Tonic Electromyogram Density in Multiple System Atrophy with Predominant Parkinsonism and Parkinson's Disease

Yi Wang[1,2], Yun Shen[1,2], Kang-Ping Xiong[1,2], Pei-Cheng He[1,2], Cheng-Jie Mao[1,2], Jie Li[1,2], Fu-Yu Wang[1,2], Ya-Li Wang[1,2,3], Jun-Ying Huang[1,2], Chun-Feng Liu[1,2,3]

[1]Department of Neurology and Sleep Center, The Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215004, China
[2]Suzhou Clinical Research Center of Neurological Disease, The Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215004, China
[3]Institute of Neuroscience, Soochow University, Suzhou, Jiangsu 215123, China

Abstract

Background: Both Parkinson's disease (PD) and multiple system atrophy (MSA) have associated sleep disorders related to the underlying neurodegenerative pathology. Clinically, MSA with predominant parkinsonism (MSA-P) resembles PD in the manifestation of prominent parkinsonism. Whether the amount of rapid eye movement (REM) sleep without atonia could be a potential marker for differentiating MSA-P from PD has not been thoroughly investigated. This study aimed to examine whether sleep parameters could provide a method for differentiating MSA-P from PD.

Methods: This study comprised 24 MSA-P patients and 30 PD patients, and they were of similar age, gender, and REM sleep behavior disorder (RBD) prevalence. All patients underwent clinical evaluation and one night of video-polysomnography recording. The tonic and phasic chin electromyogram (EMG) activity was manually quantified during REM sleep of each patient. We divided both groups in terms of whether they had RBD to make subgroup analysis.

Results: No significant difference between MSA-P group and PD group had been found in clinical characteristics and sleep architecture. However, MSA-P patients had higher apnea-hypopnea index (AHI; 1.15 [0.00, 8.73]/h vs. 0.00 [0.00, 0.55]/h, $P = 0.024$) and higher tonic chin EMG density (34.02 [18.48, 57.18]% vs. 8.40 [3.11, 13.06]%, $P < 0.001$) as compared to PD patients. Subgroup analysis found that tonic EMG density in MSA + RBD subgroup was higher than that in PD + RBD subgroup (55.04 [26.81, 69.62]% vs. 11.40 [8.51, 20.41]%, $P < 0.001$). Furthermore, no evidence of any difference in tonic EMG density emerged between PD + RBD and MSA - RBD subgroups ($P > 0.05$). Both disease duration ($P = 0.056$) and AHI ($P = 0.051$) showed no significant differences during subgroup analysis although there was a trend toward longer disease duration in PD + RBD subgroup and higher AHI in MSA - RBD subgroup. Stepwise multiple linear regression analysis identified the presence of MSA-P ($\beta = 0.552$, $P < 0.001$) and RBD ($\beta = 0.433$, $P < 0.001$) as predictors of higher tonic EMG density.

Conclusion: Tonic chin EMG density could be a potential marker for differentiating MSA-P from PD.

Key words: Multiple System Atrophy with Predominant Parkinsonism; Parkinson's Disease; Polysomnography; Tonic Chin Electromyogram Density

INTRODUCTION

Both Parkinson's disease (PD) and multiple system atrophy (MSA) have associated sleep disorders related to the underlying neurodegenerative pathology, such as abnormal sleep architecture, rapid eye movement sleep behavior disorder (RBD), excessive daytime sleepiness, restless legs syndrome, periodic limb movement disorder, and circadian dysfunction.[1-3] RBD is common in and strongly correlated with alpha-synucleinopathies (SPs), with the prevalence varying by diseases: 30–50% in PD and 80–95% in MSA.[4] In addition, idiopathic RBD is considered a harbinger of neurodegenerative disorders.

Rapid eye movement sleep without atonia (RSWA) is an essential diagnostic feature of RBD on polysomnography (PSG), with either excessive sustained elevation of electromyogram (EMG) tone or excessive phasic EMG

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activity in the rapid eye movement (REM) stage. Previous research has reported that higher surface EMG activity was associated with longer PD disease duration and greater disease severity and has suggested higher surface EMG activity as a PD biomarker.[5] However, little is known about the clinical correlates of RSWA in MSA. One study found that RSWA percentage was higher in MSA than that in PD.[6] MSA is characterized by prominent autonomic dysfunction with combinations of predominant parkinsonism (MSA-P), predominant cerebellar ataxia, and corticospinal disorders. Clinically, MSA-P resembles PD in the manifestation of prominent parkinsonism. Whether the amount of RSWA could be a potential marker for differentiating MSA-P from PD has not been thoroughly investigated. In this study, we explored the association between RSWA and SPs by manually quantifying chin EMG activity during REM sleep, and then, we compared the results in the MSA-P group to those of the PD group to determine if any significant differences exist and whether these differences could be used to distinguish MSA-P from PD.

METHODS

Patients

This study was a retrospective study evaluating the medical records of all MSA-P patients and case-matched PD patients from September 2010 to May 2015 in Center of Parkinsonism and Movement Disorder, The Second Affiliated Hospital of Soochow University. All patients meeting the clinical probable diagnostic criteria for MSA-P[7] were enrolled. We then searched for patients that satisfied the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria[8] and matched the MSA-P patients for age, gender, and RBD percentage. RBD was diagnosed according to the International Classification of Sleep Disorders (ICSD-II) criteria. It requires the combination of clinical characteristics (either by history or by abnormal REM sleep behaviors captured during video monitoring) and the presence of RSWA during video-polysomnography (vPSG). Patients who were taking selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, melatonin, or clonazepam were excluded from the study as these medications can alter EMG tone.[9,10] Patients continued taking their medications for parkinsonism as usual. Drug dosages were converted to daily levodopa equivalent doses (LEDs) for the purpose of data collection.[11]

All patients underwent a clinical evaluation, including a comprehensive neurological examination, the Mini Mental Status Examination (MMSE), the Montreal Cognitive Assessment (MOCA, Beijing version), the Epworth Sleepiness Scale (ESS), and the Pittsburgh Sleep Quality Index (PSQI). The PD patients were evaluated by the Unified Parkinson's Disease Rating Scale and Hoehn and Yahr scale during the medication "on" state. All patients provided written informed consent to participate in this study and signed additional consent forms agreeing to the use of their vPSG for scientific purposes. This study was approved by the Ethical Committee of The Second Affiliated Hospital of Soochow University.

Polysomnography

All patients underwent a night of standard vPSG (Compumedics-E series, Australia) monitoring in the sleep center. The basic recordings included electroencephalogram (F3-A2, F4-A1, C3-A2, C4-A1, O1-A2, and O2-A1), electrooculogram (EOG, LOC-A2, and ROC-A1), chin EMG, electrocardiogram, nasal-oral pressure transducer airflow, thermal oronasal airflow, thoracic and abdominal respiratory efforts, oxyhemoglobin saturation, snoring sound, and body position. All the vPSGs were manually scored by experienced technologists according to the American Academy of Sleep Medicine guidelines.

The following vPSG data were obtained and analyzed: awakenings; total sleep time (TST); sleep efficiency (SE); sleep latency (SL); REM sleep latency (REML); wake after sleep onset (WASO); percentage of sleep spent in non-REM sleep stage (NREM) 1, NREM2, NREM3, and REM sleep; arousal index; apnea-hypopnea index (AHI); minimal oxygen saturation (SaO_2); mean SaO_2; and the percentage of time spent at $SaO_2 <90\%$ (time$-[SaO_2 <90\%]$).

Analysis of electromyogram activity

The tonic and phasic chin EMG activity was quantified manually in each patient. RSWA was scored according to a previously published method:[12] each 20 s REM sleep epoch was scored as tonic depending on the presence of chin EMG activity for more than 50% of each epoch, with an amplitude of at least twice that of background activity or >10 μV. Phasic EMG activity was scored with 2 s mini-epochs containing bursts of EMG activity lasting between 0.1 s and 5.0 s, with an amplitude of at least four times the background EMG activity. Bursts of phasic activity occurring simultaneously with tonic activity were required to have an amplitude of twice the background tonic EMG activity within the same 2 s mini-epoch to be scored as phasic activity.[13] We calculated separately the percentage of 20 s epochs with tonic and 2 s mini-epochs with phasic EMG activity as tonic chin EMG density and phasic chin EMG density, respectively. All chin EMG activity correlating with arousals or respiratory events was carefully eliminated from the quantification.

Statistical analysis

SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Data were presented as mean ± standard deviation (SD), median (Q1, Q3), or frequencies (percentages). The qualitative data were analyzed using Chi-squared test or Fisher's exact test, as appropriate. Comparison of continuous variables in the two groups was conducted using Student's t-test. If the data were not in a normal distribution, the Mann-Whitney U-test was used. Four subgroups comparisons were performed using one-way analysis of variance or Kruskal-Wallis test. Stepwise multiple linear regression analysis was performed to determine the predictors of higher tonic EMG density. The independent variables included age, gender, BMI, TST, SE, SL, REML,

WASO, NREM1%, NREM2%, NREM3%, REM%, AHI, arousal index, P%, ESS, and MOCA. Statistical significance was defined as $P < 0.05$.

RESULTS

Demographic and clinical characteristics

Demographic and clinical characteristics of individuals are presented in Table 1. Among the 24 MSA-P patients, 12 were male. The MSA-P group had a mean age of 64.9 ± 8.0 years (range: 46–77 years), mean body mass index (BMI) of 22.40 ± 3.66 kg/m^2 (range: 15.80–33.10 kg/m^2), mean disease duration of 38.00 ± 19.75 months (range: 6–72 months), sleep apnea-hypopnea syndrome (SAHS) prevalence of 33.3%, and mean LEDs of 433.77 ± 251.38 mg/d (range: 50–1139 mg/d). According to the ICSD-II criteria, 16 (66.7%) of 24 MSA-P patients were diagnosed with RBD, all of whom had clinical history of abnormal sleep behaviors and definite vPSG-captured dream enactment behavior during REM stage. The remaining eight MSA-P without RBD patients had no clinical history of sleep-related injurious or disruptive behaviors. Thirty PD patients with similar age, gender, and RBD prevalence were recruited. The PD group had a mean age of 65.3 ± 5.5 years (range: 50–79 years), mean BMI of 22.79 ± 3.11 kg/m^2 (range: 16.60–28.40 kg/m^2), mean disease duration of 43.97 ± 29.37 months (range: 9–128 months), SAHS prevalence of 10.0%, mean LEDs of 372.47 ± 147.05 mg/d (range: 37.50–65.00 mg/d), and 18 (60.0%) of 30 PD patients were diagnosed with RBD according to the ICSD-II criteria. We found no significant differences in BMI ($P = 0.674$), disease duration ($P = 0.398$), LEDs ($P = 0.297$), ESS score ($P = 0.720$), PSQI score ($P = 0.614$), MMSE score ($P = 0.984$), or MOCA score during the medication "on" state ($P = 0.430$) between the two groups.

Polysomnography data

The PSG data are presented in Table 2. MSA-P group had higher AHI (1.15 [0.00, 8.73]/h vs. 0.00 [0.00, 0.55]/h, $P = 0.024$), lower minimal SaO$_2$ (89.33 ± 3.81% vs. 91.60 ± 2.93%, $P = 0.017$), lower mean SaO$_2$ (94.79 ± 1.91% vs. 95.77 ± 1.61%, $P = 0.047$), greater percentage of time spent at SaO$_2$ <90% (0.05 [0.00, 3.43]% vs. 0.00 [0.00, 0.00]%, $P = 0.007$), and higher tonic chin EMG density (34.02 [18.48, 57.18]% vs. 8.40 [3.11, 13.06]%, $P < 0.001$), compared with the PD group. No statistically significant differences in awakenings ($P = 0.202$), TST ($P = 0.350$), SE ($P = 0.162$), SL ($P = 0.103$), REML ($P = 0.195$), WASO ($P = 0.376$), NREM1 ($P = 0.930$), NREM2 ($P = 0.458$), NREM3 ($P = 0.893$), REM ($P = 0.243$), arousal index ($P = 0.195$), and phasic chin EMG density ($P = 0.638$) were found between the two groups.

Subgroups analysis

As tonic chin EMG activity and AHI showed significant difference between MSA-P group and PD group, both of them had great associations with RBD, so we divided both groups into with (MSA + RBD; PD + RBD) or without RBD (MSA - RBD; PD - RBD) subgroups to make other comparisons.

The results are displayed in Table 3. Tonic and phasic EMG density subgroup comparisons are shown in Figures 1 and 2. Both disease duration ($P = 0.056$) and AHI ($P = 0.051$) showed no significant differences during subgroup analysis although there was a trend toward longer disease duration in PD + RBD subgroup and higher AHI in MSA - RBD subgroup. Tonic and phasic EMG density showed significant differences between PD + RBD subgroup and PD - RBD subgroup ($Z = -3.979$, $P < 0.001$; and $Z = -3.726$, $P < 0.001$), MSA + RBD subgroup and MSA - RBD subgroup (Z

Table 1: Demographics and clinical features of patients with MSA-P and PD

Characteristics	PD group (n = 30)	MSA-P group (n = 24)	Statistical values	P
Age (years)	65.3 ± 5.5	64.9 ± 8.0	0.227*	0.821
Male	14 (46.7)	12 (50.0)	0.059†	0.808
BMI (kg/m^2)	22.79 ± 3.11	22.40 ± 3.66	0.422*	0.674
Disease duration (months)	43.97 ± 29.37	38.00 ± 19.75	0.852*	0.398
RBD	18 (60.0)	16 (66.7)	0.254†	0.614
SAHS	3 (10.0)	8 (33.0)	3.152†	0.076
ESS score	6.50 ± 4.02	6.92 ± 4.44	−0.361*	0.720
PSQI score	8.03 ± 4.00	7.43 ± 4.58	0.507*	0.614
MMSE score	25.93 ± 3.55	25.92 ± 2.32	0.021*	0.984
MOCA score	23.20 ± 4.96	22.21 ± 3.98	0.796*	0.430
LEDs (mg/d)	372.47 ± 147.05	433.77 ± 251.38	−1.059*	0.297
UPDRS III score	21.73 ± 9.40	NA	NA	NA
UPDRS total score	34.87 ± 13.42	NA	NA	NA
Hoehn-Yahr stage	2.00 (1.38, 3.00)	NA	NA	NA

The data are shown as mean ± SD, or n (%). *Student's t-test; †Chi-squared test. PD: Parkinson's disease; MSA-P: Multiple system atrophy with predominant parkinsonism; BMI: Body mass index; RBD: Rapid eye movement sleep behavior disorder; SAHS: Sleep apnea-hypopnea syndrome; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index; MMSE: Mini Mental Status Examination; MOCA: Montreal Cognitive Assessment. UPDRS: Unified Parkinson's Disease Rating Scale; LEDs: Levodopa equivalent doses; NA: Not applicable; SD: Standard deviation.

Table 2: Polysomnographic data in patients with MSA-P and PD

Parameters	PD group (n = 30)	MSA-P group (n = 24)	Statistical values	P
Awakenings (n)	22.00 ± 9.42	18.92 ± 7.73	1.292*	0.202
TST (min)	356.95 ± 101.64	334.88 ± 59.02	0.943*	0.350
SE (%)	68.32 ± 15.78	62.75 ± 12.30	1.419*	0.162
SL (min)	5.25 (0.50, 17.63)	12.75 (4.50, 26.38)	−1.630†	0.103
REML (min)	126.72 ± 84.28	161.50 ± 110.55	−1.312*	0.195
WASO (min)	116.53 ± 81.65	134.88 ± 65.88	−0.892*	0.376
NREM1 (%)	21.92 ± 17.22	22.29 ± 12.85	−0.088*	0.930
NREM2 (%)	44.83 ± 14.84	41.74 ± 15.37	0.748*	0.458
NREM3 (%)	16.68 ± 10.35	16.28 ± 11.54	0.135*	0.893
REM (%)	16.58 ± 7.17	19.68 ± 11.96	−1.180*	0.243
Arousal index	5.60 (2.10, 9.38)	7.00 (3.85, 11.85)	−1.297†	0.195
AHI (/h)	0.00 (0.00, 0.55)	1.15 (0.00, 8.73)	−2.261†	0.024
Minimal SaO$_2$ (%)	91.60 ± 2.93	89.33 ± 3.81	2.473*	0.017
Mean SaO$_2$ (%)	95.77 ± 1.61	94.79 ± 1.91	2.034*	0.047
Time spent at SaO$_2$ <90% (%)	0.00 (0.00, 0.00)	0.05 (0.00, 3.43)	−2.674†	0.007
Tonic EMG density (%)	8.40 (3.11, 13.06)	34.02 (18.48, 57.18)	−4.169†	<0.001
Phasic EMG density (%)	4.85 (1.67, 9.36)	5.78 (1.12, 17.99)	−0.470†	0.638

The data are shown as mean ± SD or median (Q1, Q3). *Student's t-test; †Mann-Whitney U-test. PD: Parkinson's disease; MSA-P: Multiple system atrophy with predominant parkinsonism; TST: Total sleep time; SE: Sleep efficiency; SL: Sleep latency; REML: Rapid eye movement sleep latency; WASO: Wake after sleep onset; REM: Rapid eye movement; NREM: Non-REM; AHI: Apnea-hypopnea index; SaO$_2$: Oxygen saturation; EMG: Electromyogram; SD: Standard deviation.

Table 3: Comparisons of demographics and chin EMG density among the four subgroups

Parameters	PD + RBD subgroup (n = 18)	PD - RBD subgroup (n = 12)	MSA + RBD subgroup (n = 16)	MSA - RBD subgroup (n = 8)	Statistical values	P
Age (years)	65.9 ± 6.4	64.4 ± 3.9	64.5 ± 9.2	65.8 ± 5.0	0.198*	0.897
Male	9 (50.0)	5 (41.7)	7 (43.8)	5 (62.5)	1.075†	0.800
BMI (kg/m²)	23.46 ± 3.02	21.80 ± 3.10	22.63 ± 3.62	21.95 ± 3.95	0.713*	0.549
Disease duration (months)	53.67 ± 32.19	29.42 ± 16.96	39.31 ± 20.53	35.38 ± 19.16	2.691*	0.056
AHI (/h)	0.00 (0.00, 1.75)	0.00 (0.00, 0.43)	0.65 (0.00, 4.30)	14.20 (0.08, 36.48)	7.789‡	0.051
Tonic EMG density (%)	11.40 (8.51, 20.41)§,‖	1.82 (0.63, 5.51)	55.04 (26.81, 69.62)§	11.19 (2.94, 28.88)‖	35.262‡	<0.001
Phasic EMG density (%)	8.30 (5.15, 15.19)§	1.67 (1.26, 2.59)	8.08 (3.57, 25.18)§	0.57 (0.00, 8.36)‖	17.424‡	0.001

The data are shown as mean ± SD or median (Q1, Q3). *One-way analysis of variance; †Chi-squared test; ‡Kruskal-Wallis test followed by Mann-Whitney U-test, with Bonferroni correction α' = 0.05/(4×[4−1]/2) = 0.0083; §P<0.05 versus PD-RBD subgroup; ‖P<0.05, versus MSA + RBD subgroup. PD: Parkinson's disease; MSA: Multiple system atrophy; RBD: Rapid eye movement sleep behavior disorder; BMI: Body mass index; AHI: Apnea-hypopnea index; EMG: Electromyogram; SD: Standard deviation.

= −3.123, P = 0.002 and Z = −2.635, P = 0.008), MSA + RBD subgroup and PD - RBD subgroup (Z = −4.457, P < 0.001 and Z = −3.251, P = 0.001), which was easy to understand as it was because of the presence of RBD. The most interesting result was the significant difference of tonic EMG density between MSA + RBD and PD + RBD subgroups (Z = −4.244, P < 0.001). Another concern was that we failed to present a difference of tonic EMG density between PD + RBD and MSA - RBD subgroups. Age, gender, and BMI showed no differences among four subgroups.

Regression analysis

To further explore the associations of clinical factors and the presence of higher tonic EMG density, the data including age, gender, BMI, disease type, disease duration, TST, SE, SL, REML, WASO, NREM1, NREM2, NREM3, REM, arousal index, AHI, phasic EMG density, ESS score, MOCA score, and LEDs were subjected to regression analysis. Table 4 shows that the presence of MSA-P (β = 0.552, P < 0.001) and RBD (β = 0.433, P < 0.001) was associated with higher tonic EMG density.

Discussion

The main finding was that the MSA-P group had higher tonic tone than the PD group, irrespective of whether there was clinical RBD or not. In addition, we identified the presence of MSA-P and RBD as independent predictors of higher tonic EMG density.

Subgroup analysis showed that the disease duration had a trend toward being significant, and we might see a longer disease duration in PD + RBD subgroup, which could
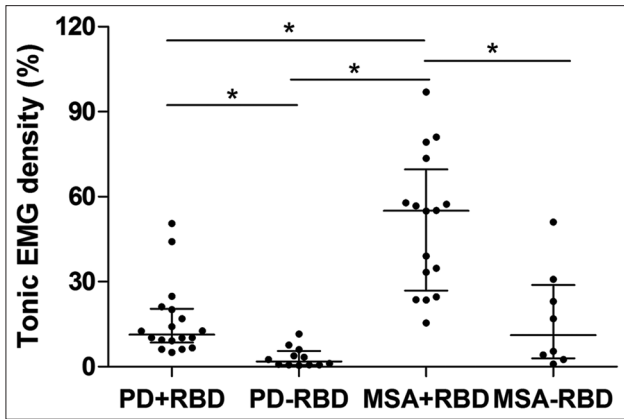
Figure 1: Subgroup comparisons of tonic electromyogram density among four subgroups. Tonic electromyogram density (%) obtained from patients with Parkinson's disease or multiple system atrophy with predominant parkinsonism is plotted. The long and short horizontal bars represent the median and interquartile range. *P < 0.05.
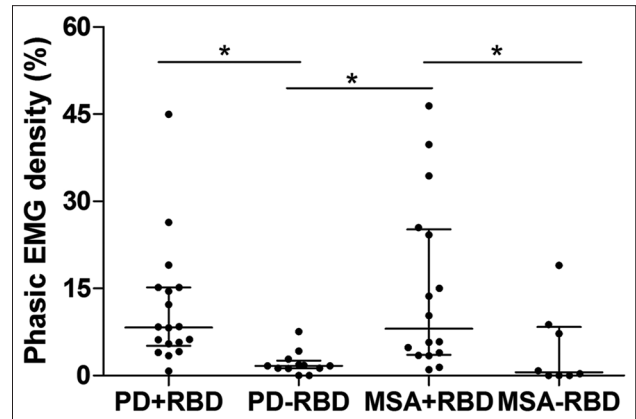
Figure 2: Subgroup comparisons of phasic electromyogram density among four subgroups. Phasic electromyogram density (%) obtained from patients with Parkinson's disease or multiple system atrophy with predominant parkinsonism is plotted. The long and short horizontal bars represent the median and interquartile range. *P < 0.05.

Table 4: Stepwise multiple linear regression analysis of factors associated with higher tonic EMG density					
Model	β	t	P	R^2	Adjusted R^2
MSA-P	0.552	5.701	<0.001	0.525	0.506
RBD	0.433	4.476	<0.001		

MSA-P: Multiple system atrophy with predominant parkinsonism; RBD: Rapid eye movement behavior disorder; EMG: Electromyogram.

be attributed to the fact that the RBD symptoms seem to gradually increase during the course of PD.[14]

Only a few studies have evaluated the difference in RSWA between MSA and PD. In a study of 26 MSA and 45 PD patients with a mean disease duration of 4.5 ± 2.3 years and 9 ± 5.3 years (P < 0.001), respectively, Iranzo et al.[6] found that the MSA group, as compared to the PD group, exhibited increased RSWA ($68.8 \pm 29.3\%$ vs. $39.4 \pm 31.6\%$, P < 0.001) and submental phasic EMG activity ($30.6 \pm 20\%$ vs. $22.1 \pm 11.2\%$, P > 0.05). Their finding of a higher RSWA percentage in MSA patients was consistent with our results, but their values of RSWA were higher than those found in this study. The RSWA metrics in the research seemed quite low for SPs, especially for the Montreal 20S scoring approach. In our previous study, Gong et al.[15] identified the tonic EMG density in PD + RBD to be 13.88 (3.07–39.96)%. Some other studies analyzing Asian patients have shown similar results. Zhou et al.[16] showed tonic EMG density in Chinese RBD patients was $20.6 \pm 16.9\%$, and in their previous study, they found significant lower values of EMG activity as well.[17] Therefore, we speculated the lower EMG activity in Chinese patients with RBD might be attributed to ethnical differences. We further grouped both groups into with and without RBD to make subgroup comparisons to eliminate the influence of RBD on tonic EMG density. Moreover, we showed that not only MSA + RBD subgroup had a higher tonic EMG density than PD + RBD subgroup but also the MSA - RBD subgroup had the tonic EMG density close to

that of PD + RBD subgroup. That was MSA-P group had higher tonic tone than the PD group, irrespective of whether there was clinical RBD or not.

It has demonstrated that lesions in the sublaterodorsal nucleus (SLD) cause RSWA. The proposed pathophysiology of RBD in humans suggested by Boeve et al.[18] included lesions in the SLD and altered locomotor drive. As loss of REM atonia is the essential feature of RBD, some researchers believed that a higher tonic chin EMG density during REM sleep could indicate a greater RBD severity[19] and resulted from more severe neurodegeneration of the associated brainstem structure. The study showed higher tonic chin EMG density in the MSA-P group, which could be attributed to the more rapid and widespread neurodegenerative pathology in MSA-P as compared to that in PD.

Moreover, the tonic chin EMG activity might be partially due to the RBD, and it might also reflect the severity of basal ganglia (BG) dysfunction. Takakusaki et al.[20] demonstrated that the GABAergic substantia nigra pars reticulata (SNr)-pedunculopontine nucleus (PPN) projections could control the muscle tone of movements during wakefulness and modulate REM-sleep atonia by activating the cholinergic PPN neurons. Studies have shown that loss of cholinergic neurons in the PPN occurs in both PD and MSA and the degree of cholinergic neuron loss correlates with the severity of motor symptoms in PD. In parkinsonism, globus pallidus interna hyperactivity results in more inhibitory GABAergic input to the PPN, leading to reduced activity of the glutamatergic PPN neurons, which project to the reticulospinal neurons of brainstem and spinal cord, causing abnormal changes in locomotion and muscle tone.[21] MSA has more rapid and widespread pathology than PD. We suspected that the SLD, PPN, and BG are affected earlier and more severely in MSA-P than PD, resulting in a higher REM sleep tonic chin EMG density in MSA-P. We anticipate future research focusing on the

relationship between abnormal BG output and tonic EMG activity during REM sleep.

We found a significant difference in tonic chin EMG density, but not in phasic chin EMG density between the two groups. In our previous study, we found tonic RSWA was more closely correlated with PD severity than phasic RSWA,[22] which was consistent with the results of this study. Similarly, a case report by Tachibana and Oka[23] described a 60-year-old MSA patient, whose PSGs indicated tonic chin EMG activity that increased as the patient's disease progressed, whereas the patient's phasic chin EMG activity remained relatively suppressed. Postuma et al.[19] analyzed the baseline PSG data of the patients who first presented with RBD and later developed neurodegenerative diseases; the researchers found that the severity of tonic chin EMG density on baseline PSG predicted the development of PD. Researchers have suggested that tonic RSWA might reflect degeneration of the SLD,[24-26] whereas phasic RSWA results from activation of locomotor generators during sleep and alterations of the intermediate ventromedial medulla pathways.[18] Dysfunction of brainstem structures, such as the PPN or BG, can also alter muscle tone. Because of the different mechanisms underlying tonic and phasic chin EMG activities, we found no contradiction in the existence of a strong correlation between tonic chin EMG activity and neurodegenerative pathology of SPs in the brainstem and the absence of a correlation between phasic chin EMG activity and SPs.

There were some limitations of this study. First, the sample size was not sufficiently large enough to determine the cutoff value for tonic chin EMG activity. Second, recognizing MSA early in the disease progression is difficult. The patients in this study were not in the earliest stages of disease progression. Future studies should focus on patients who first manifest idiopathic RBD and are subsequently diagnosed with an SP, to examine the evolution of RSWA in search of conversion predictors.

In conclusion, the results showed that the MSA-P patients had higher AHI and higher tonic chin EMG density as compared to PD patients. Moreover, the presence of MSA-P and RBD were associated with higher tonic EMG density. Given these results, the tonic EMG density could be a potential marker for differentiating MSA-P from PD.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Abbott SM, Videnovic A. Sleep disorders in atypical parkinsonism. Mov Disord Clin Pract 2014;1:89-96. doi: 10.1002/mdc3.12025.
2. Suzuki K, Miyamoto M, Miyamoto T, Hirata K. Parkinson's disease and sleep/wake disturbances. Curr Neurol Neurosci Rep 2015;15:8. doi: 10.1007/s11910-015-0525-5.
3. Videnovic A, Golombek D. Circadian and sleep disorders in Parkinson's disease. Exp Neurol 2013;243:45-56. doi: 10.1016/j.expneurol.2012.08.018.
4. Howell MJ, Schenck CH. Rapid eye movement sleep behavior disorder and neurodegenerative disease. JAMA Neurol 2015;72:707-12. doi: 10.1001/jamaneurol.2014.4563.
5. Chahine LM, Kauta SR, Daley JT, Cantor CR, Dahodwala N. Surface EMG activity during REM sleep in Parkinson's disease correlates with disease severity. Parkinsonism Relat Disord 2014;20:766-71. doi: 10.1016/j.parkreldis.2014.04.011.
6. Iranzo A, Santamaría J, Rye DB, Valldeoriola F, Martí MJ, Muñoz E, et al. Characteristics of idiopathic REM sleep behavior disorder and that associated with MSA and PD. Neurology 2005;65:247-52. doi: 10.1212/01.wnl.0000168864.97813.e0.
7. Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology 2008;71:670-6. doi: 10.1212/01.wnl.0000324625.00404.15.
8. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181-4.
9. Winkelman JW, James L. Serotonergic antidepressants are associated with REM sleep without atonia. Sleep 2004;27:317-21.
10. McCarter SJ, St Louis EK, Sandness DJ, Arndt K, Erickson M, Tabatabai GM, et al. Antidepressants increase REM sleep muscle tone in patients with and without REM sleep behavior disorder. Sleep 2015;38:907-17. doi: 10.5665/sleep.4738.
11. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010;25:2649-53. doi: 10.1002/mds.23429.
12. Montplaisir J, Gagnon JF, Fantini ML, Postuma RB, Dauvilliers Y, Desautels A, et al. Polysomnographic diagnosis of idiopathic REM sleep behavior disorder. Mov Disord 2010;25:2044-51. doi: 10.1002/mds.23257.
13. Frauscher B, Iranzo A, Gaig C, Gschliesser V, Guaita M, Raffelseder V, et al. Normative EMG values during REM sleep for the diagnosis of REM sleep behavior disorder. Sleep 2012;35:835-47. doi: 10.5665/sleep.1886.
14. Nomura T, Inoue Y, Högl B, Uemura Y, Yasui K, Sasai T, et al. Comparison of the clinical features of rapid eye movement sleep behavior disorder in patients with Parkinson's disease and multiple system atrophy. Psychiatry Clin Neurosci 2011;65:264-71. doi: 10.1111/j.1440-1819.2011.02201.x.
15. Gong Y, Xiong KP, Mao CJ, Shen Y, Hu WD, Huang JY, et al. Clinical manifestations of Parkinson disease and the onset of rapid eye movement sleep behavior disorder. Sleep Med 2014;15:647-53. doi: 10.1016/j.sleep.2013.12.021.
16. Zhou J, Zhang J, Du L, Li Z, Li Y, Lei F, et al. Characteristics of early- and late-onset rapid eye movement sleep behavior disorder in China: A case-control study. Sleep Med 2014;15:654-60. doi: 10.1016/j.sleep.2013.12.020.
17. Zhang J, Lam SP, Ho CK, Li AM, Tsoh J, Mok V, et al. Diagnosis of REM sleep behavior disorder by video-polysomnographic study: Is one night enough? Sleep 2008;31:1179-85.
18. Boeve BF, Silber MH, Saper CB, Ferman TJ, Dickson DW, Parisi JE, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. Brain 2007;130(Pt 11):2770-88. doi: 10.1093/brain/awm056.
19. Postuma RB, Gagnon JF, Rompré S, Montplaisir JY. Severity of REM atonia loss in idiopathic REM sleep behavior disorder predicts Parkinson disease. Neurology 2010;74:239-44. doi: 10.1212/WNL.0b013e3181ca0166.
20. Takakusaki K, Obara K, Nozu T, Okumura T. Modulatory effects of

the GABAergic basal ganglia neurons on the PPN and the muscle tone inhibitory system in cats. Arch Ital Biol 2011;149:385-405. doi: 10.4449/aib.v149i4.1383.

21. Benarroch EE. Pedunculopontine nucleus: Functional organization and clinical implications. Neurology 2013;80:1148-55. doi: 10.1212/WNL.0b013e3182886a76.

22. Shen Y, Xiong KP, Li J, Mao CJ, Chen J, He PC, *et al.* Clinical correlates of rapid eye movement sleep without atonia in Parkinson's disease. Clin Neurophysiol 2015;126:1198-203. doi: 10.1016/j.clinph.2014.09.014.

23. Tachibana N, Oka Y. Longitudinal change in REM sleep components in a patient with multiple system atrophy associated with REM sleep behavior disorder: Paradoxical improvement of nocturnal behaviors in a progressive neurodegenerative disease. Sleep Med 2004;5:155-8.

doi: 10.1016/j.sleep.2003.09.007.

24. Gjerstad MD, Boeve B, Wentzel-Larsen T, Aarsland D, Larsen JP. Occurrence and clinical correlates of REM sleep behaviour disorder in patients with Parkinson's disease over time. J Neurol Neurosurg Psychiatry 2008;79:387-91. doi: 10.1136/jnnp.2007.116830.

25. Ding Y, Hu YQ, Zhan SQ, Li CJ, Wang HX, Wang YP. Comparison study of polysomnographic features in multiple system atrophy-cerebellar types combined with and without rapid eye movement sleep behavior disorder. Chin Med J 2016;129:2173-7. doi: 10.4103/0366-6999.189903.

26. Zhang JR, Chen J, Yang ZJ, Zhang HJ, Fu YT, Shen Y, *et al.* Rapid eye movement sleep behavior disorder symptoms correlate with domains of cognitive impairment in Parkinson's disease. Chin Med J 2016;129:379-85. doi: 10.4103/0366-6999.176077.