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Sleep Onset—REM and NREM Sleep

The Frequency of Multiple Sleep Onset REM Periods Among Subjects With No Excessive Daytime Sleepiness

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Summary: The multiple sleep latency test (MSLT) is a valuable tool in the assessment of excessive daytime sleepiness (EDS). Additionally, multiple sleep onset rapid eye movement periods (SOREMPs) are a frequent occurrence in patients with narcolepsy. To date, however, few studies have evaluated the frequency of SOREMPs in a population of healthy control subjects. Subjects participating in a variety of sleep studies were screened with a nocturnal clinical polysomnogram, followed by the MSLT. Subjects were required to be drug free and have no sleep-related symptoms or medical or psychiatric conditions. Of the 139 subjects who were screened, 24 (17%) had two or more SOREMPs. These individuals were more likely to be male, younger, and sleepier than those with one or zero SOREMPs. The etiology of two or more SOREMPs in healthy controls was not apparent from the clinical or polysomnographic evaluation. Although it is possible that these findings are early signs of narcolepsy, subjects reported being free of any sleep-related complaints. Further investigations into the determinants of multiple SOREMPs and their reliability among asymptomatic populations are warranted. **Key Words:** Multiple sleep latency test (MSLT)—Narcolepsy—Excessive daytime sleepiness (EDS)—Sleep onset REM periods (SOREMPs).

The consensus among sleep researchers and clinicians is that sleepiness is a basic physiological state (1). It is believed that sleepiness is determined by quantity and quality of sleep, circadian rhythms, central nervous system (CNS) depressant drugs, and CNS diseases. In this context, the multiple sleep latency test (MSLT) has been shown to be useful in the quantification of sleepiness for both research and clinical purposes. Thus, it has become the most widely used tool in the determination of level of sleepiness. The MSLT is also useful in the diagnosis of excessive daytime sleepiness (EDS) (2). For example, patients with narcolepsy and obstructive sleep apnea (OSA) are known to have a heightened propensity to fall asleep. Although sleepiness among OSA patients is the result of sleep fragmentation (due to sleep-disordered breathing), sleepiness among narcoleptic patients is a result of CNS pathology. In addition, multiple sleep onset rapid eye movement (REM) periods (SOREMPs) are more frequent among narcoleptic patients when compared to other patient populations (3,4). Furthermore, these findings have been shown to be a reliable feature among narcoleptic patients (5), even when tested at several-year intervals. Despite the consistent polysomnographic findings documented among narcoleptics, the base rate of multiple SOREMPs among healthy controls remains largely unknown. The purpose of this study was to determine the base rate of multiple SOREMPs among healthy subjects with no reported complaints of EDS or any other sleeping disorder.

METHODS

Subjects

The participants were 139 (67 females and 72 males) consecutive subjects who were screened for one of four ongoing sleep research protocols. Subjects were screened for these studies between June 15, 1994 and August 1, 1995.

Procedure

Individuals responding to advertisements in area newspapers were screened over the telephone to determine if they qualified for further consideration.

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They were questioned about their sleep habits, napping behavior, medical and psychiatric problems, and drug history. Subjects reporting regular nocturnal sleep habits, no regular napping, and no evidence of EDS or other sleep disorder-related symptoms were given an appointment for further evaluation at the sleep center. All subjects gave informed consent and were told they were being screened for one of four available sleep research protocols. Three of the protocols involved the administration of a psychopharmacological agent, and the fourth involved manipulations of time in bed. Subjects completed a medical, sleep, and psychiatric evaluation, which included a history and physical examination. Subjects were in good health, with no evidence of medical or psychiatric conditions. To assure drug-free status, individuals were asked to give urine samples for toxicology examination. Subjects with a positive drug screen were excluded from further screening. If eligible, the subjects were scheduled for a nocturnal clinical polysomnogram (NCPSG) and MSLT. They were asked to refrain from consuming alcohol or caffeine the evening before the NCPSG and during the MSLT day.

On screening nights, subjects underwent an 8-hour polysomnogram (PSG) (all subjects were up by 0800 hours) that included two unipolar electroencephalographic (EEG) channels (C3 and Oz), two channels for electrooculography (EOG), chin electromyogram (EMG), a nasal/oral thermistor, and one lead for EMG of the tibialis anterior. Subjects were required to have no indication of sleep-disordered breathing, periodic leg movements, or any other sleep pathologies during the nocturnal recording.

The day following the screening PSG, subjects were administered the MSLT to determine their level of sleepiness/alertness (6). The standard clinical MSLT was utilized, in which subjects were instructed at 0930, 1130, 1330, and 1530 hours (or 1000, 1200, 1400, and 1600 hours if their bedtime was terminated after 0730 hours) to lie down in a quiet and darkened bedroom environment and try to fall asleep. Standard EEGs, including unipolar central (C3) and occipital placements (Oz), chin EMG, and EOG were recorded during the naps, which lasted 20 minutes if sleep did not occur. If sleep occurred, subjects were allowed to sleep for 15 minutes. Subjects were tested using the sleep/wake activity inventory (SWAI) and the Epworth sleepiness scale the morning of the MSLT day.

Polysomnographic recordings were scored in 30-second epochs according to the standards of Rechtschaffen and Kales (7) by trained technicians who were blind to the intentions of the study. The interrater reliability was maintained at ≥90%. Data were grouped based on the presence of multiple SOREMPs. Analyses for the sleep variables were conducted using independent t tests. Where applicable, analysis of variance (ANOVA) in the MGL Hypothesis testing portion of Systat (version 5.2) was used. Where appropriate, the probabilities reported were corrected by the Greenhouse-Geisser method. Post-hoc contrasts were performed using Tukey's procedure.

RESULTS

Subjects

Of the 139 subjects, 24 (17%) were found to have two or more SOREMPs. Eight (6%) subjects demonstrated one SOREMP, and 107 (77%) participants did not have any SOREMPs. Subjects with zero and one sleep onset REM period (NSOREMP) were compared to those with two or more sleep onset REM periods (SOREMP). Age and gender are presented in Table 1.

On weekdays, the SOREMP group averaged a reported time in bed (TIB) of 8.0 ± 1.6 hours, versus 8.0 ± 0.98 hours for the NSOREMP group [$t = 0.130$; not significant (NS)]. Their reported total sleep times (TST) on weekdays were also comparable (SOREMP group, 7.6 ± 1.6 hours; NSOREMP group, 7.4 ± 0.97 hours; $t = 0.619$, NS). On weekends the SOREMP group reported a TIB of 8.5 ± 1.4 hours and TST of 7.9 ± 1.7 hours, similar to those of NSOREMP subjects, who reported a mean TIB of 8.4 ± 0.94 hours and TST of 7.9 ± 1.3 hours ($t = 0.368$, NS; $t = 0.177$, NS, respectively). Subjects were required not to take naps on a regular basis in order to be eligible for participation. Napping one to three times per week was not different between the two groups (SOREMP group, 21%; NSOREMP group, 25%; $\chi^2 = 0.16$, NS). The daytime subjective measures of sleepiness (the SWAI and the Epworth scales) failed to differentiate the two groups, as seen in Table 1.

Nocturnal screening evaluation

Data on sleep architecture are presented in Table 1. The sleep efficiencies and sleep architecture were comparable for both groups. Differences between the two groups emerged on their latency to stage 1 non-rapid eye movement (NREM) sleep. The latency to stage 1 NREM sleep for the SOREMP group was 7.5 ± 6.2 minutes; for the NSOREMP group, it was 13.4 ± 12.7 minutes ($t = 2.22$; $p < 0.05$). There were no significant differences among the two groups on measures of sleep continuity (number of awakenings, entries to stage 1 NREM sleep, and entries to wake) (see Table 1).

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TABLE 1. *Characteristics of SOREMP versus NSOREMP groups*

	SOREMP group	NSOREMP group
Age[a]	27.9 ± 9.5	34.6 ± 12.2
Gender[b]	18 males, 6 females	54 males, 61 females
Sleep efficiency	90.8 ± 9.7	89.9 ± 6.8
Stage 1 NREM sleep %	12.4 ± 7.8	10.3 ± 6.7
Stage 2 NREM sleep %	54.8 ± 9.1	54.6 ± 9.6
Stage 3/4 NREM sleep %	12.8 ± 5.9	15.9 ± 9.0
REM %	20.0 ± 6.1	19.2 ± 5.5
Latency to stage 1 sleep[a] (minutes)	7.5 ± 6.2	13.4 ± 12.7
Latency to PS[a] (minutes)	12.5 ± 13.0	21.4 ± 21.2
Latency to REM sleep (minutes)	74.1 ± 38.6	92.0 ± 44.1
Number of entries to stage 1 sleep	18.1 ± 13.6	13.3 ± 11.8
Number of entries to wake	17.4 ± 8.8	16.3 ± 7.8
Mean MSLT score[a]	6.2 ± 2.9	10.8 ± 4.5
SWAI score	60.8 ± 9.2	62.2 ± 9.1
Epworth score	7.1 ± 3.4	7.1 ± 4.4

SOREMP, sleep onset rapid eye movement period; individuals in the SOREMP group had two or more SOREMPs. NSOREMP, no sleep onset rapid eye movement periods; individuals in the NSOREMP group had one or zero SOREMPS. NREM, non-rapid eye movement; REM, rapid eye movement; PS, persistent sleep; MSLT, multiple sleep latency test; SWAI, sleep/wake activity inventory; Epworth score refers to the Epworth sleepiness scale.

[a] $p < 0.05$.

[b] χ^2; $p < 0.05$.

Daytime evaluations

The latency to sleep on each nap was submitted to a repeated-measures ANOVA, with the between-groups variable being the SOREMP group. There was an overall main effect of group (F = 14.45, df 1,95, $p < 0.01$). The SOREMP group had a shorter mean MSLT score (6.2 ± 2.9 minutes) when compared to the NSOREMP group (10.8 ± 4.5 minutes). The latencies for the SOREMPS group were 5.3 ± 5.3, 5.8 ± 4.5, 6.3 ± 5.5, and 7.1 ± 5.7 minutes for naps 1–4, respectively. The latencies for the NSOREMP group were 9.4 ± 6.0, 9.6 ± 6.4, 11.0 ± 6.4, and 11.2 ± 6.1 minutes, respectively. No main effect of nap (F = 1.60, df 3,285, NS) or group-by-nap interaction was demonstrated (F = 0.126, df 3,285, NS).

The distribution of SOREMPs across all sleep onset opportunities (nocturnal sleep onset and four MSLT naps) was assessed with Friedman's test. An overall main effect of time was documented (F = 20.71, $p < 0.01$). The rate of SOREMPs was shown to be comparable across naps (nap 1, 27%; nap 2, 32.2%; nap 3, 15.3%; nap 4, 23.7%) and higher compared to the rate of SOREMPs on the NCPSG (1.7%).

DISCUSSION

The present results demonstrate a surprisingly high frequency of multiple SOREMPs among asymptomatic healthy volunteers. There have only been isolated case reports where SOREMPs have been encountered in otherwise healthy volunteers (8,9). From a clinical perspective, no evidence was documented that might explain this finding. Subjects were screened to report regular sleep schedules with no regular napping behavior, although there were no actigraphic recordings to validate regular sleep schedules prior to PSG evaluation. NCPSG failed to document any evidence of sleep-disordered breathing. No subject was identified as having intermittent snoring that resulted in a pattern of frequent arousals. Subjects were screened to determine drug-free status, and the absence of REM rebound in the SOREMP group is consistent with the lack of evidence of drug effects. The possible role of chronic insufficient sleep may also be considered a potential explanation for the findings. However, subjects with SOREMPs did not differ in their subjective reports of sleep time or on their overnight PSG characteristics. Another potential explanation for these findings may be that these subjects in fact have "evolving narcolepsy" (10). However, the number of subjects with multiple SOREMPs far exceeded the expected base rate of narcolepsy in the general population (11).

The present findings should caution clinicians on the unrestricted use of PSG features for the diagnosis of narcolepsy, in particular among patients with no evidence of auxiliary symptoms. Although the latter group of patients has been shown to have symptoms of EDS, sleepiness, reliable PSG features (even when tested across time), and a higher than expected association with the human leukocyte antigen (HLA) DR2 (12), the present results require further research to determine the clinical significance of SOREMPs.

REFERENCES

1. Kryger M, Roth T, Dement W, eds. *Principles and practice of sleep medicine.* Philadelphia: WB Saunders, 1994.
2. Zorick F, Roehrs T, Koshorek G, et al. Patterns of sleepiness in

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various disorders of excessive daytime somnolence. *Sleep* 1982;5:S165–74.
3. Van den Hoed J, Kraemer H, Guilleminault C, et al. Disorders of excessive daytime sleepiness: polygraphic and clinical data for 100 patients. *Sleep* 1981;4:23–37.
4. Richardson G, Carskadon M, Flagg W, van den Hoed J, Dement W, Mitler M. Excessive daytime sleepiness in man: multiple sleep latency measurement in narcoleptic and control subjects. *Electroencephalogr Clin Neurophysiol* 1978;45:621–7.
5. Folkerts M, Rosenthal L, Roehrs T, Krstevska S, Murlidhar A, Zorick F, Wittig R, et al. The reliability of the diagnostic features in patients with narcolepsy. *Biol Psychiatry* 1996;40:208–14.
6. Carskadon MA. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. *Sleep* 1986;9:519–24.
7. Rechtschaffen A, Kales A. *A manual of standardized terminology, techniques, and scoring system for sleep stages of human subjects.* Washington DC: Public Health Service Publication No. 204, U.S. Government Printing Office, 1968.
8. Carskadon M. The second decade. In: Guilleminault C, ed. *Sleeping and waking disorders: indications and techniques.* Menlo Park: Addison-Wesley, 1982:99–125.
9. Rosenthal L, Folkerts M, Roehrs T, Zorick F, Roth T. Sleepiness and sleep onset REM periods in the absence of clinical symptomatology. *Biol Psychiatry* 1994;36:341–3.
10. Montplaisir J, Poirier G. HLA in disorders of excessive daytime sleepiness without cataplexy in Canada. In: Honda Y, Juji T, eds. *HLA in narcolepsy.* Berlin: Springer-Verlag, 1988:186–90.
11. Hublin C, Kaprio J, Partinen M, et al. The prevalence of narcolepsy: an epidemiological study of the Finnish twin cohort. *Ann Neurol* 1994;35:709–16.
12. Rosenthal L, Roehrs T, Hayashi H, et al. HLA DR2 in narcolepsy with sleep-onset REM periods but not cataplexy. *Biol Psychiatry* 1991;30:830–6.

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