The Prevalence of Multiple Sleep-Onset REM Periods in a Population-Based Sample

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Study Objective: The presence of 2 or more sleep-onset rapid eye movement periods (SOREMPs) on a Multiple Sleep Latency Test (MSLT) has been used as 1 of the criteria for the diagnosis of narcolepsy and is thought to be specific to this disorder. However, previous studies have shown the prevalence of SOREMPs in healthy volunteers and apneic patients to be higher than expected. The present study determined the prevalence of 2 or more SOREMPs in a representative sample of the population from southeast Michigan and investigated potential associations with other sleep-related variables.

Design: Cross-sectional laboratory-based analysis.

Settings: Sleep disorders clinic.

Participants: Population-based sample.

Interventions: N/A.

Measurements: A population-based sample of 333 subjects was assessed by nocturnal polysomnography and daytime MSLT (5 naps), and an additional 206 subjectively sleepy people were also assessed (total = 539). Sample demographics were comparable to the 2000 census. Epworth Sleepiness Scale scores were also determined. Groups were formed based on a median split of each sleep variable (Epworth Sleepiness Scale, MSLT, total sleep time from nocturnal polysomnography) for comparisons of SOREMPs in each group.

Results: The prevalence of 2 or more SOREMPs was 3.9%. Only mean sleep latency on the MSLT was a discriminator for the presence of 2 or more SOREMPs (short latency = 6.3%, long latency = 1.9%, p < .05). Among the subjects who had an MSLT of 5 minutes or less (an indicator of a pathologic level of sleepiness), 9.5% had 2 or more SOREMPs.

Conclusions: The overall prevalence of 2 or more SOREMPs in our sample is 3.9%. Interestingly, of the variables assessed (MSLT, Epworth Sleepiness Scale, and total sleep time from nocturnal polysomnography), objective sleepiness, as determined by the MSLT, was the only measure significantly associated with 2 or more SOREMPs. Therefore, subpopulations with excessive sleepiness (eg, shift workers, young adults, patients with apnea) are likely to have a greater prevalence of SOREMPs.

Keywords: Multiple SOREMPs, population based sample, sleepiness

Citation: Singh M; Drake CL; Roth T. The prevalence of multiple sleep-onset REM periods in a population-based sample. SLEEP 2006;29(7): 890-895.

INTRODUCTION

PHYSIOLOGICALLY, THE ONSET OF SLEEP UNDER NORMAL CONDITIONS IN NORMAL ADULTS IS THROUGH NON-RAPID EYE MOVEMENT (NREM) SLEEP.1 Thus, a predictable pattern of sleep has been described, with sleep onset occurring with NREM sleep, and rapid eye movement (REM) sleep occurring approximately 90 minutes thereafter. NREM and REM sleep then alternate in a cyclic fashion every 90 minutes through the night. This was initially described by Dement and Kleitman and remains essentially unchanged. This fundamental principle of normal human sleep reflects a highly reliable finding and is important when considering normal versus “pathologic” sleep.2

The occurrence of sleep-onset REM was first described by Vogel in 1960 and subsequently linked to narcolepsy by Rechtschaffen et al in 1963.3,4 During the 1960s, on overnight sleep studies as well as single daytime nap recordings, sleep-onset REM was found to be exclusively associated with narcolepsy.4,7 In addition, with the First International Symposium on Narcolepsy, held in 1975, a clear consensus on the definition of narcolepsy was established to include REM abnormalities.8 This led to the idea that polysomnographically identified sleep-onset REM periods (SOREMPs) could be used to diagnose narcolepsy. The development of the Multiple Sleep Latency Test (MSLT) in 1976 provided an opportunity to analyze multiple sleep-onset episodes and, therefore, the potential for multiple sleep-onset REM episodes, in a single test.9 Early studies confirmed that the prevalence of multiple SOREMPs (i.e., ≥ 2) on the MSLT were found to occur exclusively with narcolepsy10 and were considered “highly diagnostic” of narcolepsy.10,11 In addition, many reports have confirmed that multiple SOREMPs are very rare in normal subjects tested in standard conditions.12-15

However, in the 1980s, these reports were brought into question by studies done in healthy young adults, as well as in patients with frequent periodic limb movements and sleep apnea, among whom multiple SOREMPs were found to be relatively common.16-19 Bishop et al found the frequency of multiple SOREMPs to be 17% in a study done in healthy young adults.16 In a series of 187 patients with sleep apnea, 25% were found to have multiple SOREMPs.18 Recently, 4.7% of 1145 patients with obstructive sleep apnea were found to have multiple SOREMPs.19 Multiple SOREMPs have also been seen among patients with Prader-Willi syndrome,20 Kleine-Levin syndrome,21 Parkinson disease,22 and periodic limb movements of sleep.17 Thus, recent data suggest that multiple SOREMPs are not pathognomonic for narcolepsy.

Despite this increasingly large body of work, the prevalence
We also investigated the associations of sleep-related variables with multiple SOREMPs. Bishop et al. consisted of healthy young adults with no sleep-wake sensory or mental impairment were excluded from the sample.

**METHODS**

Subjects

The current study was performed as a part of a larger study of excessive daytime sleepiness. Participants were drawn from the general population of the tricounty Detroit area. The tricounty area includes 84% of the population of southeastern Michigan and is similar to the United States as a whole, with the exception of a different racial/ethnic distribution (Table 1). Our sample is therefore representative of southeastern Michigan. The research design was composed of 2 components: (1) a random digit dial, computer-assisted, telephone survey and (2) a laboratory-based evaluation. This is depicted in Figure 1.

For eligibility, the calling address had to be a residence and the participant an adult between the ages of 18 and 65 years. A random-probability selection procedure was used to determine the sex of the target adult. If 2 or 3 adults within a target sex were present in a household, a random-probability selection procedure was used to determine the target respondent. If 4 or more adults with the target sex were present in a household, a random-probability selection procedure was used to determine the target sex of the target adult. If 2 or more adults with the target sex were present, last-birthday method was used to determine the target respondent. In order to maintain an unbiased sample, only individuals who could not answer the questionnaire due to sensory or mental impairment were excluded from the sample.

**Figure 1**—Flow chart summary of the study sampling methods and sleep-onset rapid eye movement periods (SOREMPs)’ sleepiness prevalence.*Mean latency of a Multiple Sleep Latency Test.

**Table 1**—Sociodemographic Characteristics of the Study Sample and Comparative Data From the 2000 United States Census

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sample (N=3283)</th>
<th>Tri county (N=4,043,467)</th>
<th>US Census (N=281,421,906)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>50.3</td>
<td>48.5</td>
<td>49.1</td>
</tr>
<tr>
<td>Women</td>
<td>49.7</td>
<td>51.5</td>
<td>50.9</td>
</tr>
<tr>
<td>Annual income, in thousands of ($)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10</td>
<td>6.4</td>
<td>8.5</td>
<td>9.5</td>
</tr>
<tr>
<td>10-15</td>
<td>4.4</td>
<td>5.1</td>
<td>6.3</td>
</tr>
<tr>
<td>15-25</td>
<td>11.1</td>
<td>11.0</td>
<td>12.8</td>
</tr>
<tr>
<td>25-35</td>
<td>11.3</td>
<td>11.1</td>
<td>12.8</td>
</tr>
<tr>
<td>35-50</td>
<td>14.5</td>
<td>15.8</td>
<td>16.5</td>
</tr>
<tr>
<td>50-75</td>
<td>22.6</td>
<td>20.2</td>
<td>19.5</td>
</tr>
<tr>
<td>&gt; 75</td>
<td>29.8</td>
<td>29.1</td>
<td>22.4</td>
</tr>
<tr>
<td>Race/Ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>68.1</td>
<td>68.7</td>
<td>75.1</td>
</tr>
<tr>
<td>African American</td>
<td>24.9</td>
<td>25.2</td>
<td>12.3</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>1.9</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Native American</td>
<td>0.9</td>
<td>0.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Other/refused</td>
<td>3.4</td>
<td>3.0</td>
<td>7.9</td>
</tr>
<tr>
<td>Age, (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-24</td>
<td>10.9</td>
<td>18.7</td>
<td>21.0</td>
</tr>
<tr>
<td>25-34</td>
<td>21.4</td>
<td>22.5</td>
<td>21.4</td>
</tr>
<tr>
<td>35-44</td>
<td>24.9</td>
<td>25.0</td>
<td>24.3</td>
</tr>
<tr>
<td>45-54</td>
<td>24.9</td>
<td>21.0</td>
<td>20.2</td>
</tr>
<tr>
<td>55-64</td>
<td>17.8</td>
<td>12.7</td>
<td>13.0</td>
</tr>
</tbody>
</table>

Data for the socioeconomic status are presented in percentage of “households.”

*5% of individuals refused to answer any 1 of the questions

United States Census and Tricounty census data from this category included individuals ages 15-17 years, which accounted for the increased percentages in these categories.

From 4682 eligible participants, 3283 individuals completed the telephone survey (response rate calculated by the number of interviews that were conducted relative to the number of eligible participants was 70.1%). The demographic details of the sample including race, age, and socioeconomic status are shown in Table 1 and are nearly identical to the 2000 census data for the area.23

Of the 3283 subjects, 333 were randomly selected for a laboratory-based evaluation. Further, as this study was a part of a larger study on daytime sleepiness, we also selected 206 high scorers (sleepy subjects) on the Daytime Sleepiness Scale24 to be brought into the laboratory.

The institutional review board approved all procedures, and informed consent was obtained from all participants. Individuals were paid for study participation.

**Procedures**

Participants completed a 20-minute telephone interview, which included questions related to sleep and health habits, along with general information regarding medical and psychiatric status and use of medications. They also reported on subjective sleepiness by answering questions on the Daytime Sleepiness Scale.24 Subjects who were chosen to come into the laboratory, completed a 2-week sleep diary describing their sleep-wake patterns, and came into the laboratory at the end of the 2 weeks. They were instructed to continue all medications, including REM-suppressant.
medications. All subjects received an 8.5-hour polysomnogram prior to the MSLT procedure. The nocturnal recordings included 4 electroencephalographic channels (C2, 3 and O1 and O2), 2 channels for electrooculography (bilateral horizontal), chin electromyogram, a nasal/oral thermistor, an electrocardiogram-recording channel, and an anterior tibialis electromyogram channel. All recordings were made using standard sleep laboratory procedures and were scored according to standard criteria.24 Nocturnal polysomnographic variables included total sleep time (TST); sleep latency; REM latency; percentages of stage 1, 2, 3/4, and REM sleep; and the respiratory event index. Following the nocturnal recording, subjects were administered a 5-nap clinical MSLT. In accordance with the standard procedures, sleep latency and the presence or absence of REM sleep was determined.25 In addition, on the morning of the MSLT, subjects filled out various sleep- and health-related questionnaires, including the Epworth Sleepiness Scale.26

Analysis

For the first part of the analysis, we calculated the mean sleep latency (MSLT) as well as the prevalence of multiple SOREMPs in both groups of subjects n = 333 (random sample) and n = 206 (subjectively sleepy). Toward our second objective, we investigated the potential associations of multiple SOREMPs with various other sleep-related variables. Specifically, we looked at sleepiness, both objective sleepiness as measured by a mean latency on the MSLT and self-reported sleepiness as measured by the Epworth Sleepiness Scale. We also looked at various polysomnographic variables, including TST; sleep efficiency; stage 1 latency; REM latency; percentages of stage 1, 2, 3, 4, and REM sleep; and the respiratory event index. For this part of the analysis, groups were formed based on a median split of the data within each variable and then compared for the prevalence of multiple SOREMPs using the χ² test. Respiratory event index scores were used to divide the sample into 2 groups based on a cutoff of >5

Table 2—Sleep-Related Polysomnography Variables for the Entire Sample and Each of the SOREMP Groups

<table>
<thead>
<tr>
<th>PSG variable</th>
<th>Entire Sample Mean latency (MSLT)</th>
<th>0 SOREMP</th>
<th>1 SOREMP</th>
<th>≥ 2 SOREMP</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESS, score</td>
<td>8.3±4.19</td>
<td>9.8±4.8</td>
<td>9.3±4.7</td>
<td>10.9±4.8</td>
<td>.001</td>
</tr>
<tr>
<td>TST (PSG), min</td>
<td>427.48±64.24</td>
<td>425.0±66.0</td>
<td>439.5±54.94</td>
<td>442.3±51.8</td>
<td>.22</td>
</tr>
<tr>
<td>SE (PSG), %</td>
<td>83.84±12.43</td>
<td>83.3±12.7</td>
<td>86.0±10.9</td>
<td>86.5±9.4</td>
<td>.15</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD unless otherwise indicated. SOREMP refers to sleep-onset rapid eye movement periods; PSG, polysomnography; MSLT, Multiple Sleep Latency Test; TST, total sleep time; ESS, Epworth Sleepiness Scale; REM, rapid eye movement.

RESULTS

Since the results (ie, the prevalence of multiple SOREMPs and the mean MSLT latency) did not statistically differ for the 2 groups (Daytime Sleepiness Scale high scorers and randomly selected subjects), we combined our groups for a final number of subjects of 539. (Figure 1)

The prevalence of multiple SOREMPs in our population-based sample (n = 539) was 3.9%. The actual number (and prevalence) of subjects with 0, 1, 2, 3, 4, and 5 SOREMPs is as follows: 491 (86.7%), 53 (9.4%), 14 (2.5%), 6 (1.1%), 1 (0.2%), and 1 (0.2%) subjects, respectively. The age and sex distribution of the subjects who had 0, 1, or 2 or more SOREMPs on their MSLT is presented in Table 3 and did not differ significantly.

Table 3—Mean Age and Sex Distribution for Each SOREMP Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of SOREMPs</th>
<th>χ² test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, % men</td>
<td>47.7</td>
<td>49.2</td>
</tr>
<tr>
<td>Mean age, y ± SD</td>
<td>42.0±12.4</td>
<td>38.1±14.4</td>
</tr>
</tbody>
</table>

No statistical differences were present between groups (p > .05); SOREMP refers to sleep-onset rapid eye movement periods on the Multiple Sleep Latency Test.

For the first part of the analysis, we calculated the mean sleep latency (MSLT) as well as the prevalence of multiple SOREMPs in both groups of subjects n = 333 (random sample) and n = 206 (subjectively sleepy). Toward our second objective, we investigated the potential associations of multiple SOREMPs with various other sleep-related variables. Specifically, we looked at sleepiness, both objective sleepiness as measured by a mean latency on the MSLT and self-reported sleepiness as measured by the Epworth Sleepiness Scale. We also looked at various polysomnographic variables, including TST; sleep efficiency; stage 1 latency; REM latency; percentages of stage 1, 2, 3, 4, and REM sleep; and the respiratory event index. For this part of the analysis, groups were formed based on a median split of the data within each variable and then compared for the prevalence of multiple SOREMPs using the χ² test. Respiratory event index scores were used to divide the sample into 2 groups based on a cutoff of >5.
higher prevalence of multiple SOREMPs. Specifically, subjects with a shorter mean latency on the MSLT had a higher frequency of multiple SOREMPs (Figure 2). For the remaining sleep-related variables tested, none of the groups differed statistically in their association with the frequency of multiple SOREMPs. A breakdown of the mean and standard deviations of these variables in the 3 groups (0, 1, and 2 or more SOREMPs), is presented in Table 2.

In addition, the 3 groups, based on the presence of 0, 1, and 2 or more SOREMPs, did not differ statistically on self-reported TST, as measured by a 2-week diary. Specifically, groups having 0, 1, and 2 or more SOREMPs had a mean TST of 7.3 ± 3.0, 7.0 ± 1.5, and 7.4 ± 1.5 hours, respectively (p > .05).

Forty-eight subjects (8.6%) were on REM-suppressant medications. Groups with 1 or 2 or more SOREMPs did not differ in their association with REM-suppressant medications (0 SOREMPs – 9.2%, 1 SOREMP – 10.6%, ≥ 2 SOREMPs – 10.0% (p > .05)).

Of the individuals who had a mean latency of less than 5 minutes (n = 63), 9.5% had multiple SOREMPs, versus 3.2% of individuals (n=476) who had a mean latency of 5 minutes or longer (p < .005). Similarly, 7.8% of individuals who had a mean latency of 8 minutes or shorter (n = 178) had multiple SOREMPs, versus 2.1% of those who had a mean latency of longer than 8 minutes (n = 387) (p < .005).

Among the SOREMP-frequency groups, mean latency on the MSLT and number of SOREMPs had an inverse relationship; as the number of SOREMPs increased, mean latency decreased, revealing a linear trend (p < .05) (Figure 3).

Finally, our hypothesis that NREM latency and REM latency would not differ was rejected when looking at individuals who had only 1 SOREMP (p < .004) (Table 4). Specifically, in individuals who had only 1 SOREMP, the sleep latency on the REM naps was significantly shorter, as compared with that on the NREM naps (p < .05) (Table 4). However, in individuals who had multiple SOREMPs, the mean latency in NREM and REM naps did not differ.

DISCUSSION

The presence of multiple SOREMPs on an MSLT was once considered to be diagnostic for narcolepsy, provided that other causes of SOREMPs have been excluded, including drug withdrawal, REM sleep deprivation, obstructive sleep apnea, alcoholism, major depression, and sleep-wake schedule abnormalities. Though various studies have evaluated the diagnostic value of using the MSLT for narcolepsy, it is difficult to interpret the specificity and sensitivity of this criterion without determining the prevalence of multiple SOREMPs in the general population. Our study was aimed at calculating the prevalence of multiple SOREMPs in a population-based sample of southeastern Michigan and was found to be 3.9%. This is, in fact, much higher than the prevalence of narcolepsy in the general population (0.05%).

In clinical situations, therefore, the sole reliance on the presence of multiple SOREMPs on the MSLT for the diagnosis of narcolepsy, in the absence of auxiliary symptoms of the disease (cataplexy, sleep paralysis, hypnagogic hallucinations), should continue to be discouraged. The prevalence of 3.9% was also found to be much lower than the 17% previously found among healthy young adults. This previous study done by Bishop et al was done on a sample of convenience. Young adults are known to be sleepier, which may explain the higher prevalence of multiple SOREMPs in the Bishop et al study. Indeed, this association of sleepiness and multiple SOREMPs was a robust finding in our analysis. The prevalence of 3.9% in our population-based sample is comparable with the 4.7% found among apneic patients, who are known to be objectively sleepy.

The second part of our study investigated which sleep-related variables were associated with multiple SOREMPs. Of all the variables tested, only objective sleepiness, as measured by a low mean latency, was associated with multiple SOREMPs. Again, SOREMPs were not related to nocturnal sleep but, rather, to excessive daytime sleepiness. Thus, the SOREMPs seen in apneic patients may not be due to sleep fragmentation as much as to excessive daytime sleepiness.

Self-reported sleepiness did not have a significant relationship with multiple SOREMPs, which is not surprising given that self-reported sleepiness does not accurately correlate with objective sleepiness.

The presence of multiple SOREMPs in a patient with narcolepsy has been thought to reflect a higher REM pressure. However, our results would imply that any condition associated with sleepiness would be associated with multiple SOREMPs. Therefore, shift-workers, apneic patients, sleep-deprived individuals, etc. would have an elevated prevalence of multiple SOREMPs,
The number of SOREMPs is linearly related to how objective sleepiness an individual is. This result can imply 2 things. Either sleepier individuals are more likely to have more SOREMPs or the mean latency to REM sleep is shorter than that to NREM sleep. To clarify this result, we looked at the sleep latency on REM versus NREM naps within each SOREMP-frequency group. We found that, among individuals who had multiple SOREMPs, sleep latency did not significantly differ between NREM versus REM naps. However, within individuals with a single SOREMP, the REM nap had a significantly shorter latency versus the NREM naps. This is an interesting finding. In the past, the presence of multiple SOREMPs has frequently been attributed to a high REM pressure, which leads to REM intrusions into wakefulness and NREM sleep stages. This higher REM pressure has been described as REM sleepiness and was found to be associated with a shorter latency on REM naps versus NREM naps among 12 untreated patients with narcolepsy. Thus, the idea that REM sleepiness versus NREM sleepiness might be 2 separate processes was advanced. However, in the largest study done to date on this topic, in 103 narcoleptics, sleep latency did not differ on REM naps versus NREM naps. Consistent with this finding, in our study, individuals with multiple SOREMPs did not differ on REM versus NREM latencies. Thus, a shorter mean latency on the MSLT and its association with multiple SOREMPs seem to imply true sleepiness rather than higher REM pressure. To be more specific, this implies that sleepier individuals have more SOREMPs and not the other way around, i.e., the presence of more SOREMPs results in a shorter mean latency on the MSLT, secondary to a higher REM pressure intruding into wakefulness. In contrast, REM pressure appears to be higher in individuals with only 1 SOREMP. This may imply that REM pressure gets masked by the higher degree of sleepiness in sleepy individuals who have multiple SOREMPs.

In summary, “2 or more SOREMPs” have been thought to be pathognomonic of narcolepsy. However, our finding that higher SOREMP-frequency groups have lower mean sleep latency would imply that, as sleepiness increases, the number of SOREMPs would increase even in the absence of narcolepsy and thus “2 or more SOREMPs” does not appear to have any specific pathognomonic significance.

ACKNOWLEDGEMENTS

Support for this study was provided by MH grants MH59338 and MH068372 to Drs Roth and Drake.

REFERENCES


Table 4—REM and NREM latency in individuals who had 1 SOREMP and multiple SOREMPs on the Multiple Sleep Latency Test

<table>
<thead>
<tr>
<th>Number of SOREMPs</th>
<th>Nap Type</th>
<th>Time, (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n = 53)</td>
<td>REM nap</td>
<td>5.67 ± 4.8</td>
</tr>
<tr>
<td></td>
<td>NREM nap</td>
<td>8.19 ± 4.4</td>
</tr>
<tr>
<td>≥ 2</td>
<td>REM nap</td>
<td>5.80 ± 3.0</td>
</tr>
<tr>
<td></td>
<td>NREM nap</td>
<td>6.70 ± 4.0</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD unless and are based on the results of t-tests.

*p< .05 versus non-rapid eye movement (NREM) naps; REM refers to rapid eye movement; SOREMP, sleep-onset REM periods on the Multiple Sleep Latency Test (MSLT). Naps with 0 SOREMPs are excluded by definition, as there are no REM onsets to compare MSLT values.
27. Sleep Disorders Classification Committee, Roffwarg HP, Chairman. Diagnostic classification of sleep and arousal disorders. Sleep 1979;2:1-139.