Increased REM Density in Narcolepsy-Cataplexy and the Polysymptomatic Form of Idiopathic Hypersomnia

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ABSTRACT: The present work is focused on REM sleep density in patients with primary hypersomnia in comparison with non-hypersomnia subjects. 28 unmedicated patients with narcolepsy-cataplexy (NC) and 10 unmedicated patients suffering from the polysymptomatic form of idiopathic hypersomnia (IH) and their age- and sex-matched controls were included in the study. The clinical diagnosis was confirmed by MSLT and nocturnal PSG, HLA typing was performed in a respective group of narcoleptic patients. Polygraphical recordings were visually scored with particular regard to the two most characteristic phasic features of REM sleep: the number of rapid eye movements (REMs) and chin muscle twitches (Tws) per minute. These events were evaluated according to recognized criteria; a closer look was taken at both their frequency and their distribution across all the nocturnal REM periods (REMPs). The following main differences between hypersomniac patients (of both groups examined) and healthy controls were found in terms of phasic activity: (I) REM density (expressed in REMs/min and Tws/min in each REM period) was significantly increased in the hypersomniac patients in comparison with the controls. (p>0.05), (II) The intra-night phasic activity distribution was found rising more conspicuously in the hypersomniacs than in the controls.

Key words: Narcolepsy; idiopathic hypersomnia; REM sleep; REM density

INTRODUCTION

APART FROM THE TIMING, LATENCY, AND DURATION OF EACH EPISODE, REM SLEEP IS DEFINED BY PHASIC PARAMETERS, conventionally referred to as REM density, including the number of episodic rapid eye movements (REMs), bursts of EMG activity (Tws=muscle twitches) as well as saw-tooth waves. Aserinsky suggested that REM density increased across successive REM episodes, approaches its maximum value after 7.5—10 hours of sleep in normal subjects. According to him, REM density might be considered to be an index of sleep satiety. The correlation between sleep duration and REM density in the case of sleep extended beyond its normal length was confirmed by Feinberg et al. Later, the same authors found REM density reduced during recovery sleep after total sleep deprivation, hypothesising an inverse relationship between REM density and sleep depth. Antonioli’s observations showed that increased need for REM sleep, produced by selective REM sleep deprivation, took the form of decreased REM latency, increased REM proportion, and reduced REM density during the recovery night. However, Lucidi found a linear relationship between the amount of sleep curtailment and the decrease in REM density in the ensuing recovery night; he suggested that REM density could be seen as a measure of sleep need. Considering the hypothetical relationship between sleep need/depth and REM density, we focused our attention on two REM sleep phasic components—REMs and Tws—as measurable objective indicators independent of the patient’s self report or the clinician’s observations, in two groups of hypersomniacs: 1) in narcoleptic patients (NC) and 2) patients suffering from the polysymptomatic form of idiopathic hypersomnia (IH).

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METHODS

Subjects

Two groups of hypersomniac patients were included in the study (Table 1). One consisted of 28 patients with narcolepsy—cataplexy (7 male, 21 female, mean age 34±11.2). Their average age at the onset of narcoleptic symptoms was 22.6±10.1 years. They were selected on the basis of a clinical history of sleep attacks and cataplexy, while the presence of further symptoms was not unconditional. Sleep paralysis was present in 12 cases (43%), hypnagogic hallucinations in 15 subjects (54%). In 25 patients (89%) the disease commenced with sleep attacks, while in three (11%) sleep attacks and cataplexy began at the same time. The other group consisted of 10 patients suffering from the polysymptomatic form of idiopathic hypersomnia (three men, seven women, mean age 37.5±8.3 years). The age at the onset of the disease varied between 5 and 23 years, with the exception of one woman, whose illness began at the age of 39 years (mean:...
The required length of nocturnal sleep ranged between 10 and 18 hours, signs of sleep drunkenness on morning awakening (lasting 20—120 min) were present in all subjects. EDS was also present in each subject, in three patients sleepiness could be overpowered, five patients usually spent one to two hours sleeping, two of them needed more than two hours of sleep per day. Familial predisposition to the illness was found in five subjects (50%). All the patients had been referred to the Sleep Disorders Center of the Department of Neurology, 1st Medical Faculty, Charles University, Prague in the 1996—2000 period. All of them: (1) had completed a detailed sleep questionnaire (NC patients—Stanford Sleep Inventory, IH patients - Berner Schlaf-Fragebogen); (2) had undergone diagnostic PSG and a subsequent MSLT (with a mean sleep latency of 10 minutes); (3) were given no sedating or REM-suppressing drugs at the time of polygraphic evaluation; such medication was discontinued at least two weeks prior to the recording; (4) had no medical or psychiatric condition that could possibly account for sleepiness, while IH patients underwent psychological examinations (shortened version of the Minnesota Multiphasic Personality and Freiburger Persönlichkeitsinventar); and (5) were diagnosed to have only one sleep disorder. The control group consisted, in both cases, of age- and sex-matched healthy volunteers (seven male, 21 female, mean age 29±7.4 years) with no complaint of either insomnia or EDS, receiving no sedatives or stimulants and reporting subjectively normal day and night sleep and wake habits.

### Polygraphic Recordings

After one adaptation night spent on the ward under standard conditions, all subjects were instructed to avoid napping after 17:00, they were under intermittent staff supervision until 21:00, when recording preparations and continuous supervision started.

A Schwarzer polygraph was used for the recording. All polygraphic recorders were made using the standard placement of electrodes for EEG (F4-C4, C4-F8, C4-P4, F3-C3, C3-F7, C3-P3, C3-A2), sub-mental EMG and horizontal EEG, ECG, as well as airflow at the nose and mouth (thermistors), bilateral anterior tibialis EMG, and infrared video camera. The recording protocol was the same for patients and for controls. The sleep stages were visually scored according to the criteria of Rechtschaffen and Kales9 by scorers blinded with respect to the diagnosis of the patient. The scoring of phasic events in the study was done by a single scorer.

For REM, the definition from Hishikawa et al.10 was adopted: a REM was scored for any deflection in the horizontal EOG tracing with an amplitude larger than 20 µV and an angle against the horizontal larger than 69 deg., at a paper speed of 1 cm/sec and a gain of 7 mm/50 µV (low cut 0.3 sec, high cut 30 Hz).

An m. mentalis twitch10 was scored for each phasic increase in the chin EMG provided it was shorter than one second and reached three times the level of the surrounding muscle tone, but at least 20 µV. Twitches found within 3 sec before or after a substantial change in muscle tone as well as movement arousals were discounted.

REM density was defined as the average number of horizontal REMs or Tws per minute of REM sleep period (REMP).

### Statistics

Standard statistical software Statgraphics was used for data analysis. Using data from the first four REMPs with no absent observations, successive REM periods were compared by means of multiple range analysis as well as by means of the Tukey method and Friedman analysis wherever appropriate. Data from the fifth REMP—when available—were evaluated similarly. Comparisons between the groups in each period of REM sleep were performed using the one-way analysis of variance (ANOVA) and, subsequently, the Tukey analysis. The Kruskal-Wallis analysis was applied for control purposes.

### RESULTS

The sleep macrostructure of both hypsomniac groups is described in Table 2. The sleep parameters are compared with the control group.

### Narcolepsy-Cataplexy (NC)

The NC patients and the controls had approximately the same total sleep time (TST) and the percentage of paradoxical sleep was not different either, although the patients' REM periods were more often interrupted by sequences of NREM sleep and/or waking stage. The results show significantly shorter REM latencies in NC patients (17±8 vs. 77±29, p<0.01). Statistical analysis points to a significant difference between NC patients and controls as regards the mean REM and Tws count per minute: as for REMs, the mean was 9.73 ranging from 6.12 to 14.17 vs. 4.88 ranging from 2.41 to 7.86 (p<0.05) (Figure 1); as for Tws, the mean value was 1.02 ranging from 0.56 to 1.11 vs. 0.46 ranging from 0.16 to 0.84 (p<0.05) (Figure 2). The patients exhibited a greater increase in REM density than the nonhypsomniac subjects.

### Table 1—Clinical data in narcolepsy-cataplexy (NC) and in polysymptomatic form of idiopathic hypersomnia (IH) in comparison with a control group

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>IH (n=10)</th>
<th>NC (n=28)</th>
<th>Controls (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female: Male</td>
<td>7:3</td>
<td>21:7</td>
<td>21:7</td>
</tr>
<tr>
<td>Age at recording (years, mean±SD)</td>
<td>37.5 ± 8.3</td>
<td>34 ± 11.2</td>
<td>29 ± 7.4</td>
</tr>
<tr>
<td>Age at onset of the disease (years, mean±SD)</td>
<td>16.4 ± 7.2</td>
<td>22.6 ± 10.1</td>
<td>-</td>
</tr>
<tr>
<td>Length of night sleep</td>
<td>10-18 hrs</td>
<td>7-9 hrs</td>
<td>6-9 hrs</td>
</tr>
<tr>
<td>First symptom - sleep attacks</td>
<td>10 (100%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sleep paralysis</td>
<td>-</td>
<td>12 (43%)</td>
<td>-</td>
</tr>
<tr>
<td>Hypnagogic hallucinations</td>
<td>-</td>
<td>15 (54%)</td>
<td>-</td>
</tr>
<tr>
<td>Sleep drunkeness</td>
<td>10 (100%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Familial occurrence</td>
<td>5 (50%)</td>
<td>3 (11%)</td>
<td>-</td>
</tr>
</tbody>
</table>

16.4±7.2. The required length of nocturnal sleep ranged between 10 and 18 hours, signs of sleep drunkenness on morning awakening (lasting 20—120 min) were present in all subjects. EDS was also present in each subject, in three patients sleepiness could be overpowered, five patients usually spent one to two hours sleeping, two of them needed more than two hours of sleep per day. Familial predisposition to the illness was found in five subjects (50%). All the patients had been referred to the Sleep Disorders Center of the Department of Neurology, 1st Medical Faculty, Charles University, Prague in the 1996—2000 period. All of them: (1) had completed a detailed sleep questionnaire (NC patients—Stanford Sleep Inventory, IH patients - Berner Schlaf-Fragebogen); (2) had undergone diagnostic PSG and a subsequent MSLT (with a mean sleep latency of 10 minutes); (3) were given no sedating or REM-suppressing drugs at the time of polygraphic evaluation; such medication was discontinued at least two weeks prior to the recording; (4) had no medical or psychiatric condition that could possibly account for sleepiness, while IH patients underwent psychological examinations (shortened version of the Minnesota Multiphasic Personality and Freiburger Persönlichkeitsinventar); and (5) were diagnosed to have only one sleep disorder. The control group consisted, in both cases, of age- and sex-matched healthy volunteers (seven male, 21 female, mean age 29±7.4 years) with no complaint of either insomnia or EDS, receiving no sedatives or stimulants and reporting subjectively normal day and night sleep and wake habits.
Idiopathic Hypersomnia (IH)

As for IH patients, the total nocturnal sleep time was significantly longer than in the controls (563±75 versus 423±52, p<0.05). Also the proportion of REM sleep was greater in the group of hypersomniacs, though the difference was non-significant. Fig.1 illustrates the patients' REM density expressed as the mean REMs count/min, Figure 2 as the number of Tws/min. The results showed twice as many REMs and Tws per minute in each REM period as in the controls: as for REMs, the mean value was 12.75 (10.0-16.4) against 4.88 (2.41-7.86) (p<0.05); as for Tws, the mean was 1.13 (ranging from 0.6 to 1.78) as distinct from 0.46 (0.16-0.84) (p<0.05). The density of both phasic events increased during the night in both the IH patients and the controls, except that in the former group the increase was statistically higher, especially in the second half of the sleeptime period (p<0.05). The greatest difference in the mean REM count between successive REMPs was found in the second and third REM periods. No significant difference was found between narcoleptic patients and IH patients as regards these two phasic parameters.

**DISCUSSION**

Our results show the following main phasic activity differences between hypersomniacs of both groups (i.e., narcoleptics, and idiopathic hypersomniacs) and healthy controls: (1) REM

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**Table 2**—Polygraphic and genetic findings in narcolepsy-cataplexy (NC) and in polysymptomatic form of idiopathic hypersomnia (IH) in comparison with a control group. *P* = level of significance for differences between patients’ and controls’ groups (p<0.05 vs. TST in IH and control group, p<0.01 vs. REM latency in NC and control group).

<table>
<thead>
<tr>
<th>Polysomnographic parameter</th>
<th>IH (n=10)</th>
<th>NC (n=28)</th>
<th>Controls (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST (min)</td>
<td>563±75*</td>
<td>426±47.3</td>
<td>423±52</td>
</tr>
<tr>
<td>Sleep efficiency (NREM1 (%TST))</td>
<td>94.3±4%</td>
<td>86.5±7%</td>
<td>92.4±5%</td>
</tr>
<tr>
<td>NREM2 (%TST)</td>
<td>4.7±2</td>
<td>6.2±3</td>
<td>3.4±3</td>
</tr>
<tr>
<td>SWS (%TST)</td>
<td>53.6±8</td>
<td>43.4±5</td>
<td>48.6±7</td>
</tr>
<tr>
<td>REM (%TST)</td>
<td>13±6</td>
<td>10±5</td>
<td>16±4</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>22±5</td>
<td>14±6</td>
<td>17±5</td>
</tr>
<tr>
<td>REM latency (min)</td>
<td>28±12</td>
<td>11.9±5</td>
<td>29±16</td>
</tr>
<tr>
<td>Mean sleep latency on MSLT (min)</td>
<td>62±23</td>
<td>17±8**</td>
<td>77±29</td>
</tr>
<tr>
<td>#SOREMPs on MSLT</td>
<td>6.2±3</td>
<td>2±1.2</td>
<td>not tested</td>
</tr>
<tr>
<td>HLA findings DQB1*0602</td>
<td>-</td>
<td>2-5</td>
<td>not tested</td>
</tr>
<tr>
<td>(nr of positives/total tested)</td>
<td>not tested</td>
<td>14/15</td>
<td>not tested</td>
</tr>
</tbody>
</table>

**Figure 1**—Density of REM sleep (mean REMs count/min) in narcolepsy-cataplexy (NC) and in polysymptomatic idiopathic hypersomnia (IH) over successive REM periods (REMPs) compared with controls. NC: as for REMPs 1-4 n=28, REMP 5 n=19. IH: REMPs 1-4 n=10, REMP 5 n=8. Controls: REMPs 1-4 n=28, REMP 5 n=12.
density (number of REMs/min and Tws/min) is increased in both
groups of hypersomniac patients in comparison with the control
group; however, there is no significant difference between the
two particular groups of patients. (2) Each examined group
shows an increase in the number of nocturnal REMs and Tws per
minute, albeit a considerably greater one in the hypersomniacs
than in the controls (Figure 1,2). The mean REM values and Tws
count remained very much the same in both groups of hyper-
somniac patients. To the best of our knowledge, increased REM
density in the polysymptomatic form of idiopathic hypersomnia
has not as yet been described in literature.

The data suggest an increased REM sleep density in primary
hypersonnias. With respect to the REM density in narcolepsy-
cataplexy, our results comply well with those reported in litera-
ture - most authors found REM density to be greater in
polysymptomatic narcolepsy cases than in normal healthy sub-
jects,11,12,13 despite the fact that the difference was not actually
significant in all of the studies.10 also a significant nocturnal
increase has also been found in healthy subjects,10,11 though some
authors describe REM density to remain at a plateau14 or even
decreased.15 As regards the intra-night distribution of phasic
activity in healthy adults, an increase in REM density during suc-
cessive nocturnal REM periods has also been recorded.16 No sig-
nificant correlation between REM density and other REM sleep
parameters such as REM time has been found so far.17 This inde-
pendence of REM density was observed also after selective para-
doxical sleep deprivation,7 or in response to cholinergic drugs.18

Hence, the frequency of oculomotor activity during paradoxi-
cal sleep does not seem to be regulated by simple homeostatic
processes. The factor that may account for the pathophysiology
of primary hypersonnias is the central arousal level. Though the
etiology of IH is unknown, a disorder of the arousal mechanisms
clinically manifested as sleep drunkenness on awakening—
should be present.

In narcolepsy, the pathologically facilitated REM/waking
transition may be one such pathophysiological mechanism.
That much seems to follow (e.g., from the higher proportion
of wakefulness seen in the form of “microawakenings” in the
REM periods of narcoleptics).11,19 The results of other studies
indicating that REM sleep may function as “agating period” for
wakefulness appear to corroborate this assumption (are consist-
tent with this). Spontaneous arousals from sleep are reportedly
more likely to occur in REM sleep than in other sleep stages.20
Subjects who were asked to wake up at a specific time, without
the aid of an external alarm, tended to wake up mainly from para-
doxical sleep.21 According to some studies, NREM sleep attacks
in narcolepsy represent a sudden transition from wakefulness to
NREM sleep while cataplexy appears to represent a sudden par-
tial manifestation of REM sleep during wakefulness. Sleep paral-
ysis would then be an incomplete form of awakening with per-
sistent REM sleep atonia.22 In MSLT the lapse into REM sleep
directly from wakefulness during daytime is also a frequently
seen phenomenon.

To go by the clinical picture, there is a measure of overlapping
between the two primary hypersonnias under study. Some
patients with narcoleptic symptoms do not have any periods of
REM at sleep onset,2 some narcoleptics may not have cataplexy
or may develop it years or decades after the onset of excessive
daytime sleepiness.23,24

The diagnostic criteria of primary hypersonnia could then

Figure 2—Density of REM sleep (mean Tws count/min) in narcolepsy-cataplexy (NC) and in polysymptomatic idiopathic hypersonnia (IH) over successive REMPs
compared with controls. NC: REMPs 1-4 n=28, REMP 5 n=19. IH: REMP s 1-4 n=10, REMP 5 n=8. Controls: REMPs 1-4 n=28, REMP 5 n=10.
hardly be extended by a closer scrutiny of REM density because no significant differences were found between the two groups of patients.

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