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EXCESSIVE DAYTIME SLEEPINESS IN MAN: MULTIPLE SLEEP LATENCY MEASUREMENT IN NARCOLEPTIC AND CONTROL SUBJECTS

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Summary

Excessive daytime sleepiness is a complaint characterizing many disorders of the wakefulness—sleep cycle. This paper addresses the complaint of sleepiness objectively by an attempt to differentiate a group of control subjects from a group of patients with unambiguous narcolepsy. Fourteen control and 27 narcoleptic subjects were evaluated by one of three protocols involving nocturnal recordings, detailed interviews, and 5 or more 20-min opportunities to sleep offered at 2-h intervals beginning at 10.00 o'clock, ±30 min. Each 20-min opportunity to sleep was given to subjects lying in a darkened quiet room and asked to try to fall asleep. Polysomnographic variables were monitored and sleep was scored in 30-sec epochs by standard criteria. The interval from the start of each test to the first epoch of NREM (including stage 1 sleep) or REM sleep was called sleep latency. In two of the protocols, the subjects were awakened immediately after sleep onset. In the third protocol, the subjects were awakened after 10 min of sleep. Narcoleptics consistently fell asleep much more readily than did control subjects. We conclude that the Multiple Sleep Latency test, in addition to providing opportunities to clinically document sleep onset REM sleep periods, can demonstrate pathological sleepiness. Based on these data, we suggest that an average sleep latency less than 5 min be set as the minimum cutoff point for pathological sleepiness.

Excessive daytime sleepiness (EDS) is a complaint characterizing many disorders of the wakefulness—sleep cycle (Guilleminault and Dement 1977). Despite the potential dangers to life and property of EDS, complaints are frequently unevaluated by physicians because there are few objective tools available to confirm pathological sleepiness.

Traditional approaches to the study of sleepiness have included performance tests such as those developed to evaluate the consequences of sleep deprivation and various work-rest schedules (e.g., Wilkinson el al. 1968), and pupillography (Yoss et al. 1969). These approaches rely on a statistical relationship between an operational definition of sleep deprivation or a subjective measurement of sleepiness on the one hand and a behavioral or psychophysiological parameter on the other hand.

More recently, Carskadon and Dement (1977) suggested that sleep latency (defined as the time between the point when an individual tries to sleep and the point when electroencephalographic patterns of sleep first develop) measured repeatedly in controlled nap situations might prove a useful tool in evaluating pathological sleepiness.

Such a multiple nap procedure offers several advantages over performance testing, subjective tests, and pupillography. First, the concept of sleep latency as a measure of sleepiness has face validity, since presumably one who is sleepy will fall asleep more quickly than one who is not sleepy. Second, the use of sleep latency as a measurement of sleepiness is less subject to the confounding influences of muscle fatigue, motivation and practice than are performance tests.

Third, in addition to evaluating pathological sleepiness, repeated sleep latency measurements allow opportunities to chock for sleep onset REM sleep periods. These abnormal sleep onsets are commonly thought to be diagnostic of narcolepsy (e.g., Passouant 1976). Normals usually have 60–120 min of NREM sleep before REM sleep is seen. A REM sleep period that occurs 0–15 min after sleep begins constitutes REM sleep with an abnormally short latency. Such short latency REM sleep is commonly called sleep onset REM sleep (Wilson et al. 1973). The finding of two or more such episodes of REM sleep occurring during normal waking hours, or just after nocturnal sleep begins, can confirm the diagnosis of narcolepsy.

This paper summarizes quantitative differences between patients with unambiguous narcolepsy and control subjects with respect to sleep latencies measured at discrete intervals during the day. The data strongly suggest that multiple measurements of sleep latency can differentiate narcoleptics from control subjects.

Methods

Study 1

A total of 9 control subjects who did not normally nap (mean age 44.1 (S.D. = 5.8), 8 males) and 8 narcoleptic subjects (mean age 44.6 (S.D. = 13.6), 4 males) served in one of two protocols. The narcoleptics were selected a priori on the basis of a medical history consistent with the diagnosis of narcolepsy. Moreover, in a post hoc evaluation, no narcoloptic failed to show two or more sleep onset REM sleep periods in a series of 6–14 20-min opportunities to fall asleep offered over a 1–2-day period. Subjects were asked to refrain from, taking sedative or stimulant medication and to limit their intake of stimulating or depressing beverages for 1 week prior to testing. Both protocols involved at least two successive all-night polysomnographic monitorings and two successive days of sleep latency tests. In protocol A (10 subjects) bedtime was at 23.00 o'clock and subjects were awakened at 08.00 o'clock. Sleep latency tests were administered at 09.30, 11.30, 13.30, 15.30,17.30, 19.30 and 21.30 o'clock. For protocol B (7 subjects) the corresponding nocturnal bedtimes were 23.30 and 08.00 o'clock. Sleep latency tests were administered at 10.00, 12.00, 14.00, 16.00, 18.00 and 20.00 o'clock.

For both protocols, meal times were 08.00, 12.00, 18.00 ± 30 min. Every sleep latency test was done while the subjects lay in a darkened, quiet room and were asked to try to fall asleep. Polysomnographic variables included monopolar C_3 or C_4 and O_1 or O_2 electroencephalograms, electro-oculogram from the right and left outer canthi (half amplitude cutoffs: 0.3–35 Hz), and the electromyogram from muscles on and beneath the chin (half amplitude cutoffs: 10–70 Hz). Resulting data were scored by 30-sec epochs using standard criteria (Rechtschaffen and Kales 1968). Sleep latency was considered to be the interval from the start of the test to first epoch of NREM (including stage 1 NREM sleep) or REM sleep. The REM sleep latency was taken as the interval between sleep onset and the first epoch of REM sleep. Subjects were awakened after 1 min of sleep. If the subject did not fall asleep on a particular sleep latency test, that test was terminated after 20 min and given a score of 20 min. Between sleep latency tests, subjects were out of bed and wakefulness was maintained by experimenter observation.

Study 2

Five control subjects who did not normally nap (mean age = 30 (S.D. = 7.2) 2 males) and 19 narcoleptic subjects (mean age = 44.9 (S.D. = 7.1), 12 males) participated in this study. Narcoleptics were selected post hoc from a series of patients with the complaint of excessive daytime sleepiness. As in study 1, this selection was done on the basis of the presentation of two or more sleep onset REM sleep periods and a history-consistent with narcolepsy. Subjects with any evidence of nocturnal myoclonus or respiratory abnormalities during sleep were

excluded either by nocturnal diagnostic polysomnograms or by careful interview procedures. After a reportedly normal night's sleep either at home or in the sleep laboratory, sleep latencies were measured at 10.00, 12.00, 14.00, 16.00 and 18.00 o'clock using the criteria of study 1, with the exception that subjects were allowed 10 min of sleep on each test. Thus, each sleep latency test could be as short as 20 min (in the case where no sleep occurred), or as long as 30 min (if sleep onset occurred during the 20th min of the test). The subjects were asked to stay awake during the intervals between tests, and a technician ensured that inter-test sleep was kept to a minimum.

Results

Study 1

Results of the nocturnal sleep analysis for traditional sleep parameters are summarized in Table I. The data are consistent with numerous other observations that the nocturnal sleep of narcoleptics is structurally different from that of control subjects. In summary, the narcoleptics fell asleep more readily, had less total sleep, more wake time after sleep onset and more body movements than did controls. However, the narcoleptics did not differ from the controls in terms of latency to nocturnal REM sleep and had significantly less nocturnal REM sleep than did the controls. Finally, it should be noted that in spite of these clear differences in nocturnal sleep, we found no reliable parameter of nocturnal sleep that could be used to unambiguously diagnose narcolepsy.

Inspection of the daytime nap data from protocol A and protocol B disclosed no systematic difference between the two procedures; thus data for the 6 naps were combined. Table II summarizes study 1 sleep latencies, as functions of group, day and nap number. Inspection of Table I disclosed no systematic differences between naps on day 1 and naps on day 2, within the two groups of subjects. Between groups, narcoleptics fell asleep more readily than did controls (all t's > 2.70, all df's =15, all P's < 0.1). Note also the afternoon dip formed by the 6 mean sleep latencies for both narcoleptics and controls. The ordering of means is characterized by the lowest sleep latencies for both groups occurring on naps 3 and 4, and the highest sleep latencies on naps 1 and 6.

Study 2

Table III summarizes results for study 2, as functions of nap time and group. As can be seen, this study showed that narcoleptics fell asleep more readily than did controls (all t's > 2.7, all df's = 22, all P's < 0.1). As in study 1, the trend is for naps 3 and 4 to show shorter sleep latencies for both narcoleptics and controls, and for naps 1 and 5 to show longer sleep latencies.

The major procedural difference between study 1 and study 2 was that in study 2 subjects throughout the 5 opportunities to sleep were allowed a total of 50 min of sleep, whereas in study 1 total sleep time throughout the 6 opportunities to sleep could never total more than about 6 min. However, an inspection of means for studies 1 and 2, summarized in Tables II and III respectively, discloses no systematic differences between the first 5 naps of study 1 and the naps of study 2. Statistical examination revealed no difference between study 1 and study 2 narcoleptics, on any comparable nap (all t's < 1, all df's = 25, all P's not significant) and no differences between control subjects in study 1 and study 2 on any comparable nap (all t's < 1, all df's = 12, all P's not significant). Therefore, to summarize overall results as succinctly as possible, we combined the first 5 naps on day 1 of study 1 with the 5 naps of study 2. Fig. 1 presents mean ± S.E.M. sleep latencies for all narcoleptic and all control subjects evaluated. The distinction between the 5 naps for controls and narcoleptics is clearly demonstrated by Fig. 1. Furthermore, note again the afternoon dip for both groups in sleep latencies.

Discussion

The nocturnal sleep data of study 1 suggest that the sleep of narcoleptics is structured differently than that of control subjects. The narcoleptics showed reduced sleep latency, reduced total sleep time, increased wakefulness after sleep onset, and increased body movements. However, the latency to nocturnal REM sleep was not significantly shorter for narcoleptics than for control subjects and narcoleptics had *less* total REM sleep during the night than did controls. These trends in REM sleep parameters may be explained by a 'ceiling effect' related to reduced total sleep time for narcoleptics. Similar findings of disrupted nocturnal sleep in narcoleptics has often been observed (e.g., Montplaisir 1976).

Of more importance is the fact that the daytime sleep latency data differentiated narcoleptic subjects from controls with enough clarity to be useful diagnostically. The daytime results are also consistent with those reported by Mitler and Dement (1978) for narcoleptic and normal dogs given successive 20-min opportunities for sleep separated by 40 min of enforced wakefulness.

The Multiple Sleep Latency approach appears to be insensitive to the methodological differences characteristic of study 1 versus study 2 and provides valid results concerning the relative sleepiness of narcoleptics and control subjects. We plan to continue using the protocol of study 2 as a clinical diagnostic tool. The procedure is quite simple to carry out and can be done with a polygraph in any comfortable setting. Furthermore, the repeated test nature of the procedure minimizes the chance of false negative and positive results that can characterize one-trial sleep electroencephalographic evaluations of EDS patients.

In this vein, we are now compiling a separate report on patients who complain of EDS but who do not qualify as narcoleptics either by history or by presenting two or more sleep onset REM sleep periods in a Multiple Sleep Latency test. To date we have noticed a great heterogeneity among such patients in terms of medical history and mean sleep latency.

Two typical examples may be of interest. One 37-year-old man had a long history of poor performance and daytime somnolence with no clear experiences of cataplexy or other signs of narcolepsy. His sleep latencies were 4, 3, 0.5, 2 and 2 ($\hat{x}$ = 2.3, S.D. = 1.3). Yet there was no REM sleep onset. Clearly, this man's pathological sleepiness was confirmed, but choice of a diagnostic category remains problematic. Another 31-year-old female complained bitterly of excessive daytime sleepiness; yet, at the height of the complaint, she presented sleep latencies of 20, 20, 20, 17.5 and 20 ($\hat{x}$ = 19.5, S.D. = 1.1). That is, she did not sleep at all in 4 of 5 20-min opportunities to sleep. Neither did she show any abnormal REM sleep latencies. We have no certain explanation for findings on this woman. One possibility is that the condition the patient refers to as 'sleepiness' is a substantially different set of psychophysiological circumstances than those that predispose most of us to sleep, and she is misusing the word 'sleepy'.

Nevertheless, the issues raised by the results with non-narcoleptic EDS subjects aside, we conclude that the Multiple Sleep Latency test, in addition to providing several opportunities to check for sleep onset REM sleep periods, can demonstrate pathological sleepiness in narcoleptics. The procedure can also be useful in patients who complain of excessive daytime sleepiness. As a preliminary guideline, we are clinically using a mean sleep latency of less than 5 min as the minimum cutoff point for documentation of the complaint of pathological sleepiness.

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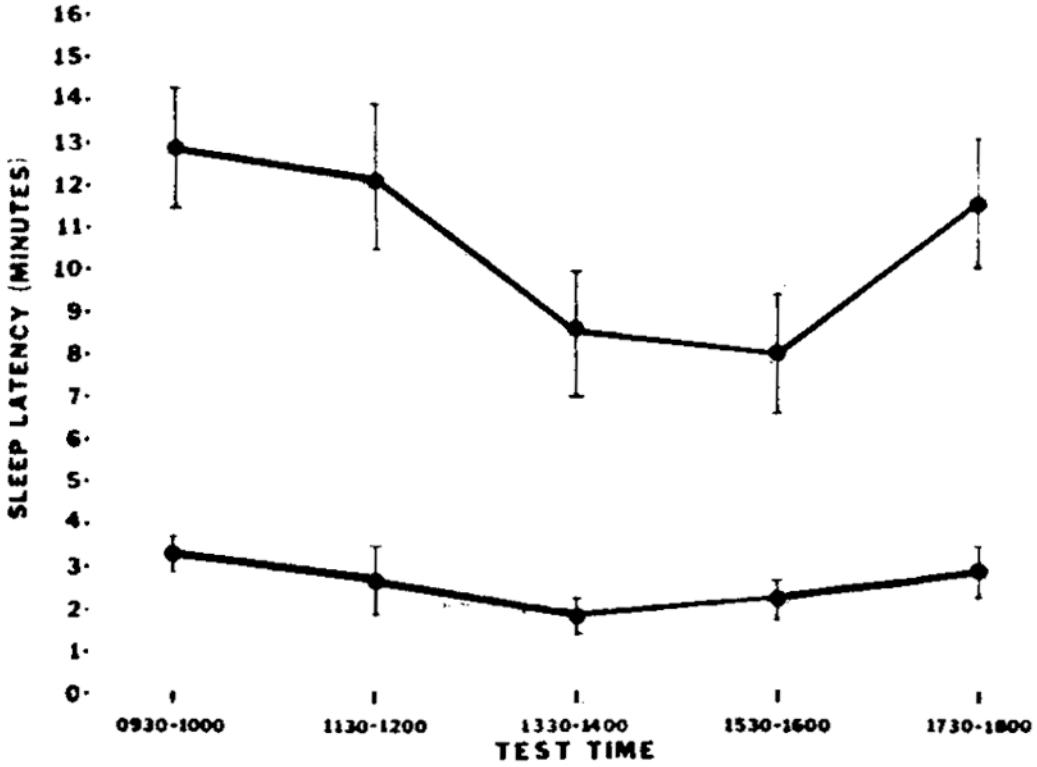

Fig. 1.

Mean (± S.E.M.) sleep latencies for control (upper curve) and narcoleptic (lower curve) subjects. For each opportunity to sleep, narcoleptics fell asleep significantly more quickly than did control subjects.

TABLE I

Mean (± S.D.) of selected nocturnal sleep parameters for narcoleptic and control subjects in study 1.

	Narcoleptics (N = 8)	Controls (N = 9)	*t*	*df*	*P*<
Sleep latency (min)	6.9 ± 9.5	15.8 ± 10.9	1.8	15	0.05
Total sleep time (min)	417.2 ± 42.7	469.8 ± 33.4	2.8	15	0.01
REM sleep latency (min)	68.4 ±61.0	79.6 ± 20.9	<1	15	NS
REM sleep time (min)	71.5 ± 19.9	91.2 ± 15.9	2.3	15	0.025
Wake time after sleep onset (min)	97.7 ± 38.2	62.3 ± 29.6	2.1	15	0.025
Number of body movements	117.3 ± 45.9	70.9 ± 44.7	2.1	15	0.025

TABLE II

Sleep latency summary, study 1.

Group		Nap No.					
		1 (09.30–10.00)	2 (11.30–12.00)	3 (13.30–14.00)	4 (15.30–16.00)	5 (17.30–18.00)	6 (19.30–20.00)
Narcoleptics	Day 1	3.4	2.2	1.4	1.3	2.4	3.5
N = 8	Day 2	2.3	3.2	1.6	2.3	1.9	3.3
Nap mean		2.8	2.7	1.5	1.8	2.2	3.4
S.D.		2.0	2.6	1.3	2.1	1.9	4.4
Controls	Day 1	13.8	12.3	9.4	8.3	11.2	12.2
N = 9	Day 2	15.2	12.8	10.2	6.5	11.1	17.7
Nap mean		14.5	12.5	9.8	7.4	11.2	14.9
S.D.		5.3	5.9	6.6	5.5	6.6	5.1

TABLE III

Sleep latency summary, study 2

Group	Nap No.				
	1 **10.00**	**2** **12.00**	**3** **14.00**	**4** **16.00**	**5** **18.00**
Narcoleptics (N = 19)					
Nap Mean	3.1	2.9	2.0	2.6	3.2
S.D.	2.4	4.7	2.1	2.8	4.3
Controls(N = 5)					
Nap Mean	11.4	11.7	7.0	7.3	12.1
S.D.	5.9	8.8	2.9	4.5	6.0