Comparison Study of Polysomnographic Features in Multiple System Atrophy-cerebellar Types Combined with and without Rapid Eye Movement Sleep Behavior Disorder

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Abstract

Background: The brain stem is found to be impaired in multiple system atrophy-cerebellar types (MSA-C). Rapid eye movement (REM) sleep behavior disorder (RBD) is reported as a marker of progressive brain stem dysfunction. Few systematic studies about the sleep disturbances in MSA-C patients combined with or without RBD were reported. This study aimed to explore the polysomnographic (PSG) features of sleep disturbances between MSA-C patients with and without RBD.

Methods: Totally, 46 MSA-C patients (23 with RBD, and 23 without RBD) were enrolled in this study. All patients underwent a structured interview for their demographic data, history of sleep pattern, and movement disorders; and then, overnight video-PSG was performed in each patient. All the records were evaluated by specialists at the Sleep Medicine Clinic for RBD and the Movement Disorder Clinic for MSA-C. The Student’s t-test, Mann-Whitney U-test for continuous variables, and the Chi-square test for categorical variables were used in this study.

Results: MSA-C patients with RBD had younger visiting age (52.6 ± 7.4 vs. 56.7 ± 6.0 years, P = 0.046) and shorter duration of the disease (12.0 [12.0, 24.0] vs. 24.0 [14.0, 36.0] months, P = 0.009) than MSA-C patients without RBD. MSA-C with RBD had shorter REM sleep latency (111.7 ± 48.2 vs. 157.0 ± 68.8 min, P = 0.042), higher percentage of REM sleep (14.9% ±4.0% vs. 10.0% ± 3.2%, P = 0.019), and lower Stage I (9.5% ±7.2% vs. 15.9% ±8.0%, P = 0.027) than MSA-C without RBD. Moreover, MSA-C patients with RBD had more decreased sleep efficiency (52.4% ±12.6% vs. 65.8% ±15.9%, P = 0.029) than that without RBD.

Conclusions: In addition to the RBD, MSA-C patients with RBD had other more severe sleep disturbances than those without RBD. The sleep disorders of MSA patients might be associated with the progress of the disease.

Key words: Behavior Disorder; Multiple System Atrophy-cerebellar Types; Rapid Eye Movement Sleep; Video-polysomnography

Introduction

Multiple system atrophy (MSA) is a group of intractable neurodegenerative disorders characterized by cerebellar ataxia, as well as various combinations of parkinsonism, autonomic failure, and pyramidal dysfunction. Several researches are trying to understand the development of MSA, and looking for early signs of system atrophy, which might be treatable at an early stage. In the past decades, several studies reported that rapid eye movement (REM) sleep behavior disorder (RBD) was strongly associated with MSA and might precede the development of neurodegenerative syndromes by several years. Therefore, studies about RBD in MSA patients might help to investigate the mechanisms, diagnosis, and treatment of MSA.

RBD is characterized by the loss of muscular atonia and prominent motor behaviors during REM sleep. It can cause sleep disruption and abnormal violent behaviors. Polysomnographic (PSG) features of RBD are the presence of chin or limb electromyographic (EMG) activity during REM sleep.

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sleep with concomitant vigorous behavioral manifestations in accordance with videotape recording and REM sleep without atonia (RSWA). Since the 1970s, RSWA was reported in patients with MSA,[7] and a study confirmed a strong association between these two disorders.[8] Since then, RBD was detected in patients with MSA by PSG.[7] Moreover, RBD was demonstrated to be common in MSA and Parkinson’s disease (PD).[9,10] Subsequently, RBD is associated with these neurodegenerative disorders and should be considered as a part of the diseases.[2,10] It can also occur in other diseases involving brainstem lesions. For instance, RBD was reported in pontine stroke[11] and brainstem cavernous hemangioma.[12] The mechanism might be due to the decreased hypocretinergic input to pontine structures, which was associated with muscle atonia in REM. The brainstem structures mainly included locus coeruleus-subcoeruleus complex, pedunculopontine nucleus, dorsal vagus nucleus, and dorsal raphe nucleus.[13,14]

Therefore, RBD can be found in diseases involving dorsal midbrain and pons.[15] MSA is a member of a diverse group of neurodegenerative disorders termed α-synucleinopathies[16] characterized by the abnormal accumulation of α-synuclein aggregates in neurons, nerve fibers, or glial cells. The pathological hallmark of all clinical subtypes of MSA is the presence of α-synuclein-positive glial cytoplasmic inclusions in oligodendroglia, which was observed in a widespread distribution throughout the brain. The clinical subtypes of MSA, MSA-parkinsonian type (MSA-P), and MSA-cerebellar type (MSA-C) are generally reflective of the brain regions with significant pathological change. In MSA-P, the striatogniral regions are predominantly affected, while in MSA-C, it is the olivopontocerebellar regions.[17] Other two main types of α-synucleinopathy, PD, and dementia with Lewy bodies have multiple clinical phenotypes, with these phenotypes differing in the dynamic distribution of their underlying neuropathologies.[18]

In other words, these three main types of α-synucleinopathy had different sequences for the susceptible site. Several studies demonstrated that RBD can be earlier, equal, or later than the syndromes of parkinsonism.[19-21] Similarly, recent studies demonstrated that RBD can be earlier, equal, and later than the symptoms of MSA, indicating that brainstem can be involved in different stages of MSA.[22] The occurrence of RBD in MSA suggested that the brainstem was involved in the process of the disease. The brainstem was a part of the central regulation of sleep.[21] Moreover, the olivopontocerebellar regions in the brainstem are mainly involved in MSA-C.[17] Therefore, there might be some differences in sleep features between MSA-C with and without RBD. Since few systematic studies about the sleep disturbances in MSA-C patients combined with or without RBD were reported, this study was performed to explore the sleep problems in these patients by overnight video-synchronized PSG (vPSG).

**Methods**

**Ethics approval**

The study protocol was complied with Declaration of Helsinki and China’s Regulations and Guidelines on Good Clinical Practice and approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University (Clinical Research Trial [2016] No. 008). All the patients agreed to take part in the study and signed an informed consent including the video assessment.

**Patients and diagnosis**

Totally, 46 MSA-C patients (23 with RBD and 23 without RBD) from the Center for Sleep Medicine and Movement Disorder Clinic in Xuanwu Hospital, Capital Medical University (China) between March 2013 and March 2015 were consecutively enrolled in this study.

The diagnosis of probable or possible MSA-C was established based on the second consensus criteria:[24] (1) a sporadic, progressive, and adult (>30 years) onset disease characterized by a cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction), and (2) at least one of the additional features as follows: parkinsonism (bradykinesia and rigidity); atrophy of putamen, middle cerebellar peduncle, or pons on magnetic resonance imaging (MRI); hypometabolism on fluorodeoxyglucose-positron emission tomography (FDG-PET) in putamen; and presynaptic nigrostriatal dopaminergic denervation on single photon emission computed tomography (SPECT) or PET.

RBD was diagnosed based on the International Classification of Sleep Disorders, 3rd Edition (ICSD-3).[23] The presence of RSWA on overnight PSG and either sleep-related injurious, potentially injurious, or disruptive behaviors by history, and/ or abnormal REM sleep behavior documented during PSG monitoring. In addition, there must be an absence of epileptiform activity on electroencephalography (EEG) during REM sleep unless RBD could be clearly distinguished from any concurrent REM sleep-related seizure disorders, and the sleep disorders could not be better explained by any other sleep disorders, medical or neurological disorders, mental disorders, and medication or substance use.

Inclusion criteria included: (1) patients were diagnosed with probable MSA-C combined with or without RBD based on the above-mentioned criteria, (2) patients can finish the interviews and PSG examination, (3) the brain MRI was normal, and (4) all the patients gave their informed consent.

Exclusion criteria included: (1) patients with signs or symptoms of any other neurologic diseases; (2) RBD secondary to any other diseases or medications; (3) patients being regularly taking sleeping pills or antipsychotics and sedative-hypnotic drugs or alcohol cannot withdraw by 1 week; and (4) patients had other sleep disorders, such as severe sleep apnea, hypopnea syndrome, or narcolepsy.

**Structured interview**

A structured face-to-face interview was conducted with the patients and checked with their close relatives to obtain the history of sleep patterns and disorders, the demographic and phenotypic details including body mass index (BMI), age at visiting and onset of MSA-C or RBD, duration of the
disease, presenting symptoms and signs, Unified Multiple System Atrophy Rating Scale (UMSARS) score, and other relevant past and family histories.

**Overnight video-polysomnography**

The vPSG was performed in each patient using a standard system (E-Series, Compumedics Limited, Abbotsford, Australia) with video monitoring of patient behavior, diagnostic PSG recordings, and measurements, including four channels of the scalp EEG (C3/A2, C4/A1, O1/A2, and O2/A1), two electrooculograms, arterial O₂ saturation (SaO₂) recording taken by oximeter, amplification of snoring sounds using a microphone, chest/abdominal respiratory effort, and anterior tibialis EMGs for leg movements. Nighttime sleep recordings started immediately after connecting the patient and calibration with lights off at 21:00 and ended at 6:00 the next morning. The parameters were set as our previous study.[26] Total sleep time (TST, min), sleep efficiency (SE, %), sleep latency (SL, min), ratio of individual sleep stages (%), arousals, isolated, and periodic movements, and snore and respiratory events were scored. Sleep macroarchitecture analysis was carried out. The indices for the apnea-hypopnea, periodic limb movement (PLM), awaking time and frequency, and fastest and average heart rate (HR) in sleep were calculated. BWD was verified by vPSG. The PSG technologists were on continuous duty during the PSG recording. Subsequently, the PSG was evaluated page by page by the investigator (Yan Ding) with special emphasis on any marked/reported events. All the patients were documented with an infrared video recording synchronized to the PSG.

**Statistical analysis**

The Statistical Package for Social Sciences (SPSS) software 16.0 (SPSS Inc., Chicago, USA) was used for statistical analyses. Normality of continuous data was checked. Normally distributed variables were expressed as mean ± standard deviation (SD) and analyzed using the Student’s t-test; skewed distributed variables were shown as median (Q₁, Q₃) and analyzed using Mann-Whitney U-test. The Chi-square test was used for categorical variables. To adjust for the difference in age, analysis of covariance was used to analyze the TST, SE, ratio of individual sleep stages, REM SL, PLM index, SaO₂, and other variables for MSA-C with and without RBD groups. All calculated P values were two-tailed, and statistical significance was set at a P < 0.05.

**Results**

**Basic characteristics**

The demographic data and clinical phenotype of the MSA-C patients with RBD and those without RBD were shown in Table 1. The mean age at visiting the clinic of MSA-C with RBD was younger than that of MSA-C without RBD (52.6 ± 7.4 vs. 56.7 ± 6.0 years, P = 0.046). The duration of MSA-C with RBD was significantly shorter than that in MSA-C without RBD (12.0 [12.0, 24.0] vs. 24.0 [14.0, 36.0] months, P = 0.009). No significant difference was found in gender ratio, age at onset, height, weight, BMI, score of UMSARS between the MSA-C with and without RBD.

**Polysomnography features**

After adjusted for the difference in age by analysis of covariance, a shorter REM latency was found in MSA-C with RBD than MSA-C without RBD (111.7 ± 48.2 vs. 157.0 ± 68.8 min, P = 0.042). The percentage of REM sleep in the TST was significantly higher in MSA-C with
RBD than without RBD (14.9% ± 4.0% vs. 10.0% ± 3.2%, 
\( P = 0.019 \)). In the contrary, the percentage of Stage I in
the TST was higher in MSA-C patients without RBD than
with RBD (15.9% ± 8.0% vs. 9.5% ± 7.2%, \( P = 0.027 \)).
Moreover, MSA-C patients with RBD had more decreased
SE (52.4% ± 12.6% vs. 65.8% ± 15.9%, \( P = 0.029 \)) than
that without RBD. No significant difference was found in
TST, SL, awakening time and frequency, percentage of other
sleep stages in the TST, apnea-hypopnea index, PLM index,
baseline and minimum SaO\(_2\), and the fastest and average
HR between the MSA-C with and without RBD [Table 1].

**Discussion**

This study found that MSA-C patients with RBD showed
significantly shorter REM latency and a higher percentage
of REM sleep in TST than that in MSA-C without
RBD (\( P = 0.042 \) and \( P = 0.019 \)). The finding was consistent
with a previous study demonstrated that MSA patients with
probable depression had shorter REM latency.\(^{[27]}\) Sleep can
be considered as a restorative process. As a homeostatic
process, sleep allows the body to return to equilibrium
when it is disturbed.\(^{[21]}\) The central regulation of sleep in
brainstem was involved in MSA-C with RBD that activated
the self-regulating system to maintain the normal sleep or
compensate the inadequate sleep. However, the central
regulation of sleep might be affected slightly or not in
MSA-C without RBD, the self-regulating system plays a
marginal role in the process. The compensation of a deficit
occurs mainly by an increase in sleep intensity rather than
by the prolongation of sleep duration.\(^{[28]}\) REM sleep played
an important role in the overall sleep. Although the SE
of MSA-C patients with RBD decreased obviously, the
proportion of REM sleep was relatively increased when
compared with MSA-C without RBD. The finding was
consistent with the results reported by Sixel-Döring et al.,
which demonstrated that the proportion of REM sleep was
higher in PD patients with RBD than without RBD.\(^{[29]}\) The
mechanism might be associated with the balance between
brainstem norepinephrine and serotonin systems and
acetylcholine systems. In addition, REM SL of MSA-C
with RBD was relatively shorter than MSA-C without RBD,
indicating that the body tried hard to maintain a relatively
“normal” sleep. Of course, slow-wave sleep (SWS) also
plays a very important role in the self-regulation of sleep.
Our research showed an increase in the proportion of Stage
III sleep in MSA-C with RBD compared to MSA-C without
RBD, but there was no significant difference. The increase
in the percentage of Stage III and REM sleep resulted in a
reduction in the proportion of shallow sleep. The significantly
lower percentage of Stage I sleep in MSA-C with RBD than
those without RBD showed that the body tried to sacrifice
shallow sleep to ensure SWS and REM sleep that was likely
to be the result of self-regulation for sleep.

This study also found that the SE of MSA-C patients
with RBD was significantly lower than those without
RBD (\( P = 0.029 \)). It was different with the characteristics in
PD patients with RBD from Sixel-Döring et al.’s study,\(^{[26]}\) in
which a higher SE in PD patients with RBD was shown than
those without RBD. Several reasons might contribute to the
difference: (1) MSA-C patients with RBD might have more
diffuse range and severely damaged extent of sleep center
in brainstem than PD with RBD, (2) more severe clinical
symptoms of MSA-C with RBD affected the quality of
sleep from the mental and physical aspects, and (3) different
developmental sequences of susceptible site between PD
and MSA-C.

Another interesting finding of this study was that the duration
of MSA-C with RBD was significantly shorter than MSA-C
without RBD under the situation that the age-onset and
UMSARS scores were similar between the two groups. The
finding suggested that the development of the disease for
MSA-C patients with RBD was faster than those without
RBD, resulted in the younger visiting age in MSA-C patients
with RBD. The finding could reflect the potential severity of
the disease. The previous studies suggested that RBD was
considered as a red flag for the diagnosis of MSA\(^{[30]}\) and might
either antedate or follow the onset of parkinsonism, cerebellar
syndrome, and dysautonomia\(^{[31]}\) that might be due to inchoate
structural lesion which damages REM regulating regions of
brain (lower brainstem and limbic system mainly).\(^{[32]}\) The
occurrence of RBD in MSA suggested that the brainstem
was involved in the process of the disease. If MSA-C patients
had both movement disorders and RBD, more diffuse brain
areas might be involved than MSA-C without RBD. Then,
the symptoms of MSA-C patients with RBD might be more
severe than those without RBD as a result visiting age was
earlier. The above finding was similar to the study about
RBD in PD. The symptom of PD patients with RBD was
more severe than PD without RBD, especially movement
disorders.\(^{[33]}\) Besides, the development of the symptoms
for PD with RBD was faster than those without RBD.\(^{[29,64]}\) These
studies suggested that PD patients with RBD might have more
diffuse lesions than those without RBD, resulting in a faster
development of disease that was consistent with our study.

The present study has several strengths, including (1) the
detailed demonstration of sleep differential by vPSG between
MSA-C with and without RBD by comparative analysis
using the latest ICSD-3 diagnostic criteria for RBD, (2) it
assisted to understand the process of MSA-C through RBD,
which might be the red flag for the development of MSA-C,
and (3) it favored the RBD in MSA-C to cause more attention
for sleep disorders in MSA. Nevertheless, several limitations
of this study should be also considered: (1) all patients with
MSA-C or RBD were enrolled at a tertiary referral center,
which was not a population-based study, (2) the present
study was a cross-sectional study, which did not include
the whole process of the disease, and (3) it considered the
whole process of the disease, and (3) only 46 MSA-C
patients were recruited. A multi-center, prospective study
is necessary in the future.

In conclusion, MSA-C patients with RBD had other more
severe sleep disturbances besides RBD than those without

RBD. The sleep disorders of MSA patients might be associated with the progress of the disease.

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**Conflicts of interest**
There are no conflicts of interest.

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