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Sleep-Wake Abnormalities in Narcolepsy

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Summary: To evaluate the degree to which sleep (REM vs. NREM) intrudes into wake and wake intrudes into sleep in narcolepsy, 103 patients with narcolepsy were compared to 105 patients with other diagnoses of disorders of excessive sleep (DOES). Narcoleptic patients had more frequent REM onsets on the multiple sleep latency test (MSLT) and nocturnal polysomnograms. But the MSLT latencies to REM versus NREM in narcoleptic patients did not differ. Nocturnal measures of REM pressure, percentage of REM, and REM latency excluding the REM onsets, did not differ among patient groups. With respect to the intrusion of wake into sleep, narcoleptic patients had more and longer awakenings compared with other DOES patients, but the distribution of wake into REM and NREM sleep did not differ among groups. These data suggest that narcolepsy is not exclusively a REM-related disorder, but involves an inability to sustain a specific neural state for periods comparable to those in normal subjects or other DOES patients. **Key Words:** Narcolepsy—Sleep-wake disorders—Multiple sleep latency test—REM sleep—Disorders of excessive daytime sleepiness.

Daytime and nighttime sleep in narcoleptic subjects tends to begin with sleep onset REM periods (appearance of REM within 10–15 min of sleep onset). First observed by Vogel (1) in 1960 and studied systematically by Rechtschaffen et al. (2) in 1963, this finding since has been confirmed in a large number of patients (1–4). Sleep onset REM is the sign that differentiates narcolepsy from other disorders of excessive daytime sleepiness (DOES). Since the associated symptoms of narcolepsy (cataplexy, hypnagogic hallucinations, and sleep paralysis) are considered to be manifestations of REM sleep, many have concluded that narcolepsy is primarily a dysfunction of REM (5). An alternative hypothesis is that narcolepsy is an abnormality involving the reciprocal inhibition between wake and both REM and NREM sleep (6). The REM phenomena stand out only because they are not seen in other DOES conditions and are specific to narcolepsy. However, the specificity of REM onsets to narcolepsy need not indicate that a REM dysfunction is the sole abnormality of narcolepsy.

To test these alternatives, narcoleptic subjects were evaluated to determine the degree to which sleep intrudes into wakefulness, and, equally important, the degree to which wakefulness intrudes into sleep. Additionally, the degree to which the sleep intrusions of wake were specific to REM sleep was assessed. Finally, all of the above anlayses were made in comparison with other DOES patients to determine the degree to which these findings were specific to narcolepsy.

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METHODS

Subjects

The subjects were 208 patients, 103 with a diagnosis of narcolepsy and 105 with other DOES diagnoses. All had undergone comprehensive diagnostic evaluation at the Henry Ford Hospital Sleep Disorders and Research Center. The mean age of patients with narcolepsy was 43.7 years, and the mean age of the other DOES patients was 41.7 years.

Procedure

The diagnostic evaluation consisted of medical and sleep histories, physical examination, questionnaires, and nocturnal polysomnography followed the next day by MSLT. Before visiting the clinic, all patients completed sleep questionnaires eliciting the history and symptoms of their sleep complaints. A 2-week diary of sleep habits, including usual weekday and weekend bed and rising times, was maintained. At the clinical interview, the questionnaire and diary were reviewed, a medical and psychiatric history was taken, and the Cornell Medical Index and the Minnesota Multiphasic Inventory were completed.

Then one all-night polysomnogram was obtained from each patient. Seven days before the polysomnogram, all sedative and stimulant medications were discontinued. Diuretics, antihypertensives, and digitalis were allowed if medically indicated. On the day of the polysomnogram, patients were instructed to refrain from using alcohol or caffeine after 5 p.m. The polysomnogram included the standard central and occipital electroencephalogram (EEGs), electro-oculogram (EOG), submental electromyogram (EMG), electrocardiogram recorded with a V5 lead, respiratory flow recorded with a nasal-oral thermistor, and left tibialis EMG. Depending on the diagnostic impression, additional tracings included respiratory effort recorded by abdominal strain gauges, and oxygen saturation monitored by Biox II ear oximeters or tibialis EMG activity recorded from both left and right legs. All recordings were scored for sleep stages according to the standards of Rechtschaffen and Kales (7). Scorers were not aware of the results of the clinical interview and maintained a within-laboratory interscorer reliability of $>90\%$.

For the MSLT, patients were instructed at 1000, 1200, 1400, and 1600 h to lie down on a bed in a dark, quiet room and try to fall asleep. Standard EEGs (always including an occipital placement, Oz), EMG, and EOG were recorded during the naps. Each nap test lasted 20 min if sleep did not occur. If sleep occurred, the nap was terminated 15 min after sleep onset. Patients were instructed not to sleep between naps and were monitored by technicians to assure wakefulness.

The patient diagnoses, made on the basis of the entire clinical evaluation, were derived from the Association of Sleep Disorders Centers Diagnostic Classification of Sleep Disorders, and each was a consensus diagnosis of two clinical polysomnographers. All patients in this study had received a single diagnosis; excluded were those meeting criteria for more than one diagnostic category. Polysomnographic evidence necessary for a diagnosis of narcolepsy was the presence of at least two REM onsets, defined as the appearance of REM sleep within 15 min of the initiation of the recording, and pathological sleepiness. These criteria have been shown previously to differentiate patients with narcolepsy from all others (3).

To evaluate the intrusion of sleep, REM, and NREM into wake, all 103 patients with narcolepsy were compared to 85 patients with DOES diagnoses other than narcolepsy or sleep apnea syndrome. To evaluate the intrusion of wake into sleep, 20 patients with narcolepsy, 20 with sleep apnea syndrome, and 20 with chronic insufficient sleep or idiopathic hypersomnolence were chosen randomly from the total 208 patients for comparison.

TABLE 1. *Frequency of REM latencies and REM percentages*

	Latencies in 15-min blocks							Percentage of REM in 5% blocks				
	<15	16–30	31–45	46–60	61–75	76–90	>90	<10	11–15	16–20	21–25	>26
Narcolepsy	46	2	4	10	13	7	21	15	28	26	26	8
Other DOES	2	1	6	12	10	12	42	16	14	28	20	7

DOES, disorders of excessive sleep.

Multiple control groups are necessary because DOES populations differ in the degree to which their sleep is fragmented by brief arousals or wakefulness. For example, patients with sleep apnea syndrome have highly fragmented sleep as they arouse frequently to resume breathing, while patients with chronic insufficient sleep or idiopathic central nervous system hypersomnolence have highly consolidated sleep (8,9).

RESULTS

Intrusion of sleep (REM vs. NREM) into wake

Patients with narcolepsy had frequent sleep onset REM periods, 70% on the MSLT and 45% on nocturnal recordings. The specificity of this sign is seen in comparison to the other DOES patients who showed sleep onset REM on 8% of MSLTs and 3% of nocturnal recordings. Comparison of the smallest difference between groups, that on nocturnal recordings, was statistically significant ($\chi^2 = 48.67$, $p < 0.01$). In addition, the latency to REM on the MSLT was significantly shorter for narcoleptic patients; on the average it was 5.7 min for narcoleptic patients and 11.8 min for the other DOES patients ($t = 3.1$, $p < 0.01$).

At issue is whether REM onsets in narcolepsy are indicative of abnormal REM pressure or simply reflective of the inability to inhibit the intrusion of REM into wake. To evaluate this problem, the traditional measures of REM pressure, REM percentage during the night, and REM latency were compared between diagnostic groups. Table 1 presents a frequency distribution of REM latencies in 15-min blocks and REM percentages in 5% blocks for the two patient groups. When sleep-onset REM periods (appearance of REM within 15 min) were excluded from the analysis, no significant differences were found in the REM latencies of the patient groups. The groups also did not differ in REM percentage. Finally, patients with narcolepsy did not show a selective pressure for REM intrusions into wake. The sleep latency on MSLT with REM onsets was 2.3 min; it was similar on latency tests with NREM sleep only (3.2 min) and not statistically different ($t = 1.93$, $p > 0.10$).

Intrusion of wake into sleep

Patients with narcolepsy had a mean of 25.4 awakenings per night, similar to the patients with apnea (36.4) and significantly more than the mean of 10.8 awakenings of the other DOES patients ($t = 4.10$, $p < 0.01$). The majority (65%) of the awakenings of narcolepsy patients were longer than 30 s, which differs significantly from apnea patients ($t = 3.42$, $p < 0.01$), in whom 50% of awakenings were longer than 30 s. The other DOES patients had 55% awakenings longer than 30 s. While the frequency and duration of awakenings differed among patient groups, their distribution in REM and NREM did not. Awakenings per minute (to correct for differential amounts of each sleep state) occurred 2.8 times as frequently from REM compared with NREM in narcoleptic patients, and the ratio was similar in the apnea patients (2.2) and in the other DOES patients (1.6).

TABLE 2. *Sleep stages in the three patient groups*

	Other DOES	Narcolepsy	Apnea
Stage 1 (%)	12.8 (6.5)	23.3[a,b] (8.9)	62.6 (20.0)
Stage 2 (%)	57.8 (8.8)	48.0[a,b] (7.7)	28.1 (16.9)
Stages 3 and 4 (%)	9.0 (7.4)	7.9 (6.5)	3.9 (7.7)
REM (%)	18.7 (6.5)	21.5[b] (6.4)	11.6 (5.7)
Sleep efficiency	93.9 (5.7)	87.9[a] (6.4)	86.7 (8.5)

Data are means and (standard deviations). DOES, disorders of excessive sleep.
[a]Differs from other DOES, $p < 0.01$.
[b]Differs from apnea, $p < 0.01$.

The subjective data yielded results similar to the results of the polysomnographic data. Patients with narcolepsy reported significantly more awakenings (3.2) than the other DOES patients (1.3) per night ($t = 2.39$, $p < 0.05$). They also rated their sleep as being lighter than in the other groups ($\chi^2 = 14.14$, $p < 0.01$).

The standard sleep stage parameters for these three patient groups are presented in Table 2 for comparison. As seen in Table 2, the sleep efficiency of patients with narcolepsy was reduced compared with the other DOES patients ($t = 3.13$, $p < 0.01$) and similar to that of the apnea patients. The patients with narcolepsy had a greater percentage of stage 1 sleep than the other DOES patients ($t = 4.26$, $p < 0.01$), but less percentage of stage 1 sleep than the apnea patients ($t = 8.00$, $p < 0.01$). There were no differences in percentage of stage 3 and 4 sleep, and only patients with apnea showed different amounts (a reduction) of stage REM sleep. Differences in percentage of stage 2 sleep were reciprocal to the large differences in percentage of stage 1 sleep; that is, patients with narcolepsy had less percentage of stage 2 sleep than the other DOES patients ($t = 3.84$, $p < 0.01$) and a greater percentage than the apnea patients ($t = 4.79$, $p < 0.01$).

DISCUSSION

These comparative studies of different DOES patients support the hypothesis that the sleep disorder of narcolepsy is not exclusively a REM-related phenomenon. First, both REM and NREM sleep intrude into wakefulness. While patients with narcolepsy showed a higher frequency of REM onsets, they did not show any of the polysomnographic features associated with increased REM pressure. This is consistent with a recent report of more REM onsets in narcoleptic subjects but no difference in REM density from age-matched normal subjects (10). Also, NREM intrusions into wake with latencies similar to REM were seen in these data. That is, on the MSLT there was no difference in sleep latencies on naps which had REM sleep and those which had NREM sleep.

Second, long periods of wakefulness intrude into the sleep of narcoleptic patients. In this study, frequent long awakenings from both REM and NREM sleep were found. The distribution of the awakenings was not specific to either REM or NREM sleep. Additionally, the sleep stage data showed evidence of increased arousal, in that stage 1 sleep was elevated compared with the other DOES patients.

In summary, the pathology in these patients seems to relate not to REM sleep exclusively but to an inability to sustain a specific neural state for a period comparable with that of normal subjects or other DOES patients. That is not to say that there is no REM dysfunction in narcolepsy, but only that the REM dysfunction of narcolepsy is not the only pathology.

REFERENCES

1. Vogel G. Studies in the psychophysiology of dreams. III. The dream of narcolepsy. *Arch Gen Psychiatry* 1960;3:421–8.
2. Rechtschaffen A, Wolpert E, Dement W, Mitchell S, Fisher C. Nocturnal sleep of narcoleptics. *Electroencephalogr Clin Neurophysiol* 1963;15:599–609.
3. Zorick F, Roehrs T, Koshorek G, et al. Patterns of sleepiness in various disorders of excessive daytime somnolence. *Sleep* 1982;5:S165–74.
4. Mitler M, van den Hoed J, Carskadon M, et al. REM sleep episodes during the multiple sleep latency test in narcoleptic patients. *Electroencephalogr Clin Neurophysiol* 1979;46:479–81.
5. Gillin JC, Horowitz D, Wyatt RJ. Pharmacologic studies of narcolepsy involving serotonin, acetylcholine, and monoamine oxidase. In: Guilleminault C, Dement WC, Passouant P, eds. *Narcolepsy*. New York: Spectrum, 1976.
6. Vogel G. Mentation reported from naps of narcoleptics. In: Guilleminault C, Dement WC, Passouant P, eds. *Narcolepsy*. New York: Spectrum, 1976.
7. Rechtschaffen A, Kales A, eds. *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects*. Los Angeles: Brain Information Service/Brain Research Institute, University of California at Los Angeles, 1968.
8. Roehrs T, Zorick F, Sicklesteel J, Wittig R, Roth T. Excessive daytime sleepiness associated with insufficient sleep. *Sleep* 1983;6:319–25.
9. Zorick F, Roehrs T, Conway W, Fujita S, Wittig R, Roth T. Effects of uvulopalatopharyngoplasty on the daytime sleepiness associated with sleep apnea syndrome. *Bull Eur Physiopathol Respir* 1983;19:600–3.
10. Vogel G. REM latency in obsessive compulsive disorder, panic disorder and generalized anxiety disorder. Presented at the annual meeting of the Sleep Research Society. Seattle: 1985.