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

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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]

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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]

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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.[9,14] The affected brain areas vary between the two subtypes, with typically olivopontocerebellar atrophy in MSA-C and striatonigal 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.[15] 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. 2015236). 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.[16] Patients were screened for spinocerebellar ataxia (SCA) genes, including SCA1, 2, 3, 6, and 7, to exclude the common forms of SCA. Brain magnetic resonance imaging was also performed to exclude other neurological disorders. After excluding patients with <6 years of education and those with incomplete data, 165 patients who met the clinical diagnostic criteria of "probable" MSA were finally included in the study.[17]

All patients underwent a face-to-face interview by experienced movement disorder specialists. Demographic and clinical data including sex, age, weight, height, educational years, subtype (MSA-P or MSA-C), age at onset, disease duration, symptom onset, medication use (levodopa, dopamine agonist), and levodopa equivalent daily doses (LEDD) were collected. Patients with MSA were categorized into two subtypes (MSA-P and MSA-C) according to whether they had predominantly parkinsonian or cerebellar symptoms. Age at onset referred to the age at which symptoms appeared. Symptom onset referred to the initial presentation of symptoms, including motor symptoms (parkinsonian or cerebellar symptoms) and autonomic symptoms. Disease severity was evaluated by the total score of the Unified Multiple System Atrophy Rating Scale (UMSARS).[18] Orthostatic hypotension was defined as a 30 mmHg decrease in systolic blood pressure or 15 mmHg decrease in diastolic blood pressure after standing from the recumbent position. Cardiovascular disease was excluded as the cause of orthostatic hypotension. The body mass index (BMI) was calculated as body weight (kg) divided by heights squared (m^2). Overweight was defined as a BMI of ≥ 24 kg/m^2. The LEDD was calculated by the commonly used protocol.[19] Executive function was assessed using the Frontal Assessment Battery (FAB).[20] Global cognitive function was evaluated using the Montreal Cognitive Assessment (MoCA), which includes seven domains: visuospatial and executive function, naming, attention, language, abstraction, delay recall, and orientation.[21] The Hamilton Depression Rating Scale-24 (HDRS-24) was used to screen for depression, and a score of >20 indicated depression.[22] The Hamilton Anxiety Rating Scale (HARS) was used to screen for anxiety, and a score of > 14 indicated anxiety.[23] The Fatigue Severity Scale (FSS) was used to screen for fatigue,[24] and a score of ≥36 indicated fatigue.

In the current study, we focused on three sleep-related symptoms: Parkinson's disease (PD)-related sleep problems (PD-SP), EDS, and RBD. PD-SP were evaluated using the PD Sleep Scale-2 (PDSS-2).[25] Patients who obtained a score of ≥18 were considered to have PD-SP. EDS was evaluated using the Epworth Sleepiness Scale (ESS).[26] EDS was defined as an ESS score of ≥10. RBD was evaluated using the RBD Screening Questionnaire (RBDSQ),[27] and patients with a score of ≥5 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 (40.39–78.81)	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)	15.50 (2.0–34.0)	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)	–1.014*	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].

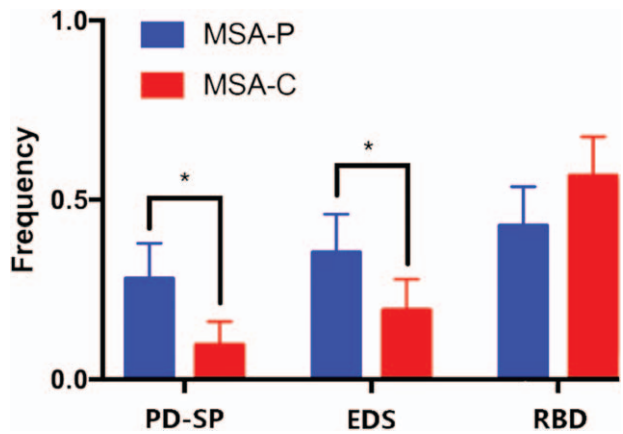

Figure 1: Comparison of frequency sleep-related symptoms in two subtypes of patients with multiple system atrophy (MSA). EDS: Excessive daytime sleepiness; MSA-C: Cerebellar subtype of MSA; MSA-P: Parkinsonism subtype of MSA; PD-SP: Parkinson's disease-related sleep problems; RBD: Rapid eye movement sleep behavior disorder.

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,

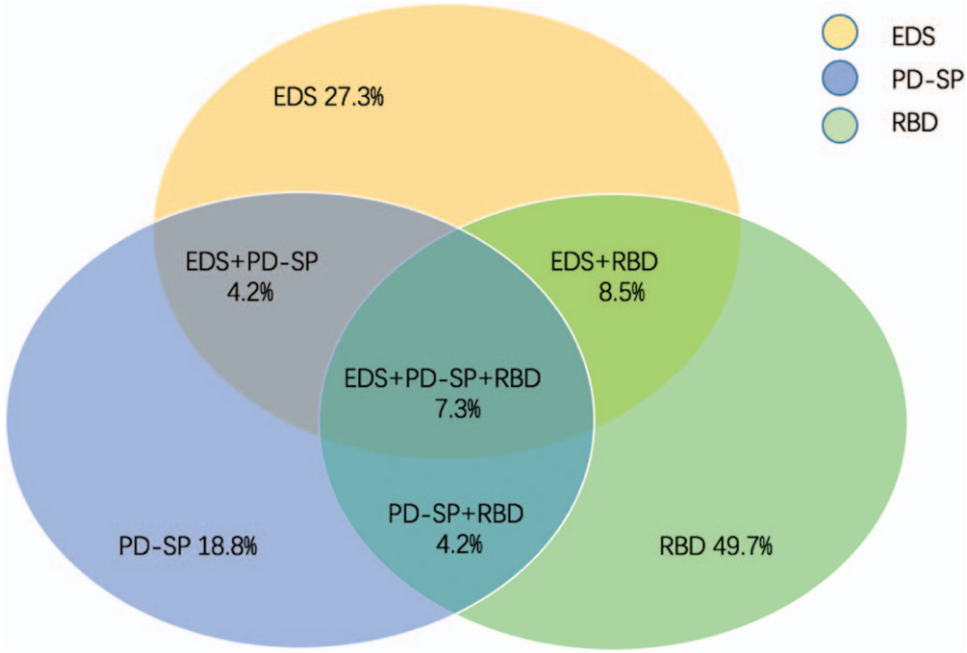

Figure 2: Prevalence and overlap of sleep-related symptoms in patients with multiple system atrophy (MSA). EDS: Excessive daytime sleepiness; PD-SP: Parkinson's diseaserelated sleep problems; RBD: Rapid eye movement sleep behavior disorder.

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.[11] Another study showed that 23.1% of patients with MSA had RLS.[29] 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 (28% of Caucasian patients with MSA[9] and 24% of Japanese patients with MSA[10]). RBD was found to be the most common sleep disorders,[30] comfirming the important role of RBD in

Table 2: Demographic and clinical features of the MSA patients with and without PD-SP, EDS, and RBD.

Variables	With PD-SP	Without PD-SP	Statistical values	*P* value	With EDS	Without EDS	Statistical values	*P* value	With RBD	Without RBD	Statistical values	*P* value
Subtype (MSA-P/MSA-C)	23/8	59/75	9.163†	0.002	29/16	53/67	5.383†	0.020	35/47	47/36	3.208†	0.073
Male sex, *n* (%)	16 (51.6)	80 (59.7)	0.677†	0.411	33 (73.3)	63 (52.5)	5.838†	0.016	57 (69.5)	39 (47.0)	8.601†	0.003
Mean age (years)	63.64 (44.75–77.27)	61.32 (40.39–79.69)	−1.312*	0.190	64.59 (47.99–76.97)	60.88 (40.39–79.69)	−2.089*	0.037	60.14 (40.76–77.27)	63.19 (40.39–79.69)	−1.812*	0.070
Age of onset (years)	60.08 ± 8.16	59.24 (38.76–76.96)	−0.893*	0.372	61.75 (39.55–75.15)	59.23 (38.76–76.96)	−1.979*	0.048	57.32 (38.76–75.15)	60.61 (39.59–76.96)	−1.957*	0.050
Disease duration (years)	2.75 (0.49–5.81)	2.27 (0.31–7.00)	−1.039*	0.299	2.14 (0.32–7.00)	2.34 (0.31–5.67)	−0.104*	0.917	2.36 (0.31–7.00)	2.13 (0.32–5.61)	−1.025*	0.305
Educational year	11.0 (6.0–16.0)	9.0 (6.0–20.0)	−0.530*	0.596	11.0 (6.0–16.0)	9.0 (6.0–20.0)	−1.472*	0.141	9.0 (6.0–19.0)	9.0 (6.0–20.0)	−0.391*	0.696
Overweight, *n* (%)	5 (16.1)	22 (16.4)	0.002†	0.969	10 (22.2)	17 (14.2)	1.552†	0.213	19 (23.2)	8 (9.6)	5.519†	0.019
Orthostatic hypotension, *n* (%)	13 (41.9)	47 (35.1)	0.512†	0.474	18 (40.0)	42 (35.0)	0.354†	0.552	32 (39.0)	28 (33.7)	0.499†	0.480
Motor onset/ Autonomic onset	22/9	85/49	0.627†	0.428	27/18	80/40	0.638†	0.424	47/35	60/23	4.056†	0.044
UMSARS-I	20.0 (9.0–34.0)	14.0 (2.0–35.5)	−3.404*	0.001	19.0 (9.0–34.0)	14.0 (2.0–35.0)	−3.869*	<0.001	17.0 (5.0–35.0)	13.0 (2.0–34.0)	−4.222*	<0.001
UMSARS-II	20.0 (8.0–35.0)	17.5 (6.0–36.0)	−2.334*	0.020	19.0 (8.0–35.0)	18.0 (6.0–36.0)	−1.462*	0.144	19.0 (7.0–36.0)	17.0 (6.0–35.0)	−2.443*	0.015
UMSARS-IV	2.0 (1.0–5.0)	2.0 (1.0–4.0)	−3.392*	0.001	2.0 (1.0–5.0)	2.0 (1.0–4.0)	−2.144*	0.032	2.0 (1.0–5.0)	2.0 (1.0–5.0)	−0.514*	0.607
Total UMSARS score	41.0 (18.0–71.0)	33.0 (12.0–75.0)	−3.322*	0.001	40.0 (18.0–71.0)	33.0 (12.0–75.0)	−3.059*	0.002	37.0 (14.0–75.0)	32.0 (12.0–72.0)	−3.385*	0.001
FAB score	14.0 (8.0–18.0)	15.0 (4.0–18.0)	−1.423*	0.155	14.0 (7.0–18.0)	15.0 (4.0–18.0)	−0.533*	0.594	15.0 (7.0–18.0)	15.0 (4.0–18.0)	−0.076*	0.940
MoCA												
Visuospatial and executive function	3.0 (0–5.0)	4.0 (0–5.0)	−1.559*	0.119	4.0 (0–5.0)	3.0 (0–5.0)	−0.318*	0.750	3.5 (0–5.0)	3.0 (0–5.0)	−0.664*	0.507
Naming	3.0 (1.0–3.0)	3.0 (1.0–3.0)	−1.871*	0.061	3.0 (1.0–3.0)	3.0 (1.0–3.0)	−0.250*	0.803	3.0 (1.0–3.0)	3.0 (1.0–3.0)	−1.013*	0.311
Attention	5.0 (2.0–6.0)	6.0 (1.0–6.0)	−1.566*	0.117	5.0 (2.0–6.0)	6.0 (1.0–6.0)	−0.613*	0.540	6.0 (1.0–6.0)	6.0 (2.0–6.0)	−0.423*	0.673
Language	2.0 (0–3.0)	2.0 (0–3.0)	−0.127*	0.899	2.0 (0–3.0)	2.0 (0–3.0)	−0.084*	0.933	2.0 (0–3.0)	2.0 (0–3.0)	−0.039*	0.969
Abstraction	1.0 (0–2.0)	1.0 (0–2.0)	−1.110*	0.267	1.0 (0–2.0)	1.0 (0–2.0)	−0.401*	0.688	1.0 (0–2.0)	1.0 (0–2.0)	−0.231*	0.817
Delay recall	3.0 (0–5.0)	3.0 (0–5.0)	−1.215*	0.224	3.0 (0–5.0)	3.0 (0–5.0)	−0.668*	0.504	3.0 (0–5.0)	3.0 (0–5.0)	−0.545*	0.586
Orientation	6.0 (2.0–6.0)	6.0 (1.0–6.0)	−0.548*	0.584	6.0 (2.0–6.0)	6.0 (1.0–6.0)	−0.881*	0.378	6.0 (2.0–6.0)	6.0 (1.0–6.0)	−1.254*	0.210
Total MoCA score	22.0 (8.0–28.0)	24.0 (8.0–30.0)	−1.642*	0.101	24.0 (8.0–28.0)	23.0 (8.0–30.0)	−0.105*	0.917	24.0 (10.0–30.0)	23.0 (8.0–30.0)	−0.042*	0.966
FSS score	54.0 (9.0–63.0)	42.0 (9.0–63.0)	−3.417*	0.001	54.0 (14.0–63.0)	41.5 (9.0–63.0)	−3.905*	<0.001	50.5 (9.0–63.0)	41.0 (9.0–63.0)	−2.275*	0.023
HDRS-24 score	16.0 (3.0–41.0)	8.0 (0–32)	−5.097*	<0.001	13.0 (2.0–41.0)	10.0 (0–32.0)	−2.033*	0.042	12.0 (0–40.0)	10.0 (0–41.0)	−1.008*	0.313
HARS score	14.0 (0–26.0)	7.0 (0–33.0)	−4.503*	<0.001	10.0 (0–26.0)	7.0 (0–33.0)	−2.346*	0.019	8.0 (0–28.0)	7.0 (0–33.0)	−1.139*	0.255
LEDD (mg/d)	150.0 (0–750.0)	0 (0–750.0)	−1.870*	0.061	150.0 (0–750.0)	0 (0–750.0)	−1.694*	0.090	0 (0–750.0)	0 (0–750.0)	−0.772*	0.440
Dopamine agonist, *n* (%)	7 (22.6)	25 (18.7)	0.248†	0.619	14 (31.1)	18 (15.0)	5.434†	0.020	12 (14.6)	20 (24.1)	2.362†	0.124
Levodopa, *n* (%)	17 (54.8)	48 (35.8)	3.814†	0.051	22 (48.9)	43 (35.8)	2.336†	0.126	31 (37.8)	34 (41.0)	0.172†	0.678

*Mann-Whitney *U* test. †Chi-square test. EDS: Excessive daytime sleepiness (ESS ≥ 10); 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.

Table 3: Demographic and clinical features of the MSA-P patients with and without PD-SP, EDS, and RBD.

Variables	With PD-SP (*n* = 23)	Without PD-SP (*n* = 59)	Statistical values	*P* value	With EDS (*n* = 29)	Without EDS (*n* = 53)	Statistical values	*P* value	With RBD (*n* = 35)	Without RBD (*n* = 47)	Statistical values	*P* value
Male sex, *n* (%)	9 (39.1)	35 (59.3)	2.713†	0.100	18 (62.1)	26 (49.1)	1.276†	0.259	21 (60.0)	23 (48.9)	0.988†	0.320
Mean age (years)	63.28 (44.75–77.27)	62.61 (40.39–78.81)	−0.046*	0.963	64.55 (47.99–76.97)	61.96 (40.39–78.81)	−1.081*	0.280	61.58 (47.99–77.27)	63.89 (40.39–78.81)	−0.708*	0.479
Age of onset (years)	60.00 (39.55–74.27)	60.10 (39.59–75.18)	−0.212*	0.832	61.75 (39.55–73.51)	59.38 (39.59–75.18)	−1.188*	0.235	59.08 (39.55–74.27)	60.83 (39.59–75.18)	−0.970*	0.332
Disease duration (years)	2.31 (0.49–4.56)	2.67 (0.32–7.00)	−0.470*	0.639	2.31 (0.32–7.00)	2.67 (0.49–5.67)	−0.461*	0.645	2.67 (0.49–7.00)	2.59 (0.32–5.61)	−0.389*	0.697
Educational year	9.0 (6.0–16.0)	9.0 (6.0–20.0)	−0.886*	0.376	11.2 ± 3.1	9.0 (6.0–20.0)	−1.575*	0.115	9.0 (6.0–16.0)	11.0 (6.0–20.0)	−1.293*	0.196
Overweight, *n* (%)	3 (13.0)	11 (18.6)	–	0.747	8 (27.6)	6 (11.3)	–	0.073	7 (20.0)	7 (14.9)	0.369†	0.543
Orthostatic hypotension, *n* (%)	8 (34.8)	16 (27.1)	0.470†	0.493	12 (41.4)	12 (22.6)	3.179†	0.075	11 (31.4)	13 (27.7)	0.138†	0.711
Motor onset/ Autonomic onset	18/5	41/	0.631†	0.427	19/10	40/13	0.920†	0.337	25/10	34/13	0.008†	0.928
UMSARS-I	20.0 (9.0–34.0)	14.0 (2.0–28.0)	−3.171*	0.002	19.0 (9.0–34.0)	14.0 (2.0–28.0)	−3.388*	0.001	18.0 (10.0–34.0)	14.0 (2.0–31.0)	−3.002*	0.003
UMSARS-II	20.0 (8.0–35.0)	18.0 (7.0–32.0)	−1.981*	0.048	19.0 (8.0–35.0)	18.0 (7.0–34.0)	−1.798*	0.072	19.0 (7.0–34.0)	18.0 (7.0–35.0)	−1.639*	0.101
UMSARS-IV	3.0 (1.0–5.0)	2.0 (1.0–4.0)	−3.152*	0.002	2.0 (1.0–5.0)	2.0 (1.0–4.0)	−2.998*	0.003	2.0 (1.0–4.0)	2.0 (1.0–5.0)	−1.576*	0.115
Total UMSARS score	42.0 (19.0–71.0)	33.0 (16.0–60.0)	−2.964*	0.003	41.0 (19.0–71.0)	32.0 (16.0–65.0)	−3.033*	0.002	40.0 (18.0–71.0)	33.0 (16.0–71.0)	−2.388*	0.017
FAB score	14.0 (8.0–18.0)	16.0 (8.0–18.0)	−1.318*	0.187	14.0 (8.0–18.0)	15.0 (8.0–18.0)	−0.715*	0.475	15.0 (8.0–18.0)	15.0 (8.0–18.0)	−0.719*	0.472

(*continued*)

Table 3

(continued).

Variables	With PD-SP ($n=23$)	Without PD-SP ($n=59$)	Statistical values	P value	With EDS ($n=29$)	Without EDS ($n=53$)	Statistical values	P value	With RBD ($n=35$)	Without RBD ($n=47$)	Statistical values	P value
MoCA												
Visuospatial and executive funct function	3.0 (1.0–5.0)	4.0 (1.0–5.0)	–1.890*	0.059	4.0 (1.0–5.0)	4.0 (1.0–5.0)	–0.095*	0.924	3.0 (1.0–5.0)	4.0 (1.0–5.0)	–0.863*	0.388
Naming	3.0 (1.0–3.0)	3.0 (1.0–3.0)	–2.089*	0.037	3.0 (1.0–3.0)	3.0 (1.0–3.0)	–0.285*	0.776	3.0 (1.0–3.0)	3.0 (1.0–3.0)	–0.619*	0.536
Attention	5.0 (2.0–6.0)	6.0 (1.0–6.0)	–1.513*	0.130	5.0 (2.0–6.0)	6.0 (1.0–6.0)	–0.492*	0.623	5.0 (1.0–6.0)	6.0 (2.0–6.0)	–0.526*	0.599
Language	2.0 (0–3.0)	2.0 (0–3.0)	–0.164*	0.870	2.0 (0–3.0)	2.0 (0–3.0)	–0.267*	0.790	2.0 (0–3.0)	2.0 (0–3.0)	–0.104*	0.917
Abstraction	1.0 (0–2.0)	1.0 (0–2.0)	–1.150*	0.250	1.0 (0–2.0)	1.0 (0–2.0)	–0.692*	0.489	1.0 (0–2.0)	1.0 (0–2.0)	–0.684*	0.494
Delay recall	3.0 (0–5.0)	3.0 (0–5.0)	–1.166*	0.244	3.0 (0–5.0)	3.0 (0–5.0)	–0.155*	0.877	3.0 (0–5.0)	3.0 (0–5.0)	–0.077*	0.938
Orientation	6.0 (2.0–6.0)	6.0 (3.0–6.0)	–0.465*	0.642	6.0 (2.0–6.0)	6.0 (3.0–6.0)	–0.007*	0.994	6.0 (4.0–6.0)	6.0 (2.0–6.0)	–1.132*	0.258
Total MOCA score	23.0 (8.0–28.0)	25.0 (9.0–30)	–1.823*	0.068	25.0 (8.0–28.0)	24.0 (9.0–30)	–0.078*	0.938	24.0 (11.0–29.0)	24.0 (8.0–30.0)	–0.475*	0.635
FSS score	54.0 (9.0–63.0)	40.0 (9.0–63.0)	–3.116*	0.002	54.0 (14.0–63.0)	37.0 (9.0–63.0)	–3.785*	<0.001	54.0 (9.0–63.0)	42.0 (9.0–63.0)	–2.119*	0.034
HDRS-24 score	16.0 (10.0–41.0)	10.0 (0–25.0)	–4.455*	<0.001	13.0 (2.0–41.0)	11.0 (0–25.0)	–2.078*	0.038	12.0 (0–40)	12.0 (0–41.0)	–0.225*	0.822
HARS score	14.0 (0–26.0)	7.0 (0–33.0)	–3.803*	<0.001	10 (0–26.0)	7.0 (0–33.0)	–2.071*	0.038	8.0 (0–26.0)	7.0 (0–33.0)	–0.385*	0.700
LEDD (mg/d)	300.0 (0–750.0)	200.0 (0–750.0)	–0.893*	0.372	300.0 (0–750.0)	150.0 (0–750.0)	–1.448*	0.148	300.0 (0–750.0)	150.0 (0–750.0)	–0.907*	0.364
Dopamine agonist, *n* (%)	7 (30.4)	21 (35.6)	0.196†	0.658	14 (48.3)	14 (26.4)	3.984†	0.046	11 (31.4)	17 (36.2)	0.201†	0.654
Levodopa, *n* (%)	16 (69.6)	32 (54.2)	1.602†	0.206	20 (69.0)	28 (52.8)	2.011†	0.156	24 (68.6)	24 (51.1)	2.533†	0.111

*Mann-Whitney *U* test. †Chi-square test. EDS: Excessive daytime sleepiness (ESS ≥ 10); 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.

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

Variables	With PD-SP ($n=8$)	Without PD-SP ($n=75$)	Statistical values	P value	With EDS ($n=16$)	Without EDS ($n=67$)	Statistical values	P value	With RBD ($n=47$)	Without RBD ($n=36$)	Statistical values	P value
Male sex, *n* (%)	7 (87.5)	45 (60.0)	–	0.248	15 (93.8)	37 (55.2)	8.193†	0.004	36 (76.6)	16 (44.4)	9.006†	0.003
Mean age (years)	66.14 (53.44–76.18)	59.45 (40.76–79.69)	–1.829*	0.067	65.06 (48.15–76.18)	57.43 (40.76–79.69)	–1.662*	0.096	56.90 (40.76–76.73)	62.43 (45.86–79.69)	–1.636*	0.102
Age of onset (years)	62.81 (49.78–75.15)	58.54 (38.76–76.96)	–1.466*	0.143	62.09 (45.15–75.15)	56.72 (38.76–76.96)	–1.374*	0.170	54.66 (38.76–75.15)	59.76 (44.33–76.96)	–1.636*	0.102
Disease duration (years)	3.57 (1.02–5.81)	2.08 (0.31–4.79)	–1.852*	0.064	2.08 (0.47–5.81)	2.26 (0.31–4.98)	0.208*	0.835	2.33 (0.31–5.81)	1.82 (0.47–4.66)	–1.571*	0.116
Educational year	12.5 (6.0–16.0)	9.0 (6.0–19.0)	–1.804*	0.071	11.0 (6.0–16.0)	9.0 (6.0–19.0)	–0.376*	0.707	9.0 (6.0–19.0)	9.0 (6.0–16.0)	–0.794*	0.427
Overweight, *n* (%)	2 (25.0)	11 (14.7)	–	0.605	2 (12.5)	11 (16.4)	–	1.000	19 (23.2)	8 (9.6)	7.990†	0.005
Orthostatic hypotension	5 (62.5)	31 (41.3)	–	0.284	6 (37.5)	30 (44.8)	0.278†	0.598	21 (44.7)	15 (41.7)	0.075†	0.784
Motor onset/ Autonomic onset	4/4	44/31	–	0.716	8/8	40/27	0.498†	0.480	22/25	26/10	5.399†	0.020
UMSARS-I	16.0 (9.0–28.0)	15.0 (2.0–35.0)	–1.283*	0.199	16.50 (9.0–28.0)	14.0 (2.0–35.0)	–1.839*	0.066	17.0 (5.0–35.0)	12.5 (2.0–34.0)	–3.186*	0.001
UMSARS-II	19.5 (8.0–23.0)	17.0 (6.0–36.0)	–1.005*	0.315	17.0 (8.0–26.0)	18.0 (6.0–36.0)	–0.012*	0.991	19.0 (7.0–36.0)	15.0 (6.0–34.0)	–2.043*	0.041
UMSARS-IV	2.0 (1.0–5.0)	2.0 (1.0–4.0)	–1.016*	0.310	2.0 (1.0–5.0)	2.0 (1.0–4.0)	–0.599*	0.549	2.0 (1.0–5.0)	2.0 (1.0–4.0)	–0.531*	0.595
Total UMSARS score	37.5 (18.0–56.0)	33.0 (12.0–75.0)	–1.413*	0.158	36.0 (18.0–56.0)	34.0 (12.0–75.0)	–0.918*	0.358	37.0 (14.0–75.0)	30.0 (12.0–72.0)	–2.635*	0.008
FAB score	13.0 (9.0–16.0)	14.0 (4.0–18.0)	–1.329*	0.184	14.50 (7.0–18.0)	14.0 (4.0–18.0)	–0.628*	0.530	15.0 (7.0–18.0)	13.50 (4.0–18.0)	–1.185*	0.236
MoCA												
Visuospatial and executive function	3.0 (0–5.0)	3.0 (0–5.0)	–0.826*	0.409	3.5 (0–5.0)	3.0 (0–5.0)	–0.071*	0.944	4.0 (0–5.0)	3.0 (0–5.0)	–2.067*	0.039
Naming	3.0 (1.0–3.0)	3.0 (1.0–3.0)	–0.365*	0.715	3.0 (1.0–3.0)	3.0 (1.0–3.0)	–0.708*	0.479	3.0 (1.0–3.0)	3.0 (1.0–3.0)	–0.842*	0.400
Attention	5.0 (4.0–6.0)	6.0 (2.0–6.0)	–0.475*	0.635	5.0 (4.0–6.0)	6.0 (2.0–6.0)	–0.285*	0.775	6.0 (3.0–6.0)	5.5 (2.0–6.0)	–1.076*	0.282
Language	1.50 (0–3.0)	2.0 (0–3.0)	–1.088*	0.277	2.0 (0–3.0)	2.0 (0–3.0)	–0.283*	0.777	2.0 (0–3.0)	2.0 (0–3.0)	–0.038*	0.969
Abstraction	1.0 (0–2.0)	1.0 (0–2.0)	–0.537*	0.591	1.0 (0–2.0)	1.0 (0–2.0)	–1.544*	0.123	1.0 (0–2.0)	1.0 (0–2.0)	–0.413*	0.680
Delay recall	2.5 (0–4.0)	3.0 (0–5.0)	–1.084*	0.278	2.5 (0–4.0)	3.0 (0–5.0)	–1.223*	0.221	3.0 (0–5.0)	3.0 (0–5.0)	–0.440*	0.660
Orientation	6.0 (4.0–6.0)	6.0 (1.0–6.0)	–0.433*	0.665	5.5 (3.0–6.0)	6.0 (1.0–6.0)	–1.867*	0.062	6.0 (2.0–6.0)	6.0 (1.0–6.0)	–0.308*	0.758
Total MOCA score	18.0 (15.0–27.0)	23.0 (8.0–30.0)	–1.184*	0.237	21.50 (13.0–27.0)	23.0 (8.0–30.0)	–0.862*	0.388	23.0 (10.0–30.0)	23.0 (8.0–30.0)	–0.852*	0.394
FSS score	52.5 (9.0–63.0)	43.0 (9.0–63.0)	–1.315*	0.189	45.5 (14.0–63.0)	44.0 (9.0–63.0)	–1.339*	0.181	47.0 (9.0–63.0)	37.0 (9.0–63.0)	–1.353*	0.176
HDRS-24 score	16.0 (3.0–24.0)	8.0 (0–32.0)	–2.149*	0.032	11.0 (2.0–24.0)	8.0 (0–32.0)	–0.393*	0.694	12.0 (0–32.0)	7.5 (1.0–27.0)	–1.256*	0.209
HARS score	12.0 (7.0–22.0)	7.0 (0–28.0)	–2.412*	0.016	9.0 (0–24.0)	7.0 (0–28.0)	–1.290*	0.197	8.0 (0–28.0)	5.5 (0–23.0)	–1.404*	0.160
LEDD (mg/d)	0 (0–450.0)	0 (0–600.0)	–0.449*	0.653	0 (0–450.0)	0 (0–600.0)	–0.893*	0.372	0 (0–450.0)	0 (0–600.0)	–1.415*	0.157
Dopamine agonist, *n* (%)	0	4 (5.3)	–	1.000	0	4 (6.0)	–	1.000	1 (2.1)	3 (8.3)	–	0.312
Levodopa, *n* (%)	1 (12.5)	16 (21.3)	–	1.000	2 (12.5)	15 (22.4)	–	0.126	7 (14.9)	10 (27.8)	2.078†	0.149

*Mann-Whitney *U* test. †Chi-square test. EDS: Excessive daytime sleepiness (ESS ≥ 10); 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.

Table 5: Factors associated with sleep-related symptoms in MSA patients.

Variable	OR	95% CI	*P* value
PD-SP*			
Subtype (MSA-P = 1, MSA-C = 0)	3.861	1.499–9.941	0.005
Total UMSARS score	1.042	1.006–1.080	0.022
Anxiety	4.755	1.833–12.336	0.001
EDS†			
Sex (male = 1, female = 0)	3.309	1.441–7.602	0.005
Total UMSARS score	1.036	1.003–1.070	0.032
Subtype (MSA-P = 1, MSA-C = 0)	2.733	1.251–5.973	0.012
Fatigue	3.654	1.493–8.943	0.005
RBD‡			
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, total UMSARS score, anxiety, depression, fatigue were included as co-variables. †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 (PDSS-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.

α-synucleinopathies.[31] 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. After adjusting for age, disease duration, and LEDD, the current study showed that patients with the MSA-P subtype had a higher frequency of PD-SP and EDS, but not RBD, than patients with the MSA-C subtype. Our findings suggest that different sleep-related symptoms are associated with different MSA subtypes, and these different symptoms may be related to the underlying pathophysiological characteristics of each subtype.

No studies have investigated the factors associated with PD-SP and RBD in patients with MSA, and few studies have investigated the factors associated with EDS in patients with MSA. One study showed that EDS in Caucasian patients with MSA was associated with a decreased sleep duration and SDB.[9] Another study of Japanese patients with MSA found no relationship between EDS and SDB but revealed a dose-dependent effect of antiparkinson drugs.[10] The current study revealed that a higher total UMSARS score (*ie*, greater disease severity) was associated with PD-SP, 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-

ric, and more pronounced striatonigral degeneration in patients with MSA-P than MSA-C[35] and more diffuse DAT loss in patients with MSA-C than MSA-P.[36] In addition, neurodegenerative changes may affect the central autonomic nervous system, including the hypothalamus, noradrenergic and serotoninergic brainstem nuclei, nucleus ambiguus, dorsal nucleus of the vagus nerve, and Onuf's nucleus.[1] 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,[37] cholinergic neurons in the laterodorsal tegmental and pedunculopontine tegmental nuclei in the pons,[38] putative wake-active dopaminergic neurons in the ventral periaqueductal gray matter,[39] and serotonergic neurons of the rostral raphe[40]; 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,[41] but not with the degree of loss of mesopontine cholinergic neurons.[38]

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,[17] 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 apneas as well as periodic limb movements were not included in the analysis. Because the occurrence of stridor might contribute to shortened survival,[42] 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.

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Conflicts of interest

None.

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