Sleep-related symptoms in multiple system atrophy: determinants and impact on disease severity

Jun-Yu Lin, Ling-Yu Zhang, Bei Cao, Qian-Qian Wei, Ru-Wei Ou, Yan-Bing Hou, Kun-Cheng Liu, Xin-Ran Xu, Zheng Jiang, Xiao-Jing Gu, Jiao Liu, Hui-Fang Shang

Department of Neurology, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China.

Abstract

Background: Sleep disorders are common but under-researched symptoms in patients with multiple system atrophy (MSA). We investigated the frequency and factors associated with sleep-related symptoms in patients with MSA and the impact of sleep disturbances on disease severity.

Methods: This cross-sectional study involved 165 patients with MSA. Three sleep-related symptoms, namely Parkinson’s disease (PD)-related sleep problems (PD-SP), excessive daytime sleepiness (EDS), and rapid eye movement sleep behavior disorder (RBD), were evaluated using the PD Sleep Scale-2 (PDSS-2), Epworth Sleepiness Scale (ESS), and RBD Screening Questionnaire (RBDSQ), respectively. Disease severity was evaluated using the Unified MSA Rating Scale (UMSARS).

Results: The frequency of PD-SP (PDSS-2 score of ≥18), EDS (ESS score of ≥10), and RBD (RBDSQ score of ≥5) in patients with MSA was 18.8%, 27.3%, and 49.7%, respectively. The frequency of coexistence of all three sleep-related symptoms was 7.3%. Compared with the cerebellar subtype of MSA (MSA-C), the parkinsonism subtype of MSA (MSA-P) was associated with a higher frequency of PD-SP and EDS, but not of RBD. Binary logistic regression revealed that the MSA-P subtype, a higher total UMSARS score, and anxiety were associated with PD-SP; that male sex, a higher total UMSARS score, the MSA-P subtype, and fatigue were associated with EDS; and that male sex, a higher total UMSARS score, and autonomic onset were associated with RBD in patients with MSA. Stepwise linear regression showed that the number of sleep-related symptoms (PD-SP, EDS, and RBD), disease duration, depression, fatigue, and total Montreal Cognitive Assessment score were predictors of disease severity in patients with MSA.

Conclusions: Sleep-related disorders were associated with both MSA subtypes and the severity of disease in patients with MSA, indicating that sleep disorders may reflect the distribution and degree of dopaminergic/non-dopaminergic neuron degeneration in MSA.

Keywords: Multiple system atrophy; Sleep disorders; Disease severity; Subtype

Introduction

Multiple system atrophy (MSA) is a neurodegenerative disorder characterized by autonomic dysfunction in combination with parkinsonism and/or cerebellar ataxia. It has been pathologically confirmed to be an α-synucleinopathy based on the presence of α-synuclein in the glial cytoplasmic inclusions (GCI). Once the misfolded α-synuclein is released by oligodendrocytes, it may be taken in by neighboring neurons to form neuronal cytoplasmic inclusions, which cause neuronal death and subsequent reactive astrogliosis. The spread of the toxic α-synuclein leads to multisystem neuronal involvement, which is typical of MSA.[1] MSA is categorised into a parkinsonism subtype (MSA-P) and a cerebellar subtype (MSA-C) according to the predominant motor symptom.[2]

Besides motor symptoms, MSA is also characterized by nonmotor symptoms such as urinary disorders, orthostatic hypotension, erectile dysfunction in men, sleep disorders, and constipation.[3] Among these nonmotor symptoms, sleep disorders are common and even can arise before any overt motor symptoms develop. Sleep disorders in patients with MSA include rapid eye movement sleep behavior disorder (RBD), excessive daytime sleepiness (EDS), and nocturnal sleep disturbances.[4] Previous studies showed that 69% to 100% of patients with MSA experience RBD.[5-8] Additionally, EDS was reported in 28% of Caucasian patients with MSA[9] and 24% of Japanese patients with MSA.[10] The European Multiple System Atrophy registry reported that 19% of patients with MSA suffered from insomnia.[11] Previous studies have also revealed that sleep disorders are related to poor quality of life in patients with MSA.[12,13]

Correspondence to: Dr. Hui-Fang Shang, Department of Neurology, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China
E-Mail: hfshang2002@126.com

Copyright © 2020 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2021;134(6)
However, few studies have focused on the factors associated with sleep disorders in patients with MSA. To our knowledge, two studies have shown that sleep-disordered breathing (SDB)\(^9\) and antiparkinson drugs\(^10\) are associated with EDS in patients with MSA, respectively, while no study has revealed factors associated with RBD or nocturnal sleep disturbances in patients with MSA. In addition, no study has investigated whether sleep disorders would have an impact on the severity of the disease.

Our previous study revealed that nonmotor symptoms are more severe and common in patients with MSA-P than MSA-C, and that sleep/fatigue symptoms are important determinants of poor quality of life in patients with MSA-P but not MSA-C.\(^12\) A few studies have shown a higher prevalence of restless legs syndrome (RLS) in patients with MSA-P than in those with MSA-C.\(^13\) The affected brain areas vary between the two subtypes, with typically olivopontocerebellar atrophy in MSA-C and striatonigral degeneration in MSA-P. The different underlying neuropathologies of the two subtypes might contribute to specific sleep disorders. However, few studies have focused on the association between specific sleep disorders and MSA subtypes.\(^14\) Therefore, studying the relationships between sleep disorders and MSA subtypes will help to achieve a better understanding of the underlying neuropathology and improvements in clinical practice.

In the current study, we aimed to explore the frequency of three main sleep-related symptoms in patients with MSA and with each MSA subtype, the factors associated with different sleep-related symptoms in patients with MSA and with each MSA subtype, and the impact of sleep-related symptoms on the severity of MSA.

**Methods**

**Patients evaluation**

This cross-sectional study was approved by the Ethics Committee of West China Hospital of Sichuan University (No. 20152356). Written informed consent was obtained from all recruited participants. Patients with MSA were consecutively recruited from the Department of Neurology, West China Hospital of Sichuan University from March 2018 to November 2019. All patients received a detailed clinical evaluation including a medical history, physical examination, and neurological examination with special attention to gait, coordination, and muscle tone. Progression of motor symptoms, response to antiparkinson medications, and nonmotor features including symptoms of cardiovascular, gastrointestinal, genitourinary, and sudomotor dysfunction were collected.\(^15\) Patients were screened for PD-SP, EDS, and RBD Screening Questionnaire (RBDSQ),\(^27\) and patients with a score of ≥3 were considered to have RBD. The Chinese versions of these scales, which have shown good validity and reliability, were used in this study.

**Statistical analysis**

First, we compared the demographic and clinical characteristics between patients with the two subtypes of MSA (MSA-P and MSA-C). Because most of the data were not normally distributed, the Mann–Whitney U test was used for continuous variables. The Chi-squared test or Fisher exact test was used for categorical variables. When comparing the frequency of the three types of sleep disorders between patients with MSA-P and MSA-C, differences were adjusted by age, disease duration, and LEDD using logistic regression analysis.\(^28\) The demographic and clinical characteristics were then compared between patients with and without PD-SP, EDS, and RBD, respectively. The variables with significant differences served as independent variables, while the presence or absence of PD-SP, EDS, and RBD
### Table 1: Demographic and clinical features of the patients with MSA-P and MSA-C subtypes.

| Variables                  | MSA            | MSA-P          | MSA-C          | Statistical value | P value |
|----------------------------|----------------|----------------|----------------|-------------------|---------|
| Number, n (male/female)    | 165 (96/69)    | 82 (44/38)     | 83 (52/31)     | 1.371*            | 0.242   |
| Mean age (years)           | 62.05 (40.39–79.69) | 62.69 (40.39–79.81) | 60.48 (40.76–79.69) | –1.421*          | 0.155   |
| Age of onset (years)       | 59.60 (38.76–76.96) | 60.04 (39.55–75.18) | 59.43 (38.76–76.96) | –1.178*          | 0.239   |
| Disease duration (years)   | 2.31 (0.31–7.00) | 2.65 (0.32–7.00) | 2.22 (0.31–5.81) | –1.465*          | 0.143   |
| Educational year (years)   | 9.0 (6.0–20.0)  | 9.00 (6.0–20.0) | 9.0 (6.0–19.0)  | –0.777*          | 0.437   |
| Overweight, n (%)          | 27 (16.4)      | 14 (17.1)      | 13 (15.7)      | 0.060†            | 0.807   |
| Motor onset/Autonomic onset| 107/58         | 59/23          | 48/35          | 3.608†            | 0.058   |
| Orthostatic hypotension, n (%) | 60 (36.4) | 24 (29.3)      | 36 (43.4)      | 3.546†            | 0.060   |
| UMSARS-I                   | 15.0 (2.0–35.0) | 15.0 (2.0–35.0) | 15.0 (2.0–35.0) | –0.549*          | 0.583   |
| UMSARS-II                  | 18.0 (6.0–36.0) | 18.0 (7.0–35.0) | 18.0 (6.0–36.0) | –1.111*          | 0.266   |
| UMSARS-IV                  | 2.0 (1.0–5.0)  | 2.0 (1.0–5.0)  | 2.0 (1.0–5.0)  | –1.403*          | 0.161   |
| Total UMSARS score         | 35.0 (12.0–75.0) | 36.0 (16.0–71.0) | 35.0 (12.0–75.0) | –0.104*          | 0.311   |
| FAB score                  | 15.0 (4.0–18.0) | 15.0 (8.0–18.0) | 14.0 (4.0–18.0) | –1.839*          | 0.066   |
| Total MoCA score           | 24.0 (8.0–30.0) | 24.0 (8.0–30.0) | 23.0 (8.0–30.0) | –1.802*          | 0.071   |
| FSS score                  | 45.0 (9.0–63.0) | 45.0 (9.0–63.0) | 44.0 (9.0–63.0) | –1.197*          | 0.231   |
| HDRS-24 score              | 11.0 (0–41.0)  | 12.0 (0–41.0)  | 8.0 (0–32.0)   | –1.127*          | 0.260   |
| HARS score                 | 7.0 (0–33.0)   | 7.0 (0–33.0)   | 7.0 (0–28.0)   | –0.586*          | 0.558   |
| Levodopa, n (%)            | 65 (39.4)      | 48 (58.5)      | 17 (20.5)      | 25.019†          | <0.001  |
| Dopamine agonist, n (%)    | 32 (19.4)      | 28 (34.1)      | 4 (4.8)        | 22.694†          | <0.001  |
| LEDD (mg/d)                | 0 (0–750.0)    | 225.0 (0–750.0) | 0 (0–600.0)    | –5.608*          | <0.001  |

*Mann-Whitney U test; †Chi-square test. FAB: Frontal Assessment Battery; FSS: Fatigue Severity Scale; HDRS-24: Hamilton Depression Scale; HARS: Hamilton Anxiety Scale; MSA: Multiple system atrophy; MSA-P: Multiple system atrophy with predominately parkinsonism; MSA-C: Multiple system atrophy with predominately cerebellar ataxia; LEDD: Levodopa equivalent daily doses; MoCA: Montreal Cognitive Assessment; PDSS-2: PD Sleep Scale-2; PD-SP: PD-related sleep problems (PDSS-2 ≥ 18); RBDSQ: RBD Screening Questionnaire; RBD: Rapid eye movement behavior disorder (RBDSQ ≥ 5); UMSARS: Unified multiple system atrophy rating scale.

served as dependent variables in the following binary logistic regression exploring the factors associated with these three sleep-related symptoms. Further, the demographic and clinical characteristics were compared between patients with and without different sleep-related symptoms regarding to MSA subtypes. Finally, a stepwise regression analysis was performed to predict disease severity (total UMSARS score) using the following independent variables: sex, age, subtype, disease duration, fatigue, depression, anxiety, MoCA score, and number of sleep-related symptoms (0–3; PD-SP, EDS, or RBD). All analyses were performed using the SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Two-tailed P values of <0.05 were considered statistically significant.

### Results

The demographic and clinical characteristics of all patients with MSA and of patients with the two subtypes of MSA are shown in Table 1. The analysis included 165 patients with probable MSA (96 male, 69 female) with a mean disease duration of 2.56 ± 1.34 years. Eighty-two patients (49.7%) had MSA-P and 83 patients (50.3%) had MSA-C. The frequency of PD-SP, EDS, and RBD was 18.8%, 27.3%, and 49.7%, respectively. After adjusting for age, disease duration, and LEDD, the frequencies of PD-SP and EDS were significantly higher in patients with MSA-P than in patients with MSA-C. The frequency of RBD was not significantly different between patients with MSA-P and MSA-C [Figure 1]. The frequency of overlap of two of the three sleep-related symptoms varied from 4.2% to 8.5%. The frequency of coexistence of all three sleep-related symptoms was 7.3% [Figure 2].

The demographic and clinical characteristics of patients with MSA with and without the three sleep-related symptoms (PD-SP, EDS, and RBD) are shown in Table 2. Compared with patients without PD-SP, those with PD-SP showed a higher frequency of the MSA-P subtype and had higher UMSARS, FSS, HDRS-24, and HARS scores. Compared with patients without EDS, those with EDS had a higher frequency of the MSA-P subtype and male sex; older age; older age at onset; higher UMSARS, FSS, HDRS-24, and HARS scores; and a higher proportion of dopamine agonist use. Compared with patients without RBD, those with RBD had a higher frequency of male sex.
overweight, and autonomic onset and higher UMSARS and FSS scores.

Comparisons between patients with and without sleep-related symptoms with respect to MSA subtypes are shown in Tables 3 and 4. Among patients with MSA-P, patients with PD-SP had higher UMSARS, FSS, HDRS-24, and HARS scores and a lower score of the naming domain of the MoCA than did patients without PD-SP. Among patients with MSA-P, patients with EDS had higher UMSARS, FSS, HDRS-24, and HARS scores and a higher proportion of dopamine agonist use than did patients without EDS. Among patients with MSA-P, patients with RBD had higher UMSARS and FSS scores than did patients without RBD. Among patients with MSA-C, patients with PD-SP had higher HDRS-24 and HARS scores than did patients without PD-SP. Among patients with MSA-C, patients with EDS showed a higher frequency of male sex than did patients without EDS. Among patients with MSA-C, patients with RBD showed a higher frequency of male sex, overweight, and autonomic onset and higher UMSARS scores scores than did patients without RBD.

The binary logistic regression showed that the MSA-P subtype (OR = 3.861; P = 0.005), a higher total UMSARS score (OR = 1.042; P = 0.022), and anxiety (OR = 4.755; P = 0.001) were associated with PD-SP; that male sex (OR = 3.309; P = 0.005), a higher total UMSARS score (OR = 1.036; P = 0.032), the MSA-P subtype (OR = 2.733; P = 0.012), and fatigue (OR = 3.654; P = 0.005) were associated with EDS; and that male sex (OR = 2.614; P = 0.005), a higher total UMSARS score (OR = 1.052; P = 0.001), and autonomic onset (OR = 0.486; P = 0.044) were associated with RBD in patients with MSA [Table 5].

To investigate the impact of sleep disturbances on disease severity, we performed a stepwise linear regression analysis. The total UMSARS score was used to represent disease severity and acted as the dependent variable, while the number of sleep-related symptoms (0–3; PD-SP, EDS, or RBD) acted as the independent variable. Other covariables included sex, age, subtype, disease duration, fatigue, depression, anxiety, and MoCA score. The tolerance of all independent variables was <0.2 and the variance inflation factor was >5, suggesting that there was no multicollinearity in the model. The final model showed that the disease duration, depression, fatigue, total MoCA score, and number of sleep-related symptoms (PD-SP, EDS, and RBD) were significant predictors of disease severity in patients with MSA [Table 6].

**Discussion**

In this cross-sectional study, the frequency of PD-SP, EDS, and RBD was 18.8%, 27.3%, and 49.7%, respectively. The type of sleep-related symptoms differed between the two subtypes of MSA. Sleep disturbances had an impact on the severity of MSA.

The PDSS-2 is mainly used to evaluate the nocturnal sleep quality of patients with parkinsonism. It evaluates disorders including motor symptoms at night, insomnia, RLS, and disturbed sleep. The European Multiple System Atrophy registry reported that 19% of patients with MSA suffered from insomnia. Another study showed that 23.1% of patients with MSA had RLS. The frequency of PD-SP observed in our study (18.8%) is similar to those observed in previous studies. The proportion of patients with MSA who had EDS in our study (27.3%) is also similar to that in previous studies. RBD was found to be the most common sleep disorders, confirming the important role of RBD in
|                        | With RBD | Without RBD | With PD-SP | Without PD-SP |
|------------------------|----------|-------------|------------|---------------|
| **Subtype (MSA-P/MSA-C)** | 23/8     | 59/75       | 9.163      |
| **P value**            |          |             |            |
| **Age of onset (years)** | 60.08    | 0.893       |
| **Disease duration (years)** | 2.75 (0.49 | 2.27 (0.31 |
|                        | 5.81)    | 0.917       |
|                        | 2.36 (0.31 | 11.0 (6.0 |
|                        | 0.917    | 0.607       |
|                        |          |             | 2.443      |
|                        |          |             | 0.050      |
|                        |          |             | 0.638      |
|                        |          |             | 0.084      |
|                        |          |             | 0.423      |
|                        |          |             | 0.042      |
|                        |          |             | 0.126      |
|                        |          |             | 0.172      |
|                        |          |             | 2.089      |
|                        |          |             | 0.708      |
|                        |          |             | 0.212      |
|                        |          |             | 0.267      |
|                        |          |             | 0.042      |
|                        |          |             | 0.969      |
|                        |          |             | 0.507      |
|                        |          |             | 0.155      |
|                        |          |             | 3.385      |
|                        |          |             | 0.039      |
|                        |          |             | 0.001      |
| **Total MoCA score**   | 22.0     | 8.000       |
| **HDRS-24 score**      | 16.0     | 7.000       |
| **HARS score**         | 14.0     | 14.000      |
| **Orientation**        | 6.0      | 2.000       |
| **executive function** |          |             | 3.0        |
| **Dopamine agonist**   |          |             | 3.0        |
| **UMSARS**             |          |             | 18.0       |
| **PDQ-39**             |          |             | 15.0       |
| **Depression questionnaire** |           |             | 13.0       |
**Table 3**  
(continued)

| Variables | With PD-SP (n = 23) | Without PD-SP (n = 59) | Statistical values | P value |
|-----------|---------------------|-----------------------|--------------------|---------|
| MoCA      | 3.0 (1.0–5.0)       | 4.0 (1.0–5.0)         | -1.89              | 0.059   |
| Vissuospatial and executive function | 4.0 (1.0–5.0) | 4.0 (1.0–5.0) | -0.095† | 0.924 |
| Naming    | 3.0 (1.0–3.0)       | 3.0 (1.0–5.0)         | -0.203             | 0.037   |
| Attention | 5.0 (2.0–4.0)       | 5.0 (2.0–6.0)         | -0.51               | 0.130   |
| Language  | 2.0 (0.0–3.0)       | 2.0 (0.0–3.0)         | -0.16               | 0.870   |
| Abstraction| 1.0 (0.0–2.0)      | 1.0 (0.0–2.0)         | -1.15               | 0.250   |
| Delay recall| 3.0 (0.0–5.0)     | 3.0 (0.0–3.0)         | -0.24               | 0.241   |
| Orientation| 6.0 (2.0–6.0)       | 6.0 (3.0–6.0)         | -0.46               | 0.642   |

**Table 4: Demographic and clinical features of the MSA-C patients with and without PD-SP, EDS, and RBD.**

| Variables | With PD-SP (n = 3) | Without PD-SP (n = 7) | Statistical values | P value |
|-----------|-------------------|-----------------------|--------------------|---------|
| Male sex, n (%) | 7 (2.5)          | 45 (60.0)             | 0.248              | 15 (19.3) |
| Age (years) | 66.14 (54-74.18)  | 59.40 (67-79.89)      | -0.65              | 0.067   |
| Overweight (%) | 3.0 (0.0-5.0)   | 2.0 (0.0-3.0)         | 0.31               | 0.250   |
| Motor onset/ Autonomic dysfunction | 12.5 (6.0-16.0)  | 9.0 (6.0-14.0)        | -0.80              | 0.071   |
| UMSARS 1 | 37.5 (18.0-56.0)  | 33.0 (12.0-75.0)      | 0.13               | 0.413   |
| UMSARS 2 | 13.0 (9.0-16.0)  | 14.0 (9.0-18.0)       | 0.32               | 0.184   |
| MoCA     | 3.0 (5.0-5.0)     | 4.0 (1.0-3.0)         | -0.82              | 0.409   |
| Vissuospatial and executive function | 3.0 (1.0-5.0)   | 3.0 (1.0-3.0)         | 0.06               | 0.944   |
| Naming    | 3.0 (1.0-3.0)       | 3.0 (1.0-5.0)         | -0.36              | 0.715   |
| Attention | 3.0 (1.0-2.0)       | 3.0 (1.0-4.0)         | -0.31              | 0.591   |
| Language  | 2.0 (0.0-3.0)       | 2.0 (0.0-4.0)         | -0.08              | 0.277   |
| Abstraction| 1.0 (0.0-2.0)      | 1.0 (0.0-2.0)         | -1.51              | 0.130   |
| Delay recall| 2.0 (0.0-3.0)     | 2.0 (0.0-4.0)         | -0.28              | 0.777   |
| Orientation| 6.0 (2.0-6.0)       | 6.0 (3.0-6.0)         | -0.82              | 0.066   |
| UMSARS 1 | 37.5 (18.0-56.0)  | 33.0 (12.0-75.0)      | 0.13               | 0.413   |
| UMSARS 2 | 13.0 (9.0-16.0)  | 14.0 (9.0-18.0)       | 0.32               | 0.184   |

**Table 5: Clinical features of the MSA-C patients with and without PD-SP, EDS, and RBD.**

| Variables | With PD-SP (n = 23) | Without PD-SP (n = 59) | Statistical values | P value |
|-----------|---------------------|-----------------------|--------------------|---------|
| Male sex, n (%) | 7 (2.5)          | 45 (60.0)             | 0.248              | 15 (19.3) |
| Age (years) | 66.14 (54-74.18)  | 59.40 (67-79.89)      | -0.65              | 0.067   |
| Overweight (%) | 3.0 (0.0-5.0)   | 2.0 (0.0-3.0)         | 0.31               | 0.250   |
| Motor onset/ Autonomic dysfunction | 12.5 (6.0-16.0)  | 9.0 (6.0-14.0)        | -0.80              | 0.071   |
| UMSARS 1 | 37.5 (18.0-56.0)  | 33.0 (12.0-75.0)      | 0.13               | 0.413   |
| UMSARS 2 | 13.0 (9.0-16.0)  | 14.0 (9.0-18.0)       | 0.32               | 0.184   |

**Table 6: Clinical features of the MSA-C patients with and without PD-SP, EDS, and RBD.**

| Variables | With PD-SP (n = 23) | Without PD-SP (n = 59) | Statistical values | P value |
|-----------|---------------------|-----------------------|--------------------|---------|
| Male sex, n (%) | 7 (2.5)          | 45 (60.0)             | 0.248              | 15 (19.3) |
| Age (years) | 66.14 (54-74.18)  | 59.40 (67-79.89)      | -0.65              | 0.067   |
| Overweight (%) | 3.0 (0.0-5.0)   | 2.0 (0.0-3.0)         | 0.31               | 0.250   |
| Motor onset/ Autonomic dysfunction | 12.5 (6.0-16.0)  | 9.0 (6.0-14.0)        | -0.80              | 0.071   |
| UMSARS 1 | 37.5 (18.0-56.0)  | 33.0 (12.0-75.0)      | 0.13               | 0.413   |
| UMSARS 2 | 13.0 (9.0-16.0)  | 14.0 (9.0-18.0)       | 0.32               | 0.184   |
The frequency of RBD observed in our patients with MSA (49.7%) was the highest among different the various sleep-related symptoms, also confirming the above-mentioned role of RBD. In addition, overlap exists among the three sleep-related disorders. Among all patients with MSA, 7.3% developed all three sleep-related symptoms simultaneously, which has never been studied. The findings of our study and previous studies suggest that sleep-related symptoms are common in patients with MSA. Such symptoms should receive more attention in clinical practice.

Few studies have focused on the differences in sleep-related symptoms between the two MSA subtypes. For example, a higher prevalence of RLS was found in MSA-P than in MSA-C,[9,14] while no differences in the prevalence or severity of RBD were observed between the two MSA subtypes.[8,32-34] However, whether EDS differs between the two MSA subtypes has never been studied. The stepwise linear regression model showed that in patients with MSA, a higher total UMSARS score ( ie, greater disease severity) was associated with PD-SP and EDS, and RBD. Moreover, the MSA-P subtype was associated with PD-SP and EDS, and male sex was associated with RBD and EDS. In addition, RBD was more likely to develop in patients with than without anxiety and in patients with than without autonomic onset, and EDS was more likely to develop in patients with than without fatigue. The stepwise linear regression model showed that in addition to the disease duration, depression, fatigue, and total MoCA score, an increased number of sleep-related symptoms (PD-SP, EDS, and RBD) was significantly correlated with the disease severity. Our study is the first to demonstrate that an increased number of sleep-related symptoms (PD-SP, EDS, and RBD) has a significant impact on the severity of MSA.

Some studies focusing on the patterns of dopamine transporter (DAT) imaging have shown uneven, asymmet-

| Table 5: Factors associated with sleep-related symptoms in MSA patients. |
|-------------------------|-----------------|-----------------|-----------------|
| Variable                | OR              | 95% CI          | P value         |
| ---                     | ---             | ---             | ---             |
| PD-SP†                  | 3.861           | 1.499–9.941     | 0.005           |
| Subtype (MSA-P = 1, MSA-C = 0) |           |                 |                 |
| Total UMSARS score      | 1.042           | 1.006–1.080     | 0.022           |
| Anxiety                 | 4.755           | 1.833–12.336    | 0.001           |
| EDS†                    | 3.309           | 1.441–7.602     | 0.005           |
| Sex (male = 1, female = 0) |           |                 |                 |
| Total UMSARS score      | 1.036           | 1.003–1.070     | 0.032           |
| Subtype (MSA-P = 1, MSA-C = 0) |           |                 |                 |
| Fatigue                 | 2.733           | 1.251–5.973     | 0.012           |
| RBD‡                    | 3.654           | 1.493–8.943     | 0.005           |
| Total UMSARS score      | 1.052           | 1.021–1.083     | 0.001           |
| Sex (male = 1, female = 0) | 2.614           | 1.331–5.132     | 0.005           |
| Symptom onset (Motor onset = 1, Autonomic onset = 0) | 0.486 | 0.241–0.980 | 0.044 |

†P value was calculated by a binary logistic regression model, with subtype, sex, age, total UMSARS score, anxiety, depression, fatigue were included as co-variables. ‡P value was calculated by a binary logistic regression model, with sex, overweight, symptom onset, total UMSARS score, fatigue were included as co-variables. EDS: Excessive daytime sleepiness (ESS ≥ 10); MSA: Multiple system atrophy; PD-SP: Parkinson’s disease-related sleep problems (PDDS-2 ≥ 18); RBD: Rapid eye movement behavior disorder (RBDSQ ≥ 5); UMSARS: Unified multiple system atrophy rating scale.

| Table 6: Stepwise linear regression analysis of the Total UMSARS score in patients with MSA. |
|-------------------------|-----------------|-----------------|-----------------|
| Variable                | Standardised regression coefficient | Standard error | P value         |
| ---                     | ---             | ---             | ---             |
| Disease duration        | 0.228 (0.096 to 0.359) | 0.603 | 0.001           |
| Depression              | 0.197 (0.062 to 0.333) | 2.437 | 0.004           |
| Fatigue                 | 0.147 (0.008 to 0.286) | 1.749 | 0.038           |
| Total MoCA score        | -0.281 (-0.411 to -0.151) | 0.164 | <0.001          |
| Number of sleep problems| 0.251 (0.114 to 0.389) | 0.931 | <0.001          |

MSA: Multiple system atrophy; MoCA: Montreal Cognitive Assessment; Number of sleep-related symptoms (PD-SP, EDS or RBD); UMSARS: Unified multiple system atrophy rating scale.
ic, and more pronounced striatonigral degeneration in patients with MSA-P than MSA-C, and more diffuse DAT loss in patients with MSA-C than MSA-P. In addition, neurodegenerative changes may affect the central autonomic nervous system, including the hypothalamus, noradrenergic and serotonergic brainstem nuclei, nucleus ambiguus, dorsal nucleus of the vagus nerve, and ONU’s nucleus. Sleep disorders have been found to be associated with the brainstem and hypothalamus. Both dopaminergic and non-dopaminergic mechanisms may be involved in the underlying mechanism. EDS is reportedly correlated with loss of hypocretin/orexin neurons in the lateral hypothalamus, cholinergic neurons in the laterodorsal tegmental and pedunculopontine tegmental nuclei in the pons, putative wake-active dopaminergic neurons in the ventral periaqueductal gray matter, and serotonergic neurons of the rostral raphe; therefore, the positive correlation between the MSA-P subtype and EDS may indicate the underlying aetiology and neuropathology of subtype formation of MSA, such as a wider range of areas affected in MSA-P or a different distribution of brain neuron degeneration. Our finding that an increased number of sleep-related symptoms had a significant impact on the severity of MSA may reflect the degree of brain neuron degeneration, which is consistent with the findings of previous studies: RBD has been shown to be correlated with the degree of loss of striatal monoaminergic neurons, but not with the degree of loss of mesopontine cholinergic neurons.

The strengths of this study include its large sample size, comprehensive evaluation of demographic and clinical characteristics, and a multiple study design. In addition, this is the first study to systematically investigate the factors associated with three common sleep problems (PD-SP, EDS, and RBD) in patients with MSA and their impact on MSA subtypes and disease severity. The findings imply a potential association between sleep disorders and the distribution and degree of dopaminergic/non-dopaminergic neuron degeneration, which may give inspiration to future aetiology studies. Despite these strengths, however, several limitations should be acknowledged. First, the patients’ diagnoses of MSA were not confirmed by autopsy. However, all patients included in the current study were diagnosed according to strict diagnostic criteria, and patients who met the criteria for a “possible” diagnosis of MSA were excluded from the final analysis. The second limitation was the lack of polysomnography for objective assessment of RBD, SDB disorders, and periodic limb movements. As a result, SDB disorders such as nocturnal stridor and obstructive sleep apnea as well as periodic limb movements were not included in the analysis. Because the occurrence of stridor might contribute to shortened survival, future studies that include patients with stridor are needed. Third, this was a cross-sectional study, which can only offer correlations rather than causality. Further prospective studies are needed to confirm the impact of sleep-related disorders on disease severity or survival.

**Conclusions**

Our study showed that the MSA-P subtype, male sex, autonomic onset, anxiety, fatigue, and a higher total UMSARS score tended to be associated with sleep-related symptoms in patients with MSA. This study also indicated that there may be a link between MSA subtypes and specific sleep disorders, which may reflect the underlying differences in the neuropathologies of the two MSA subtypes. In addition, a higher number of sleep-related symptoms was found to have an impact on the disease severity in patients with MSA, which emphasizes the importance of clinical assessment and management of sleep-related symptoms in patients with MSA.

**Acknowledgements**

The authors thank the patients and their families for their participation in the study.

**Funding**

This study was supported by a grant from the 1.3.5 project for disciplines of excellence–Clinical Research Incubation Project, West China Hospital, Sichuan University (No. 2019HXFH016).

**Conflicts of interest**

None.

**References**

1. Fanciulli A, Wenning GK. Multiple-system atrophy. N Engl J Med 2015;372:249–263. doi: 10.1056/NEJMra1311488.
2. Wenning GK, Colosimo C, Geser F, Poewe W. Multiple system atrophy. Lancet Neurol 2004;3:93–103. doi: 10.1016/S1474-4422(03)00662-8.
3. Colosimo C. Nonmotor presentations of multiple system atrophy. Nat Rev Neurol 2011;7:295–298. doi: 10.1038/nrneurol.2011.5.
4. Abbott SM, Videnovic A. Sleep disorders in atypical parkinsonism. Mov Disord Clin Pract 2014;1:89–96. doi: 10.1002/mdc3.12025.
5. Plazzi G, Corsini R, Proveni F, Pierangeli G, Martinelli P, Montagna P, et al. REM sleep behavior disorder in multiple system atrophy. Neurology 1997;48:1094–1097. doi: 10.1212/ WNl.48.4.1094.
6. Vetrugno R, Proveni F, Cortelli P, Plazzi G, Lotti EM, Pierangeli G, et al. Sleep disorders in multiple system atrophy: a correlative videopolysomnographic study. Sleep Med 2004;5:21–30. doi: 10.1016/s1470-sleep.2003.07.002.
7. Tachibana N, Kimura K, Katajima K, Shinde A, Kimura J, Shibasaki H. REM sleep motor dysfunction in multiple system atrophy: with special emphasis on sleep talk as its early clinical manifestation. J Neurol Neurosurg Psychiatry 1997;63:678–681. doi: 10.1136/jnpp.63.5.678.
8. Palma JA, Fernandez-Cordon C, Coon EA, Low PA, Miglis MG, Jarach S, et al. Prevalence of REM sleep behavior disorder in multiple system atrophy: a multicenter study and meta-analysis. Clin Auton Res 2015;25:69–75. doi: 10.1007/s10286-015-0279-9.
9. Moreno-Lopez C, Santamaria J, Salamero M, Del Sorbo F, Albanese A, Pellechia MT, et al. Excessive daytime sleepiness in multiple system atrophy (SLEEMSA study). Arch Neurol 2011;68:223–230. doi: 10.1001/archneurol.2010.359.
10. Shimohata T, Nakayama H, Tomita M, Ozawa T, Nishizawa M. Daytime sleepiness in Japanese patients with multiple system atrophy: prevalence and determinants. BMC Neurosci 2012;12:130. doi: 10.1186/1471-2277-12-130.
11. Stefanova N, Bucke P, Duerr S, Wenning GK. Multiple system atrophy: an update. Lancet Neurol 2009;8:1172–1178. doi: 10.1016/S1474-4422(09)70288-1.
12. Zhang L, Cao B, Ou R, Wei QQ, Zhao B, Yang J, et al. Non-motor symptoms and the quality of life in multiple system atrophy with different subtypes. Parkinsonism Relat Disord 2017;35:63–68. doi: 10.1016/j.parkreldis.2016.12.007.
