Objective: Rapid eye movement (REM) sleep behavior disorder (RBD) is commonly associated with Lewy body disease, narcolepsy, or depression. In contrast, the relationship between REM sleep without atonia (RWA), which is a hallmark of RBD on polysomnography, and clinical characteristics remains unclear. The purpose of this study is to investigate the clinical features of psychiatric patients exhibiting RWA and its relevance to Lewy body disease.

Methods: Of 55 consecutive patients who underwent polysomnography at the psychiatric ward, 25 patients with sleep apnea syndrome were excluded, and 12 patients exhibiting RWA were identified. The clinical profiles were compared between the groups with and without RWA.

Results: The mean age and the frequency of neurocognitive disorders were significantly higher in 12 patients with RWA than in 18 without. Only five of the 12 patients exhibiting RWA had episodes of dream-enactment behavior, and fulfilled the clinical criteria for RBD. Two young patients were diagnosed with narcolepsy, while the other middle-aged and older patients fulfilled the clinical criteria for Parkinson’s disease (n=1), dementia with Lewy bodies (n=4), idiopathic RBD (n=2), and major depressive disorder (MDD) (n=3). The patients with MDD exhibited constipation and/or olfactory dysfunction. Moreover, neuroimaging examinations in the patients with MDD revealed isolated occipital hypoperfusion in three patients and mild dopamine transporter deficit in one patient.

Conclusions: Rapid eye movement sleep without atonia itself may be associated with specific clinical profiles, even when dream-enactment behavior is absent. Continued follow-up of the patients with MDD exhibiting RWA is warranted to determine if they represent the prodromal Parkinson’s disease/dementia with Lewy bodies. Copyright © 2015 John Wiley & Sons, Ltd.

Key words: Parkinson’s disease; Dementia with Lewy bodies; depression; dopamine transporter; constipation; REM sleep behavior disorder

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Introduction

Lewy body disease (LBD), including Parkinson’s disease (PD) and dementia with Lewy bodies (DLB), is defined pathologically as degeneration in the central, peripheral, and autonomic nervous system associated with Lewy bodies (Halliday et al., 2010; Hyman et al., 2012). The common pathological basis suggests that PD and DLB share common prodromal symptoms with LBD, allowing us to use a common strategy for identifying individuals with an underlying pathophysiology of LBD (Fujishiro et al., 2015). Dysautonomia, olfactory dysfunction, rapid eye movement (REM) sleep behavior disorder (RBD), and psychiatric symptoms antedate the development of the full clinical syndrome by years or even decades in patients with PD/DLB (Postuma et al., 2009; Chiba et al., 2012; Boeve, 2010; Iranzo et al., 2013). The prodromal psychiatric symptoms include depression, anxiety, and hypochondrias, raising the possibility that some
psychiatric patients may exhibit prodromal state of PD/DLB (Alonso et al., 2009; Leentjens et al., 2003; Weisskopf et al., 2003; Onofrj et al., 2010; Fujishiro et al., 2015).

REM sleep behavior disorder is a parasomnia characterized by repeated episodes of dream-enactment behavior, and is commonly associated with neurodegenerative disease, narcolepsy, or depression (Olson et al., 2000; Gagnon et al., 2006; Ju et al., 2011; Lam et al., 2010; Teman et al., 2009; Frauscher et al., 2014). These clinical conditions are defined as secondary RBD. In contrast, this condition is classified as idiopathic RBD when it occurs in the absence of any other known conditions. Considering the profoundly high risk of neurodegenerative disease associated with idiopathic RBD in older people, RBD is mainly described in association with neurodegenerative disease (Boeve, 2013; Fujishiro et al., 2015). REM sleep without atonia (RWA) is the polysomnographic hallmark of RBD in which the physiological atonia during REM sleep is absent or greatly diminished. The clinical diagnosis of RBD requires the presence of RWA using polysomnography (PSG), although there is no description regarding the quantitative character of RWA in the American Academy of Sleep Medicine (AASM) Manual (2007). Recent clinicopathological studies confirmed that RWA is closely associated with α-synucleinopathy, especially Lewy body pathology, in a large number of patients with episodes of dream-enactment behavior (Boeve et al., 2013). When considering the association between RBD and neurodegenerative disorders in the middle-aged and older patients, the concept of subclinical RBD is attracting attention for early detection of RBD. Schenck and Mahowald (2008) suggested that the criteria of subclinical RBD should include PSG abnormalities alone or with nonclinical behaviors in REM sleep such as limb twitching and jerking, and simple behavior. Moreover, some recent studies revealed the cutoff values for RWA, establishing a clear definition of RBD accompanying abnormal dream-enactment behavior (Montplaisir et al., 2010; Frauscher et al., 2013; Sasai-Sakuma et al., 2014). Eisensehr et al. (2003) demonstrated the continuum of reduced striatal dopamine transporters among controls, subclinical RBD, and clinically manifest RBD. A recent study reported that substantia nigra hyperechogenicity was present in four of 14 subjects with subclinical RBD, and one subject developed dream-enactment behaviour during observation period (Stefani et al., 2015). These facts suggest that the presence of RWA as an incidental finding may lead us to suspect the pathophysiology of neurodegeneration, even when a clinical history of dream-enactment behaviour is absent.

In the present study, we reviewed the clinical profiles of 12 patients exhibiting RWA at a psychiatric ward; only five patients had a clinical history of dream-enactment behaviour, and the remaining seven patients had RWA as an incidental finding. The clinical profiles of the 12 patients were consistent with the characteristics of patients with RBD. In this series, the presence of RWA in middle-aged and older psychiatric patients may be indicative of the underlying pathophysiology of LBD, even when dream-enactment behavior is absent. The purpose of this study was to investigate the clinical features of middle-aged and older psychiatric patients exhibiting RWA and the relevance of RWA to LBD.

Methods

Subjects and clinical evaluation

We retrospectively reviewed the clinical profiles of all consecutive 55 patients who underwent PSG from April 2013 to December 2014 at our psychiatric ward at Nagoya University Hospital. The present study was approved by the Ethics Committee of the Nagoya University Graduate School of Medicine. Twenty four patients had sleep apnea (Apnea–Hypopnea Index > 5/h) based on PSG reports, and one patient received effective treatment with continuous positive airway pressure therapy. These patients with sleep apnea were excluded from further analysis. Finally, 18 men and 12 women with a mean age of 43 ± 22 (range: 14–81) years were included in this study. The primary reasons for polysomnographic workup were as follows: suspected sleep-related breathing disorders (n = 3), suspected sleep-related movement disorder (n = 8), suspected excessive daytime sleepiness (n = 8), insomnia (n = 7), and circadian rhythm disorder (n = 4). For each patient, the clinical diagnosis was made in a consensus conference that included the Japanese Society of Sleep Research specialists and the Japanese Society of Psychiatry and Neurology specialists. Clinical diagnoses were made according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013), the Third Consortium on DLB clinical criteria for the clinical diagnosis of DLB (McKeith et al., 2005), the United Kingdom’s Parkinson’s Disease Society’s Brain Bank criteria for the clinical diagnosis of idiopathic PD (Hughes et al., 1992), or the criteria from the 2nd edition of the International...
Classification of Sleep Disorder (2005) for the clinical diagnosis of RBD. The presence or absence of sleep-related behavior that has been potentially injurious and/or dream-enactment behavior was obtained from all the patients exhibiting RWA and his or her bed partner. The mini-mental state examination was used to assess cognitive ability. The motor subset of the Unified Parkinson’s Disease Rating Scale was used as an index of extrapyramidal motor signs (Fahn and Elton, 1987). Parkinsonism was considered to be present if any patient had a score of two or greater in at least two of the following cardinal features of Parkinson’s disease: rigidity, bradykinesia, rest tremor, and postural instability.

Sleep analysis

All the patients underwent standard PSG (Embla N7000; Natus, USA). Polysomnographic recording and scoring were performed according to the AASM Manual. All PSG studies involved continuous video synchronized to standard PSG monitoring using the following montage: electroencephalogram (EEG), two electro-oculograms, mentalis and bilateral anterior tibialis electromyograms (EMGs), electrocardiogram, nasal/oral airflow, chest and abdominal wall motion using respiratory inductance plethysmography, an oximetry sensor for percutaneous oxygen saturation, snore microphone, and position sensor.

The amount of REM sleep and the proportion of RWA from the submentalis and/or anterior tibialis EMG were visually checked for each patient. The tonic and phasic components of RWA were separately evaluated. Tonic EMG activity was scored only in the mentalis muscle using full 30-s epochs of REM sleep. This activity was scored when the increased sustained EMG activity was present in >50% of the total 30-s epoch duration with an amplitude of at least twice the background EMG muscle tone or >10 μV. Phasic EMG activity was scored in 3-s mini-epochs in the mentalis muscle and anterior tibialis muscles. Artifacts in EMG channels were carefully examined and excluded from the analysis. EMG activity in the muscle that occurred either before or during arousals related to any type of respiratory events was excluded from the analysis. No EEG epileptiform activity during sleep was confirmed. When the presence of RWA was found, increased EMG activity was manually quantified in the mentalis muscle and anterior tibialis muscles as the percentages of RWA during REM sleep. These results were compared with the optimal cutoff values of correct diagnosis of RBD by the Sleep Innsbruck Barcelona group (Frauscher et al., 2012).

Evaluation of regional cerebral blood flow

The $^{99m}$Tc-ethyl cysteinate dimer brain perfusion single-photon emission computed tomography (SPECT) was performed to investigate regional cerebral blood flow (rCBF) in a subset of patients. Each subject was placed in the supine position on the scanning bed with eyes closed during injection and during the subsequent scanning period in a quiet examination room. The $^{99m}$Tc-ethyl cysteinate dimer tracer was injected intravenously at a maximum dose of 600 MBq. The images were acquired over 5 min after injection on a multiheaded gamma camera (Symbia T; SIEMENS, Tokyo, Japan) with a low energy high-resolution collimator, and calibrated using the 140 keV photopeak and a +10.5% energy window. The acquisition parameters were as follows: 3.3 mm pixel size, $\times 1.45$ zoom factor, $128 \times 128$ matrix, and 30 min for spent time. A Butterworth filter (Order 8, cutoff 0.4 cycles/cm) was used to filter the projections. The SPECT images were prepared using attenuation correction according to Chang’s method.

An easy Z-score imaging system (eZIS) as the statistical image analysis method was used to investigate the changes in relative regional Tc-99m ECD uptake (Matsuda et al., 2004, 2007a). A database of normal volunteers of various age groups has been built in eZIS and is widely used in Japan. The utility of eZIS for discrimination of early-stage Alzheimer's disease from controls is confirmed by using different acquisition parameters for the four cameras in a multicenter study (Matsuda et al., 2007b). Each SPECT image of the subjects after anatomical standardization was compared with the mean and SD of the SPECT images of the age-matched normal controls already incorporated in the eZIS program as a normal database using voxel-by-voxel Z-score analysis after voxel normalization to global mean values: $Z$-score = (control mean – individual value)/control SD. A positive $Z$-score means lower rCBF of a patient than that of the control database. eZIS images with the lower threshold of a $Z$-score map of 2 were used to evaluate rCBF.

Evaluation of cardiac sympathetic nervous activity

Some patients underwent cardiac $^{123}$I-metaiodobenzylguanidine (MIBG) scintigraphy to examine the presence of underlying LBD (Miyamoto et al., 2008).
123I-MIBG (111 mBq) was injected intravenously. Static images were acquired using a scintillation camera (Symbia S; SIEMENS, Tokyo, Japan) equipped with low-energy to medium-energy general purpose (LMEGP), parallel-hole collimators. A 5-min static acquisition was made in the anterior view at 15 min (early) and at 3 h (delayed) after the injection of 123I-MIBG. Energy discrimination was centered on 159 keV with a 7.5% window. On each anterior planar 123I-MIBG image, regions of interest were manually placed on the whole heart and the mediastinum of the front image. The ratio of the 123I-MIBG uptake in the region of interest of the heart to that in the mediastinum (H/M ratio) was calculated. The H/M ratios from early and delayed images were measured.

Evaluation of nigrostriatal dopamine innervation

Some patients underwent 123I-N-fluoropropyl-2β-carboxymethoxy-3β-(4-iodophenyl)nortropane (123I-FP-CIT) SPECT imaging for the dopamine transporter (DAT) to allow differentiation between normality and neurodegenerative causes using presynaptic imaging. Each patient was intravenously injected with [123I]-FP-CIT (185 MBq). The images were acquired 3–4 h after injection on a multiheaded gamma camera (Symbia T; SIEMENS, Tokyo, Japan) with a low-energy to medium-energy general purpose collimator, and calibrated using the 159 keV photopeak and a +10% energy window. The acquisition parameters were as follows: 14 cm radius of rotation, 128 × 128 matrix, 4° view angle, and 28 min for spent time. Subsequently, reconstruction was performed using Flash 3D software, with postfiltering that employed the Gaussian filter. The specific binding ratio was calculated as the quantitative evaluation using DaTview analysis. This method consisted of collecting the whole radioactivity from the striatum of each hemisphere, and estimating the background radioactivity from the whole brain minus that from the striatum (Tossici-Bolt et al., 2006).

Statistical analysis

Data were analyzed with SIGMAPLOT 11.0 (Systat Software, Inc., Point Richmond, CA, USA), and the significance level was set at p < 0.05. The patients with and without RWA on PSG were compared with respect to the following variables: age, sex ratios, sleep questionnaire scores, frequency of each clinical diagnosis, the proportion of patients taking each drug, and polysomnographic findings. The Student’s t-test or the Mann–Whitney sum rank test was performed as appropriate for age, sleep questionnaire scores, and polysomnographic findings. The Fisher’s exact test or the χ² test was performed as appropriate for sex ratios, frequency of each clinical diagnosis, and the proportion of patients taking each drug.

Results

Clinical diagnose of patients exhibiting RWA on PSG

We identified 12 patients exhibiting RWA. Two young patients (aged 14 and 15) fulfilled the clinical criteria for narcolepsy. The other middle-aged and older psychiatric patients fulfilled the clinical criteria for probable DLB (n = 4), PD (n = 1), idiopathic RBD (n = 2), and major depressive disorder (MDD) (n = 3) (Table 1). In this series, only one patient exhibiting RWA first visited our hospital with a chief complaint of dream-enactment behavior without clinical psychiatric history, but the other middle-aged and older patients with RWA had a clinical history of psychiatric illnesses, mainly MDD (70%) (Table 1). The clinical history of dream-enactment behaviour was obtained as one of prodromal PD/DLB symptoms instead of a chief complaint (Table 2). The disease durations of these psychiatric illnesses until PSG recording approximately ranged from approximately 2 months to 30 years. In contrast, none of the 18 patients without RWA fulfilled the clinical criteria for PD, DLB, or idiopathic RBD. Only one patient had episodes of dream-enacting behaviors, but RWA was not observed in his PSG recording. This may be a result of the short period of REM sleep (15 min) during his overnight examination.

Only five of 12 patients exhibiting RWA on PSG had a clinical history of dream-enacting behavior and fulfilled the clinical criteria for RBD. The movement of extremities during REM sleep was observed in the patients on time-synchronized video. In contrast, the remaining seven patients exhibited no episode of dream-enactment behavior but nevertheless exhibited a small amount of RWA, which is consistent with subclinical RBD. The movement of extremities during REM sleep was not observed in the patients on time-synchronized video. A quantification of muscle activity was performed to differentiate between RBD and non-RBD according to previous reports (Frauscher et al., 2012; Sasai-Sakuma et al., 2014). The percentages of each type of EMG activities during REM sleep are shown in Figure 1. The optimal cutoff values of muscle activities for a diagnosis of RBD are also shown.
Clinical pro-
files of three patients with major depressive disorder and subclinical RBD. Although three MDD patients with subclinical RBD were suspected of having LBD based on the presence of cognitive changes and prodromal LBD symptoms (Chiba et al., 2012; Fujishiro et al., 2013a, 2015), they failed to meet the clinical criteria for PD/DLB. The magnetic resonance imaging findings of the brains of the patients with MDD were unremarkable, but brain perfusion SPECT revealed mild decreases in rCBF extending from the bilateral parietal cortex to occipital cortex, which is the preferentially affected region in the patients with full DLB syndrome (Waragai et al., 2008). The other clinical findings were summarized in Table 1. In two patients with MDD, DAT scan was not detected (Nakajima et al., 2012). [123I]-FP-CIT SPECT revealed mild dopamine transporter deficits in Patient 8, which is similar to those of a patient with probable DLB and a patient with idiopathic RBD. In contrast, Patient 10 exhibited normal DAT binding. The three patients with MDD partially shared common prodromal symptoms and radiological findings with PD/DLB (Tables 1 and 2). As for primary psychiatric diagnoses, the proportion of neurocognitive disorders was significantly higher in the patients with RWA than in those without (Table 3). However, the differences in sex ratio, sleep questionnaire scores, or the prevalence of psychiatric symptoms were not remarkable between the patients with and without RWA on PSG.

Table 1: Demographics and clinical profile in middle-aged and older patients with REM sleep without atonia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>MMSE</th>
<th>UPDRS</th>
<th>Final clinical feature (time from first visit to PSG recording)</th>
<th>Main psychiatric feature (symptomatic duration)</th>
<th>Clinical history of RBD</th>
<th>Cardiac [123I]-MIBG scintigraphy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>M</td>
<td>14</td>
<td>NA</td>
<td>Probable DBL</td>
<td>Depression (8 years)</td>
<td>Present (NA)</td>
<td>Early H/M ratio: 1.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypophagia (4 years)</td>
<td>Present (12 years)</td>
<td>Delayed H/M ratio: 1.24</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>M</td>
<td>24</td>
<td>12</td>
<td>Idiopathic DBL</td>
<td>Depression (2 years)</td>
<td>Absent</td>
<td>DAT scan: SBR (right, left)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Parkinson’s disease</td>
<td>Depression (8 years)</td>
<td>Delayed H/M ratio: 1.56</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>F</td>
<td>26</td>
<td>1</td>
<td>Idiopathic DBL</td>
<td>Depression (30 years)</td>
<td>Present (2 years)</td>
<td>Early H/M ratio: 4.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Major depressive disorder</td>
<td>Absent</td>
<td>Delayed H/M ratio: 5.01</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>F</td>
<td>22</td>
<td>15</td>
<td>Idiopathic DBL</td>
<td>Depression (8 years)</td>
<td>Absent</td>
<td>DAT scan: SBR (right, left)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Major depressive disorder</td>
<td>Depression (7 years)</td>
<td>Delayed H/M ratio: 3.33</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>73</td>
<td>M</td>
<td>30</td>
<td>14</td>
<td>Major depressive disorder</td>
<td>Depression (8 years)</td>
<td>Absent</td>
<td>DAT scan: SBR (right, left)</td>
</tr>
<tr>
<td>6</td>
<td>66</td>
<td>M</td>
<td>25</td>
<td>11</td>
<td>Major depressive disorder</td>
<td>Depression (2 months)</td>
<td>Absent</td>
<td>DAT scan: SBR (right, left)</td>
</tr>
<tr>
<td>7</td>
<td>83</td>
<td>M</td>
<td>27</td>
<td>4</td>
<td>Major depressive disorder</td>
<td>Depression (30 years)</td>
<td>Absent</td>
<td>DAT scan: SBR (right, left)</td>
</tr>
<tr>
<td>8</td>
<td>69</td>
<td>F</td>
<td>26</td>
<td>1</td>
<td>Major depressive disorder</td>
<td>Depression (2 months)</td>
<td>Absent</td>
<td>DAT scan: SBR (right, left)</td>
</tr>
<tr>
<td>9</td>
<td>56</td>
<td>M</td>
<td>30</td>
<td>0</td>
<td>Probable DBL</td>
<td>Depression (8 years)</td>
<td>Absent</td>
<td>DAT scan: SBR (right, left)</td>
</tr>
<tr>
<td>10</td>
<td>55</td>
<td>M</td>
<td>27</td>
<td>2</td>
<td>Probable DBL</td>
<td>Depression (8 years)</td>
<td>Absent</td>
<td>DAT scan: SBR (right, left)</td>
</tr>
</tbody>
</table>

MMSE, Mini-Mental State Examination; UPDRS III, The Unified Parkinson’s Disease Rating Scale part III; DBL, dementia with Lewy bodies; PD, Parkinson’s disease; RBD, REM sleep behavior disorder; N.A., not available; MIBG scintigraphy, metaiodobenzylguanidine scintigraphy; H/M ratio, heart-to-mediastinum ratio; DAT scan, dopamine transporter scan; SBR, specific binding ratio.

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REM sleep without atonia and Lewy body disease

As for primary psychiatric diagnoses, the proportion of neurocognitive disorders was significantly higher in the patients with RWA than in those without. The differences in sex ratio, sleep questionnaire scores, or the prevalence of psychiatric symptoms were not remarkable between the patients with and without RWA on PSG. When demographics and clinical profiles were compared between the patients with and without RWA, the mean age was significantly higher in the patients with RWA than in those without (Table 3). However, the differences in sex ratio, sleep questionnaire scores, or the prevalence of psychiatric symptoms were not remarkable between the patients with and without RWA on PSG.
Lewy-related symptoms were listed based on the Third Consortium on Dementia with Lewy bodies (DLB) clinical criteria for the clinical diagnosis of DLB in middle-aged and older patients with REM sleep without atonia. Asterisks show the optimal cutoff values for diagnosis of rapid eye movement sleep behavior disorder based on the previous study by Frauscher et al. (2012). Either + or − represents the presence or absence of each LB-related symptom. The time that each LB-related symptom preceded polysomnography recording is listed (years). PD, Parkinson's disease; iRBD, idiopathic REM sleep behavior disorder; MDD, major depressive disorder.

When polysomnographic features were compared between the patients with and without RWA, there were no differences in the proportion of primary reason for a polysomnographic workup between them (Table 4). The patients with RWA showed a trend toward a higher proportion of insomnia compared with those without RWA, but it did not reach statistical significance. On PSG, the patients with RWA had significantly lower sleep period times, less total sleep time, and a higher percentage of wake ups after sleep onset. The reasons for these different sleep parameters remain unknown, but the older age or the higher proportion of insomnia in the patients with RWA has been implicated as one of the factors involved in this difference.

**Discussion**

There is limited data regarding the prevalence of subclinical RBD. This is a result of the lack of a widely

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**Figure 1** Distribution of the percentages of each electromyographic activity in middle-aged and older 12 patients with rapid eye movement sleep without atonia. Asterisks show the optimal cutoff values for diagnosis of rapid eye movement sleep behavior disorder based on the previous study by Frauscher et al. (2012). Filled circles represent patients who had dream-enactment behaviors, and open circles represent patients who had no dream-enactment behaviors, which is consistent with subclinical rapid eye movement sleep behavior disorder.
accepted consensus of quantitative scoring rules and cutoff values of EMG activity for the clinical diagnosis of RBD. Although the variable scoring methods for RWA exist (Montplaisir et al., 2010; Frauscher et al., 2013), we defined RWA more strictly so as to detect a small amount of RWA according to the AASM Manual because it is the more widely used standard. It is of note that the cutoff values of muscle activities for the correct diagnosis of RBD based on previous studies (Frauscher et al., 2012; Sasai-Sakuma et al., 2014) were nearly valid in psychiatric patients as well. The present study demonstrated that RWA itself may be associated with specific clinical profiles, even when dream-enactment behavior is absent. Moreover, the presence of RWA in middle-aged and older psychiatric patients may be indicative of the underlying pathophysiology of LBD.

In the present study, the majority of middle-aged and older patients with RWA exhibited occipital hypoperfusion, which is a supportive feature for clinical diagnosis of DLB. Although there is limited data of radiological findings at prodromal PD/DLB state, recent studies reported that nondemented patients with glucose hypometabolism in the primary visual cortex exhibit certain other clinical features of DLB, mainly probable RBD (Fujishiro et al., 2012). Moreover, continued follow-up study revealed that glucose hypometabolism in the primary visual cortex is present in the patients with prodromal DLB.

Figure 2. The 99mTc-ethyl cysteinate dimer brain perfusion single-photon emission computed tomography findings using an easy Z-score imaging system. Compared with four patients with dementia and Lewy bodies (A), three patients with major depressive disorder (B) exhibited isolated occipital hypoperfusion. DLB, dementia with Lewy bodies; MDD, major depressive disorder.
Although the time course of the hypoperfusion in the occipital cortex remains unknown, isolated occipital hypoperfusion in three patients with MDD and subclinical RBD may represent prodromal DLB state. Of 18 patients with clinically diagnosed PD at an early stage, five patients
had normal or only slightly reduced cardiac tracer accumulation, and three patients had normal DAT binding (Spiegel et al., 2000; Boot et al., 2012; Postuma et al., 2013; Frauscher et al., 2014). In the present study, the most frequent clinical history of psychiatric illness was MDD in middle-aged and older patients exhibiting RWA. Although antidepressants can produce a loss of the normal atonia of REM sleep and dream-enactment behavior (Winkelman and James, 2004; McCarter et al., 2015), the reason for this connection remains unclear. Recent studies, however, reported that antidepressants might trigger an RBD of a subclinical status. Postuma et al. (2013) demonstrated that markers of underlying LBD were present in patients with antidepressant-associated RBD; dysautonomia, olfactory dysfunction, color vision abnormalities, and motor dysfunction were observed. Moreover, naturalistic follow-up studies suggested that dream-enactment behaviors and the presence of RWA findings persisted despite discontinuing or switching antidepressants (Lam et al., 2010). Because there were no differences in the prevalence of antidepressant usage between the patients with and without RWA in this study, it is unlikely that the neurochemical effects mediated by antidepressants cause a reversible state of RWA. Wing et al. (2015) recently demonstrated reduced striatal dopamine transmission and impaired olfactory function in RBD comorbid with MDD. They concluded that the development of dream-enactment behaviors in the patients with MDD might represent an early phase of neurodegeneration instead of a merely antidepressant-induced condition. A clinicopathological study by Tsopelas et al. (2011) revealed that late-in-life depression was significantly associated with the presence of subcortical Lewy bodies, supporting the link between depression and RBD. The long prodromal phase of PD/DLB provides a critical opportunity for potential intervention with disease-modifying therapy, but only if we are able to clearly identify the patients with underlying LBD. Because it remains unknown whether the patients with MDD and subclinical RBD are presenting the prodromal state of PD/DLB, a continued follow-up of the patients will be needed.

### Conflict of interest

None declared.

### Key points

- The relationship between RWA and LBD remains unclear.
- Of the 10 middle-aged and older patients exhibiting RWA, seven patients fulfilled the clinical criteria for PD, DLB, and idiopathic RBD.
- The remaining three patients with major depressive disorder partially shared common prodromal symptoms and radiological findings with LBD.
- RWA itself may be associated with LBD in middle-aged and older psychiatric patients, even when dream-enactment behavior is absent.

### References


