NEW RESEARCH

JCSM
Journal of Clinical Sleep Medicine

http://dx.doi.org/10.5664/jcsm.2490

Night-to-Night Variability of Automatic Quantitative Parameters of the Chin EMG Amplitude (Atonia Index) in REM Sleep Behavior Disorder

Raffaele Ferri, M.D.[1]; Sara Marelli, Psy.D., Ph.D.[2]; Filomena I.I. Cosentino, M.D.[1]; Francesco Rundo, M. Eng[1]; Luigi Ferini-Strambi, M.D.[2]; Marco Zucconi, M.D.[2]

[1]Sleep Research Centre, Department of Neurology I.C., Oasi Institute for Research on Mental Retardation and Brain Aging (IRCCS), Troina, Italy; [2]Sleep Disorders Center, Department of Neurology, Scientific Institute and University Ospedale San Raffaele, Vita-Salute University, Milan, Italy

Study Objectives: To analyze the night-to-night variability of REM sleep electromyographic (EMG) features of REM sleep behavior disorder (RBD) by using the automatic quantitative method known as *atonia index* (AI), and to evaluate the improvement in sensitivity and specificity of AI for the diagnosis of RBD when a second recording night is available.

Setting: Sleep research center.

Interventions: N/A.

Methods: A group of 17 idiopathic RBD patients was recruited for whom 2 all-night polysomnographic (PSG) recordings were available. Thirty normal controls were also recruited and subgrouped into Young (< 45 years of age) or Aged (> 45 years). Chin EMG analysis was run on all recordings; night-to-night variability of both AI and number of chin EMG activations/h during REM sleep was additionally quantified as the absolute difference between the 2 nights standardized as the percentage of their mean.

Measurements and Results: Night-to-night variability of AI was higher in RBD patients (19.7%) than in the 2 groups of controls (Young 1.8% and Aged 2.8%). The values of variability of chin EMG activations were much higher than those of AI, especially in the Aged controls. Sensitivity of AI ≤ 0.9 for RBD was always higher than 82% and reached 88.9% for the combined-night analysis; specificity was also high, with a value of 92.3% for the combined-value analysis.

Conclusion: The night-to-night variability of AI seems to be very low in normal controls and remains under 20% in RBD patients; that of the number of EMG activations is higher. However, even a single PSG recording provides high values of sensitivity and specificity when a threshold value of AI ≤ 0.9 is used to define abnormal chin EMG levels during REM sleep that increase only moderately when a second night recording is available.

Keywords: REM sleep behavior disorder, RBD, REM sleep without atonia, atonia index, chin EMG analysis, night-to-night variability

Citation: Ferri R; Marelli S; Cosentino FII; Rundo F; Ferini-Strambi L; Zucconi M. Night-to-night variability of automatic quantitative parameters of the chin EMG amplitude (atonia index) in REM sleep behavior disorder. *J Clin Sleep Med* 2013;9(3):253-258.

SCIENTIFIC INVESTIGATIONS

The presence of excessive amounts of sustained or intermittent elevations of submentalis muscle electromyography (EMG) tone or excessive phasic submentalis muscle twitching (or upper/lower limbs) is a required polysomnographic (PSG) feature for the diagnosis of REM sleep behavior disorder (RBD).[1] However, the general and non-quantitative nature of this criterion has prompted a number of studies aiming at establishing more quantitative parameters for the definition of the so-called REM sleep without atonia (RSWA); based on both visual[2-4] and automatic[5-8] approaches.[9] These methods seem to show sufficient sensitivity and specificity for their application in both clinical practice and research settings and probably provide comparable results.[10]

However, one of the aspects that needs to be further clarified is that of the night-to-night variability of RSWA. The availability of the above quantification methods now allows exploration of this aspect of RBD, which was previously limited to subjective evaluation of "excessive" amounts of activity during REM sleep. The night-to-night variability of the clinical manifestations of RBD is well known; however, it has been reported that PSG EMG activity seems to be more stable than video-recorded behavioral manifestations across nights, and the combination of information obtained from one video-PSG might be sufficient for the diagnosis.[11-13] Regarding EMG activity, in particular,

BRIEF SUMMARY

Current Knowledge/Study Rationale: Automatic quantitative parameters for the definition of the so-called REM sleep without atonia (RSWA) are now available which seem to show sufficient sensitivity and specificity for their application in both clinical practice and research settings. The scope of this study was to analyze the night-to-night variability of the REM sleep electromyographic (EMG) features of RBD by using our automatic quantitative method for quantifying RSWA, also known as atonia index (AI).

Study Impact: This study shows that the night-to-night variability of AI seems to be very low in normal controls and moderately low in RBD patients; on the contrary, that of the number of EMG activations is higher. Moreover, this study also supports the idea that a single PSG recording provides high values of sensitivity and specificity for the detection of RSWA in RBD patients; these values increase only moderately when a second night recording is available.

phasic muscle activity has been reported to be more variable than tonic muscle activity.[13]

All the data available in full-length articles on night-to-night variability of the EMG activity of RBD have been produced by means of visual quantification methods. Thus, the primary scope of this study was to analyze the night-to-night variability of the REM EMG features of RBD by using our automatic quantitative method also known as *atonia index* (AI).[7,8,10,14,15] This index can vary from zero (i.e., complete absence of EMG atonia) to one (stable EMG atonia) and can be calculated for any sleep stage. In addition, in the same method sequences of consecutive mini-epochs with values > 2 μV are counted as movements. The second aim of this study was to evaluate the improvement in sensitivity and specificity of AI for the diagnosis of RBD when a second recording night was available.

METHODS

Subjects

Patients with idiopathic RBD (iRBD) for whom ≥ 2 PSG recordings were available, under constant pharmacological treatment, were consecutively and retrospectively recruited for this study and gave their permission for the use of their data in this analysis. The diagnosis of iRBD was based on the International Classification of Sleep Disorders, 2nd Edition (ICSD-2) criteria for RBD, including presence of REM sleep without atonia, sleep related injurious-disruptive behaviors by history or abnormal sleep behaviors documented during PSG monitoring, absence of EEG epileptiform activity during REM sleep, and sleep disturbance not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.[1] Secondary forms of RBD were excluded on the basis of historical data, neurologic examination, and cerebral MRI findings. All RBD patients with at least one subtentorial vascular lesion or ≥ 2 vascular supratentorial lesions > 0.5 cm were excluded.

Normal controls were also recruited. The exclusion criteria for the control group were the same as described for iRBD patients; additionally, the presence of subjective sleep complaints (insomnia, daytime sleepiness, restless legs syndrome, RBD symptoms, snoring, or witnessed apnea) was also ruled out. None of the controls was taking hypnotics or benzodiazepines.

This study was approved by the local ethics committee and all subjects provided informed consent according to the Declaration of Helsinki.

Nocturnal Polysomnography

Nocturnal video-PSG was carried out in a standard sound-attenuated (noise level to a maximum of 30 dB nHL) sleep laboratory room. Subjects were not allowed caffeinated beverages the afternoon preceding the recording and were allowed to sleep until their spontaneous awakening in the morning. Lights-out time was based on individual habitual bedtime and ranged between 21:30 and 23:30. The following signals were recorded: EEG (≥ 2 channels, one central and one occipital, referred to the contralateral earlobe; however, multiple-channel EEG was available for patients at their first diagnostic assessment in order to exclude the presence of frontal lobe seizures); electrooculogram (electrodes placed 1 cm above the right outer canthus and 1 cm below the left outer canthus and referred to A1); electromyogram (EMG) of the submentalis muscle (bipolar derivations with 2 electrodes placed 3 cm apart and affixed using a collodion-soaked gauze pad); EMG of the right and left tibialis anterior muscles; and ECG (one derivation). Impedance was kept < 10 KΩ (typically < 5 KΩ). Sleep signals were sampled at 200 or 256 Hz and stored on hard disk for further analysis. The sleep respiratory pattern of each patient was monitored using oral and nasal airflow thermistors and/or nasal pressure cannula, thoracic and abdominal respiratory effort strain gauge, and by monitoring oxygen saturation (pulse oximetry). This was performed in all subjects in a previous recording (within 1 week) or during the study recording; patients with an apnea-hypopnea index > 5 were not included. Sleep stages were scored following standard criteria[16] on 30-s epochs; since muscle atonia can be absent in RBD, REM sleep was scored without submental EMG atonia, using electroencephalogram and electrooculogram only. According to a method specifically developed for RBD,[2,17] onset of a REM sleep period was defined as the occurrence of the first rapid eye movement in the presence of an EEG signal characteristic of REM sleep (low amplitude mixed frequencies, absence of sleep spindles and K complexes). Offset of a REM sleep period was determined by the occurrence of a specific EEG feature indicative of another stage (K complex, sleep spindle, or EEG signs of arousal) or absence of rapid eye movements during 3 consecutive minutes. Epochs containing technical artifacts or extremely elevated muscle activity causing saturation of amplifiers were carefully detected and marked for exclusion from the subsequent quantitative EMG analysis.

Two recordings were obtained from each patient, with a variable time lag between them (see results); however, drug therapy was the same in both nights. For normal controls, 2 consecutive nocturnal PSG recordings were obtained.

Quantification of the Submentalis Muscle EMG Amplitude

For the computer quantitative analysis of the submentalis muscle EMG activity we used our established automatic scoring algorithm.[7,8,14] The submentalis muscle EMG signal was digitally band-pass filtered at 10-100 Hz, with a notch filter at 50 Hz and rectified. Subsequently, each REM sleep epoch included in the analysis was divided into 30 1-sec mini-epochs. The average amplitude of the rectified submentalis muscle EMG signal was then obtained for each mini-epoch. After a noise reduction procedure,[8] the values of the submentalis muscle EMG signal amplitude in each 1-s mini-epoch were used to compute the percentage of values in the following 20 amplitude (amp) classes (expressed in μV): amp ≤ 1, 1 < amp ≤ 2, …, 18 < amp ≤ 19, amp > 19. Muscle atonia is expected to be reflected by high values of the first class (amp ≤ 1), while phasic and tonic activations are expected to increase the value of the other classes. As proposed in previous studies, an index summarizing in a single value the degree of preponderance of the first class was used in REM sleep:

$$\text{Atonia Index} = \text{amp} \leq 1 \,/\, (100 - 1 < \text{amp} \leq 2).$$

Mathematically, this index can vary from 0 (absence of mini-epochs with amp ≤ 1), i.e., complete absence of EMG atonia, to 1 (all mini-epochs with amp ≤ 1) or stable EMG atonia in the epoch.

Table 1—Sleep architecture parameters

	Young (n = 16)		Aged (n = 14)		iRBD (n = 17)		Aged vs. iRBD ANCOVA
	mean	SD	mean	SD	mean	SD	p <
Time in bed, min	483.5	50.24	504.4	89.88	446.1	16.51	0.0015
Sleep period time, min	457.7	42.05	473.6	90.33	417.6	31.87	0.006
Total sleep time, min	424.9	64.79	381.6	92.80	345.9	55.13	NS
Sleep latency, min	16.4	17.37	21.4	24.97	23.1	21.59	NS
REM latency, min	95.2	64.66	98.0	42.05	95.2	53.28	NS
Stage shifts/hour	10.4	3.41	13.1	3.88	16.4	11.99	NS
Awakenings/hour	3.8	2.40	4.2	2.23	5.4	5.57	NS
Sleep efficiency, %	88.0	11.32	75.7	11.88	77.7	12.91	NS
WASO, %	7.3	10.29	19.2	13.15	17.1	12.55	NS
S1, %	3.8	2.47	6.5	3.87	8.5	6.69	NS
S2,%	48.6	7.76	41.0	10.54	42.5	7.42	NS
SWS, %	17.7	8.44	17.3	8.56	14.4	8.75	NS
REM, %	22.6	7.00	16.0	4.95	17.6	7.93	NS

WASO, wakefulness after sleep onset; S1, sleep stage 1; S2, sleep stage 2; SWS, sleep stages 3+4.

In addition, sequences of consecutive mini-epochs with values > 2 μV were counted as movements. The algorithm was run blind to the condition of the subject, even though no manual modifications of the parameters is possible.

Statistical Analysis

For the comparison of sleep architecture parameters, the analysis of covariance was used and age of the subjects served as a covariate; while for the comparison of AI and number of chin EMG activations/h during REM sleep obtained in the 3 groups of subjects, the Kruskal-Wallis ANOVA was first carried out, followed by the Mann-Whitney test used as a post hoc test.

The analysis of the night-to-night variability of AI and number of chin EMG activations/h during REM sleep was first carried out by means of the Kendall W coefficient of concordance, which expresses the simultaneous association (relatedness) between different sets of rankings. The range of Kendall concordance is from 0 to 1; values close to 0 represent lack of agreement in the rankings of the variables among nights in this case, while values close to 1 represent perfect agreement. Night-to-night variability of both AI and number of chin EMG activations/h during REM sleep were additionally quantified as the absolute difference between the 2 nights, standardized as the percentage of the mean of the 2 nights. These values were compared by means of the Kruskal-Wallis ANOVA, followed by the Mann-Whitney test used as a post hoc assessment.

Finally, sensitivity, specificity, positive predictive value, and negative predictive value of AI ≤ 0.9 for the diagnosis of iRBD vs. Aged controls were computed for the first and second recording nights, separately or combined (AI ≤ 0.9 in either the first or the second recording night).

RESULTS

For this study, 17 consecutive iRBD patients were retrospectively recruited (14 men and 3 women, mean age 66.0 ± 4.93 years). Average disease duration was 9.1 ± 12.86 years at the time of the first recording. All patients were taking clonazepam (0.5-1 mg) at bedtime.

A group of 30 normal controls (15 men and 15 women) was also retrospectively recruited and then subdivided into 2 age groups, based on age below or above 45 years. The younger subgroup (Young) included 16 subjects (mean age 30.6 ± 6.86 years), while the older subgroup (Aged) was formed by the remaining 14 subjects (mean age 58.2 ± 9.63 years).

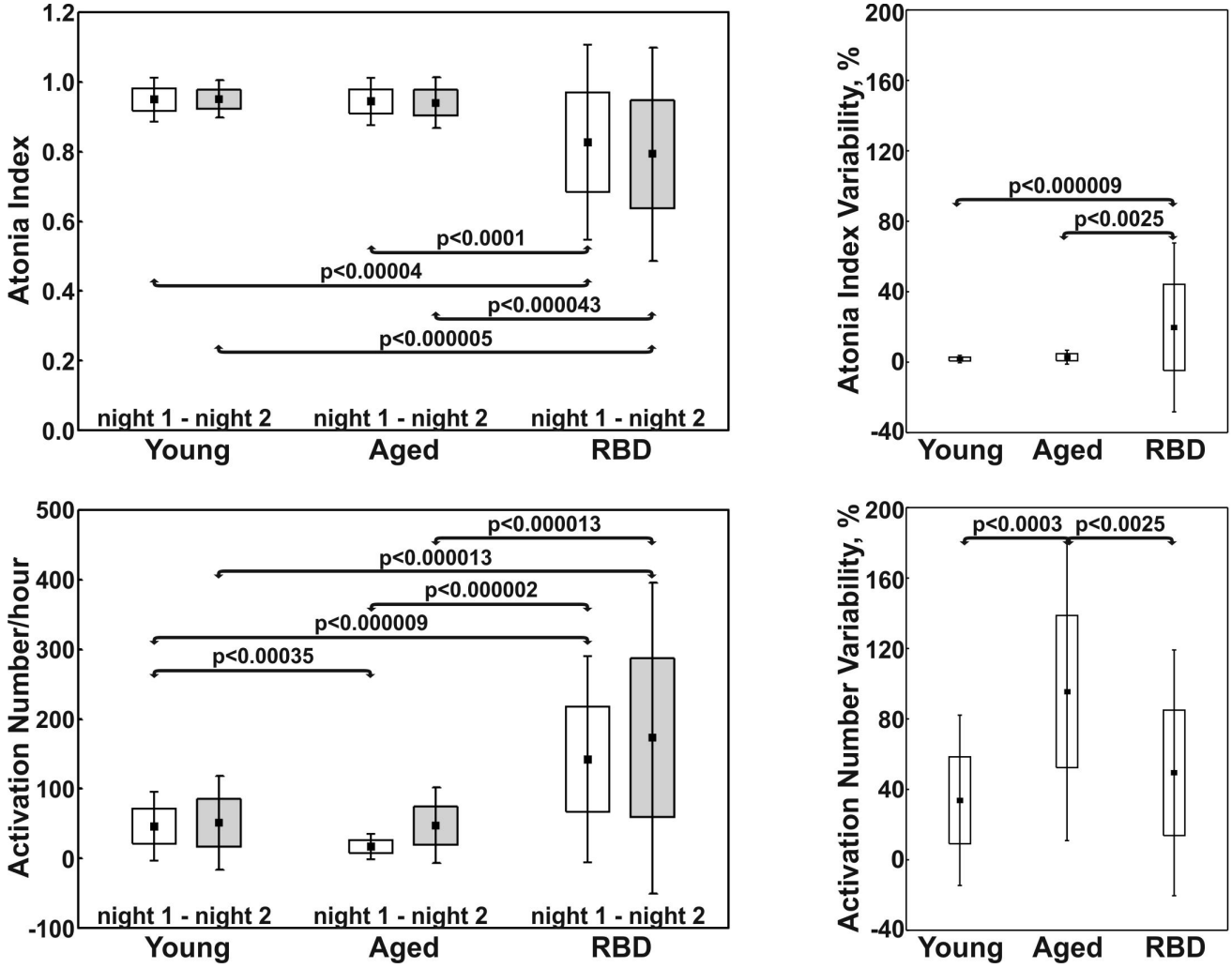
Patients and controls differed for their gender composition, but we have previously reported that our chin EMG measurement seems to be independent of gender[14,15]; in this new study, the number of women in the RBD group was too low to allow us to control for the influence of this factor.

Table 1 shows the descriptive statistics of sleep architecture parameters obtained from the first recording available for each subject in these 3 groups of subjects. A comparison was also run between iRBD and Aged controls by means of the analysis of covariance, to take into account the age of the subjects in the 2 groups, using age as a covariate. Time in bed and sleep period time were significantly shorter in iRBD patients.

As mentioned above, the 2 PSG recordings available for iRBD patients were not consecutive; the second PSG recording was obtained with an average time lag of 2.5 ± 1.17 years after the first. Two consecutive recordings were available for all controls.

The left panels of **Figure 1** shows the comparison of the chin EMG amplitude parameters (AI and number of chin EMG activations/h during REM sleep) found during the 2 PSG recordings among subject groups. As expected, in iRBD patients, AI was significantly lower and the number of chin EMG activations/h was significantly higher than those of both groups of controls in both recordings. However, night-to-night variability (top right panel of **Figure 1**) of AI was higher in iRBD patients (19.7%) than in the 2 groups of controls (Young 1.8%, Aged 2.8%). The values of variability of chin EMG activations were generally much higher than those of AI, especially in the Aged controls. The Kendall W coefficient of concordance between the 2 nights (**Table 2**) showed high (Young) to moderate (iRBD patients) values, which reached

Figure 1—Comparison of the different chin EMG amplitude parameters found during the two polysomnographic recordings in the groups of subjects



Data are shown as mean (black-filled squares) and box (standard deviation) and whiskers (95% confidence intervals) plots.

statistical significance for AI of both control groups and for the number of EMG activations of only Young controls.

Finally, an analysis of sensitivity, specificity, positive predictive value, and negative predictive value of AI ≤ 0.9 for the diagnosis of iRBD vs. Aged controls was run (**Table 3**). These parameters were computed for the first and second recording nights, separately or combined (AI ≤ 0.9 in either the first or the second recording night). Sensitivity was always higher than 82% and reached 88.9% for the combined-night analysis; specificity was also high, with a value of 92.3% for the combined-value analysis. Overall, the combined-night analysis gave better results, but the values obtained for the single nights were also high, and the improvement obtained by using the combined nights was relatively small.

DISCUSSION

It has been reported that, using a visual quantification of the chin EMG amplitude during REM sleep and video-analysis of behaviors, only increased tonic chin muscle activity can be considered to be a relatively stable measure for RBD diagnosis; conversely, enhanced phasic chin muscle activations and motor and vocal behaviors are more variable between nights.[13] We have now extended this type of night-to-night variability analysis to our automated quantification method and have found that, similar to the above study, AI is a more stable feature than the number of chin muscle activations in both normal controls and iRBD patients. These results underline once more the concordance between visual and automatic analysis of the chin EMG amplitude during REM sleep in RBD,[7] with the added value of speed and strict objectivity of the automatic analysis.

The retrospective nature of our analysis is the major limitation of this study, which allowed us to collect the second recording of iRBD patients obtained only after a long period from the first; consecutive night recordings were available for normal controls. This might mean that consecutive recordings in iRBD patients (if available) might have yielded more stable results; but this is only a speculative consideration that needs to be checked in

Table 2—Concordance of the different chin EMG amplitude parameters found during the two polysomnographic recordings in the groups of subjects

	Kendall W	Chi-square	p <
Young			
Atonia Index	0.847	25.412	0.045
EMG activations	0.912	27.353	0.026
Aged			
Atonia Index	0.745	22.352	0.05
EMG activations	0.585	17.538	NS
iRBD			
Atonia Index	0.605	19.353	NS
EMG activations	0.591	18.922	NS

Table 3—Analysis of sensitivity, specificity, positive predictive value, and negative predictive value of AI ≤ 0.9 for the diagnosis of iRBD vs. aged controls

	AI ≤ 0.9		Sensitivity, %	Specificity, %	PPV, %	NPV, %
	yes	no				
1st night						
iRBD	14	3	82.3	86.7	87.5	80
Aged	2	12				
2nd night						
iRBD	15	2	88.2	92.8	93.7	86.7
Aged	1	13				
Combined nights						
iRBD	16	1	88.9	92.3	94.1	85.7
Aged	2	12				

PPV, positive predictive value; NPV, negative predictive value. The results are shown for the first and second recording nights, separately or combined (AI ≤ 0.9 in either the first or the second recording night).

future studies. Another important limitation deriving from the retrospective nature of the study was the impossibility of arranging an adequately age-matched control group. This was partially controlled for by using the ANCOVA for some comparisons. However, it should also be underlined that we have already reported that in adulthood, AI shows relatively stable values > 0.9 in normal controls[15] (this was true also in the present study); thus, we believe that our analyses can still be considered as reliable.

Finally, after a technical improvement of our method to compute AI,[8] we have indicated a normality threshold value of > 0.9 for this parameter, because the vast majority of normal adults provide scores above this threshold. We have also previously reported that using this AI threshold, a sensitivity of 74.3% and a specificity 91.4% were obtained for iRBD patients compared to controls; in the same study we found both sensitivity and specificity of 100% for multiple system atrophy.[8] More recently, we have applied the same type of analysis in a group of Parkinson disease patients with or without RBD and have obtained sensitivity 93.8% and specificity 90.6%.[10] In the present study, we have found that sensitivity ranged from 82.3% to 88.2% and specificity 88.2% to 92.8% in the two nights. Only a moderate improvement was obtained when either night was used to detect AI ≤ 0.9 (sensitivity 88.9, specificity 92.3%). All these results were obtained from studies which only involved limited numbers of patients, if considered singularly; however, taken together, they involved 48 patients with iRBD, 27 with Parkinson disease, and 10 with multiple system atrophy—a nontrivial total number of patients. Thus, they show a convincing convergence toward high values of sensitivity and specificity for AI ≤ 0.9 and seem to support the conclusion that a single recording night might be considered sufficient for the diagnostic work-up of RBD, especially if we take into account that other video-PSG and clinical parameters contribute to its definition.[11-13]

REFERENCES

1. American Academy of Sleep Medicine. *International classification of sleep disorders, 2nd ed.: diagnostic and coding manual*. Westchester, IL: American Academy of Sleep Medicine, 2005.
2. Lapierre O, Montplaisir J. Polysomnographic features of REM sleep behavior disorder: development of a scoring method. *Neurology* 1992;42:1371-4.
3. Montplaisir J, Gagnon JF, Fantini ML, et al. Polysomnographic diagnosis of idiopathic REM sleep behavior disorder. *Mov Disord* 2010;25:2044-51.
4. Frauscher B, Iranzo A, Gaig C, et al. Normative EMG Values during REM Sleep for the Diagnosis of REM sleep behavior disorder. *Sleep* 2012;35:835-47.
5. Burns JW, Consens FB, Little RJ, Angell KJ, Gilman S, Chervin RD. EMG variance during polysomnography as an assessment for REM sleep behavior disorder. *Sleep* 2007;30:1771-8.
6. Mayer G, Kesper K, Ploch T, et al. Quantification of tonic and phasic muscle activity in REM sleep behavior disorder. *J Clin Neurophysiol* 2008;25:48-55.
7. Ferri R, Manconi M, Plazzi G, et al. A quantitative statistical analysis of the submentalis muscle EMG amplitude during sleep in normal controls and patients with REM sleep behavior disorder. *J Sleep Res* 2008;17:89-100.
8. Ferri R, Rundo F, Manconi M, et al. Improved computation of the atonia index in normal controls and patients with REM sleep behavior disorder. *Sleep Med* 2010;11:947-9.
9. Fulda S, Plazzi G, Ferri R. Scoring atonia during normal and pathologic REM sleep: Visual and automatic quantification methods. *Sleep Biol Rhythms* 2012; in press.
10. Ferri R, Fulda S, Cosentino FI, Pizza F, Plazzi G. A preliminary quantitative analysis of REM sleep chin EMG in Parkinson's disease with or without REM sleep behavior disorder. Sleep Med 2012;13:707-13.
11. Frauscher B, Gschliesser V, Brandauer E, et al. Video analysis of motor events in REM sleep behavior disorder. *Mov Disord* 2007;22:1464-70.
12. Zhang J, Lam SP, Ho CK, et al. Diagnosis of REM sleep behavior disorder by video-polysomnographic study: is one night enough? *Sleep* 2008;31:1179-85.
13. Cygan F, Oudiette D, Leclair-Visonneau L, Leu-Semenescu S, Arnulf I. Night-to-night variability of muscle tone, movements, and vocalizations in patients with REM sleep behavior disorder. *J Clin Sleep Med* 2010;6:551-5.
14. Ferri R, Franceschini C, Zucconi M, et al. Searching for a marker of REM sleep behavior disorder: submentalis muscle EMG amplitude analysis during sleep in patients with narcolepsy/cataplexy. *Sleep* 2008;31:1409-17.
15. Ferri R, Bruni O, Fulda S, Zucconi M, Plazzi G. A quantitative analysis of the submentalis muscle EMG amplitude during REM sleep across the lifespan. *J Sleep Res* 2012;21:257-63.
16. Rechtschaffen A, Kales A, eds. A *manual of standardized terminology, techniques, and scoring system for sleep stages of human subjects.* Washington, DC: 1968.
17. Dauvilliers Y, Rompre S, Gagnon JF, Vendette M, Petit D, Montplaisir J. REM sleep characteristics in narcolepsy and REM sleep behavior disorder. *Sleep* 2007;30:844-9.

ACKNOWLEDGMENTS

This work was carried out at the Oasi Institute for Research on Mental Retardation and Brain Aging (IRCCS), Troina, Italy and the Scientific Institute and University Ospedale San Raffaele, Vita-Salute University, Milan, Italy. This study was supported by the Italian Ministry of Health ("Ricerca Corrente").

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication July, 2012
Submitted in final revised form September, 2012
Accepted for publication September, 2012
Address correspondence to: Raffaele Ferri, M.D., Sleep Research Centre, Department of Neurology I.C., Oasi Institute for Research on Mental Retardation and Brain Aging (IRCCS), Via C. Ruggero 73, 94018 Troina, Italy; Tel: +30-0935-936111; Fax: +39-0935-936694; E-mail: rferri@oasi.en.it

DISCLOSURE STATEMENT

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