Loss of Rapid Eye Movement Sleep Atonia in Patients with REM Sleep Behavioral Disorder, Narcolepsy, and Isolated Loss of REM Atonia

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Study Objectives: To compare the amounts of REM sleep without atonia (RSWA) between patients with REM sleep behavior disorder (RBD), "isolated loss of REM atonia," narcolepsy, and control subjects and determine if there were threshold values for the amount of RSWA that differentiate each group from controls.

Methods: Retrospective analyses of polysomnography (PSG) records were used employing strict quantitative criteria for the measurement of phasic and tonic EMG activity during REM sleep. The PSG recordings of 47 individuals were analyzed (RBD 16, isolated loss of REM atonia 11, narcolepsy 10, control 10).

Results: Patients with the diagnosis of isolated loss of REM atonia had significantly lower levels of EMG activity during REM sleep than those with RBD but higher than control subjects. RSWA was higher in narcolepsy than in loss of REM atonia but lower than for RBD patients. Receiver operating characteristic (ROC) curves provided threshold values

with high specificity and sensitivity in all patient groups with a cutoff value $\geq 1.22\%$ (100% correctly classified) for phasic and $\geq 3.17\%$ for tonic (92% correctly classified) EMG activity in RBD.

Conclusion: Quantification of REM sleep EMG activity can successfully differentiate RBD and isolated loss of REM atonia patients from controls. The consistently increased amount of RSWA in patients with narcolepsy indicates that this can be an additional marker for a diagnosis of narcolepsy. Longitudinal studies of patients with isolated loss of REM atonia are needed to evaluate if these patients are at risk of developing RBD or neurodegenerative disorders.

Keywords: REM sleep behavior disorder (RBD), REM sleep, narcolepsy, EMG, polysomnography

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REM sleep behavior disorder (RBD) is a parasomnia characterized by loss of normal muscle atonia during REM sleep with abnormal motor activity that is proposed to be associated with dream content.¹ RBD is associated with neurodegenerative disorders and in particular with synucleinopathies such as Parkinson disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) (secondary RBD). Long-term follow-up studies have shown that a large proportion (38% to 65%) of patients with presumed idiopathic RBD develop Parkinsonism and/or dementia.^{2,3} EEG and neuropsychological tests have also revealed early evidence of CNS dysfunction in idiopathic RBD patients.⁴⁻⁷ Furthermore, diffusion tensor imaging has uncovered microstructural abnormalities in the brain areas responsible for REM sleep regulation in idiopathic RBD patients.⁸

In addition to neurodegenerative disease, RBD is also associated with other sleep disorders. Periodic limb movements of sleep (PLMS) are highly prevalent (70%) in patients with RBD.⁵ In addition, RBD is frequently seen in patients with narcolepsy.^{9,10} REM sleep without atonia (RSWA) in narcolepsy was first described in 1992.¹⁰ RBD and/or RSWA are thought to be common in narcolepsy with cataplexy and rare in narcolepsy without cataplexy.^{11,12} It has been proposed that hypocretin deficiency plays an essential role for both RBD and cataplexy in narcolepsy.¹³

BRIEF SUMMARY

Current Knowledge/Study Rationale: There are currently no widely accepted criteria for abnormally elevated level of submental EMG activity during REM sleep. The study aimed to determine if the amount of REM sleep atonia in patients with isolated loss of REM atonia and RBD was significantly different from control subjects and to set the criteria of REM sleep without atonia for the diagnosis of RBD, isolated loss of REM atonia and narcolepsy.

Study Impact: The criteria used to quantify REM sleep without atonia found reliable cut off values for differentiating patients with RBD, isolated loss of REM atonia as well as narcolepsy from control subjects. The study suggests that there is continuum pathological process that may lead to neurodegeneration and can be detected early as REM sleep atonia loss.

Isolated loss of REM atonia or RSWA is a condition usually identified incidentally in patients during polysomnography. The loss of REM atonia is an electrophysiological finding without accompanying abnormal motor behavior during REM sleep. Although the condition may represent "subclinical" or "preclinical" RBD in some cases,¹⁴ there are no longitudinal data to substantiate progression to the clinical RBD or neurodegenerative disorders.

The first method for visual quantitative measuring of chin EMG activity in RBD patients was developed in 1992.¹⁵ Two different activities were measured—tonic and phasic. This method has been widely used with certain variations to quantify RSWA in both RBD and narcolepsy patients by different research groups.^{15–21} Some studies quantified tonic EMG activity in 20-s epochs and phasic in 2-s epochs^{15,16,18,20}; others used 30-s and 3-s intervals, respectively^{17,19,21}; and some studies did not indicate epoch duration²² or scored only phasic^{23,24} or tonic activity.²² Bliwise et al. and Bliwise & Rye quantified PEM (phasic electromyographic metric) in 2.5-sec intervals.^{23,24} The majority of studies have quantified chin muscle activity, and several research groups used other muscle groups as well. Chin EMG has the highest rate of activity among muscles. Frauscher et al. measured phasic activity in 3-s epochs in 13 different muscles and Iranzo et al. in 5 muscles (mentalis, right and left flexor digitorum superficialis, and right and left extensor digitorum brevis).^{25,26}

A number of computerized scoring methods have been developed to analyze increased muscle activity in REM sleep.^{27–30} However, the validity of these methods has not yet been tested. One problem is how to define loss of REM atonia; a variety of criteria have been used. The majority have defined phasic as four times baseline and tonic as two times baseline. Eisensehr et al. and Knudsen et al. quantified two other types of activities: short (0.1–0.49s) and long-lasting muscle activity (0.5–15s) in the left anterior tibialis.^{14,37}

A first cutoff (10%; sensitivity 89% and specificity 57%) was identified for combined tonic and phasic activity in RBD patients where clinical features of the disease were used as a gold standard.¹⁷ Montplaisir et al.²⁰ identified a cutoff value $\geq 30\%$ (81.9% correctly classified) for tonic and $\geq 15\%$ (83.8% correctly classified) for phasic chin EMG activity during REM sleep using a visual method of scoring. However, they found elevated levels of RSWA in control subjects as well.²⁰

There are, however, currently no widely accepted criteria for abnormally elevated level of submental EMG activity and no validated cutoff values of submental EMG activity during REM sleep for differentiation of RBD and isolated loss of REM atonia patients from normal controls. We set out to use strict criteria for loss of REM atonia in order to: (1) determine differences in measures of loss of REM atonia between patients given a diagnosis of isolated loss of REM atonia versus patients with a diagnosis of RBD, narcolepsy, and control groups; (2) evaluate if there is any correlation between the amounts of tonic and phasic EMG activity; and (3) determine diagnostic criteria (cutoff values) for the proportion of REM sleep with tonic and phasic EMG activity in each group of patients that would allow a robust way to distinguish RBD, isolated loss of REM atonia, and narcolepsy patients from controls.

METHODS

The study was performed as an audit of polysomnography (PSG) data, applying quantitative criteria to evaluate the accuracy of the clinical diagnoses of RBD and loss of REM atonia at our sleep unit. Approval for the audit was obtained by the audit committee of the National Hospital for Neurology and Neurosurgery.

Subjects

All PSG recordings used for the study were obtained from patients admitted to the telemetry unit at the National Hospital for Neurology and Neurosurgery for a sleep study from January 2009 to February 2011. The diagnoses were based on clinical review of PSG data and MSLT (for a diagnosis of narcolepsy) by consultant neurologists with a special interest in sleep disorders (SHE and MCW).

Exclusion and Inclusion Criteria

All patients with a diagnosis of RBD, isolated loss of REM atonia, or narcolepsy were considered for the study (68). In all groups we excluded those with insufficient quality PSG data, such as numerous artifacts, very short or too fragmented REM sleep (< 2 continuous epochs of REM and/or scattered single REM epochs with total amount < 5 min), or other technical problems that could interfere with accurate EMG scoring. For some patients, PSG recording could not be restored due to technical problems.

After applying exclusion criteria, PSG recordings of 47 patients were included in the study. Polysomnography reports and referrals for sleep studies were reviewed for clinical information and additional sleep parameters.

RBD

Sixteen patients with the diagnosis of RBD were included in the study. Both patients with idiopathic ($n = 10$) and secondary or symptomatic RBD ($n = 6$) were included in the study. The latter group included patients with neurodegenerative disorders (PD, MSA, probable DLB), stroke, and cognitive decline. A patient with epilepsy for whom no seizure activity was identified during the night of study was also included.

Isolated Loss of REM Atonia

Eleven patients with a diagnosis of isolated loss of REM atonia were included in the study. Two patients with a concomitant diagnosis of epilepsy were included in this group since no seizures were observed during the sleep study. In 2 patients, the use of antidepressants (citalopram, amitriptyline) was reported. In one of these patients clonazepam use was reported for other indications.

Narcolepsy

Patients with a concomitant diagnosis of neurodegenerative disorders and/or RBD were excluded. In total, 10 patients with narcolepsy with cataplexy (8) or narcolepsy without cataplexy (2) were included in the study.

Control Group

Ten patients were identified who had been admitted to the hospital with different sleep complaints—predominantly suspected NREM sleep parasomnias, insomnia, or hypersomnolence where no abnormality was found and the study demonstrated normal sleep. The patients did not have concomitant neurodegenerative disorders, narcolepsy, or other sleep disorders.

Polysomnography

As the majority of patients only had one night PSG recording, all analyses were performed on the first night's recording even

if patients were admitted for several nights to ensure consistency and avoid any potential confounders such as a first night effect. During PSG recording, 22 channels of EEG, including 2 ground electrodes and 2 reference electrodes (reference electrodes placed at Pz), were applied according to the 10-20 international placement system.³² EMG activity was recorded from the masseter muscles, submental muscle, and right and left tibialis anterior muscles. EOG was recorded bilaterally and referred to cross-linked mastoid electrodes.

PSG data was acquired using a Nicolet LTM Neurodiagnostic System – software NicoletOne v. 5.71 (Viasys Healthcare). Data were analyzed using NicVue reader software. Sleep staging was carried out on a bipolar montage including all channels and using epoch duration of 30 seconds. During clinical assessment of PSGs, sleep was scored/staged based on Rechtschaffen and Kales scoring criteria.³³ For this particular study, only epochs that had been scored as REM sleep by an experienced clinical physiologist (M-AW) during the clinical review were analyzed. EMG activity resulting from movements associated with arousals was not scored.

Scoring

The scoring process was performed by a single scorer (AK), blinded to patient group. To calculate the degree of inter-rater agreement, 2 independent readers (SHE and MCW) also assessed 7,400 seconds of REM sleep from 3 patients with RBD. The κ score for phasic events was 0.81 and for tonic epochs was 0.88. These indicate excellent agreement for event and epoch classification.

In order to minimize electrode artifact and interference so increasing signal to noise ratio, the submental muscle EMG the signal was post hoc digitally band-pass filtered at 10-100 Hz, with a notch filter at 50 Hz (mains frequency in UK). REM sleep included in the analysis was analyzed in 20-s epochs that were also subdivided into 10 2-s mini-epochs. A sensitivity of 30 μ V/cm was selected. The amount of REM sleep and proportion of REM without atonia from the submental muscle EMG were visually scored for each patient. The tonic and phasic components of REM sleep were scored separately as outlined in detail below. The tool “box cursor” was used to measure amplitudes.

Tonic Activity

Tonic submental muscle EMG activity was scored in 20-s epochs. An epoch was scored as tonic if submental muscle EMG activity > 2 times that of the background EMG was present for $\geq 50\%$ of the epoch duration. Background EMG amplitude was defined for each epoch by assessment of EMG activity on adjacent epochs of REM sleep.

Phasic Activity

Phasic submental muscle EMG activity was scored in 2-s epochs. Epochs containing submental muscle EMG activity with amplitudes > 4 times that of the background EMG activity (defined as above) and lasting from 0.1 to 10 s were scored as phasic. Phasic EMG activity could be scored both on epochs scored as tonic or atonic.

All the collected data were entered on Excel spreadsheets. For each patient and each group, we calculated the total number of 20-s epochs with tonic chin EMG activity and the number of

2-s epochs containing phasic activity. The proportion of both activities was then calculated as a percentage of the total duration of REM sleep.

Statistical Analyses

All analyses were carried out using STATA V.11. Continuous data were summarized using mean and standard deviation or median and interquartile range depending on distribution. Categorical data were summarized using count and percentages. Mean/rank differences between groups were compared using analysis of variance (ANOVA) or its nonparametric equivalent (Kruskal-Wallis test) if the assumptions required by test (normality and equal variances) were not met and no transformation of data was possible.

To analyze gender differences between groups we employed the nonparametric Fisher exact test. To compare age differences among groups, one-way ANOVA was used, followed by post hoc Bonferroni test. The Kruskal-Wallis rank test was used to compare differences of medians of tonic and phasic muscle EMG activities among all 4 groups. We then performed Mann-Whitney U test for comparisons between groups. Bonferroni corrections were used to adjust for multiple comparisons. Adjusted p-value for the 6 comparisons were calculated ($p = 0.008$). The nonparametric Spearman correlation coefficient test was used to investigate the strength of relationship between tonic and phasic submental muscle EMG activities.

ROC (receiver operating characteristic) curves were calculated to identify cutoff points for each component of EMG activity and to obtain sensitivity and specificity for these cutoff values in narcolepsy, RBD, and isolated loss of REM atonia groups.

RESULTS

Age and Gender

Demographic data are listed in **Table 1**. In the control group, there was an equal number of male and females, whereas in the RBD majority were males, and in narcolepsy groups there was a slight male predominance. Interestingly, in the isolated loss of REM atonia patients we observed a small female predominance. These differences were, however, not statistically significant (Fisher exact $p = 0.4$; **Table 2**).

Age differed (one-way ANOVA) significantly among the 4 groups ($F_{3,43} = 5.44$, $p = 0.003$; **Table 2**). Bonferroni post hoc comparisons indicate that subjects in RBD group (mean age 54 years) were significantly older than the isolated loss of REM atonia group (mean age 29.6 years), $p = 0.003$, and control group ($p = 0.047$). Comparisons between other groups were not statistically significant at $p > 0.05$.

Tonic and Phasic Submental Muscle EMG Activities in All Groups

There was a significant difference between all groups in tonic (Kruskal-Wallis test, $\chi^2(3) = 20$, $p < 0.001$) as well as phasic ($\chi^2(3) = 28$, $p < 0.001$) chin EMG activities in REM sleep (**Table 3** and **Figure 1**).

Subanalysis revealed that RBD patients have significantly (adjusted significant p -value < 0.008) higher proportions

Table 1—Demographic and clinical data of subjects

Subjects' ID	Gender	Age at study (years)	Diagnosis	Additional diagnosis	PLMS
1	M	62	RBD	Cognitive decline	Mild
2	M	49	RBD		Severe
3	M	53	RBD		
4	M	37	RBD		Mild
5	M	68	RBD		
6	M	38	RBD		
7	F	52	RBD	MSA	
8	M	60	RBD	Stroke	Moderate
9	F	64	RBD	PD with dementia	
10	M	64	RBD		Severe
11	M	80	RBD		
12	F	31	RBD		
13	M	71	RBD		Mild
14	F	39	RBD		
15	M	74	RBD	Probable DLB	Moderate
16	F	27	RBD	Epilepsy	
17	F	36	Isolated loss REM atonia		
18	F	19	Isolated loss REM atonia	Epilepsy	Mild
19	M	31	Isolated loss REM atonia		Mild
20	M	49	Isolated loss REM atonia		
21	F	22	Isolated loss REM atonia		
22	M	33	Isolated loss REM atonia		
23	F	35	Isolated loss REM atonia		Mild
24	F	32	Isolated loss REM atonia		
25	F	19	Isolated loss REM atonia	Epilepsy	
26	M	24	Isolated loss REM atonia		
27	F	26	Isolated loss REM atonia		Mild
28	M	40	Narcolepsy	N	Mild
29	F	21	Narcolepsy	N	
30	F	26	Narcolepsy	N/C	
31	F	74	Narcolepsy	N/C	Severe
32	M	68	Narcolepsy	N/C	
33	M	32	Narcolepsy	N/C	
34	M	21	Narcolepsy	N/C	
35	M	23	Narcolepsy	N/C	
36	M	70	Narcolepsy	N/C	Moderate
37	F	36	Narcolepsy	N/C	Mild
38	M	30	Control		Mild
39	M	31	Control		
40	F	74	Control		
41	F	18	Control		
42	M	27	Control		
43	M	29	Control		Mild
44	F	20	Control		
45	M	64	Control		
46	F	37	Control		
47	F	26	Control		

PLMS, periodic limb movements of sleep; M, male; F, female; RBD, REM sleep behavior disorder; PD, Parkinson disease; DLB, dementia with Lewy bodies; N, narcolepsy without cataplexy; N/C, narcolepsy with cataplexy.

of both tonic (Mann-Whitney test, $p = 0.002$) and phasic ($p = 0.002$) submental EMG activity than isolated loss of REM atonia and control groups ($p = 0.0007$ and $p = 0.0001$, respectively; **Table 3**). However, there was no significant difference between RBD patients and patients with narcolepsy in tonic ($p = 0.07$) or phasic ($p = 0.04$) activity. The highest value of

EMG activity among RBD patients was found in a patient with MSA (tonic activity 42.68%, phasic activity 21.67%). The isolated loss of REM atonia group had the least increase in tonic and phasic submental EMG activity compared to controls. In isolated loss of REM atonia patients, phasic EMG activity was significantly higher ($p = 0.0001$) than in

Table 2—Summary statistics of age (years), gender, phasic and tonic submental EMG activity

	RBD	ILRA	Narcolepsy	Controls
Mean age (SD)	54 (16)	29.6 (9)	41 (21.4)	35.6 (18.6)
Gender (male %)	11 (68.8%)	4 (36.4%)	6 (60%)	5 (50%)
Tonic activity				
Median (IQR 25%, 75%)	7.1 (3.98, 12.4)	2.36 (0, 3.5)	3.5 (1.48, 6.38)	0.44 (0, 0.79)
Mean (SD) %	9.8 (10)	2.1 (1.9)	4 (2.93)	0.53 (0.57)
Standard error	2.4	0.58	0.92	0.18
Phasic activity				
Median (IQR 25%, 75%)	6.3 (2.9, 11)	2.6 (1.4, 3)	3.2 (2.4, 4.5)	0.58 (0.24, 0.70)
Mean (SD) %	7.3 (5.28)	2.27 (0.92)	3.4 (1.79)	0.54 (0.34)
Standard error	1.3	0.27	0.57	0.1

RBD, REM sleep behavior disorder; ILRA, isolated loss of REM atonia; SD, standard deviation; IQR, interquartile range.

the control group, while there was no statistically significant ($p = 0.06$) difference in tonic component of submental muscle EMG activity. The narcolepsy patients showed an increase in both chin EMG components, which was higher than in the isolated loss of REM atonia group but lower than in RBD patients. However, the difference between narcolepsy and isolated loss of REM atonia patients in both tonic and phasic activities was not statistically significant ($p > 0.008$, corrected for multiple comparisons). Narcolepsy patients with and without cataplexy appeared to have similar elevated levels of submental EMG activity, but the groups were too small to allow any statistical comparisons.

Correlation of Tonic and Phasic Activities

The tonic and phasic chin EMG activities were correlated in all groups. Very high ($r=0.94$) and significant ($p < 0.001$) correlation between tonic and phasic EMG activity was found in RBD patients followed by loss of REM atonia group ($r=0.66$, $p = 0.02$). In narcolepsy patients and control group, there was a trend for correlation between tonic and phasic EMG activities, but this was not statistically significant ($r=0.56$, $p = 0.09$, and 0.50 , $p = 0.13$, respectively).

Results of Receiver Operating Characteristics Curve

The results of ROC curve analysis are displayed in **Table 4** and **Figure 3**. **Figure 2** illustrates individual data for tonic and phasic EMG activity in RBD, loss of REM atonia and narcolepsy groups with determined cutoff values distinguishing patients in each group from control subjects.

Cutoff values for the tonic component of REM sleep submental EMG activity in RBD patients compared to control subjects with optimal sensitivity and specificity was $\geq 3.17\%$ (87% sensitivity and 100% specificity) with an area under curve (AUC) 0.9. For phasic activity, a cutoff value of $\geq 1.22\%$ (AUC = 1) gave the best sensitivity and specificity (both 100%) for distinguishing RBD patients from control subjects. Cutoff values with high specificity and sensitivity for distinguishing between control subjects and narcolepsy and loss of REM atonia patients were also obtained, as detailed in **Table 4**. Phasic submental EMG activity had higher specificity and sensitivity than tonic activity in all three groups.

Table 3—Between group comparisons of tonic and phasic submental EMG activities using Mann-Whitney test

Comparisons	p-values	
	Tonic	Phasic
RBD vs. loss of REM atonia	0.002*	0.002*
RBD vs. narcolepsy	0.07	0.04
RBD vs. controls	0.0007*	0.0001*
Loss of REM atonia vs. narcolepsy	0.12	0.14
Loss of REM atonia vs. control	0.06	0.0001*
Narcolepsy vs. control	0.0014*	0.0015*

*Adjusted significant p-value is $p < 0.008$.

DISCUSSION

To our knowledge, this is the first study that compares the amount of RSWA in patients with isolated loss of REM atonia (subclinical RBD) versus RBD, as well as narcolepsy and control subjects. All groups did have higher amount of submental EMG activity during REM sleep compared to control subjects. The study showed that RBD patients have the highest amount of submental muscle EMG activity in REM sleep among all studied groups. As we hypothesized, the patients with isolated loss of REM atonia demonstrated significantly lower level of submental muscle activity during REM sleep than those with RBD. Patients with narcolepsy could not be reliably distinguished from those two groups, but were significantly different from controls.

Patients with loss of REM atonia demonstrated higher amount of RSWA than control subjects, suggesting that despite the lack of quantitative diagnostic criteria for isolated loss of REM atonia, patients given this diagnosis were clearly different from controls. Thus, RSWA observed in these individuals may constitute a separate clinical entity that warrants further investigation and follow-up to establish the possible association with RBD. The higher level of RSWA in RBD compared to the two other groups of patients suggests that the occurrence of dream enactment behavior seen in RBD is a consequence of more severe loss of REM atonia. Thus, the pathological process in narcolepsy patients with RSWA and loss of REM atonia patients may not

Figure 1—Box plots for tonic (left) and phasic (right) EMG muscle activity for all the studied groups

The graph displays summary of the group values of REM sleep proportion with tonic and phasic EMG activity: median, 25th and 75th interquartile ranges (IQR), minimum and maximum data values. RBD, REM sleep behavior disorder; ILRA, isolated loss of REM atonia.

Table 4—ROC data of tonic and phasic submental EMG activity

	RBD	ILRA	Narcolepsy
Phasic activity			
Sensitivity	100%	90%	90%
Specificity	100%	100%	100%
Correctly classified	100%	95%	95%
Cutoff	≥ 1.22	≥ 1.12	≥ 2.0
95% Confidence Interval	1	0.94-1	0.76-1
AUC	1	0.98	0.92
Tonic activity			
Sensitivity	87%	63%	80%
Specificity	100%	90%	90%
Correctly classified	92%	76%	85%
Cutoff	≥ 3.17	≥ 1.28	≥ 1.48
95% Confidence Interval	0.75-1	0.51-0.96	0.8-1
AUC	0.9	0.74	0.92

RBD, REM sleep behavior disorder; ILRA, isolated loss of REM atonia; AUC, area under curve.

be severe enough to allow violent movements. Moreover, the involvement of different pathways has been suggested in pathophysiology of RSWA and dream enactment behaviors in RBD. Therefore, to develop RBD, severity of the pathology or development of an additional pathological process may be needed.

The involvement of two motor systems has been suggested in the regulation of REM sleep atonia: one for generating muscle atonia and one for suppressing locomotor activity. Thus, the involvement of the processes that activate the locomotor generators, which overcome the tonic inhibition of the sublaterodorsal (SLD) or magnocellular reticular formation (MCRF) on spinal motoneurons, leading to dream enactment behaviors can also contribute.³⁴ It also has been suggested that depending on the site and size of pontine lesion, complex or simple behavior changes can be exhibited in REM sleep,³⁵ and that a lesion of the SLD may cause RSWA whereas a cell-specific lesion to vSLD can cause “dream enactment behavior.”³⁶ An impairment in the

dopaminergic system has been found in patients with isolated loss of REM atonia, but to a lesser degree than in patients with RBD and PD.³⁷ This supports the hypothesis that isolated loss of REM atonia can be considered “subclinical RBD” and may thus be a predictor for neurodegenerative disorders.

Our results demonstrate that RSWA is very common in narcolepsy both with and without cataplexy. Such a frequent occurrence of RSWA in narcolepsy patients could potentially be a further marker for the diagnosis of narcolepsy, particularly for patients without cataplexy. Although hypocretin deficiency is a suggested mechanism of RSWA in narcolepsy with cataplexy, the mechanism in narcolepsy without cataplexy is unclear.

For the first time, we obtained a cutoff value for phasic EMG activity in RBD versus control subjects (1.2%) with 100% specificity and 100% sensitivity. Contrary to a previous study, we found phasic chin muscle EMG activity to be a more reliable marker than tonic activity for RBD as well as narcolepsy and isolated loss of REM atonia. This is reasonable, considering that the main clinical symptom of RBD is dream enactment movements in REM sleep that generate phasic activity. Manni et al. reported that motor behaviors in RBD are associated with phasic activity such as rapid eye movements, bursts of sawtooth waves on EEG, and bursts of alpha rhythms.³⁸ Phasic EMG activity was a good diagnostic tool to distinguish narcolepsy patients from controls (sensitivity 90%, specificity 100%). This may be clinically useful to objectively differentiate these patient groups from control subjects.

Overall, the amounts of both tonic and phasic submental EMG activities in all groups in our study are much lower than those obtained in previous studies. This may be due to differences in criteria defining phasic and tonic EMG activity, as well as methodological differences of signal analysis.

Before scoring EMG activity, the signal was filtered to minimize the noise and artifacts that might interfere with the analyses and appear as false positive activity. Similar methods were used in recently developed computerized studies.^{11,28,29} A study that employed computerized methods and filtering of

Figure 2

(A) Dot plot of individual data for controls versus patients with RBD. For tonic activity (left), the cutoff value of amount of REM sleep with EMG activity (indicated as horizontal line on the graph) was $\geq 3.17\%$ (95% CI 0.75-1, sensitivity 87%, specificity 100%, with 92% correctly classified and area under curve = 0.92). For phasic activity (right), the cutoff value was $\geq 1.22\%$ (sensitivity, specificity, and correctly classified 100%. 95% CI 1 and area under curve = 1). **(B)** Dot plot of individual data for controls versus patients with "isolated loss of REM atonia." For tonic activity (left), the cutoff value of amount of REM sleep with EMG activity ≥ 1.28 (95% CI 0.51-0.96, sensitivity 63%, and specificity 90%, with 76% correctly classified and area under curve = 0.74). For phasic activity (right), the cutoff value was $\geq 1.12\%$ (95% CI 0.94-1, sensitivity 90%, and specificity 100%, with 95% correctly classified and area under curve = 0.98). **(C)** Dot plot of individual data for controls versus patients with narcolepsy. For tonic activity (left) the cutoff value of amount of REM sleep with EMG activity ≥ 1.48 (95% CI 0.8-1, sensitivity 80%, and specificity 90%, with 85% correctly classified and area under curve = 0.92). For phasic activity (right) the cutoff value was ≥ 2.0 (95% CI 0.76-1, sensitivity 90%, and specificity 100%, with 95% correctly classified and area under curve = 0.92).

Figure 3—Receiver operating characteristic (ROC) graphs of tonic activity (left) and phasic activity (right)

(A) RBD, (B) ILRA (isolated loss of REM atonia), and (C) narcolepsy patients. ROC curve for the tonic EMG activity in RBD (AUC-1, 95% Confidence interval -1, sensitivity, specificity, and correctly classified 100%) is not generated by the software.

signals reported mean values of phasic EMG activity in RBD, narcolepsy, and control groups that were similar to those in the present study.¹² However, it is not clear if this was performed in other studies using visual methods of scoring as well, as this was not reported.

We defined tonic activity as a two times that of background activity, whereas the previous studies that employed visual scoring methods either did not define the criteria for tonic

activity, taking any increase from the background, or defined it as either a two times increase or an increase of more than 10 μ V. As the surface EMG is considered to be an uncalibrated signal displaying large variability across subjects as well as intra-individual variability even within the same recording, using absolute amplitude may risk introduction of bias. In addition, we measured amplitude of each epoch precisely using the “box cursor” tool in PSG. This enabled us to clearly distinguish

between background EMG and activity increased compared to background. Further, we defined background activity in adjacent epochs rather than a single background level for the whole PSG recording. The main reason for this was that EMG activity may vary through the night and artifacts increase towards morning as electrode contact may be less good.

The results of the study need to be interpreted in the light of the small sample size and the fact that only one night of polysomnography was analyzed. However, it has been shown that one night of PSG study could be enough to identify RSWA.¹⁹ There was an age difference between the RBD group and isolated loss of REM atonia group, which might affect the results of the study, although it is understandable considering the prevalence of conditions in different age groups. In addition, the patient groups were of different sizes with almost twice as many subjects in the RBD group as in other groups. In two patients with loss of REM atonia, the use of antidepressants was reported. However, in one of these patients, parallel use of clonazepam also was reported. Antidepressants may change sleep architecture. There is an association of antidepressants with RBD³⁹ and with loss of REM atonia.⁴⁰ However, there is no study demonstrating the level of REM sleep atonia before and after antidepressant use.³⁹ Recent studies have suggested using EMG recordings from several different muscle groups to increase the sensitivity for detecting RBD.²⁵ Unfortunately, such recordings were not performed at our institution at the time.

The cutoff values for phasic activity separating RBD patients from control subjects with high specificity and sensitivity need to be validated in a large sample of RBD patients. This method can then be used as a reference for developing and testing new automated methods of scoring of submental EMG activity after removal of, for example, ECG artifacts. Novel methods of scoring could facilitate performing routine analysis to distinguish loss of REM atonia patients from normal individuals.

CONCLUSION

In conclusion, the EMG activity in isolated loss of REM atonia patients differed significantly from control subjects as well as the other groups studied. This suggests that there is a continuum of clinical symptoms and that there may also be different etiological factors contributing to RSWA, such as brainstem pathology, dopaminergic system and hypocretin deficiency. Further longitudinal studies of patients with isolated loss of REM atonia only are needed to establish if this truly represents “preclinical RBD.”

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