ORIGINAL ARTICLES

SOREMs in Sleep Clinic Patients: Association with Sleepiness, Alertness and Fatigue

Chris Y. Kim, Alan Ong, MD, FRCP(C), D.ABPN, D.ABSM,
Sharon A. Chung, PhD, Colin M. Shapiro, MBBCh, PhD, MRC Psych, FRCP(C)

Study objectives: Sleep-onset rapid eye movement (SOREM) during daytime naps is recognized as a main diagnostic feature of narcolepsy. However, SOREMs have been reported to occur in other disorders. This study set out to answer three questions: 1) whether the majority of patients with SOREMs are diagnosed with narcolepsy; 2) if the number of SOREMs is linked with the degree of daytime sleepiness; and, 3) whether patients with SOREMs are sleepier than patients without SOREMs.
Methods: One hundred and eighty-five charts of sleep clinic patients with SOREMs on the Multiple Sleep Latency Test (MSLT) or Maintenance of Wakefulness Test (MWT) were compared to 178 charts from clinic patients without SOREMs on the MSLT or MWT (control group). Information was collected from the initial, diagnostic sleep study.
Results: Patients with SOREMs were almost as frequently diagnosed with narcolepsy as with obstructive sleep apnea (OSA) or depression/anxiety. Subjective measures of sleepiness, alertness and fatigue were not different between the SOREM and control groups. The SOREM group did not exhibit shorter mean sleep onset latencies on the MSLT or MWT but a greater number of SOREMs was associated with increased sleepiness on the MSLT, but not on the MWT or subjective measures of sleepiness.
Conclusion: SOREMs occur across a wide variety of sleep and psychiatric disorders. Patients with SOREMs were not sleepier, more fatigued or less alert than those without SOREMs. The findings of this study indicate that SOREMs are not an accurate or specific diagnostic marker of narcolepsy. **(Sleep and Hypnosis 2012;14(1-2):20-28)**

Key words: SOREM, EDS, alertness, fatigue, narcolepsy

INTRODUCTION

Sleep onset rapid eye movement sleep (SOREM) is an abnormal sleep phenomenon characterized by having REM sleep occurrence within 15 minutes from the onset of nighttime sleep or daytime napping. SOREMs are commonly recognized as one of the main features of narcolepsy (1). However, SOREMs have been reported to occur with other sleep, psychiatric and medical disorders, such as OSA (2), major depression (3), alcoholism (4), sleep–wake schedule disturbances (5), Prader–Willi Syndrome (6), neurodegenerative disorders such as Parkinson's disease (7), schizophrenia (8), frequent periodic limb movements (9) and Kleine–Levin syndrome (10). SOREMs

Department of Psychiatry, Toronto Western Hospital, University Health Network

Address reprint requests to: Dr. Sharon A. Chung, PhD
Sleep Research Laboratory, Department of Psychiatry, Toronto Western Hospital, University Health Network, 399 Bathurst Street, 7 Main – 429 Toronto, Ontario, Canada, M5T 2S8
Tel: 416–603–5275, Fax: 416–603–5292
E–mail: sachung@uhnres.utoronto.ca

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sometimes occur in individuals who report being free of any sleep–related complaints, but this has been proposed as being an early sign of narcolepsy (11).

Although SOREMs frequently occur in patients with excessive daytime sleepiness (EDS), there has not been a clearly defined link between the number and frequency of SOREMs and the degree of sleepiness. Narcolepsy patients who are known to have severe EDS are recognized and, by some definitions (12) but not all (13), required to have more than two SOREMs recorded by MSLT. Interestingly, SOREMs are not uncommon in patients with OSA which is recognized as a much more common cause of daytime sleepiness than narcolepsy (4).

In clinical practice, excessive daytime sleepiness (EDS) is commonly interpreted as having drowsiness, low–vitality, tiredness, and uncontrollable daytime sleepiness (14). SOREMs may be linked to sleepiness as alluded to in a study of intrinsic dream mechanisms by using the Sleep Interruption Technique (15) where sleep is interrupted for one hour following 40 minutes of non–REM (NREM) in order to elicit SOREMs (16). In that study, patients who had SOREMs felt more tired than patients who did not have SOREMs.

A possible link between the appearance of SOREMs and subjective sleepiness has also been investigated. Broughton and Aguirre (17) have shown that narcolepsy patients with SOREMs rated themselves as being sleepier on the Stanford Sleepiness Scale (SSS) (18) than patients without SOREMs. The authors proposed that increased REM pressure (resulting in 'REM sleepiness') would produce greater levels of both subjective and objective sleepiness (17). In contrast, mean sleep latencies as measured by the MSLT have been shown to be a more consistent marker in diagnosing narcolepsy than is the number of SOREMs (4), suggesting that SOREMs may instead represent a non–specific feature in narcolepsy. In a recent study of EDS, Singh and colleagues (19) have found that SOREMs can occur in the general population and that two or more SOREMs may not have any particular significance in making the diagnosis of narcolepsy. In addition, there is evidence that age may play a role with regards to the number of SOREMs in patients with narcolepsy (20). In the aforementioned study, older narcolepsy patients consistently evinced fewer SOREMs on daytime tests than younger patients.

Further, there is no evidence whether or not the presence of SOREMs is associated with greater impairment of alertness. Alertness has recently been defined as being a subjective state of responsivity to both introceptive and external stimuli that has independent psychometric properties to the construct of sleepiness and is relevant in the evaluation of sleep–disordered patients (21). Two questionnaires, the Toronto Hospital Alertness Test (THAT) and the ZOGIM Alertness Scale (ZOGIM–A) (22), have been developed to assess subjective alertness.

Fatigue may be described as a subjective sensation of weariness overlapping with negative sensations of heaviness and general malaise (23,24). Fatigue is distinct from sleepiness, the latter being the subjective experience associated with the tendency to change behavioral state into sleep. Fatigue is a symptom that is a prominent in a number of medical conditions, for example multiple sclerosis (25), cancer (26), and lupus (27). There is some suggestion that SOREMs may be associated with greater subjective complaints of fatigue. In one study by Takeuchi and colleagues (16) higher levels of fatigue occurred when SOREMs were artificially induced in healthy subjects. The above finding bears further investigation.

Untreated excessive daytime sleepiness and impaired daytime alertness are linked to a high prevalence of motor–vehicle accidents, work–related injuries, increased use of the healthcare system and a reduced overall quality of life (14). Therefore, it would be useful to determine whether patients with SOREMs, regardless of the underlying sleep disorder, also present with features of EDS or impaired alertness. It is also unclear if the number and frequency of SOREMs

can be used clinically as a diagnostic marker for predicting the level of daytime sleepiness.

The current study set out to answer three questions. Firstly whether the majority of patients with SOREMs are found to have narcolepsy; secondly, whether patients with SOREMs are sleepier, less alert, and more fatigued than the patients who do not exhibit SOREMs; and, lastly, if there is a link between the number of SOREMs and the degree of daytime sleepiness.

MATERIAL AND METHODS

Study Population

Approval to conduct this retrospective study was obtained from the University Health Network Research Ethics Board. All the charts were collected from the Sleep and Alertness Clinic which is a 9–bed sleep clinic in downtown Toronto associated with a tertiary care center, the Toronto Western Hospital, University Health Network. There were approximately 1200 patient charts filed in alphabetical order either at the clinic or at a storage facility.

In this retrospective study, charts of sleep clinic patients who had completed overnight diagnostic polysomnographic (PSG) testing in the 5 years before the start of data collection, and who had undergone MSLT or MWT testing on the day following their initial sleep study were suitable for inclusion in this study. Exclusion Criteria were: charts of patients where overnight PSG or daytime testing (MSLT or MWT) were incomplete or charts where patients had not completed the ESS, SSS or FS questionnaires.

Two hundred and twenty–five charts of sleep clinic patients with at least one SOREM on their daytime tests (consisting of 4 or 5 sessions), MSLT and/or MWT were collected. SOREM was defined in this study as REM sleep occurring within 15 minutes from the onset of sleep on the MSLT or MWT. Of the charts from the 225 SOREM patients, 40 charts had to be excluded from analysis as these patients were undergoing further diagnostic testing and definitive diagnoses were as yet unavailable. This left a total of 185 evaluable charts of patients in the SOREM group. From the alphabetically filed clinic charts, the control charts were obtained by selecting the patient chart to the immediate right of the SOREM patients' charts. If that chart did not match the study inclusion/exclusion requirements, sequential charts to the right were examined until a suitable chart could be obtained. Using this procedure, 225 charts from clinic patients without SOREMs on daytime tests were initially selected for the control group, but a further 47 of these had to be excluded because the patients had a previous history of SOREMs or had SOREMs on their overnight PSG tests. For both the SOREM and control groups, charts of patients who had received any treatment for a sleep disorder prior to their initial sleep study in the clinic were excluded.

Study Design

Where clinic patients had two initial overnight sleep studies in the clinic, information from the second night of two overnight sleep studies was collected. The primary diagnosis of the SOREM patients and controls was determined from the patient's charts using the physicians' consultation notes before and after the diagnostic sleep study. This determination was made by a separate physician sleep–specialist member of our team (AO) after a thorough review of the patients' charts. Charts were reviewed for scores on the Stanford Sleepiness Scale (SSS) (18), Epworth Sleepiness Scale (ESS) (28), alertness scales (THAT, ZOGIM–A) (29) and fatigue scale (FS) (30), and sleep latencies as determined from results of the MSLT and/or MWT. Information about age, gender and current medications were also collected. PSG sleep architectural and physiological measures were noted from the sleep study including: Respiratory Disturbance Index (RDI), Arousal Index (AI), Periodic Limb Movement Index (PLMI), sleep onset latency, sleep stage duration and total sleep time.

Statistical Analyses

The SPSS software version 14.0 (SPSS Inc., Chicago, IL) was used to conduct the statistical analysis. Independent sample t–tests were used to determine if the scores on the measures of subjective (ESS and SSS) or objective (MSLT and MWT) sleepiness, subjective alertness (THAT and ZOGIM–A), and subjective (FS) fatigue differed between those patients who had SOREMs and those of the control group. The significance level was set at $p<0.001$ so as to reduce the occurrence of Type I errors resulting from multiple comparisons. Correlation analysis using the Spearman's rank–order correlation coefficient was used to determine the relationship between subjective (ESS, SSS, THAT, ZOGIM–A and FS) and objective (MSLT and MWT) measures of sleepiness and alertness and the number of SOREMs.

RESULTS

The SOREM group (185 total) consisted of 115 (62%) male and 70 female patients, and the control group (178 total) of 95 (53%) male and 83 female patients. Of the SOREM group, 119 (64.3%) patients underwent only the MSLT and 60 (32.4%) patients had both daytime tests. The mean ages of the study groups at the time of their sleep studies were: SOREM: 39.2 ± 14.5 years (range from 14 to 76 years) and controls: 45.9 ± 15.4 years (range from 15 to 98 years). The control group patients were significantly older ($p<0.001$) than the SOREM group.

Most common diagnoses of patients (n=185) in the SOREM group included narcolepsy (n= 44), OSA (n= 39) and depression and anxiety (n= 27). Two other less frequent diagnoses were acquired brain injury (n= 12) and idiopathic hypersomnia (n= 12). The diagnosis of idiopathic hypersomnia was made only when

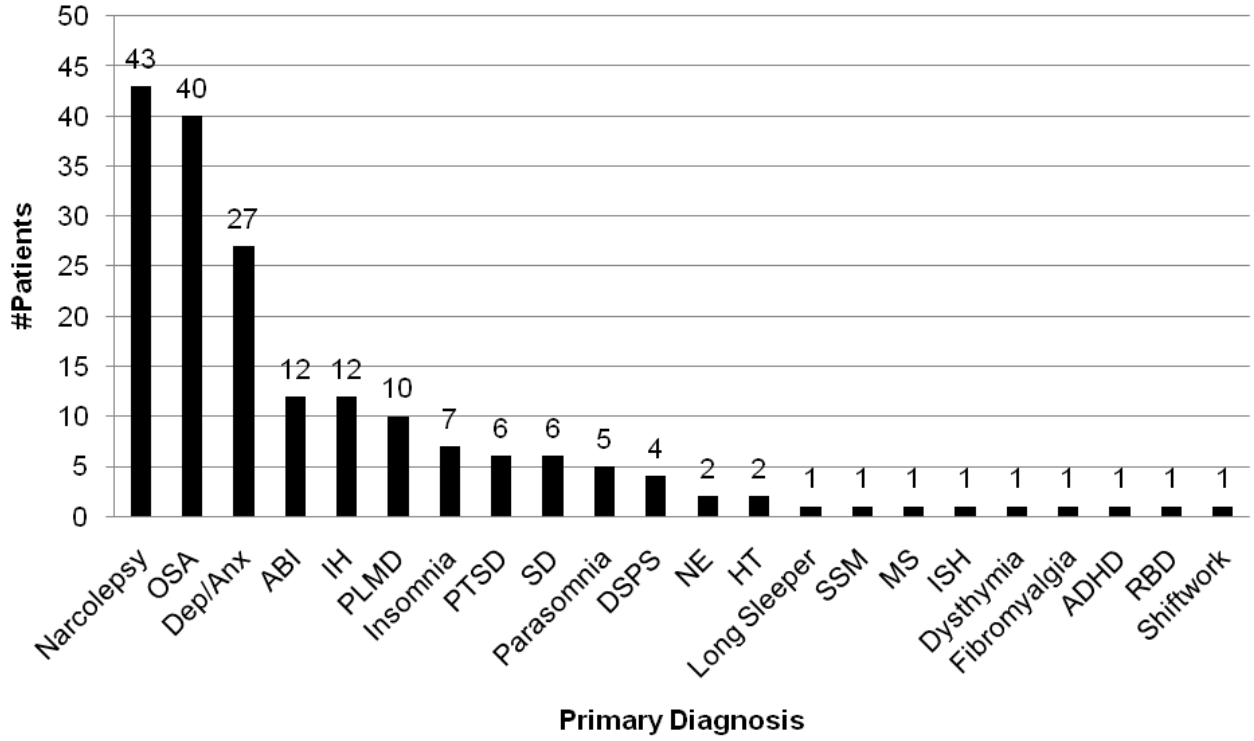

Figure 1. Diagnosis of 185 patients with SOREM on either their MSLT or MWT. The y-axis represents the percentage of SOREM patients who were diagnosed with one of the respective sleep or psychiatric disorders.
OSA = Obstructive Sleep Apnea; Dep/Anx = Depression/Anxiety; ABI = Acquired Brain Injury; IH = Idiopathic Hypersomnia; PLMD = Periodic Limb Movement Disorder; PTSD = Post-Traumatic Stress Disorder; SD = Sleep Deprivation;; DSPS = Delayed Sleep Phase Syndrome; NE = Nocturnal Epilepsy; HT = Hypothyroidism; SSM = Sleep State Misperception; MS = Marfan's Syndrome; ISH = Inadequate Sleep Hygiene; ADHD = Attention Deficit Hyperactivity Disorder; RBD = REM Behavior Disorder.

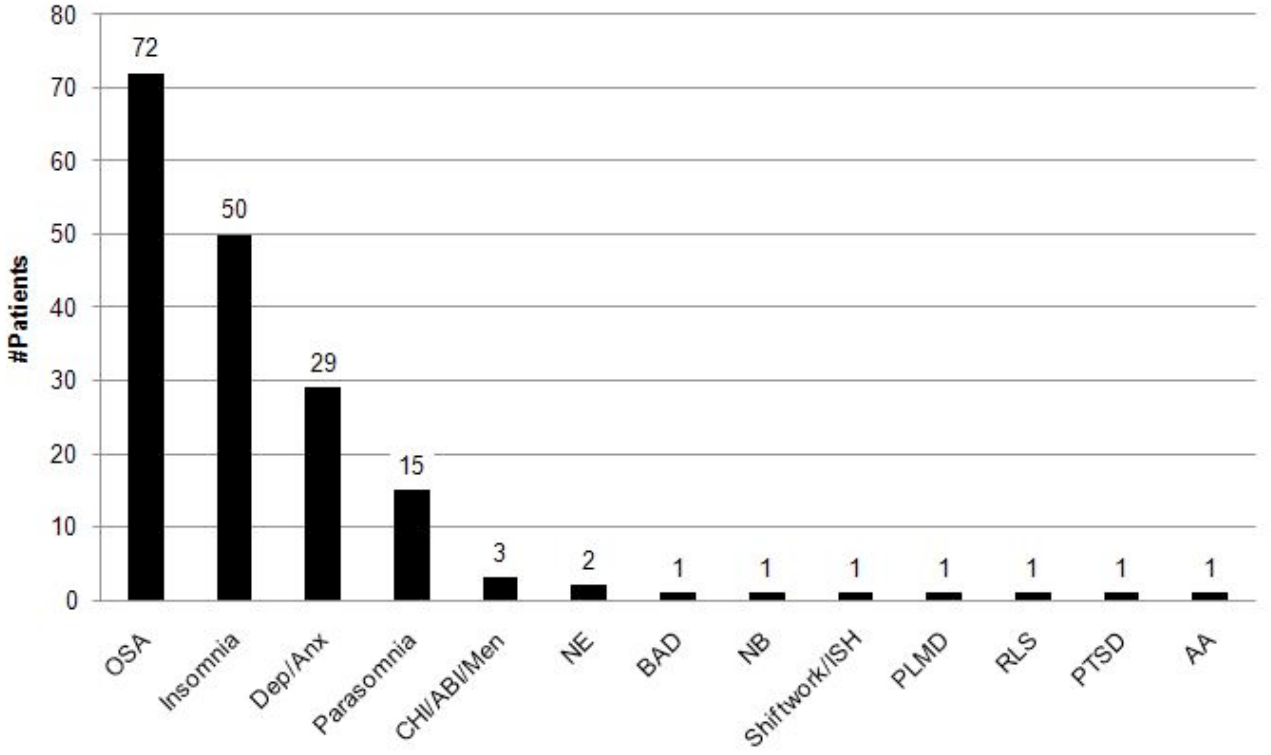

Figure 2. Diagnosis of 178 patients in the control group. The y-axis represents the percentage of control patients who were diagnosed with one of the respective sleep or psychiatric disorders.
OSA = Obstructive Sleep Apnea; Dep/Anx = Depression/Anxiety; CHI = Closed Head Injury; ABI = Acquired Brain Injury; Men = Meningitis; NE = Nocturnal Epilepsy;BAD = Bipolar Affective Disorder; NB = Nocturnal Bulimia; ISH = Inadequate Sleep Hygiene; PLMD = Periodic Limb Movement Disorder; RLS = Restless Leg Syndrome; PTSD = Post-Traumatic Stress Disorder; AA = Alcohol Abuse.

no medical reason for excessive daytime sleepiness was found, despite a thorough medical, psychiatric and sleep assessment, and where patients did not have any history of cataplexy. The distributions of diagnoses of the SOREM and control groups are listed in Figures 1 and 2.

Sleep and Sleepiness in the SOREM vs. Control Groups

The sleep variables on the overnight PSG were examined to discern any differences in sleep architectural variables between the SOREM and the control group. The overnight PSG variables for both study groups are shown in Table 1. The only significant differences in the PSG variables found between the two groups were the SOREM group having a greater percentage of slow wave sleep (SWS) ($p<0.001$), a lower arousal index (AI) ($p<0.001$), and a significantly shorter nighttime REM sleep latency ($p<0.001$). There were no differences in total sleep duration (TST), sleep efficiency (SE), periodic limb movement index (PLMI) or in the respiratory disturbance index (RDI).

As shown in Table 1, the mean subjective sleepiness scores of the SOREM group were not different from that of the control group (SSS: $p= 0.169$; ESS: $p= 0.073$). Also, the two groups did not differ significantly on mean alertness (THAT: $p= 0.292$; ZOGIM–A: $p= .0438$) or fatigue (FS: $p= .261$) scores. Compared to the control group, the SOREM group appeared to have a significantly shorter mean sleep onset latency on the MSLT (7.6 ± 4.4 min versus 10.1 ± 4.8 (control); $p < 0.001$) and MWT (16.9 ± 6.9 min versus 21.3 ± 6.0 (control); $p < 0.001$). However, a comparison of sleep onset latencies across the different age groups (Table 2) demonstrated no significant differences in MSLT and MWT latencies for the SOREM and control groups.

Table 1. PSG characteristics of the SOREM (n=185) and control (n=178) groups.

	SOREM			Control			
Variable	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**	**p**
TST (min)	375	72.5	117.5 - 515	366.5	81.8	9 - 495	0.293
Stage 1 (%)	6.9	4.36	1.1 - 29.6	7.6	6	1.4 - 65.2	0.208
Stage 2 (%)	50	11.9	11.4 - 81.9	51.1	11.5	4.8 - 80.5	0.378
Stage 3 (%)	6.8	3.6	0 – 17.9	6.1	3.5	0 – 15	0.047
Stage 4 (%)	6.5	6.1	0 – 23.4	4.8	5.2	0 – 21	0.006
SWS (%)*	13.4	7.7	0 – 40.9	10.7	7.1	0 - 38	<0.001*
Wake (%)	12.5	12.3	0.2 - 73.3	15.8	13.6	0 – 93	0.014
REM (%)	16.9	7.2	0 - 45.9	15.1	7.2	0 – 35	0.017
REM latency (min)*	94.2	63.9	0.5 - 359	122.6	93.4	0 – 428	<0.001*
AI (/h)*	14.2	11.5	0.6 - 70.0	19.8	19.1	1.5 - 152.3	<0.001*
RDI (/h)	6.7	12.8	0 – 71.7	8.4	13.6	0 - 99.4	0.225
PLMI (/h)	6.6	13.5	0 - 99.4	9	20.2	0 - 155.9	0.179
SE (%)	87.5	12.3	26.7 – 99.8	84.16	13.63	7.3 - 100	0.014
SSS	3.4	1.49	1 - 7	3.2	1.3	1 - 7	0.169
ESS	11.6	5.9	0 - 24	10.1	5.6	0 - 24	0.073
ZOGIM	31.3	8.4	4 - 50	32.2	8.1	14 - 50	0.438
THAT	24.9	9.6	5 - 47	26.3	11.5	1 - 50	0.292
FS	3.9	1.71	1 - 7	3.7	1.6	1 - 7	0.261
MSL(MSLT)	7.6	4.6	0 - 19.8	10.1	4.8	1.5 - 29.1	<0.001*
MSL(MWT)	17.3	6.9	0.9 - 21.5	21.3	6.0	5.3 - 29.4	<0.001*

SD = Standard Deviation; TST = Total Sleep Time; SWS = Slow Wave Sleep; REM = Rapid Eye Movement; RDI = Respiratory disturbance index; PLMI = Periodic Limb Movement Index; AI = Arousal Index; SE = Sleep Efficiency; SSS = Standford Sleepiness Scale; ESS = Epworth Sleepiness Scale; THAT = Toronto Hospital Alertness Test; FS = Fatigue Scale; p = t statistic that determines the statistical difference between the means of each variable. * indicates statistical significance (set at p<0.001).

Table 2. Age-adjusted comparison of the mean sleep latencies on the MSLT and MWT.

	SOREM	Control	MSL_{MSLT}	SOREM	Control	MSL_{MWT}
Decades	**MSL_{MSLT} ± SD**	**MSL_{MSLT} ± SD**	**p**	**MSL_{MWT} ± SD**	**MSL_{MWT} ± SD**	**p**
10s	9.8 ± 4.7	9.1 ± 2.8	0.312	26.2 ± 5.6	24.5 ± 6.9	0.819
20s	6.3 ± 3.0	9.8 ± 4.3	0.926	15.0 ± 7.8	22.6 ± 7.5	0.801
30s	6.7 ± 4.8	9.8 ± 4.8	0.679	18.3 ± 9.9	22.8 ± 7.6	0.065
40s	8.4 ± 4.5	10.1 ± 4.8	0.68	24.0 ± 7.5	25.7 ± 5.9	0.029
50s	8.3 ± 4.0	9.9 ± 4.8	0.186	20.8 ± 8.0	26.0 ± 5.6	0.103
60s	6.9 ± 4.7	11.4 ± 6.1	0.178	25.7 ± 6.1	28.0 ± 3.7	0.054
70s	6.6 ± 1.2	11.8 ± 6.2	0.033	25.7 ± 3.8	21.6 ± 7.5	0.039

MSL_{MSLT}= Mean Sleep Latency on MSLT; MSL_{MWT}= Mean Sleep Latency on MWT; SD= Standard Deviation.

Table 3. Correlations between the number of SOREM episodes with measures of sleepiness, alertness and fatigue.

	No. SOREMs (MSLT)		No. SOREMs (MWT)	
	r^2 value	**p**	**r^2 value**	**p**
SSS	0.047	0.58	0.029	0.79
ESS	-0.1	0.93	0.373	0.023
THAT	0.126	0.266	-0.173	0.261
ZOGIM-A	-0.09	0.277	-0.167	0.151
FS	0.109	0.156	0.032	0.759
MSLT MSL	-0.353	<0.001*		
MWT MSL			-0.087	0.426

SSS = Stanford Sleepiness Scale; ESS = Epworth Sleepiness Scale; THAT = Toronto Hospital Alertness Test; FS = Fatigue Scale; MSLT = Mean Sleep Latency Test; MSL = Mean Sleep Latency; MWT = Maintenance of Wakefulness Test. * indicates statistical significance (set at p<0.001).

Correlational Analyses

Scores on tests of subjective daytime sleepiness (SSS and ESS), alertness (THAT and ZOGIM–A) or fatigue (FS) were not correlated with the number of SOREMs on either the MSLT or MWT. No correlation between the number of SOREMs on the MWT and the sleep onset latency on that daytime test was found (r^2= –.087, p= .426). However, there was a small but significant correlation between the mean sleep latencies on the MSLT (r^2= – .353, p<.001) and the number of SOREMs on the MSLT. The statistical values for the above correlations are presented in Table 3.

DISCUSSION

Patients with SOREMs did not have a greater degree of daytime sleepiness, whether assessed with subjective (SSS and ESS) or objective (MSLT and MWT) measures of sleepiness. Our findings also suggest that self–reported measures of sleepiness are reliable in the SOREM patient population. In support of the previous literature, the SOREM group had a shorter REM latency compared to the control group. SOREMs are presumed to be a product of an increased REM pressure (31), which is typically thought to be the case in patients with narcolepsy. The shortened REM latency in the patient group with SOREMs in this study supports the hypothesis that these patients have increased REM pressure in their nighttime sleep that is reflected in the occurrence of SOREMs on daytime naps.

We observed that although patients with SOREMs were not sleepier, more fatigued or less alert than their control group counterparts, a greater number of SOREMs during the MSLT, but not MWT, was associated with shorter sleep onset latency on the MSLT. The interpretation of this latter finding is unclear. It is possible that a greater number of SOREMs on daytime naps is predictive of an increased level of objective sleepiness but this would need further investigation. Along these lines, Bonnet and Arand (32) have proposed that the MSLT may be a better measure of sleepiness whereas the MWT may reflect levels of alertness.

As reported in numerous studies (5,12), narcolepsy is often coupled with the presence of multiple SOREMs. The presence of SOREMs has been a diagnostic focus due to the REM–based phenomena, including muscle atonia (sleep paralysis or dissociated REM sleep), which are present in patients with narcolepsy. However, the present study shows that only 24% of the patients with SOREMs were diagnosed with narcolepsy. The vast majority of patients with SOREMs had other sleep, medical and psychiatric disorders, implying that for the diagnosis of narcolepsy other clinical features such as the presence of cataplexy and medical history need to be considered in addition to changes in REM latency. The fact that the majority of patients with SOREMs did not have narcolepsy would not change even if the 40 patients with SOREMs who were initially excluded from the analysis due to the lack of a definitive diagnosis were all eventually diagnosed with narcolepsy. This finding draws us to the similar conclusions made previously in the literature that the presence of SOREM is not solely associated with narcolepsy and that shortened REM latency in narcolepsy is not an accurate or specific marker in making the diagnosis (19,31). On the other hand, mean sleep latencies measured by the MSLT and MWT may have a better sensitivity and specificity in diagnosing narcolepsy (4).

In our study, patients with OSA were found to have a similar occurrence (21%) of SOREMs as in the narcolepsy patients (24%). This finding is in accordance with others (33) who determined that the presence of SOREM in OSA patients is not due to narcolepsy. SOREMs have also been reported in major depression and, surprisingly, almost one out of seven patients with SOREMs in this study was diagnosed with depression or anxiety. Of particular interest were the patients with other disorders that exhibited SOREMs, such as PTSD and acquired brain injury. There has not been any previous report of SOREMs in these disorders. Given the association between SOREMs and increased sleepiness, it appears that SOREMs can occur in patients with excessive daytime sleepiness, regardless of the underlying disorder.

Utilization of the Sleep Interruption Technique (16), designed to elicit SOREMs in normal individuals, points to another cause of SOREMs, that of sleep fragmentation. However, contrary to the findings of that study, our control patients had a greater degree of sleep fragmentation compared to the SOREM group. Our study did not observe an association between arousal index and the occurrence of SOREMs. One of the flaws with the technique used by Takeuchi and his colleagues (16) is that

their study procedure also produced sleep deprivation, which would likely have resulted in excessive daytime sleepiness.

It is important that we highlight some of the limitations of the methodology used in this study. It should be noted that although about one in seven patients with SOREMs had either anxiety or depression, the design of the study does not provide any information on the specificity and sensitivity of SOREMs as a marker of depression or anxiety. No initial attempts were made to age–match the groups and the control group was older than the SOREM group. This group difference in age was likely due to the typical early onset of narcolepsy and the later onset of disorders such as OSA. Furthermore, we did not compare the differences in the mean sleep latencies in a four–nap protocol and a five–nap protocol, although the difference becomes less significant above the age of 40 (34). If a patient presented with multiple disorders, the physician labeled the disorder that had the greatest impact on the patients' sleep or medical presentation as the primary diagnosis. We did not come across any patient charts where narcolepsy was indicated as a secondary diagnosis. Also, due to the retrospective nature of the study, it was not possible to determine the patient's quality and quantity of sleep prior to the sleep studies. We specifically excluded any charts of patients taking sedating medications and patients were routinely asked on the night of their sleep study to list any medications they had taken during that day. While our technologists are trained to detect patients under the influence of alcohol or illicit drugs, we did not conduct blood tests to screen for sedating or alerting substances that the patients may not have reported. We have tried to counterbalance the abovementioned issues as best as possible with the large sample size of patients with SOREM and control patients.

In summary, we have found in this study that patients with SOREMs are not sleepier than those without SOREMs. However, a greater number of SOREMs was associated with increased sleepiness on the MSLT, but not on the MWT or subjective measures of sleepiness. Lastly, the paper emphasizes that many patients with disorders other than narcolepsy may exhibit SOREMs during daytime testing and recommends against making the diagnosis of narcolepsy exclusively based on these phenomena.

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