Excessive Muscle Activity Increases Over Time in Idiopathic REM Sleep Behavior Disorder

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Study Objectives: Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by excessive electromyographic (EMG) activity due to dysfunction of the brainstem structures modulating REM sleep atonia. Patients with idiopathic RBD often develop a neurodegenerative disease, such as Parkinson disease, over the years, suggesting progression of an underlying pathologic process in the brainstem. It is unknown if the excessive EMG activity in REM sleep changes over time in patients with idiopathic RBD.

Setting: University hospital sleep disorders center.

Participants: Eleven patients with idiopathic RBD who were studied at baseline and after a mean follow-up of 5 years.

Interventions: NA.

Measurements and Results: Eleven patients with idiopathic RBD underwent polysomnography (PSG) at the moment of the diagnosis of RBD (PSG1) and after a mean follow-up of 5 years (PSG2). Tonic EMG activity in PSG1 and PSG2 was blindly quantified and compared in the mentalis muscle during REM sleep. Phasic EMG activity in PSG1 and PSG2 was blindly quantified and compared in the mentalis muscle, both biceps brachii, and both anterior tibialis during REM sleep. Patients were 9 men and 2 women with a mean age of 73.2 ± 5.4 years and a mean RBD duration of 10.7 ± 5.3 years at PSG2. In each of the 5 muscles and combination of muscles evaluated, phasic EMG activity was significantly greater in PSG2 than in PSG1 ($P < 0.022$ in all muscles studied). Mentalis tonic EMG activity increased from 30% to 54% ($P = 0.013$). No correlation was found between age of the patients and quantity of EMG activity at PSG1 (tonic; $P = 0.69$, phasic $P = 0.89$) and at PSG2 (tonic; $P = 0.16$, phasic; $P = 0.42$).

Conclusion: Excessive tonic and phasic EMG activity during REM sleep increases over time in subjects with idiopathic RBD. This finding suggests that, in subjects with idiopathic RBD, there is an underlying progressive pathologic process damaging the brainstem structures that modulate REM sleep.

Keywords: REM sleep behavior disorder, tonic and phasic EMG activity during REM sleep, brainstem

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RAPID EYE MOVEMENT (REM) SLEEP BEHAVIOR DISORDER (RBD) IS CHARACTERIZED BY UNPLEASANT DREAMS, DREAM-ENACTING BEHAVIOURS, and increased tonic and phasic electromyographic (EMG) activity during REM sleep. It is thought that excessive EMG activity in RBD reflects dysfunction of the brainstem structures responsible for muscle atonia during REM sleep.[1] In animals, experimental lesions in the brainstem produce increased tonic and phasic EMG activity and abnormal behaviors during REM sleep.[2-5] In humans, RBD can be idiopathic or associated with neurodegenerative diseases.[6] Follow-up of patients with idiopathic RBD shows an increased risk for developing neurodegenerative diseases such as Parkinson disease, dementia with Lewy bodies, and multiple system atrophy.[7-11] Idiopathic RBD patients with longer follow-up are more likely to be found to have these neurodegenerative diseases,[9] suggesting that a progressive pathologic process takes place in these patients. It has never been determined, however, if the excessive EMG activity during REM sleep of patients with idiopathic RBD increases with time, a finding that would likely reflect a progressive impairment of the brainstem structures that regulate REM sleep atonia. We assessed, in this study, whether the amount of excessive tonic and phasic EMG activity during REM sleep increases over time in subjects with idiopathic RBD after several years of clinical follow-up.

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PATIENTS AND METHODS

Patient Selection

Eleven patients with idiopathic RBD confirmed by audiovisual polysomnography participated in this study. All patients underwent polysomnography at the moment of the diagnosis of RBD (PSG1) and after a mean follow-up of 5 years (PSG2). Tonic and phasic EMG activity was blindly quantified and compared between PSG 1 and PSG 2. The study was approved by the ethics committee at our institution, and patients gave written informed consent.

The diagnosis of idiopathic RBD required (1) chronic history of dream-enacting behaviors, (2) audiovisual polysomnography demonstration of increased phasic and/or tonic EMG activity during REM sleep associated with abnormal motor and vocal behaviors, (3) normal neurologic examination, (4) no cognitive complaints, and (5) no abnormal findings on brain magnetic resonance imaging.[9] After the diagnosis of idiopathic RBD was confirmed by polysomnography (PSG1), all 11 patients had subsequent follow-up visits at our sleep center every 3 to 6 months. After a mean clinical follow-up of 5.0 ± 1.9 (range, 1.8-8.4) years, patients still had the idiopathic form of RBD

Table 1—Tonic and Phasic Electromyographic Activity During REM Sleep at PSG1 and PSG2

	PSG1	PSG2	P Value
Tonic activity			
Mentalis	30.7 ± 31.6	54.9 ± 34.5	0.013
Phasic activity			
Mentalis	29.3 ± 19.2	44.5 ± 22.1	0.004
Right biceps brachii	12.4 ± 11.2	24.5 ± 11.0	0.008
Left biceps brachii	9.1 ± 9.3	24.4 ± 11.8	0.003
Right tibialis anterior	5.4 ± 3.8	9.2 ± 5.6	0.016
Left tibialis anterior	5.8 ± 4.8	10.3 ± 7.0	0.013
Upper limbs	16.7 ± 13.1	35.2 ± 14.7	0.003
Lower limbs	8.7 ± 5.6	14.6 ± 7.3	0.021
Four limbs	21.3 ± 13.1	40.5 ± 13.8	0.003
Mentalis and four limbs	38.4 ± 19.8	59.0 ± 19.1	0.004

Data are presented as percentages. PSG1 refers to polysomnography performed at baseline when the diagnosis of rapid eye movement (REM) sleep behavior disorder (RBD) was confirmed; PSG2, polysomnography performed after a mean clinical follow-up of 5 years.

(none developed a neurologic disorder) and a second polysomnogram (PSG2) was performed.

Between PSG1 and PSG2, 9 patients were treated with clonazepam, and clinical response was considered successful during the follow-up visits. In all 9, the clonazepam dose was decreased gradually over an 8-week period and withdrawn 3.3 ± 1.6 (range, 2-7) weeks prior to PSG2. During clonazepam reduction, RBD symptoms returned gradually in all 9 patients. The remaining 2 patients never took clonazepam, despite reporting a mild increase in their RBD symptomatology over the years. None of the patients included in this study had been treated with melatonin, antidepressants, antidopaminergic medications, dopaminergic agents, or other medications known to influence sleep architecture and EMG activity during REM sleep.

Polysomnographic Evaluation

PSG1 and PSG2 were performed with the same digital polygraph (Deltamed, Coherence 3 NT, software version 4.0, Paris, France) and consisted of vertical and horizontal electrooculography, electroencephalography (O2-A1+A2, O1-A2+A1, C4-A1+A2, C3-A2+A1), mentalis EMG, right and left biceps brachii EMG, right and left anterior tibialis EMG, electrocardiography, nasal and oral air flow, thoracic and abdominal respiratory effort, oxygen saturation, and synchronized audiovisual recording. Sleep stages were scored according to the American Academy of Sleep Medicine criteria[12] with the allowance for REM sleep without atonia.

EMG activity was quantified during REM sleep in the mentalis muscle, right and left biceps brachii, and right and left anterior tibialis. Scoring was performed visually by a trained sleep scorer who was blind to the patient's identity and the time when polysomnography was performed (PSG1 or PSG2). The tonic EMG activity was measured in the mentalis muscle as the percentage of 30-second REM sleep epochs with sustained tonic EMG activity, as as been previously described.[13] Phasic EMG activity was evaluated in mini-epochs of 3 seconds in all 5 muscles. A phasic EMG event was defined as any burst of EMG activity lasting at least 0.1 seconds, with an amplitude exceeding twice the EMG activity background.[13,14] Each EMG channel was displayed isolated on the computer screen and scored independently. After the scoring of 1 muscle was completed, the process was repeated in the remaining muscles. Every mini-epoch in each EMG channel was scored either "0" when phasic EMG activity was absent or "1" when phasic EMG activity was present.[14] In each muscle, the mean phasic EMG activity was expressed as the percentage of the 3-second mini-epochs containing phasic EMG events in REM sleep. Phasic EMG activity percentage in each mini-epoch was calculated separately for each of the 5 muscles, for the upper limbs (right and left biceps brachii), for the lower limbs (right and left anterior tibialis), for all limbs (right and left biceps brachii plus right and left anterior tibialis), and for all 5 muscles (mentalis plus right and left biceps brachii plus right and left anterior tibialis). For example, in the upper limbs, a 3-second mini-epoch was considered "phasic" when phasic activity appeared in any of the biceps brachii channel.[15] Tonic and phasic EMG increases concurrent with respiratory arousals and snoring signal artifacts were excluded from analysis.[14,15] Periodic leg movements in sleep (PLMS) were scored, and the PLMS index (number of periodic leg movements per hour of sleep) was calculated.[12] PLMS were carefully distinguished from phasic EMG activity during REM sleep in the anterior tibialis based upon their regular periodicity and characteristic flexor withdrawal appearance by videography.[14,15] The apnea-hypopnea index was defined as the average number of apneas and hypopneas per hour of sleep.

Statistical Analysis

Tonic and phasic EMG activity during REM sleep was compared between PSG1 and PSG2 with the Wilcoxon rank-sum test. The Spearman correlation coefficient test was used to assess if there was a correlation between the clonazepam-washout period before PSG2 and the EMG activity in REM sleep at PSG2. Also, we evaluated whether there was a correlation between age of the patients and EMG activity at both PSG1 and PSG2, between RBD duration and EMG activity, and between time since last PSG with the increase in EMG activity.

RESULTS

There were 9 men and 2 women with a mean age of 73.2 ± 5.4 (range, 65-81) years and a mean reported RBD duration of 10.7 ± 5.3 (range, 5-25) years at PSG2.

In all muscles and combination of muscles evaluated, phasic EMG activity was significantly greater in PSG2 than in PSG1 (Tables 1 and 2). Phasic EMG activity increased from 29% to 44% in the mentalis (P = 0.004), from 21% to 40% in the 4 limbs (P = 0.003), and from 38% to 59% (P = 0.004) in the 5 muscles studied. Tonic EMG activity in the mentalis increased from 30% to 54% (P = 0.013). Sleep0architecture variables, including REM sleep percentage, number of REM sleep periods, and REM sleep latency, were not different between PSG1 and

Table 2—Tonic and Phasic Electromyographic Activity During REM Sleep at PSG1 and PSG2 in the 11 Patients with Idiopathic RBD

	PSG1	PSG2
Patient 1		
Mentalis tonic EMG activity	35.14	59.39
Mentalis phasic EMG activity	38.86	37.21
Four limbs phasic EMG activity	19.16	41.12
Patient 2		
Mentalis tonic EMG activity	36.70	52.50
Mentalis phasic EMG activity	25.91	39.61
Four limbs phasic EMG activity	12.26	35.70
Patient 3		
Mentalis tonic EMG activity	27.78	46.27
Mentalis phasic EMG activity	42.24	62.44
Four limbs phasic EMG activity	20.00	34.91
Patient 4		
Mentalis tonic EMG activity	00.00	02.78
Mentalis phasic EMG activity	16.71	31.32
Four limbs phasic EMG activity	12.87	31.64
Patient 5		
Mentalis tonic EMG activity	15.00	93.65
Mentalis phasic EMG activity	9.60	33.33
Four limbs phasic EMG activity	6.57	40.96
Patient 6		
Mentalis tonic EMG activity	00.00	00.00
Mentalis phasic EMG activity %	05.11	06.80
Four limbs phasic EMG activity	11.36	11.76
Patient 7		
Mentalis tonic EMG activity	06.25	25.00
Mentalis phasic EMG activity	10.36	35.73
Four limbs phasic EMG activity	11.00	52.45
Patient 8		
Mentalis tonic EMG activity	73.08	96.94
Mentalis phasic EMG activity	63.44	89.25
Four limbs phasic EMG activity	49.33	67.31
Patient 9		
Mentalis tonic EMG activity	06.25	88.64
Mentalis phasic EMG activity	16.63	32.65
Four limbs phasic EMG activity	22.73	38.10
Patient 10		
Mentalis tonic EMG activity	38.18	56.07
Mentalis phasic EMG activity	45.61	56.48
Four limbs phasic EMG activity	34.66	43.52
Patient 11		
Mentalis tonic EMG activity	99.34	82.74
Mentalis phasic EMG activity	47.60	64.37
Four limbs phasic EMG activity	33.96	48.05

Data are presented as percentages. PSG1 refers to polysomnography performed at baseline when the diagnosis of rapid eye movement (REM) sleep behavior disorder (RBD) was confirmed; PSG2, polysomnography performed after a mean clinical follow-up of 5 years; EMG, electromyography.

PSG2 (Table 3). There was an increase in the apnea-hypopnea index, but the difference was not significant (P = 0.062).

There was no correlation between clonazepam-washout period and phasic (P = 0.157) and tonic (P = 0.750) mentalis EMG activity in REM sleep at PSG2. No correlation was found between age of the patients and the quantity of mentalis EMG activity at PSG1 (tonic; P = 0.697, phasic P = 0.894) and PSG2 (tonic; P = 0.110, phasic; P = 0.433). There was no correlation between reported RBD duration and EMG activity (tonic; P = 0.819, phasic; P = 0.141) nor between time since last polysomnogram and increase in EMG activity (tonic; P = 0.769, phasic; P = 0.582).

Table 3—Sleep Architecture at PSG1 and PSG2.

	PSG1	PSG2	P Value
Sleep efficiency, %	71.6 ± 11.9	73.4 ± 11.3	0.722
TST, min	328.1 ± 66.6	337.4 ± 49.6	1.000
Sleep stage, % of TST			
1	23.1 ± 11.0	28.1 ± 15.7	0.286
2	45.3 ± 12.2	42.4 ± 7.6	0.722
3	16.0 ± 10.1	13.4 ± 10.1	0.374
REM	15.6 ± 8.4	16.1 ± 6.7	0.790
REM sleep periods, no.	2.8 ± 1.1	2.3 ± 0.8	0.132
REM sleep latency, min	115.6 ± 74.5	166.9 ± 123.9	0.182
PLMI	4.6 ± 11.0	9.7 ± 16.1	0.176
AHI	9.0 ± 13.4	17.0 ± 21.9	0.062

PSG1 refers to polysomnography performed at baseline when the diagnosis of rapid eye movement (REM) sleep behavior disorder (RBD) was confirmed; PSG2, polysomnography performed after a mean clinical follow-up of 5 years; TST, total sleep time; PLMI, periodic leg movement index; AHI, apnea-hypopnea index.

DISCUSSION

Our study shows that excessive tonic and phasic EMG activity during REM sleep increases with time in subjects with idiopathic RBD. In contrast, REM sleep percentage, number of REM sleep periods, and REM sleep latency did not change. These observations indicate that, in idiopathic RBD, an evolving pathologic process results in progressive dysfunction of the structures responsible for suppression of muscle activity in REM sleep but not for those modulating REM sleep latency and REM sleep time. This is in agreement with the observation that REM sleep latency and REM sleep time are not different between patients with idiopathic RBD and healthy control subjects.[16-18]

In normal animals and humans, there is minimal skeletal muscle activity in REM sleep. Onset and maintenance of REM sleep atonia requires active inhibition of sustained muscle tone (tonic activity) and of intermittent muscle twitches (phasic activity) by neural structures located in the dorsal mesopontine tegmentum, ventral mesopontine junction,[5] and ventromedial medulla.[19] In animals, experimental lesions in the ventral sublaterodorsal nucleus (analogous to the subcoeruleus nucleus in humans) ,[2,3] nucleus magnocellularis[4] and ventral mesopontine junction[5] produce excessive tonic and phasic muscle activity associated with orienting, searching, and aggressive behaviors during unequivocal REM sleep. In these animal models of human RBD, the location and extent of the brainstem lesion is .related to the quantity of excessive muscle activity and behavior intensity in REM sleep[2,3] Therefore, our findings might reflect a greater extent of brainstem impairment occurring with time in subjects with RBD.

In humans, RBD may be idiopathic or occurring in the setting of those neurodegenerative diseases characterized by promi-

nent neuronal loss in the brainstem, such as Parkinson disease, dementia with Lewy bodies, and multiple system atrophy.[6,15] A high proportion of patients with idiopathic RBD seen at sleep centers develop the cardinal features of Parkinson disease, dementia with Lewy bodies, and multiple system atrophy after several years of follow-up.[7-11] Prospective longitudinal studies show that this proportion increases with time of follow-up.[8,10] Conversely, some patients with Parkinson disease, dementia with Lewy bodies, and multiple system atrophy report that the onset of RBD preceded the onset of parkinsonism, cognitive impairment, and ataxia by several years.[15] This is in line with the observation that, in some Parkinson disease brains, the earliest pathologic changes may involve the ventromedial medulla and subceruleus nucleus before reaching the substantia nigra.[20] Thus, idiopathic RBD may represent an early stage of a neurodegenerative disease reflecting dysfunction or damage of the lower brainstem structures and pathways responsible for REM sleep atonia. It can be speculated that the increased tonic and phasic EMG activity seen over time in idiopathic RBD indicates a progressive impairment at the brainstem level in the absence of motor and cognitive symptomatology.

We could not assess if the increased EMG activity in REM sleep was associated with a similar worsening in RBD symptomatology because most patients in our study were treated with clonazepam after the diagnosis of idiopathic RBD. This treatment dramatically decreased the frequency and intensity of both unpleasant dreams and dream-enacting behaviors during the follow-up period.

Since clonazepam decreases REM-sleep phasic-EMG activity,[13] one could think that our findings may be explained by a rebound phenomena after discontinuation of this drug several weeks before PSG2. We do not think this was the case because there was no correlation between the duration of the clonazepam-washout period and tonic and phasic EMG activity at PSG2. Moreover, clonazepam was gradually decreased over an 8-week period, and its administration was withdrawn at least 2 weeks prior PSG2, a much longer period than 5 half-lives of the drug and its longer-acting metabolite (24 hours) .[21] Upon discontinuation of clonazepam, patients reported a gradual, but not abrupt, reappearance of RBD symptoms that did not lead to injuries or withdrawal from the study. The 2 patients included in this study who never took clonazepam had an increase in both tonic and phasic EMG activity at PSG2. Finally, it should be noted that clonazepam does not decrease tonic EMG activity[13] and that, in our study, this measure was significantly higher in PSG2 than in PSG1.

We acknowledge the limitations of our study, namely the small number of patients evaluated and the nonhomogeneous period of time elapsed between PSG1 and PSG2. The lack of correlation between time since last polysomnogram with the increase in EMG activity might be a consequence of the limitations of our study or, alternatively, may reflect interindividual differences in the pathologic process producing increases in EMG activity. The latter is supported by the lack of correlation between the percentage of EMG activity and reported duration of RBD at both PSG1 and PSG2. It cannot be excluded that passage of time by itself increases EMG activity during REM sleep, since we did not evaluate a control group over time. However, the finding in our study and others[22] that patient age is not related with the amount of EMG activity argues against this possibility.

In summary, the finding that excessive EMG activity increases with time suggests a progressive dysfunction of the brainstem structures that modulate REM sleep atonia in idiopathic RBD.

DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

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