

# Antidepressants substantially affect basic REM sleep characteristics in narcolepsy-cataplexy patients

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## Abstract

**OBJECTIVES:** Antidepressants substantially affect REM sleep characteristics and trigger manifestations of REM sleep behavior disorder (RBD) in the general, non-narcoleptic, population. Antidepressants are also frequently administered in an attempt to suppress cataplexy. We investigated the role of antidepressants in the development of RBD in narcolepsy with cataplexy (NC) patients.

**PATIENTS/METHODS:** Seventy-five patients diagnosed with NC were assessed by a structured interview (focused on RBD manifestations and the use of antidepressants) and night video-polysomnography followed by the multiple sleep latency test.

**RESULTS:** Of all 75 NC patients (36 male, 39 female; mean age  $46.1 \pm 18.5$  years), 34 cases had a history of antidepressant use (45.3%; 18 male, 16 female). In this antidepressant-positive group, 13 patients suffered from RBD (38.2%). Among antidepressant-naïve patients, only 5 subjects (12.2%) were diagnosed with RBD. Polysomnographic data showed significantly increased REM latency ( $p < 0.01$ ) and reduced percentage of REM sleep ( $p < 0.01$ ) in the antidepressant-positive group, as well as more periodic limb movements during sleep ( $p = 0.01$ ).

**CONCLUSIONS:** NC patients with a history of antidepressant use showed a three-fold higher occurrence of RBD in comparison to antidepressant-naïve patients.

## INTRODUCTION

Narcolepsy-cataplexy (NC) is a chronic neurological disorder characterized by excessive daytime sleepiness, episodes of cataplexy, sleep paralysis, hypnagogic hallucinations and disturbed nocturnal sleep. The disease is caused by a loss of hypocretin-secreting neurons (Dauvilliers *et al.* 2007). Additionally, between 45–61% of narcolepsy

patients have been reported to suffer from associated rapid eye movement (REM) sleep behavior disorder (RBD; Schenck & Mahowald 1992; Nightingale *et al.* 2005, Mattarozzi *et al.* 2008; Frauscher *et al.* 2013; Luca *et al.* 2013).

RBD is a parasomnia characterized by dream-enacting behavior and impaired motor inhibition during REM sleep (REM sleep without atonia, RWA; AASM 2005). In narcolepsy, RBD is con-

sidered a distinct phenotype with respect to idiopathic RBD, characterized by (1) the absence of gender predominance, (2) elementary rather than complex movements and less violent behavior, and (3) a younger age at the onset of motor events with a strong association to hypocretine deficiency, which is likely another manifestation of REM sleep dyscontrol in narcolepsy (Dauvilliers *et al.* 2013). Furthermore, clinical features of RBD reported in NC questionnaires are recorded less frequently by video-polysomnography than in subjects with idiopathic RBD (Dauvilliers *et al.* 2013).

Several studies have shown that antidepressants can elicit dream-enacting behavior and a loss of normal REM sleep atonia in the general population (Winkelman

& James 2004; Ju 2013; Frauscher *et al.* 2014; McCarter *et al.* 2015). Schenck and Mahowald (1992) first suggested that antidepressants may induce RBD even in narcolepsy, however confirmatory studies are still lacking. As NC is often associated with RBD and many patients are given antidepressants in attempt to treat cataplexy, we elected to investigate the effect of antidepressant therapy on REM sleep characteristics and RBD.

## METHODS

### Subjects

We retrospectively evaluated 75 consecutive adult patients with NC examined at our institution between 2007 and 2015 (36 male, 39 female; mean age 46.1±18.5 years, mean age at disease onset 23.4±11.5 years). Seventy patients were found to be HLA DQB1\*0602 positive, two patients HLA negative, and in 3 patients HLA typing was not available. Hypnagogic hallucinations were present in 35 (46.7%) and sleep paralysis in 28 (37.3%) of these subjects. The mean Epworth sleepiness score (ESS) score was 18.2±3.4. All participants underwent a structured interview focused on RBD manifestations and the use of antidepressants, a systematic medical history and a complete neurological examination. The information was assembled from patient records when available. All patients on antidepressants at the time of the video-polysomnography or with a history of prior exposure were included in the antidepressant-positive group. The study was approved by the local Ethics Committee and all patients provided signed, informed consent to the analysis of video-polysomnographic and clinical data.

### Polysomnographic recordings

All patients underwent in-lab video-polysomnography (22.00–06.00) followed by the 5-nap multiple sleep latency test (MSLT). Sleep including RWA was scored according to the AASM manual for the scoring of sleep and associated events (Iber *et al.* 2007).

## RESULTS

Eighteen of the 75 subjects analyzed suffered from RBD (24%; 12 male, 6 female). Clinical features and polysomnographic data are summarized in Table 1. Thirty-four subjects (45.3%) had a history of antidepressant treatment, including 16 patients treated by antidepressants at the time of examination, while 41 subjects were never exposed to antidepressants. Specific antidepressants used by subjects in the antidepressant-positive group included clomipramine in 14 cases, escitalopram in 8 cases, imipramine in 4 cases, tianeptin in 4 cases, venlafaxine in 3 cases, citalopram in 2 cases and sertraline in only one case (two patients were treated by two antidepressants). Thirteen patients (38.2%) from the antidepressant-positive group suffered from RBD, including 6 of the 16 patients (37.5%) on antidepressants at the time

**Tab. 1.** Comparison of clinical variables and polysomnographic data between narcolepsy with cataplexy patients with a positive history antidepressant use (NC + AD) and narcolepsy with cataplexy patients with no history of antidepressant use (NC without AD).

	NC + AD (mean ± SD)	NC without AD (mean ± SD)	p-value
<b>Clinical features</b>			
Number	34 (45.3%)	41 (54.7%)	
Sex, M/F	18/16	18/23	
Age, years	55.6±18.0	38.2±15.1	p<0.001
Age at NC onset, years	25.1±13.3	22.1±9.8	NS
ESS score	17.8±3.4	18.5±3.3	NS
HH	17/34	19/41	
SP	14/34	15/41	
<b>Polysomnographic data</b>			
TST, min.	358.5±55.2	401.4±57.3	p<0.01
Awakenings, nr	53.0±34.6	35.2±16.7	p<0.01
SOL, min.	9.1±14.9	8.4±10.4	NS
R latency, min.	81.1±92.4	31.9±55.4	p<0.01
SE, %	76.0±12.6	84.9±10.3	p<0.01
S 1, %	14.4±8.8	11.6±9.4	NS
S 2, %	36.6±11.4	38.6±10.3	NS
SWS, %	12.1±7.6	18.6±6.9	p<0.001
R duration, %	15.4±7.3	20.0±5.9	p<0.01
AHI	15.7±24.0	9.4±18.9	NS
PLM index	35.6±34.4	16.9±24.6	p=0.01
MSLT mean latency, min.	2.7±2.3	2.5±1.9	NS
MSLT SOREMP (n)	3.2±1.4	3.6±1.1	NS

AHI (apnea-hypopnea index), PLM (periodic limb movements), ESS (Epworth sleepiness scale), HH (hypnagogic hallucinations), SP (sleep paralysis), TST (total sleep time), SOL (sleep onset latency), R (REM sleep), SE (sleep efficiency), SWS (slow wave sleep), MSLT (multiple sleep latency test), SOREMP (sleep onset REM period), S1 (sleep NREM 1), S2 (sleep NREM 2), NC (narcolepsy with cataplexy), AD (antidepressants), SD (standard deviation), n (number), NS (not significant).

of polysomnography, in the antidepressant-naïve group it was only 12.2% ( $p=0.0085$ , Pearson Chi Square). We found no temporal relationship between the onset of RBD and the onset of narcolepsy.

Polysomnographic data showed significantly impaired general quality of sleep (reduced total sleep time with more awakenings, impaired sleep efficiency and decreased duration of slow wave sleep) in the antidepressant-positive NC group. This group also showed significantly increased REM sleep latency ( $p<0.01$ ) and reduced percentage of REM sleep ( $p<0.01$ ), as well as more periodic limb movements (PLM) during sleep ( $p=0.01$ ). Sleep onset REM periods on video-polysomnography were found in 15 patients in the antidepressant-positive group, irrespective of antidepressant intake status at the time of video-polysomnography and in 29 antidepressant-naïve patients. MSLT data did not show any differences between the antidepressant-positive and antidepressant-naïve groups.

## DISCUSSION

The primary finding of the present study is the three-fold higher occurrence of RBD in NC patients with a history of antidepressant use (namely selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants), regardless of antidepressant status at the time of examination. Our findings suggest that antidepressants suppress REM sleep and induce or aggravate RBD. Thus, antidepressants may considerably contribute to the development of RBD in NC patients. The increase of REM sleep latency and reduction of REM sleep percentage in NC due to antidepressants is similar to general or psychiatric populations (Winkelman & James 2004; Lam *et al.* 2010).

RBD is under-diagnosed in children and adults with NC, although it may cause significant nocturnal sleep dysfunction in these patients. Thus, adequate screening questions should be part of the initial evaluation (manifestations of RBD are not usually spontaneously described by patients as they generally do not result in injury to the patient or their partners, in contrast to idiopathic RBD or RBD associated with parkinsonism). Concurrent assessment of the RWA index (Ferri *et al.* 2008; Bušková *et al.* 2009; Khalil *et al.* 2013) during diagnostic video-polysomnography and subsequently during the course of cataplexy treatment may aid in establishing the diagnosis of RBD in narcolepsy-cataplexy. Recognition of this comorbidity could guide treatment choice, however there is no record of a prospective, double-blind, placebo-controlled trial of any specific drug to treat RBD in NC. Only a few cases of narcoleptic patients with RBD treated, generally successfully, with clonazepam have been published (Billiard *et al.* 2009). An alternative treatment such as melatonin is required when patients with RBD do not respond to or are intolerant of clonazepam, or clonazepam use is

contraindicated due to cognitive problems, sleep apnea syndrome or increased daytime sleepiness (Gagnon *et al.* 2006). Taking into account the beneficial effect of sodium oxybate on disturbed nocturnal sleep in NC, it may be also of interest to treat RBD in these patients (Mayer *et al.* 2010). A detailed history of lifetime exposure to psychotropic medication should also be elicited in the clinical evaluation of RBD. At present, long-term, follow-up studies of RBD in narcoleptic patients taking antidepressants are lacking.

We found a significantly higher PLM index in the antidepressant-positive NC group in comparison to the antidepressant-naïve NC group, which is in agreement with findings in the general population (Yang *et al.* 2005, Haba-Rubio *et al.* 2013). We also confirmed that the temporal relationship between the onset of RBD and the onset of narcolepsy is broadly variable. RBD may be an early manifestation of childhood narcolepsy-cataplexy (Nevšimalová *et al.* 2007), however it may appear 10 years after the diagnosis (Billiard 2009). Additionally, the percentage of women affected by RBD in NC is higher than in the general population (Ju 2013). Furthermore, of the 75 NC patients included in the present study, only one case (female aged 86 years) developed Parkinson disease and RBD 31 years after narcolepsy onset (Fialová *et al.* 2015). Our finding of a high number of NC patients with many years RBD duration (in the presence of only one patient with Parkinson disease) suggests that the risk of synucleinopathy development may not be as high in NC similarly to other authors (Christine *et al.* 2012; Mayer *et al.* 2013) as in idiopathic RBD cases (Gagnon *et al.* 2002; Postuma *et al.* 2013).

There are some limitations to the present study, mainly its retrospective character, which does not provide accurate information regarding dosage and the exact duration of medication use. A further limitation is the small number of NC patients on particular antidepressants. Subjects with the history of antidepressant intake were older. Finally, we cannot exclude the introduction of bias from grouping according to antidepressant intake, as one may suggest that more severely affected subjects are treated to a greater extent.

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