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Original Article

Underutilization of the MSLT in sleepy patients with a short onset REM period (SOREMP) in the sleep clinic

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ABSTRACT

Objective/Background: A nocturnal sleep onset REM period (defined as REM onset latency ≤ 15 min; SOREMP) occurs rarely and research has shown that the phenomenon is specific for type 1 and 2 narcolepsy. However, little is known about the meaningfulness of the phenotype in general sleep clinic patients because those that exhibit the phenomenon often present with few traditional narcolepsy symptoms. As such, this study aimed to (1) evaluate the rate of eventual MSLT testing for those with a SOREMP on routine PSG when the phenomenon occurred in the absence of potential explanatory factors and (2) quantify the stability of the SOREMP phenotype.

Patients/Methods: This was a retrospective analysis of a large repository of de-identified PSG and MSLT test results from 2008 to 2015. Patient records were retrieved from a repository of studies completed at a variety of sleep laboratories across the USA. A total of 118,046 baseline polysomnograms were evaluated for a PSG SOREMP (occurred in 0.7% of the sample). Patients were excluded if they indicated working either shift or night work at the time of the SOREMP or if their self-reported habitual weekday time in bed was less than 7 h. A final sample of 391 cases with a SOREMP were sequestered and previous or consecutive studies were searched for each individual.

Results: The vast majority of patients (n = 347/391; 89%) with a PSG SOREMP never received MSLT testing. Patients that *were* evaluated by MSLT (n = 44; 11%) were typically very sleepy and 82% ended up with a diagnosis of narcolepsy or had MSLTs consistent with current narcolepsy criteria (ie, including the nocturnal SOREMP). Only seven of the 140 patients (n = 5%) that with OSA that first underwent one or more PAP titrations were subsequently seen for an MSLT. Compared to those that eventually received an MSLT, patients that did not receive MSLT testing were older (52 vs. 41 years, $p < 0.001$), more likely to have moderate to severe OSA (AHI ≥ 15; 39% vs. 16%, $p < 0.001$), and were generally less likely to report severe sleepiness (ESS ≥ 16; 25% vs. 55%, $p < 0.001$) and vehicle or workplace accidents or injuries. However, 12% of those that never received an MSLT reported such extreme sleepiness that they endorsed a near-miss car accident due to sleepiness, almost twice as prevalent than that found in a random sample of matched moderate-to-severe OSA patients ($p < 0.01$). Overall, the reliability of the SOREMP phenotype was low at 9.8%, but was much higher for those diagnosed with type 2 narcolepsy (31%) compared to those without narcolepsy (IH or normal MSLTs; 0%; $p < 0.01$) or where narcolepsy status was unknown because an MSLT was not conducted (7%; $p < 0.01$).

Conclusions: The MSLT has been historically underutilized for those exhibiting a SOREMP on diagnostic PSG, a potential marker of narcolepsy. This is presumably because patients with a PSG SOREMP reported variable levels of sleepiness (although some severe) and many had some degree of OSA, which may either be a partial factor in symptomology or even obscure true narcolepsy. Some patients with a PSG SOREMP were very sleepy and most, when an MSLT was conducted, received a diagnosis of type 2 narcolepsy despite few presenting with some of the associated features of narcolepsy. Well-controlled longitudinal studies with high quality data on cataplexy and hypocretin status are needed to understand where the PSG SOREMP phenomenon falls on the hypersomnolence spectrum and to establish which comorbidities share variance with and/or potentially mask narcolepsy. However because untreated narcolepsy can have high social, functional, and financial burden, until such studies are done,

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physicians should consider a narcolepsy workup when a SOREMP is observed (especially if multiple are seen) as well as close follow-up for symptom resolution when, for example, a patient is treated for sleep apnea.

1. Introduction

Narcolepsy is a debilitating neurological condition affecting approximately 0.02%–0.05% [1] and 0.2% [2] of the population, when cataplexy is present versus absent, respectively. Narcolepsy with cataplexy (now referred to as type 1 narcolepsy) is caused by the destruction of neuropeptide hypocretin/orexin neurons [3] which function to promote wakefulness and suppress REM via direct projections to many key wake-promoting nuclei that produce histamine, norepinephrine, serotonin, dopamine, and acetylcholine [4]. Hypocretin/orexins provide state-stability via their influence on the sleep-wake and REM-NREM flip flop switches [5]. Thus, the degeneration of the hypocretin/orexin system observed in type 1 narcolepsy leads to unstable or discontinuous periods of sleep and wakefulness as well as REM-sleep intrusion into wakefulness (cataplexy, hypnogogic/pompic hallucinations, and sleep paralysis) [6]. Cataplexy, sleep paralysis, and hypnogogic hallucinations is reported by approximately 70%, 69%, and 77% of type 1 narcolepsy cases [7]. Type 2 narcolepsy is less well-understood and more heterogeneous than type 1 narcolepsy, with fewer patients reporting sleep paralysis (35%) and hypnogogic hallucinations (42%), and by definition none reporting cataplexy [7]. However, similar to type 1 narcolepsy, type 2 narcolepsy is characterized by severe sleepiness and disrupted sleep/wake continuity [8] and approximately 24% of type 2 narcolepsy patients actually have low CSF hypocretin/orexin levels [9] (thus meeting diagnostic criteria for type 1 narcolepsy) suggesting some pathophysiological overlap with type 1.

The occurrence of a nocturnal sleep onset REM period (defined as REM onset latency $\leq$ 15 min; SOREMP) has received quite a bit of attention in the last few years as recent data has shown that the otherwise rare phenomenon (typically occurring in $\leq$0.5% of the population) [2,11] is much more common in (occurring in ~50% of type 1 and 18% of type 2 narcolepsy) and highly specific for both type 1 and 2 narcolepsy [10–12]. The salience of a SOREMP was recently reflected in the International Classification of Sleep Disorders (ICSD) change for the diagnosis of narcolepsy that allows a nocturnal SOREMP to essentially "replace" one of the SOREMPs on a consecutive MSLT to fulfill the quota of $\geq$2 total SOREMPs [13]. However, much of the research on nocturnal SOREMPs has been conducted in confirmed type 1 narcolepsy cases and much remains unknown about the meaningfulness of the phenotype in the general sleep clinic setting.

Previous data from our research team found that patients with a SOREMP on routine PSG (ie, not necessarily suspected to have hypersomnia) had few of the 'hallmark' characteristics of narcolepsy, like severe sleepiness, disrupted sleep continuity, short sleep onset latency, and some of the REM-related phenomena [12]. These data suggest that, understandably so, practitioners may not be prompted to evaluate for hypersomnia when the phenomenon is observed in the absence of necessary clinical indicators. This is likely, especially in cases when the phenomenon occurs in the presence of other potentially explanatory factors, such as poor sleep timing, circadian misalignment, or restricted sleep duration. Moreover, because many patients in the sleep clinic have some degree of sleep disordered breathing, it is plausible that providers may first recommend adequate control of such before evaluating for hypersomnia.

Ultimately, it remains unknown if patients that exhibit a SOREMP on baseline PSG eventually return for MSLT testing for residual symptoms or unsatisfactory outcomes. Thus, a main aim of this study is to evaluate the rate of MSLT testing in patients that originally exhibited a nocturnal SOREMP (defined as a REM latency of $\leq$15 min) [10] on routine PSG. Also, this study aims to expand on the previous report to include data on habitual sleep habits, additional information on cataplexy, and medications, which were not available previously. Further, we aim to evaluate sleepiness-related performance decrements in SOREMP patients, such as work and driving impairment compared to a matched group of patients with moderate to severe OSA-a group commonly associated with increased risk for vehicle accidents [14]. Lastly, because only one other study has evaluated the repeatability of the SOREMP phenotype, which was demonstrably low at 11.8% [2], we will also evaluate the rate of a second SOREMP and differentiate repeatability between those diagnosed with narcolepsy and those not evaluated for hypersomnia.

2. Methods

This study was a retrospective analysis of a large repository of anonymized diagnostic polysomnograms (PSG) completed between 2008 and 2015. Studies were conducted at various sleep disorders clinics in the United States and patients were referred for testing for a variety of reasons, including to rule in/out sleep disordered breathing or other sleep pathology.

2.1. Measures

This study utilized objective data as per the patient's scored and interpreted PSG (and subsequent MSLT, if it occurred) as well as data acquired from the patient's self-reported medical intake form. The intake form assesses self-reported race/ethnicity and sex as well as previous diagnoses, sleep/wake habits, sleep complaints, and symptoms of a variety sleep disorders. Self-reported time in bed was calculated as the time elapsed between reported bedtime to wake-up time ("on weekdays/workdays, what time do you usually go to bed … wake up?"). Both workdays and non-workdays were evaluated, but we used habitual weekday (or workday) time in bed for inclusion purposes (see procedure) as people are most likely to restrict sleep on workdays. Weekday and weekend napping habits were assessed with the questions "on your work [and non-work days] do you regularly take naps [y/n]". Cataplexy-like attacks was assessed using the dichotomous [y/n] question "do you have drop or paralysis attacks"? Sleep paralysis was assessed with the question "when falling asleep, how often do you feel unable to move or paralyzed". Hypnogogic hallucinations were assessed with the question "when falling asleep, how often do you experience vivid, dreamlike scenes or hallucinations even though you are awake". Data on hypnopompic hallucinations was not available. Restless sleep was assessed with the question "during the night, how often do you have restless, disturbed sleep". The previous three questions were initially assessed using a likert item scale, but were dichotomized as present if the patient endorsed a frequency of 'sometimes or more'. Sleepiness was assessed with the Epworth Sleepiness Scale (ESS). Sleepiness-related daytime

performance metrics were evaluated using questions about driving and workplace accidents. The number of driving accidents and near-miss driving car accidents was assessed with the following questions: “how many accidents [or near miss accidents] have you had due to sleepiness in the previous six months?” Sleepiness-related workplace injuries and mistakes was acquired with the following questions: “Have you ever had work related injuries associated with sleepiness?” [yes/no] and “Have you ever had work-related mistakes associated with sleepiness?” [yes/no]. Medications were acquired from a combination of self-reported information (from the intake questionnaire) and physician documentation. Final diagnosis for each patient was retrieved from the physician's signed interpretation report.

2.2. PSG acquisition and scoring

Physiologic sleep data were acquired using a variety of native sleep systems and were converted to European data format [15] to allow for automated signal processing. Raw sleep study data (including respiratory events and limb movements) were scored according to AASM criteria using Morpheus™, an automated signal processing software [16]. Morpheus decomposes EEG data into a 4-frequency state model (high frequency, low-frequency, and mixed frequency [low or high energy]) using adaptive segmentation with fuzzy clustering and feature extraction. The following rules are applied when EEG is processed with Morpheus: (1) wakefulness is scored when obvious movements are present and/or if EEG membership is predominant in the high frequency domain, (2) N1 is scored when EEG frequencies are predominant in the low energy mixed frequency domain in the presence of relatively high EMG, (3) REM is scored similarly to N1 when rapid eye movements are present and EMG tone is at the lowest point of the recording, (4) N2 is scored when membership domain is predominant in the high energy mixed frequency state along with the presence of K-complexes and spindles, and (5) N3 is scored when EEG frequencies are predominant in the low-frequency domain with high EEG peak-to-peak amplitude. As per standard protocol, registered sleep technologists visually confirm and edit as appropriate all autoscored data (sleep staging, respiratory data, limb movements, etc.) on a 30-second epoch-by-epoch basis. Technologists also, as per standard, validate each REM period, including the start and end times and any stage transitions during each period.

2.3. Data extraction

Fig. 1 displays the schematic of how patients were extracted for analysis. The principal Morpheus database from 2008 to August of 2015 consisted of approximately 312,000 sleep studies and included a variety of types of sleep studies (PAPs, PSGs, MSLTs, MWTs, etc.). A variety of data points are held within each study, including but not limited to data raw sleep study waveforms, digitized data from the patient-reported intake questionnaire, and endpoint data from the physician interpreted sleep study (sleep onset, AHI, etc.). For the purposes of this report, SOREMP studies were excluded if the study was labeled as a positive airway pressure (PAP) or split-night study or if the patient self-reported working shift or night work. Patients with sleep disordered breathing were not excluded because we wanted to evaluate the prevalence of eventual MSLT testing in those who first underwent treatment for OSA. Children were also not excluded from the analysis as recent data has found that a SOREMP is also highly specific for narcolepsy in children as young as 6 years of age [11].

A total of 786 patients with a SOREMP (REM latency of $\leq$15 min) on baseline PSG were identified with the aforementioned criteria (Fig. 1). Patients were then excluded if they had missing or incomplete demographic information (including medications; n = 145), insufficient information on sleep/wake habits (n = 85), or if they reported a habitual weekday/workday time in bed (defined above) of less than 7 h (n = 165). This yielded a total of 391 patients for whom the principal database was then searched for additional studies that occurred either before or after the PSG with a SOREMP occurred. At this phase, we included all study types (eg, PAP titrations, MSLTs, MWTs, etc.) so patient testing history could be evaluated. If other studies were found for that individual, they were added to the testing repository and matched by their unique case number. For patients deemed to have multiple SOREMPs, blinded registered sleep technologists validated the finding by reviewing each participant's raw EEG data (all were confirmed). The study protocol was approved by Schulman Associates IRB for the protection of human subjects.

2.4. Statistical analyses

Analyses were performed using SPSS 23.0 (SPSS Inc., Chicago, IL). For continuous variables, descriptive analyses were completed to analyze the shape, central tendency, and dispersion to ensure parametric testing appropriateness. Skewness was addressed using log transformation and back transformation when appropriate. Differences in continuous variables were analyzed using univariate analysis of variance (ANOVA) with Bonferroni post-hoc comparisons when more than two groups were analyzed. Differences in categorical variables were analyzed using Chi Square analysis. When more than two categorical groups were analyzed, individual Chi Square comparisons were made only when the overall Chi Square was significant. All comparisons were two-tailed and significance was set at the 0.05 level.

3. Results

The final sample of 391 SOREMP cases was comprised of 56% females and 53% Caucasians. Mean age was 51 ± 19 years and ranged widely from 3 to 93; three patients were under the age of 6 (Fig. 2). Fig. 1 illustrates that only 44 SOREMP individuals (11%) were ever evaluated for hypersomnolence with an MSLT, many of whom presumably met some pretest criteria for hypersomnolence and were thus pre-scheduled for an MSLT the morning following their baseline study (n = 21). The remaining 23 individuals *eventually* had an MSLT. A total of 140 patients (36%) with a PSG SOREMP underwent a subsequent PAP titration for OSA, and only 7 returned for an MSLT (5%). For the 23 that *eventually* had an MSLT, median ‘delay’ between initial sleep study and MSLT was 62 days, with 70% being studied within 90 days of their initial sleep study and 30% with a delay of one year or longer. The rate at which individuals with a PSG SOREMP were evaluated with an MSLT was variable from year-to-year, and interestingly did not appear to increase in 2013 and 2014 (Fig. 3).

Table 1 illustrates the nature of the PSG SOREMP samples. The most common comorbidity was depression (overall 26%) and approximately 18% of the sample were noted to be using an antidepressant at the time of their PSG SOREMP. This included selective serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and atypical agents (eg, bupropion, etc.). An additional 4% were using an antipsychotic agent. Of those that underwent an MSLT, only 8% reported to currently using an antidepressant despite a depression diagnosis rate of 32%, suggesting many were either not treated for depression or they refrained from their medication for the MSLT. However, it is unclear exactly how many of the 8% refrained from their psychotropic medication for the days or weeks leading up to their MSLT. On average, patients reported 8.5 h of time in bed on weekdays and

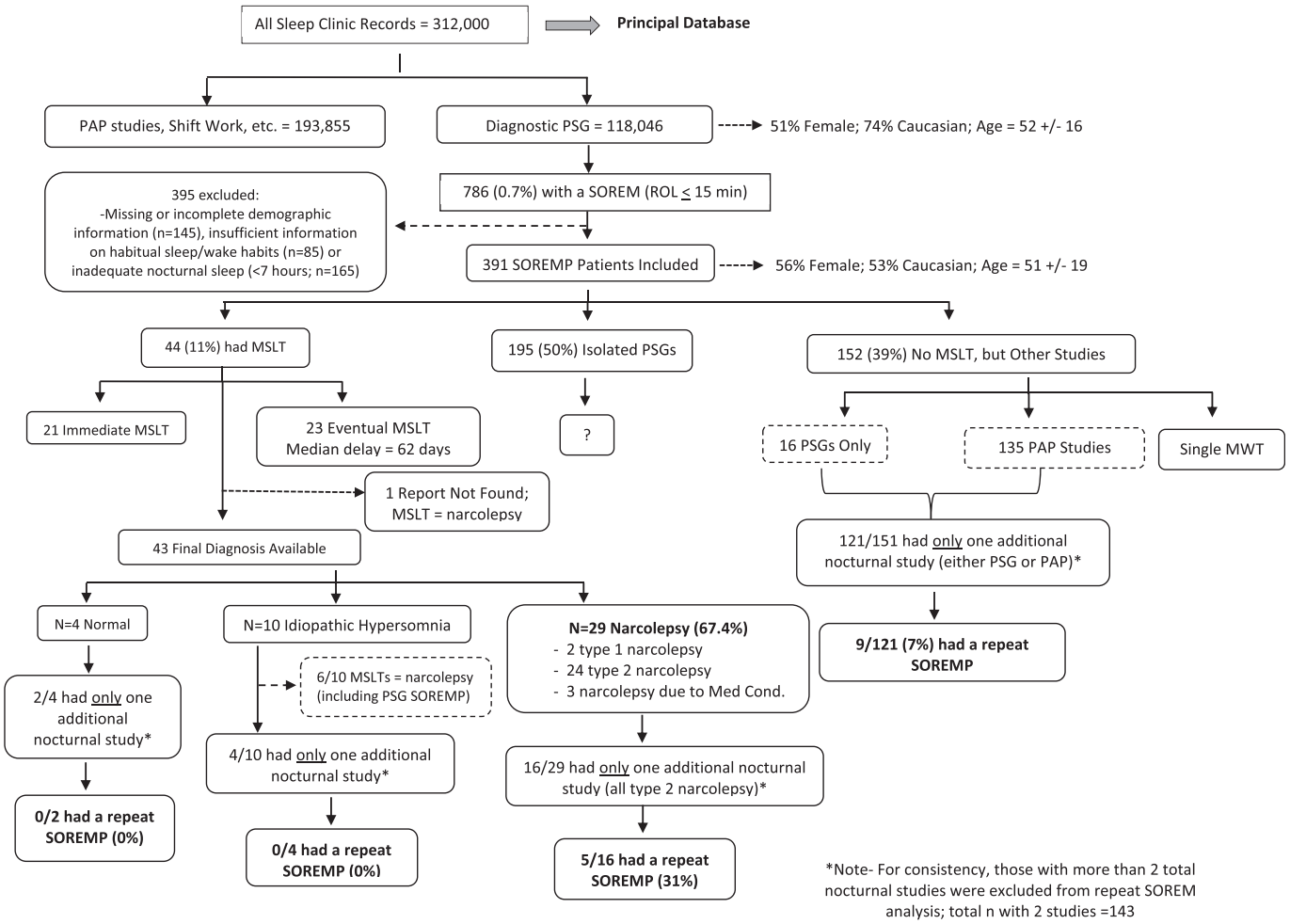

Fig. 1. The testing history for those with a SOREMP on diagnostic PSG.

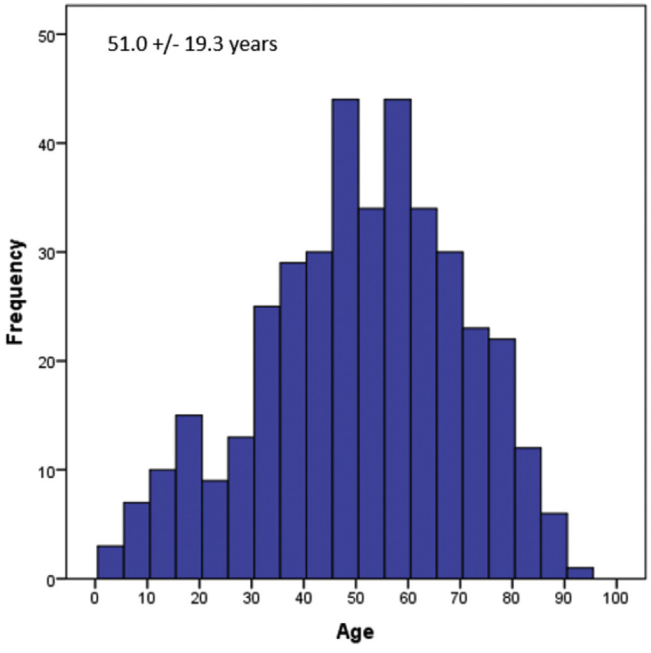

Fig. 2. Age distribution of patients with a PSG SOREMP (n = 391).

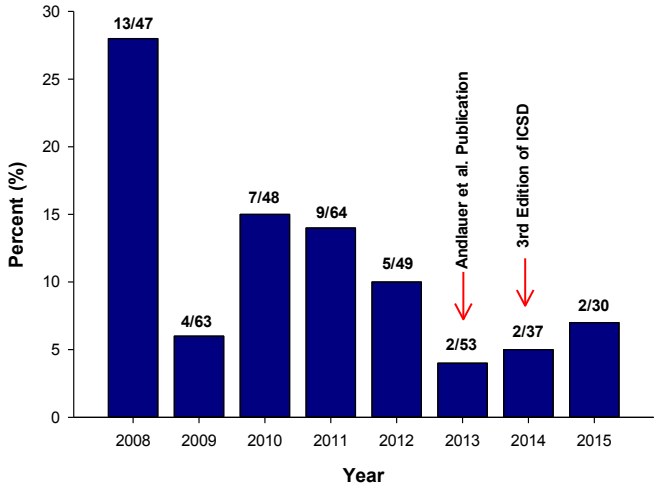

Fig. 3. Yearly variability in MSLT evaluation for patients with a PSG SOREMP.

over 9 h on weekends and approximately half reported regular weekday and weekend naps.

As Table 2 indicates, over half of those evaluated by MSLT were remarkably sleepy with Epworth scores of 16 or higher and approximately 1 out of 5 patients reported vehicle accidents due to

Table 1
Patients with a SOREMP on diagnostic PSG: comparison between those evaluated for hypersomnolence to those not evaluated for hypersomnolence.

	Evaluated by MSLT	Not evaluated by MSLT	Analyses[a]
Total sample size	44	347	
Demographics			
Sex (% female)	57%	56%	p = 1.0
Race (% Caucasian)	51%	58%	p = 0.50
Age (yr) [min–max]	41.3 ± 19.6	52.3 ± 18.9	**p < 0.001**
BMI (kg/m^2)	30.4 ± 7.5	31.9 ± 8.0	p = 0.23
Comorbidities			
Depression	32%	25%	p = 0.36
Chronic pain	23%	29%	p = 0.48
Hypertension	34%	52%	**p = 0.04**
Diabetes	18%	24%	p = 0.45
Heart disease	9%	11%	p = 1.0
Medication use			
Sedative hypnotic	13%	17%	p = 0.34
Opioid	5%	16%	p = 0.05
Anti-depressant	8%	20%	p = 0.05
Anti-psychotic	0%	8%	p = 0.06
Sleep habits			
Weekday bedtime	22:18 ± 1:11	22:21 ± 2:14	p = 0.87
Weekday wake time	6:50 ± 1:37	7:16 ± 2:09	p = 0.25
Weekday TIB[b]	8:34 ± 1:20	8:35 ± 1:51	p = 0.93
Weekend bedtime	22:51 ± 1:15	22:54 ± 1:37	p = 0.83
Weekend wake time	8:03 ± 1:46	8:04 ± 2:12	p = 0.96
Weekend TIB[b]	9:17 ± 1:36	9:07 ± 2:12	p = 0.67
Weekday naps	61%	48%	p = 0.08
Weekend naps	58%	42%	**p = 0.03**
Narcolepsy symptoms			
Cataplexy-like attacks	9%	3%	p = 0.08
Sleep paralysis	26%	8%	**p < 0.01**
Hypnogogic hallucinations	33%	15%	**p < 0.01**
Restless sleep	78%	68%	p = 0.26
PSG data			
AHI[c]	8.8 ± 20.5	13.0 ± 13.3	p = 0.11
% AHI ≥ 15	16%	39%	**p < 0.01**
RDI[d]	9.2 ± 17.8	8.8 ± 13.0	**p = 0.01**
% RDI ≥ 15	11%	35%	**p < 0.01**
REM onset latency (min)	6.3 ± 3.4	8.4 ± 4.0	**p < 0.01**
Sleep onset latency (min)	23.3 ± 40.5	45.7 ± 68.8	p = 0.04
Sleep efficiency	88.6 ± 9.6	85.4 ± 13.3	p = 0.12
Arousal index	8.8 ± 4.8	10.8 ± 8.5	p = 0.12
Wake after sleep onset (min)	46.6 ± 36.1	58.1 ± 49.1	p = 0.22
PLMI[e]	5.6 ± 13.2	8.1 ± 18.9	p = 0.40
PLMI ≥ 15	16%	17%	p = 0.55

[a] Bolded values represent comparisons that reached statistical significance; Chi Square analysis for dichotomous variables and ANOVA for continuous variables.
[b] TIB = time in bed (time elapsed between bedtime to wake time; patients with <7 h TIB were excluded from analyses).
[c] AHI = apnea hypopnea index = the average number of apneas and hypopneas per hour of sleep.
[d] RDI = respiratory disturbance index = the average number of apneas, hypopneas, and flow limited events that either terminate in an EEG arousal or a 3% desaturation per hour of sleep.
[e] PLMI = Periodic limb movement index.

sleepiness in the previous 6 months. The majority of cases received a final diagnosis of narcolepsy (67%; n = 29 out of 43 where an interpretation was available); 24 had type 2 narcolepsy and 2 cases were diagnosed with type 1. Three cases received a diagnosis of narcolepsy due to medical condition because of previously diagnosed sleep apnea. Of the remaining 14 cases evaluated by MSLT, 10 were diagnosed with idiopathic hypersomnia and 4 had normal MSLTs. Interestingly, 6 of the 10 'idiopathic hypersomnia' cases would meet current diagnostic criteria for type 2 narcolepsy as they had only 1 MSLT REM onset with a MSL ≤ 8 min. Thus, including these six cases and the one case where final diagnosis was not available but the MSLT was concordant with narcolepsy, 82% of those with a PSG SOREMP evaluated by MSLT would arguably meet diagnostic criteria for either type 1 or 2 narcolepsy (ie, 36 out of 44 possible studies).

Approximately 50% of those with a PSG SOREMP (n = 195) were only seen for their initial PSG and never appeared to have additional testing. The remaining 39% of the SOREMP sample (n = 152) went on for one or more other types of studies, the majority with a single follow-up PAP titration for sleep apnea (Fig. 1; n = 135). Compared to patients that did receive MSLT testing, those that did not have MSLT testing were approximately 10 years older and more frequently had hypertension, which was likely at least partially associated with the higher prevalence of moderate-to-severe OSA (39% vs. 16%, p < 0.01; Table 1). They were also generally less sleepy and less likely to report some of the associated features of narcolepsy like sleep paralysis and hypnogogic hallucinations (Table 1). Despite this, a subsample of individuals did report very high levels of sleepiness and indicated increased risk for sleepiness-related daytime performance decrements. For example, 25% of the cases reported very high Epworth scores (ESS ≥ 16) and, in general, the sample was almost twice as likely to report near-miss vehicle accidents compared to a random sample of patients with OSA matched for age, race, gender, and sleep habits. Importantly, these statistics were nearly identical (within ½ of a percent) when selecting only for SOREMP patients without OSA (AHI < 5), suggesting the sleepiness was present despite sleep apnea.

We next aimed to examine the stability of the SOREMP phenotype by evaluating the rate of repeat SOREMP when given the opportunity to do so (ie, on a previous or subsequent PSG or subsequent PAP titration). A total of 143 SOREMP cases were identified with only one additional nocturnal study for which the repeatability of SOREMP could be evaluated (ie, for a total of two nocturnal studies). The majority of cases (79%; n = 113/143) had a SOREMP on their 1st baseline PSG and not their second nocturnal study (often times a PAP titration) and the remaining 16 individuals had a SOREMP on their latter baseline PSG only and not their first sleep study (typically another PSG). Thus, of the 143 cases, 14 individuals (9.8%) were identified as having a repeat SOREMP. However, as you can see in Fig. 1, the rate of a repeated PSG SOREMP was remarkably higher in patients with type 2 narcolepsy (31%) than patients either without narcolepsy (idiopathic hypersomnia or normal MSLTs; 0%; p < 0.01) or where narcolepsy status was unknown because an MSLT was not conducted (7%; p < 0.01). Unfortunately, the repeatability of SOREMPs in type 1 narcolepsy could not be evaluated because neither of the type 1 patients had 2 nocturnal studies.

4. Discussion

When hypersomnolence was evaluated for, those with a PSG SOREMP were very sleepy and most received a diagnosis of type 2 narcolepsy or had abnormal MSLTs concordant with current narcolepsy nosology. However, it appears that very few individuals with a SOREMP ever get evaluated for hypersomnolence, and although we do not know if these patients have narcolepsy, a subset of individuals (even in the absence of sleep apnea) had very high levels of sleepiness and were twice as likely to report near-miss vehicle accidents due to sleepiness compared to patients with moderate to severe OSA-a group commonly associated with traffic accidents [14]. Ultimately, these data suggest that a PSG SOREMP is not a benign finding, and should be thoroughly investigated as a potential marker of central hypersomnolence when observed.

Several explanations are possible for why such few SOREMP patients were evaluated with an MSLT. First, because many patients with a SOREMP went on for one or more PAP titrations for sleep apnea, one hypothesis is that symptoms remitted after adequate treatment. Unfortunately, this hypothesis could not be adequately tested because very few patients had multiple studies where

Table 2
Sleepiness and performance measures in SOREMP cases compared to matched sleep apnea patients.

	Evaluated by MSLT	Not evaluated by MSLT	OSA sample[b]	Analyses[a]
Total sample size	44	347	400	
Sleepiness measures				
Epworth Sleepiness Scale (ESS)	15.7 ± 5.6	11.2 ± 5.9	10.9 ± 5.6	**E vs. N&O p < 0.001**; N vs. O p = 1.0
% ESS ≥ 10	89%	57%	58%	**E vs. N&O p < 0.001**; N vs. O p = 0.80
% ESS ≥ 16	55%	25%	21%	**E vs. N&O p < 0.001;** N vs. O p = 0.10
Daytime performance				
≥1 driving accidents-sleepiness	21%	4%	2%	**E vs. N&O p < 0.001;** N vs. O p = 0.10
≥2 driving accidents-sleepiness	16%	2%	0.2%	**E vs. N&O p < 0.001; N vs. O p = .04**
≥1 near-miss accidents-sleepiness	27%	12%	7%	**E vs. N&O p < 0.01; N vs. O p < 0.01**
≥2 near-miss accidents-sleepiness	18%	10%	5%	**E vs. N&O p<.001; N vs. O p<.001**
Work-related injuries-sleepiness	16%	8%	6%	**E vs. N&O p<.05;** N vs. O p = .20
Work-related mistakes-sleepiness	7%	4%	2%	Omnibus p = .08

[a] E = Evaluated by MSLT, N = Not Evaluated by MSLT, O = OSA group; bolded values represent comparisons that reached statistical significance; ANOVA with Bonferroni post-hoc comparisons for continuous variables and Chi Square analysis for dichotomous variables.
[b] OSA and SOREMP samples matched for age (Mean N = 52.3 ± 18.9 vs. O = 52.7 ± 14.8; p = 0.87), sex (N = 56% vs. O = 54% female; p = 0.67), race (both groups 39% AA), and habitual sleep habits.

adequate time elapsed to evaluate change in symptoms. Another possibility is that providers have not historically appreciated the phenotype as only recently has the ICSD formally incorporated the phenomenon into the diagnostic criteria for narcolespy [13]. However, this hypothesis was not supported by our data because the rate of MSLT evaluation did not increase after 2013/2014, when the significance of the SOREMP was publicized. This conclusion is based on the finding that most patients have historically received MSLT testing within three months of their diagnostic PSG SOREMP, thus we should have seen at least a modest increase in MSLTs by our late 2015 analysis.

Another reason for non-evaluation by MSLT may be the lack of clinical symptoms in those with a SOREMP and the compounding effect of various psychiatric, health, and/or other sleep/wake conditions that may mimic or obscure true narcolepsy. For example, research has found that REM sleep is often altered in patients with depression, many times with shortened REM latency [17]. Thus, it is not implausible that a practitioner could defer hypersomnolence testing in lieu of a psychiatric evaluation if he or she suspected undiagnosed psychopathology. For those with a previous diagnosis of depression, however, it appeared that many were either using an antidepressant and/or antipsychotic agent, thus suggesting that the shortened REM latency was not entirely due to depression-related physiology as most antidepressant and antipsychotic agents actually suppress REM [18]. Finally, it is also possible that patients underwent testing with another company or simply refused additional testing.

4.1. Lack of narcolepsy features in those with a PSG SOREMP

One of the most salient findings from this study was that, despite sometimes high levels of sleepiness, most patients with a PSG SOREMP did not present with many of the features that would trigger a clinician to suspect narcolepsy. For example, 40% did not report clinical levels of sleepiness and the rate of sleep paralysis and hypnogogic hallucinations were much lower than other published estimates of type 2 narcolepsy cases [7]. Instead, many patients reported non-specific sleep complaints like disrupted, restless sleep. Disrupted sleep continuity is common in and distressing for patients with type 1 and 2 narcolepsy [8] but is also commonly reported in other sleep disorders and can be confounded by age, comorbidities, and medication. Further, over 1/4th of the sample reported psychotropic medication use and it has been well-established that such compounds can suppress REM and REM-related phenomena such as sleep paralysis, sleep hallucinations, and cataplexy [18]. Also, patients with a SOREMP were approximately 10 years older than what has been typically documented for the diagnosis of type 2 narcolepsy [19], and 27% were over the age of 65. Thus, it is very challenging to disentangle true central hypersomnolence from other age-related confounding factors, even for highly skilled sleep medicine professionals.

Lastly, this study found that the repeatability of the SOREMP phenotype is overall quite low, but similar to that reported by Goldbart and colleagues in a smaller sample [2]. However, the sample size used in this report was large enough to allow for observation between diagnoses over several years. As suspected, those with a diagnosis of type 2 narcolepsy were more likely to have repeat episodes of short nocturnal REM latency, reinforcing the meaningfulness of the SOREMP as a marker of narcolepsy. These data also highlight the sheer rarity of the phenomenon, even when someone has a diagnosis of type 2 narcolepsy and has exhibited the phenomenon previously. Overall, these data suggest that providers should consider a narcolepsy workup when a SOREMP is observed in the absence of other explanatory factors and close follow-up for symptom resolution when, for example, a patient is treated for another sleep pathology or is not medically recommended to abstain from their psychotropic medication. This is especially the case when multiple episodes are observed. This statement is based on the rationale that narcolepsy historically has a long diagnostic delay and untreated narcolepsy can have high social, functional, and financial burden [19].

All conclusions should be made in consideration of the study's limitations. Primarily, data from this study represent that from a treatment-seeking sleep clinic patients, many times with a variety of comorbidities and many that use various medications to treat such comorbidities. Although we don't see this as a limitation, per se, one must keep the nature of the sample in mind when drawing conclusions. Also, a large portion of data was acquired from the patient's intake questionnaire and self-reported. Thus, these data are inherently subject to reporting bias, omissions, and errors like any self-report instrument. Further, our questionnaire was designed to be used with our standard of care in a sleep clinic setting and thus was never validated for the assessment of narcolepsy. Given this, it is likely that self-reported symptoms are discrepant from physician assessment for some patients. This is especially the case with cataplexy, which requires a very thorough assessment and is likely insufficiently-reflected with a single-item question which in itself was fairly limited because it did not query emotion-induced muscle weakness. Additionally, patient-reported time in bed is likely an over-estimate of actual sleep time, thus it is

likely that there were more patients with behaviorally-induced insufficient sleep or variably-timed sleep.

Despite the study's limitations, there were a number of strengths that need to be highlighted. First and foremost, this was the first study ever to evaluate the testing history of the SOREMP phenotype, which requires an enormous database due to the sheer rarity of the phenomenon. Moreover, these data are rich and diverse in terms of time, geographical distribution, age, sex, and race. Also, because our data were collected under the auspices of a single organization, data collection and processing were standardized. This study highlights the need for future studies in uncovering where the SOREMP phenotype falls on the hypersomnolence spectrum. Ultimately, well-controlled longitudinal studies with high quality data on cataplexy, hypocretin status, and daytime performance measures are needed to understand the phenotype more thoroughly and to establish which comorbidities share variance with it. Lastly, this study reinforces the essential role of the skilled sleep medicine practitioner and a thorough clinical evaluation in the diagnosis of narcolepsy.

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Conflict of interest

Drs. Bogan and Cairns have received research support from Jazz Pharmaceuticals and are employed by SleepMed, Inc. Dr. Bogan also serves on the speakers bureau for and is a consultant to Jazz Pharmaceuticals.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2016.11.023.

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