI due to DLB. Moreover, because IMP SPECT is more cost-effective and more widely used than FDG-PET in many countries, comparison of FDG PET and IMP SPECT for the differential diagnosis between AD and DLB or between MCI due to AD and MCI due to DLB would be valuable.

In the present study, we investigated patients with AD and DLB or patients with MCI due to AD and MCI due to DLB using FDG PET and IMP SPECT in order to assess CHM and CHP, respectively. We statistically analyzed regional CHM and CHP compared with each of the normal databases that we constructed, and then compared CHM and CHP between FDG PET and IMP SPECT, focusing on the occipital regions.

2. Methods

2.1. Subjects

Thirty-five patients who came to the memory clinic at Juntendo Tokyo Koto Geriatric Medical Center from March to December in 2012 were examined. They included nine AD patients (AD group), nine DLB patients (DLB group), eight MCI due to AD patients (MCI-AD group), and nine MCI due to DLB patients (MCI-DLB group). Table 1 presents the demographic characteristics of the patients and their scores on the Mini-Mental State Examination (MMSE), the Wechsler Adult Intelligence Scale third edition (WAIS-III), Wechsler Memory Scale-Revised (WMS-R). AD and DLB groups met the criteria of major neurocognitive disorder (NCD) defined in the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013), and their MMSE scores were equal to or less than 23. The MCI-AD and MCI-DLB groups met the criteria of mild NCD in DSM-5, and their MMSE scores were above 23.

A clinical diagnosis of DLB was made according to the CDLB clinical criteria (McKeith et al., 2005). In the DLB group, seven out of nine patients were diagnosed with probable DLB and the others were diagnosed with possible DLB. They met the criteria of probable or possible major NCD with Lewy bodies (NCDLB) in DSM-5.

In the MCI-DLB group all patients exhibited at least one feature of parkinsonism, visual hallucination and/or RBD, which are included in core features and suggestive features in the CDLB clinical criteria. They met the criteria of mild NCDLB in DSM-5. The prevalence of parkinsonism, visual hallucinations and RBD was investigated for both the DLB and MCI-DLB groups.

A clinical diagnosis of AD was made according to the criteria of the National Institute on Aging and the Alzheimer's Association workgroup (McKhann et al., 2011). In the AD group, all AD patients were diagnosed with probable AD, meeting the criteria of NCD due to AD (NCDAD) in DSM-5. In the MCI-AD group all patients exhibited disturbance of learning and memory, meeting the criteria of mild NCDAD in DSM-5. In order to rule out potential DLB, the AD and AD-MCI groups were followed for 3 years. Consequently, the AD group was confirmed not to convert to any other type of dementia including DLB within 3 years. The MCI-AD group was confirmed to convert to probable AD and not to convert to any other type of dementia including DLB within 3 years.

2.2. MRI procedure

Head magnetic resonance imaging (MRI) was performed for all four groups using a 1.5 T scanner (MAGNETOM Symphony; Siemens, Munich, Germany). On the MRI, brain atrophy was evaluated using the Scheltens medial temporal lobe atrophy (MTA) scale of 0–4 (Scheltens et al., 1992), and periventricular hyperintensity (PVH) and deep and subcortical white matter hyperintensity (DSWMH) were evaluated using the Fazekas scale 0–3 based on T2-weighted MRI examination (Fazekas et al., 1991). No patients scored equal to or more than 3 on the Fazekas scale.

Table 1
Demographics, MMSE score, WAIS-III scores, WMS-R scores, clinical profiles, and neuroimaging findings in the four groups.

Group	AD $N=9$	DLB $N=9$	MCI-AD $N=8$	MCI-DLB $N=9$
Mean age	72.6 ± 8.5	76.3 ± 8.5	71.6 ± 5.7	74.6 ± 5.6
Age at onset	70.1 ± 9.4	70.3 ± 4.0	69.6 ± 6.3	72.7 ± 5.4
Sex (M/F)	4/5	6/3	2/6	6/3
MMSE score	19.3 ± 5.5	17.6 ± 4.0	26.3 ± 2.3	25.3 ± 1.0
WAIS-III	$N=7$	$N=4$	$N=8$	$N=8$
Full scale IQ	95.6 ± 42.9	84.0 ± 44.8	96.6 ± 15.6	98.1 ± 34.4
Verbal IQ	99.3 ± 8.8	96.0 ± 4.7	102 ± 13.8	104.4 ± 11.3
Performance IQ	92.3 ± 9.4	74.0 ± 18.0	89.9 ± 15.7	90.3 ± 11.1
WMS-R	$N=9$	$N=4$	$N=8$	$N=8$
General memory	74.1 ± 23.0	78.3 ± 15.4	76.5 ± 9.7	84.8 ± 10.7
Verbal memory	79.6 ± 21.3	83.3 ± 13.9	80.9 ± 7.6*	89.4 ± 10.2
Visual memory	70.9 ± 20.5	73.5 ± 16.0	75.5 ± 14.6	80.6 ± 14.4
Attention/ concentration	100.6 ± 21.6	91.0 ± 9.3	107.4 ± 14.5	98.4 ± 9.8
Delayed recall	65.8 ± 18.9	75.8 ± 19.8	66.5 ± 15.2*	81.9 ± 10.4
Clinical profiles				
Visual hallucination	0%, 0/9	66.7%, 6/9	0%, 0/8	55.6%, 5/9
Parkinsonism	0%, 0/9	88.9%, 8/9	0%, 0/8	88.9%, 8/9
RBD	0%, 0/9	88.9%, 8/9	0%, 0/8	77.8%, 7/9
MRI findings				
Left MTA	1.0 [0.5, 1.5]	1.0 [0.0, 1.0]	0.0 [0.0, 1.8]	0.0 [0.0, 1.0]
Right MTA	1.0 [0.5, 1.5]	1.0 [0.0, 1.0]	0.5 [0.0, 1.0]	0.0 [0.0, 1.0]
PVH	1.0 [0.0, 1.0]	1.0 [1.0, 2.0]	0.0 [0.0, 0.8]	0.0 [0.0, 1.0]
DSWMH	1.0 [0.5, 1.5]	1.0 [0.0, 1.5]	1.0 [0.0, 1.0]	0.0 [0.0, 1.5]

The demographic data, psychological data, FDG PET and AMP SPECT findings are shown as mean ± standard deviation. MRI findings are shown as median [25%, 75%]. MTA, medial temporal atrophy; PVH, perivascular hyperintensity; DSWMH, deep subcortical white matter hyperintensity; RBD, rapid eye movement sleep behavior disorder.

* Significant difference compared with the MCI-DLB group.

2.3. Statistical analyses

All statistical analyses were performed with SPSS 20.0 and EZR (Saitama Medical Center, Jichi Medical University; http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/manual.html; Kanda, 2013), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

For age, analysis of varance was applied among the four groups. For variables with a normal distribution (age, MMSE scores, WAIS-III scores, and WMS-R scores), Student's *t*-tests were applied for comparisons between the AD and DLB groups, and between the MCI-AD and MCI-DLB groups. Additionally, for the MMSE score, Student's *t*-tests were applied for comparisons between the AD and MCI-AD groups, and between the DLB and MCI-DLB groups. Because brain MRI findings were not normally distributed, Mann–Whitney tests were used to differentiate between the AD and DLB groups, and between the MCI-AD and MCI-DLB groups. Statistical significance was set at $p < 0.05$. This study was approved by the Ethics Committee of Juntendo Tokyo Koto Geriatric Medical Center. Written informed consent was obtained from all patients or their caregivers.