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Authors

DelRosso, Lourdes
Chesson, Andrew
Hoque, Romy

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Characterization of REM Sleep without Atonia in Patients with Narcolepsy and Idiopathic Hypersomnia using AASM Scoring Manual Criteria

Lourdes M. DelRosso, M.D.; Andrew L. Chesson Jr., M.D., F.A.A.S.M.; Romy Hoque, M.D.

Department of Neurology, Division of Sleep Medicine, Louisiana State University School of Medicine Shreveport, LA

SCIENTIFIC INVESTIGATIONS

Introduction: *The AASM Manual for the Scoring of Sleep and Associated Events* (Manual) has provided standardized definitions for tonic and phasic REM sleep without atonia (RSWA). This study used Manual criteria to characterize REM sleep in patients with narcolepsy and idiopathic hypersomnia (IH).

Methods: A retrospective review of PSG data from ICSD-2 defined patients with narcolepsy or IH, performed by two board certified sleep medicine physicians. Data compiled included REM sleep epochs and the presence in REM sleep of epochs scored as sustained muscle activity (tonic), and excessive transient muscle activity (phasic) as defined by Manual criteria.

Results: PSG data from 8 narcolepsy patients (mean age: 27.5 years; age range: 11-55) showed mean ± standard deviation values for: total REM sleep epochs 205 ± 46.1; RSWA/phasic epochs 56.1 ± 25.4; and RSWA/tonic epochs 15.0 ± 10.7. PSG data from 8 IH patients (mean age: 33.1 years; age range: 20-57) showed mean ± standard deviation values of total REM sleep epochs 163.8 ± 67.9; RSWA/phasic epochs 6.2 ± 3.5; and RSWA/tonic epochs 0.2 ± 0.4. Comparison revealed intergroup differences in phasic REM sleep ($p < 0.01$) and tonic REM sleep ($p < 0.01$) were significantly increased in narcoleptics compared to IH.

Conclusion: Our retrospective analysis showed that RSWA phasic activity and RSWA tonic activity are significantly increased in patients meeting ICSD-2 criteria for narcolepsy compared to patients meeting ICSD-2 criteria for IH. This robust difference, with further validation, could be useful as electrophysiological criteria differentiating the two disorders and understanding the physiological differences.

Keywords: Narcolepsy, idiopathic hypersomnia, rapid eye movement sleep, REM sleep without atonia, phasic, tonic

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Earlier reports have presented evidence of REM dysfunction in patients with narcolepsy. Our study will evaluate electrophysiologic differences between Narcolepsy and Idiopathic Hypersomnia.

Study Impact: Our study demonstrates a robust electrophysiologic difference in both tonic and phasic REM sleep without atonia between IH and narcolepsy, independent of cataplexy status.

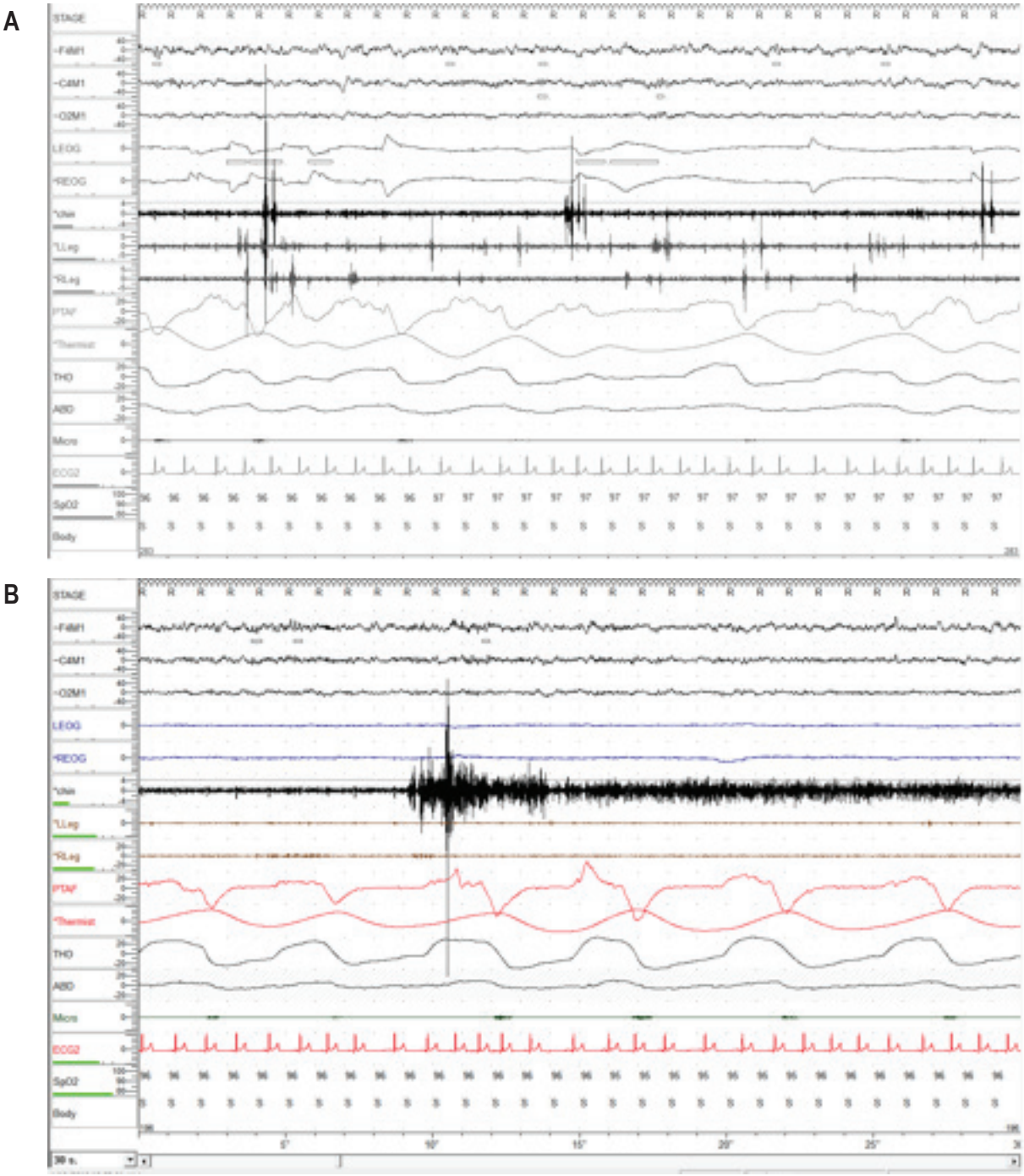
The *International Classification of Sleep Disorders*-second edition (ICSD-2) classifies narcolepsy and idiopathic hypersomnia (IH) under hypersomnias of central origin.[1] The diagnostic criteria for both conditions include at least three months of subjective excessive daytime sleepiness (EDS) occurring almost daily and a mean sleep latency of less than eight minutes in the multiple sleep latency test (MSLT). These two conditions are electrophysiologically differentiated based on the number of sleep onset REM periods (SOREMPS) in the MSLT: two or more for narcolepsy and less than two for IH. The ICSD-2 further subdivides narcolepsy into narcolepsy with cataplexy (N+C) and narcolepsy without cataplexy (N-C). For both narcolepsy and IH, medical, mental, neurological, or pharmacological causes must also be excluded. The conditions must also not be accounted for by another sleep disorder or drug use.

Several earlier reports have presented evidence of REM dysfunction in patients with narcolepsy including: different patterns in REM sleep distribution/REM density across the night, REM sleep phasic activity, and early onset REM sleep periods.[2] REM behavior disorder (RBD) has been reported in up to 36% of patients with narcolepsy, with higher prevalence in N+C.[3] On rare occasions, RBD has been the presenting complaint in patients with undiagnosed narcolepsy.[4] However, the motor manifestations of RBD in narcolepsy have been found to be both less frequent and less severe than in idiopathic RBD.[5] REM sleep without atonia (RSWA) has been previously reported in narcoleptics who do not meet criteria for RBD.[6]

Different methods have been used to assess motor dysregulation in patients with narcolepsy. Automated computerized scoring has demonstrated increased EMG activity in the chin during sleep, while video monitoring studies have shown "mild" motor behaviors in narcolepsy as opposed to full-blown violent/aggressive RBD.[7]

IH closely resembles narcolepsy both clinically and in polysomnography (PSG) features.[8] Furthermore, REM related symptoms, such as hypnagogic hallucinations and sleep paraly-

Figure 1—Examples of typical rapid eye movement sleep without atonia (RSWA) epochs



(A) RSWA - phasic activity. **(B)** RSWA - tonic activity.

sis, have been found to be higher in a subgroup of patients with IH than in the general population.[9]

The goal of this study was to analyze PSG data scored in accordance with the *American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events* (Manual) in narcolepsy and IH to evaluate electrophysiologic differences between these two conditions, with special attention to whether RSWA differs in these two conditions.[10] No prior studies of RSWA in narcolepsy have explicitly utilized the Manual criteria.

METHODS

Selection Criteria

Over a 2-year period (03.01.2010 to 03.01.2012), all patients with a new diagnosis of narcolepsy or IH were identified from patient records at the Sleep Disorders Center of the Louisiana State University Health Sciences Center in Shreveport, Louisiana. The diagnosis of IH, N-C, and N+C was made by a board certified

Table 1—Demographics

A Demographics	N Mean ± SD, (range)	IH Mean ± SD, (range)	Mann-Whitney p-values: N/IH
Age	27.5 ± 12.73, (11-55)	32.62 ± 14.34, (20-57)	0.674
ESS	19.75 ± 2.92 (16-24)	16.63 ± 3.62, (10-20)	0.074
BMI	33.69 ± 7.37, (24-43.8)	28.69 ± 5.35, (20.9-37.8)	0.156

B Demographics	N Total, % of total	IH Total, % of total
Sex (F)	4, 50%	7, 87%
Self reported dream enacting behavior	2, 25%	0
Self reported sleep talking	3, 37%	3, 37%
RLS	3, 37%	3, 37%
Caffeine intake	3, 37%	3, 37%

(A) Age, ESS, and BMI. No statistically significant differences where noted in these variables between the two groups. **(B)** Sex distribution and self-reported dream enacting behavior, self-reported sleep talking, RLS, and daily caffeine intake. ESS, Epworth Sleepiness Score; BMI, body mass index; N, narcolepsy; IH, idiopathic hypersomnia; RLS, restless legs syndrome.

Table 2—PSG data from narcoleptics and idiopathic hypersomniacs

					p-values				
					Kruskal-Wallis	Mann Whitney			
PSG variable	N Mean ± SD	N+C Mean ± SD	N-C Mean ± SD	IH Mean ± SD	N+C/N-C/IH	N/IH	N+C/IH	N-C/IH	N+C/N-C
Total REM sleep in minutes	205.75 ± 46.15	206.25 ± 65.06	205.25 ± 27.12	163.88 ± 67.92	0.236	0.104	0.270	0.126	0.564
Total Tonic REM sleep epochs	15 ± 10.74	10.5 ± 5.07	19.5 ± 13.77	0.25 ± 0.46	0.002	0.001	0.007	0.007	0.248
Total Phasic REM sleep epochs	56.13 ± 25.74	51.5 ± 27.74	60.75 ± 26.81	6.25 ± 3.54	0.003	0.001	0.007	0.007	0.564
RSWAI	42.67 ± 16.39	38.25 ± 22.09	47.09 ± 9.31	5.59 ± 3.48	0.003	0.001	0.007	0.007	0.386
REM sleep onset	21.13 ± 32.95	4.63 ± 1.6	37.63 ± 42.49	119.88 ± 54.89	0.008	0.003	0.007	0.042	0.248
Sleep latency	19.56 ± 13.19	9.88 ± 6.86	29.25 ± 10.44	40.88 ± 26.67	0.019	0.059	0.007	0.734	0.043
TST	419.56 ± 47.96	412.25 ± 35.29	426.88 ± 63.08	461.31 ± 33.35	0.107	0.036	0.062	0.126	0.885
WASO	37.94 ± 23.41	54.25 ± 19.44	21.63 ± 13.82	32.5 ± 31.91	0.128	0.372	0.107	0.865	0.043
SE	90.89 ± 5.08	87.68 ± 3.97	94.1 ± 4.13	92.49 ± 5.99	0.187	0.674	0.174	0.497	0.083
N1%	3.36 ± 3.41	4.68 ± 4.37	2.05 ± 1.86	3.06 ± 1.9	0.627	0.793	0.734	0.445	0.386
N2%	55.5 ± 14	49.47 ± 18.19	61.53 ± 5.39	61.2 ± 10.65	0.458	0.345	0.308	0.610	0.248
N3%	16.38 ± 12.5	20.58 ± 16.39	12.18 ± 6.97	17.83 ± 4.04	0.387	0.294	0.734	0.126	0.386
REM sleep %	24.76 ± 6.43	25.28 ± 9.14	24.24 ± 3.5	17.91 ± 8	0.082	0.027	0.126	0.042	0.773
PLMI	12.99 ± 22.79	5.58 ± 5.59	20.4 ± 32.15	14.53 ± 27.85	0.967	0.834	0.865	0.865	0.773

REM, rapid eye movement; RSWAI, REM sleep without atonia index; TST, total sleep time; WASO, wake after sleep onset; SE, sleep efficiency; PLMI, periodic limb movement index per hour of sleep; N, narcolepsy; N+C, narcolepsy with cataplexy; N-C, narcolepsy without cataplexy; SD, standard deviation.

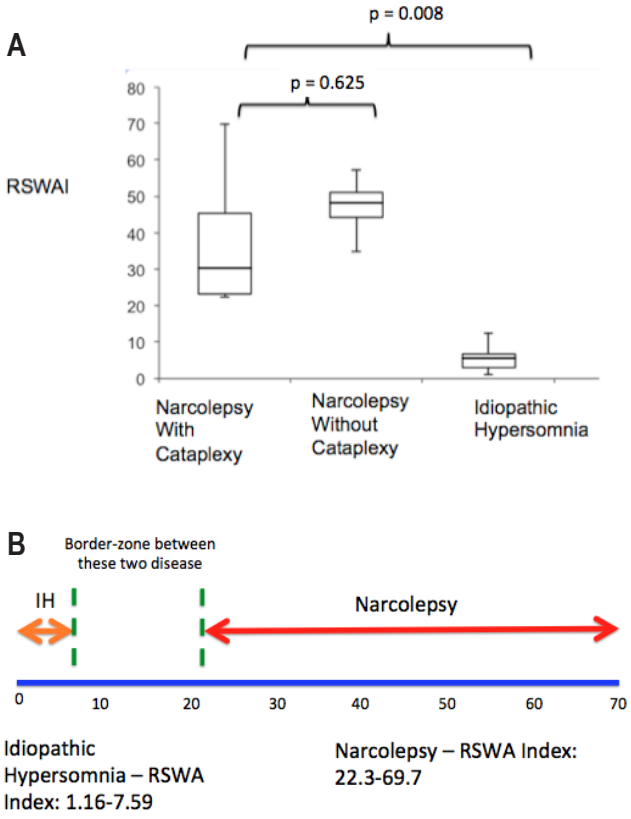
sleep medicine physician based on history, clinical symptoms, and nocturnal PSG and MSLT according to ICSD-2 criteria.[1]

To these narcolepsy and IH patient records we applied the following exclusion criteria: presence of obstructive sleep apnea defined by total sleep time (TST) apnea hypopnea index > 5, circadian disorder, insufficient sleep syndrome based on sleep diaries, positive drug screen performed with MSLT, REM sleep altering/cataplexy suppressing medications (e.g., tricyclic antidepressants, selective serotonin and/or norepinephrine reuptake inhibitors, sodium oxybate), PSG/MSLT done at another facility, psychiatric or neurological comorbidity, and PSG/MSLT recording obscured by significant artifact. The remaining patients used for the study consisted of 8 patients with IH, 4 patients with N+C, and 4 patients with N-C.

Data Acquisition

All patients had a nocturnal PSG followed by an MSLT. The PSG recordings were acquired using the Alice 5 system (Respironics, Inc., Murrysville, PA, USA) and included 6 electroencephalogram channels (F3/A2, F4/A1, C3/A2, C4/A1, O1/A2, O2/A1), vertical and horizontal electroculograms, chin and bilateral tibialis anterior muscle electromyogram, 1-channel electrocardiogram, and respiratory monitors (nasal pressure transducer, thermistor, thoracic and abdominal plethysmogra-

Figure 2—Comparison of REM sleep without atonia index (RSWAI) in narcolepsy with cataplexy, narcolepsy without cataplexy, and idiopathic hypersomnia



(A) Box-plot of RSWAI distributions. **(B)** RSWAI range in idiopathic hypersomnia and narcolepsy.

phy belts, microphone and pulse oximetry). PSG scoring was in accordance with the Manual.

Quantification of RSWA

Each PSG was scored in agreement by 2 board certified sleep medicine physicians (LD, RH) in accordance with the Manual. RSWA was scored using section 7: movement rules; Number 6: Scoring PSG features of REM sleep behavior disorder.[10] **Figures 1A** and **1B** show sample epochs with RSWA.

Calculation of RSWA Index (RSWAI)

RSWAI, the total number of RSWA epochs per hour of REM sleep, was calculated using the formula below:

RSWAI (RSWA 30 sec epochs per hour of REM sleep) = 120 (total number of RSWA 30 sec epochs/total REM sleep epochs)

The total number of RSWA epochs is the sum of the total number of epochs meeting criteria for RSWA by phasic and by tonic criteria.

Statistical Analysis

Analysis of variance for non-parametric samples was performed using the Kruskal-Wallis calculation, and assessment of statistical significance for nonparametric samples was performed using the Mann-Whitney U calculation. P-values less than 0.05 were considered statistically significant.

RESULTS

Demographics

Demographic data of the 3 patient groups is presented in **Table 1**. Mean age for the 8 narcolepsy patients was 27.5 years (range: 11-55); 4 patients were women. Four patients had N+C; 4 patients had N-C. Mean age for the 8 IH patients was 33.12 years (range: 20-57); 7 patients were women. Age, body mass index, and Epworth Sleepiness Scale score were not significantly different between the narcoleptic and IH groups. Two patients with narcolepsy had questionnaire reports of dream-enacting behavior consisting of non-injurious nocturnal arm and leg movements. No patients reported injurious parasomnias or had a primary complaint of parasomnias. Three patients with narcolepsy (all N+C) and 3 with IH reported daily ingestion of caffeinated beverages. As the PSG and MSLT studies were to establish a hypersomnia related diagnosis, all patients were off stimulants and sleep/wake or REM sleep altering medications for > 2 weeks.

PSG Data

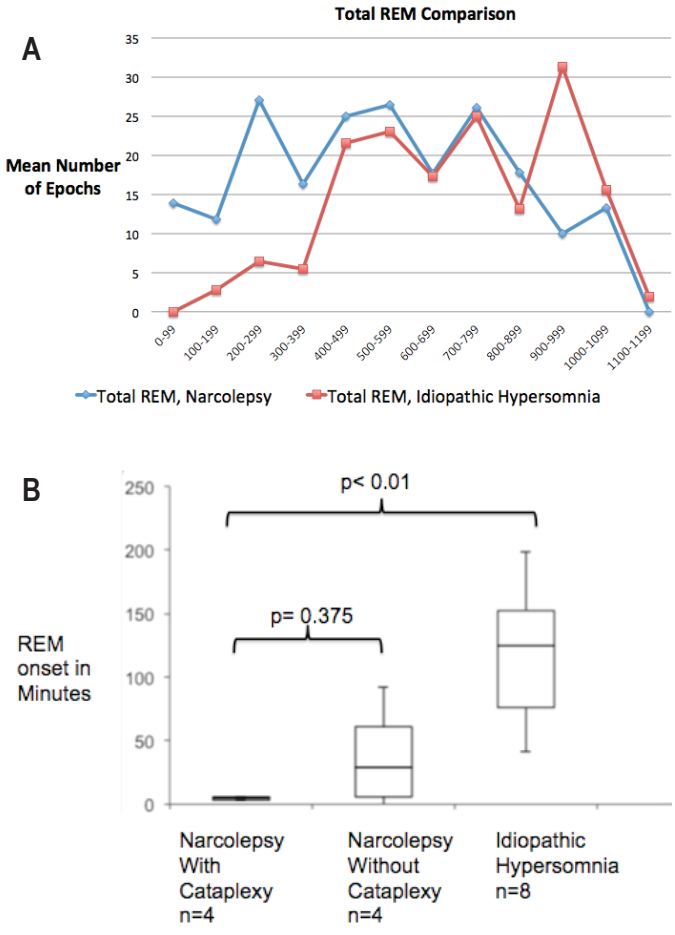
PSG data is summarized in **Table 2**. Total REM sleep in minutes was not significantly different between narcoleptics (206.75 min) and IH (163.88 min), but REM sleep % was significantly different between narcoleptics (24.76%) and IH (17.91%). The use of MSLT to support a diagnosis of narcolepsy requires TST > 6 h on the prior night.[1] Patients from both groups exceeded this amount considerably. TST was significantly different between narcoleptics and IH. The mean TST in narcoleptics was 419.56 min; it was 461.31 min in IH. The narcoleptics TST ranged from 382.5 min to 517 min. The IH TST ranged from 428 min to 532 min. Wake after sleep onset (WASO), sleep efficiency, N1 percentage, N2 percentage, N3 percentage, and periodic limb movement indices (PLMI) were not significantly different between narcoleptics and IH. Neither the narcoleptics nor the IH patients exhibited abnormal REM sleep behaviors during the video PSG recording.

Significant intergroup variances were found between IH, N+C, and N-C in total tonic REM sleep epochs, total phasic REM sleep epochs, RSWAI, and REM sleep latency at $p < 0.01$; and in sleep latency at $p < 0.05$. When comparing narcolepsy to IH, N+C to IH, and N-C to IH: significant Mann-Whitney statistical differences at $p < 0.01$ were found in total tonic epochs, total phasic epochs, and RSWAI. When comparing N+C to IH: significant statistical difference at $p < 0.01$ was found in sleep latency. RSWAI comparisons are shown in **Figure 2A**. The range of RSWAI values in narcoleptics and IH do not overlap with one another and seem to have distinct ranges (**Figures 2A** and **2B**).

No significant statistical difference was found in sleep latency when comparing narcolepsy to IH or when comparing N-C to IH. Significant statistical difference ($p < 0.05$) in sleep latency and WASO was found between N+C and N-C.

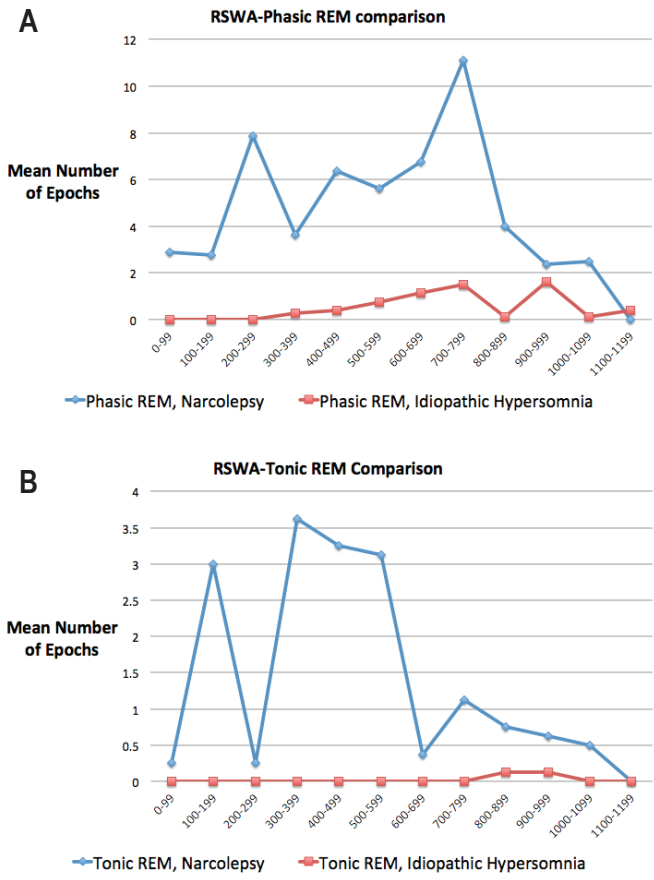
Mean REM sleep onset was 21.13 min in all narcoleptics, 4.63 min in N+C, 37.63 min in N-C, and 119.88 min in IH. Statistically significant differences in REM sleep onset at $p < 0.01$ were seen when comparing narcolepsy to IH, and when com-

Figure 3



(A) Comparison of Total REM sleep epoch distribution across the night in narcolepsy and in idiopathic hypersomnia. **(B)** REM sleep onset comparison between narcolepsy with cataplexy, narcolepsy without cataplexy and idiopathic hypersomnia.

Figure 4—Epoch distribution of REM sleep without atonia (RSWA) comparing narcolepsy and idiopathic hypersomnia



(A) Phasic RSWA epoch distribution. **(B)** Tonic RSWA epoch distribution.

paring N+C to IH. Statistically significant differences in REM sleep onset at $p < 0.05$ were seen when comparing N-C to IH. Despite the difference in mean REM sleep onset between N+C and N-C, this difference was not statistically significant.

Epoch distribution of REM sleep across the night and REM sleep onset in narcolepsy and IH are shown in **Figures 3A** and **3B**, respectively. A more even distribution of REM sleep across the night with more REM sleep earlier in the sleep period was seen in narcolepsy than in IH. IH showed REM sleep predominance later in the sleep period.

Phasic RSWA and tonic RSWA are much more prominent in narcolepsy compared to IH (**Figure 4**). In both narcolepsy and IH: phasic RSWA was more prominent than tonic RSWA; phasic RSWA was most prominent in the third quarter of night and decreases in the final quarter of the night; and tonic RSWA was more prominent in the first half of the night and decreased in the second half of the night.

DISCUSSION

In assessing PSG differences between narcolepsy and IH, this study revealed a statistically significant difference in overnight REM sleep distribution between groups. This finding is consistent with a previous study of the overnight distribution of motor episodes in patients with narcolepsy with cataplexy, which demonstrated that RBD episodes in these patients are less predictable than in patients with idiopathic RBD and independent of time of night or REM sleep period length.[11] The differences in sleep latency and REM sleep onset between narcolepsy and IH shown in our study are consistent with prior investigations.[12]

Our study demonstrates a robust electrophysiologic difference in both tonic and phasic RSWA between IH and narcolepsy, independent of cataplexy status. Recent studies in vivo suggest that the mechanism of REM sleep atonia is dependent on glutamatergic neurons from the sublaterodorsal (SLD) nucleus projecting to glycinergic neurons on the ventromedial medulla (VMM) and/or spinal cord.[13] Muscle atonia is also maintained by simultaneous withdrawal of histaminergic, serotonergic, and noradrenergic input.[14] The areas implicated in muscle atonia during REM sleep include the magnocellular reticular formation, locus ceruleus, subceruleus, pedunculopontine tegmentum, and laterodorsal tegmentum. The presence and complexity of REM sleep motor behavior exhibited in RBD may depend on the neuroanatomical site affected.[15] For example, a case of narcolepsy with RBD has been reported in association with an isolated pontine tegmental lesion.[16]

Hypocretin containing neurons, localized in the hypothalamus with widespread projections throughout the CNS,[17] not only stabilize the sleep/wake cycle but also play a role in modulating muscle atonia during REM sleep by regulating the activity of lumbar motor neurons through both pre-synaptic and post-synaptic mechanisms[18] in a sleep/wake stage dependent manner.[19] N+C patients have been found to have over 90% deficiency in hypocretin neurons, while N-C patients have been found to have a 30% deficiency in hypocretin neurons.[20] RBD in narcolepsy has been associated with hypocretin deficiency, independent of cataplexy status.[21]

Limitations of our study include: retrospective rather than prospective analysis, small patient sample, evaluation of single night PSG data from each patient, patient recruitment from a single institution, and lack of blinded comparisons. These issues may be addressed in future larger multicenter studies. The purpose of this study was to compare RSWA in hypersomnias of central origin, but future studies may also include comparisons to patients who meet ICSD-2 criteria for idiopathic RBD.

Our study may support a common putative pathology for RSWA in both narcolepsy groups that differs from IH. This finding may add an extra electrophysiologic measure, RSWAI, which can potentially be used as an extra marker in aiding in the differentiation between these two central hypersomnias. If confirmed by larger numbers of patients and other investigators, a RSWAI cutoff value obtained from a diagnostic PSG using Manual criteria may be established to help support the differential diagnosis between narcolepsy or IH.

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Address correspondence to: Lourdes DelRosso, M.D., Department of Neurology, Division of Sleep Medicine, Louisiana State University School of Medicine, 1501 Kings Highway, Shreveport, Louisiana 71103; Tel: (318) 762-2930; Fax: (318) 675-4404; E-mail: lordydel@yahoo.com

DISCLOSURE STATEMENT

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