

REM sleep without atonia in narcolepsy

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Abstract

OBJECTIVE: While there are a number of observations/quantifications indicating a greater proportion of REM sleep without atonia (RWA) in narcolepsy, the intra-night distribution of this parameter has not been evaluated.

MATERIALS AND METHODS: Thirty-four patients (15 men and 19 women; mean age 44.9 ± 18.9) with narcolepsy-cataplexy were included in this retrospective study. The clinical diagnosis was confirmed by MSLT, video-polysomnography and HLA typing. Polysomnographic recordings were scored with particular regard to REM sleep without atonia (RWA) across all the nocturnal REM periods. RWA scoring was done according to a standard method.

RESULTS: The analysis showed a significant increase in the proportion of REM sleep without atonia during successive nocturnal REM periods in narcoleptic patients ($p < 0.01$). No correlation was found between the percentage of RWA and the severity or duration of the disease, no age effect was documented.

CONCLUSION: The study demonstrates for the first time an increasing amount of RWA during the night suggesting enhanced nocturnal REM sleep motor disturbance.

INTRODUCTION

Narcolepsy is a sleep disorder characterized by daytime attacks of sleep and manifestations of dissociated rapid eye movement (REM) sleep (cataplexy, hypnagogic hallucinations, sleep paralysis) (AASM Manual, 2005). Typical of nocturnal sleep in narcoleptics is instability with frequent stage shifts or arousals and increased motor activity such as periodic leg movements in sleep (PLMS), persistence of electromyographic tone throughout REM sleep (REM sleep without atonia) and/or excessive aperiodic EMG twitching during REM sleep (Schenck and Mahowald, 1992; Montplaisir *et al.* 2000; Dauvilliers *et al.* 2007a) as well as higher REM density (Vankova *et al.* 2001; Dauvilliers *et al.* 2007b).

Abbreviations :

REM sleep - Rapid eye movement sleep
RBD - REM sleep behavior disorder
RWA - REM sleep without atonia
EMG - electromyography
PLMS - periodic leg movements in sleep

In the present study we concentrated on REM sleep without atonia (RWA). This condition is known to be associated with motor behavioral manifestations accompanying violent dreaming, a prominent feature of REM sleep behavior disorder (RBD) (AASM Manual, 2005). Indeed, RBD was recognized as a common associated symptom of narcolepsy (Nightingale *et al.* 2005). The aim of the present study was to assess the all-night distribution of RWA in narcoleptic patients without muscle atonia in REM sleep.

MATERIAL AND METHODS

Subjects

We evaluated in retrospect 95 polysomnography recordings of patients admitted in our Sleep Disorder Centre between 1998 and 2008 (77 patients with narcolepsy –cataplexy and 18 patients with isolated narcolepsy). Signs of RWA were found in 34 patients suffering from narcolepsy with cataplexy (15 men and 19 women; mean age 44.9 ± 18.9 years) and in 3 patients with isolated narcolepsy. Statistical analysis was made in 34 patients with narcolepsy-cataplexy in order to obtain the most uniform population. These 34 patients affected by narcolepsy with cataplexy were selected by the presence of REM sleep without atonia in more than 20% of the total REM sleep duration ascertained by polysomnography (PSG) (Lapierre and Montplaisir, 1992; Gagnon *et al.* 2002). Hypnagogic hallucinations (HH) were present in 22 cases (64.7%) and sleep paralysis (SP) in 14 of these patients (41.2%). Seven of them had clinically manifested RBD (4 men and 3 women; mean age 46 ± 3.6 , HH in 5 cases, SP in 3 cases). All of them, except one subject, were HLA DQB1*0602 positive, one patient refused investigation.

All patients had undergone diagnostic polysomnography and subsequent multiple sleep latency test (MSLT). They were given no medication of potential effect on REM sleep atonia; in 5 patients such medication was discontinued two weeks prior to the recording.

All subjects gave written informed consent to participate to the study.

Polysomnographic Recordings

Sleep stages (except REM) were generally scored with the Rechtschaffen and Kales method (Rechtschaffen and Kales, 1968). As EMG atonia is a mandatory criterion for REM sleep rating, we could not use it for REM sleep scoring in our patients. REM sleep was scored using EEG and electrooculography only (Lapierre and Montplaisir, 1992). The occurrence of the first REM epoch was used for determining the onset of a REM sleep period. Its end was identified by the occurrence of an EEG feature indicative of another stage (K complex, sleep spindles, arousal) or by the absence of rapid eye movements during 3 consecutive minutes. REM sleep muscle atonia was rated as follows: each 30-second epoch during REM sleep was scored as tonic

or atonic depending on whether tonic chin EMG activity was present for $\geq 50\%$ or $< 50\%$ of the epoch (Lapierre and Montplaisir, 1992). The baseline EMG signal for atonia as determined for each subject was found to be between 3 and $7 \mu\text{V}$. Any EMG signal that was twice the amplitude measured during atonia and $>10 \mu\text{V}$ was considered to be tonic. REM sleep without atonia was diagnosed if there was tonic REM submental EMG activity for more than 20% of the total REM sleep duration (total number of 30 second epochs during nocturnal REM sleep) (Gagnon *et al.* 2002).

Statistical analysis

All data are presented as mean \pm SD. The paired Wilcoxon test was used for comparisons of the mean percentage of RWA relative to the total duration of REM sleep. The Rank test was applied because of the non-Gaussian distribution of the percentage. Pearson's correlation coefficient was calculated for linear trend testing.

RESULTS

The sleep macrostructure changes found in our narcoleptic patients were as expected. The subjects showed shortened sleep latency and reduced sleep efficiency, increased wakefulness after sleep onset (WASO) and a greater PSG proportion of stage 1. Seventeen of them were diagnosed with PLMS, 8 with obstructive sleep apnea. MSLT showed shortened mean sleep latency and at least two sleep onset REM periods in all patients (Table 1).

Generally, this study confirms a high prevalence of RWA in narcolepsy (36.8%). Hypnagogic hallucinations were present in 64.7% and sleep paralysis in 41.2% patients of our study group ($n=95$). Of interest is our finding that RWA occurs in both men and women equally ($n=34$, 15 men and 19 women) in contrast to „idiopathic“ RBD cases. What came as an absolutely new finding in our study was a significant RWA increase during successive nocturnal REM periods ($p<0.01$). The average duration of each of the REM periods showed statistically significant lengthening in the course of sleep, which is why RWA time is given in percent of the total duration of REM sleep. The average duration of RWA increased significantly throughout the night (linear trend $r=0.943$, $p<0.05$) (Figure 1). No significant difference was noted between REM periods 1 vs. 2 and 3 vs. 4. REM periods 3, 4 and 5 differed significantly from REM periods 1 and 2 ($p<0.01$). Similarly, a significant increase in %RWA was found in REM 5 against REM 3 and 4. As for comparisons between men and women, the RWA analysis showed the same results ($p<0.01$). There was no evidence of any age affect on the occurrence or distribution of RWA all through the night. A similar RWA increase during the night was found also in the group of 7 patients with clinically manifest RBD ($p<0.01$). No correlation was

Tab. 1. Polysomnographic and MSLT characteristics of patients with narcolepsy (n=34)

Men / women	15 / 19
Age at PSG, years	44.9 ± 18.9
Nocturnal sleep parameters	
Total sleep time, min	396.0 ± 53.9
Sleep latency, min	5.3 ± 4.6
Sleep efficiency	82.5 ± 7.5
(% of total sleep time / sleep in bed)	
% Stage 1	14.3 ± 8.6
% Stage 2	46.9 ± 9.7
% SWS	8.6 ± 4.6
% REM	21.8 ± 11.2
Awakenings (number)	44 ± 15
Daytime sleepiness	
Sleep latency at MSLT, min	2.8 ± 1.9
SOREMPs at MSLT, min	3.4 ± 1.3
Epworth Sleepiness Scale (total score)	17.1 ± 4.3

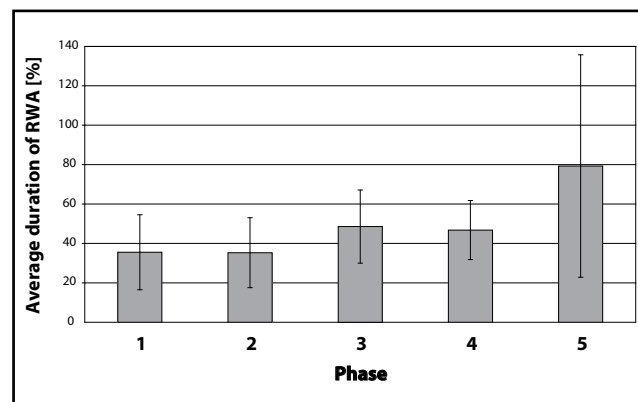
found between the percentage of RWA and the severity or duration of the disease.

DISCUSSION

This study demonstrated for the first time the nocturnal course of REM sleep without atonia. The loss of muscle atonia in REM sleep significantly increased in our patients from the first to the fourth or fifth REM periods. Previous studies similarly showed increased phasic activity during REM sleep in narcoleptics, including REM sleep density or PLMS (Montplaisir *et al.* 2000; Dauvilliers *et al.* 2007a) with similar intra-night distribution (Vankova *et al.* 2001). This might indicate growing motor disturbance throughout the night. Our data seem to point in the direction of global damage to the motor regulation inhibitory systems in narcolepsy.

Interestingly, almost all of our patients with loss of atonia in REM sleep also suffered from cataplexy (34 patients including all 7 RBD cases), except that 3 patients experienced no episode of cataplexy at all. We can conclude that patients without atonia in REM sleep, are more likely to suffer from cataplexy (loss of muscle tone when awake), where both, RWA and cataplexy, are signs of REM sleep dysregulation caused by decreased hypocretinergic tone.

Another interesting finding of our study was that the patients with RWA represented a different demographic group than those with RBD. The typical RBD patient is an elderly man (Olson *et al.* 2000). However, in this study, we confirmed a previous finding by Nightingale *et al.* namely that women are as likely to have RWA as

**Fig. 1.** The average duration of REM sleep without atonia.

men, the mean age being 44 years (Nightingale *et al.* 2005).

The close association between RBD and narcolepsy has been described previously, the frequency of RBD in narcolepsy has been estimated at between 7 and 36% (Schenck and Mahowald, 1992; Dauvilliers *et al.* 2007b; Nightingale *et al.* 2005). RBD may even be one of the first symptoms of childhood narcolepsy (Nevsimalova *et al.* 2007). Very few previous studies demonstrated a greater proportion of REM sleep without atonia (RWA) in narcolepsy (Schenck and Mahowald, 1992; Dauvilliers *et al.*, 2007b). The relation between RBD and RWA remains unclear. It is still not known whether or not an increased chin EMG tone during REM sleep, in the absence of other RBD symptoms, might represent a subclinical form of RBD with the risk of developing such symptoms in the future. Animal studies suggest that REM sleep without atonia and motor manifestations of RBD are two distinct phenomena with different anatomic substrates. Bilateral pontine tegmental lesions in cats release a state of REM sleep without atonia with a minimal increase in motor manifestations. Additional rostro-ventral damage to the midbrain is necessary to trigger obvious motor manifestations apart from a muscle tone increase (Hendricks *et al.*, 1982; Morrison *et al.* 1995).

In conclusion, there are some basic mechanism involved in both narcolepsy and RBD resulting in RWA. RBD is caused by impaired dopaminergic transmission, and dopaminergic abnormalities are critical downstream mediators of hypocretin deficiency. Dysfunctions in the hypocretin/dopaminergic system are likely to be the most important mechanisms involved in the pathophysiology of narcolepsy (Dauvilliers *et al.* 2003; Boeve *et al.* 2007).

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