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Original Article

Effects of long-term use of clonazepam on nonrapid eye movement sleep patterns in rapid eye movement sleep behavior disorder

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ABSTRACT

Objective: We aim to analyze in detail the characteristics of nonrapid eye movement (NREM) sleep in drug-free patients with idiopathic rapid eye movement sleep behavior disorder (iRBD). We compare drug-free iRBD patients to both normal controls and drug-free patients with narcolepsy/RBD and evaluate the changes following the long-term use of bedtime clonazepam.
Participants and methods: Forty-six participants were recruited: 15 with iRBD (13 men, 2 women; mean age, 65.8 ± 4.39 years), 13 with narcolepsy/RBD (10 men, 3 women; mean age, 63.0 ± 6.73 years), and 18 normal controls (10 men, 8 women; mean age 69.4 ± 7.72 years). Sleep was video polysomnographically recorded and the RBD severity scale (RBDSS) was obtained. Chin electromyography (EMG) amplitude was quantitatively assessed and the atonia index was computed. Additionally, NREM sleep instability was evaluated using an automatic quantitative analysis. Participants with iRBD were re-evaluated after 2.75 ± 1.62 years of regular therapy with 0.5 to 1-mg clonazepam at bedtime.
Results: Slow transient electroencephalography (EEG) events were increased in iRBD and decreased in narcolepsy/RBD, while fast transient events decreased in iRBD and increased in narcolepsy/RBD. During rapid eye movement (REM) sleep the atonia index was reduced in both iRBD and narcolepsy/RBD groups and during NREM sleep atonia index was increased in iRBD participants, remaining low in narcolepsy/RBD participants. After long-term therapy with clonazepam, wakefulness after sleep onset was decreased together with an increase in both slow-wave sleep (SWS) and sleep stage 2, in which the latter reached statistical significance; sleep stages 1 and 2 instability significantly decreased and the duration of EEG transients also slightly but significantly decreased. Finally, chin tone was not modified by clonazepam.
Conclusions: Our study confirms that clonazepam modifies some aspects of NREM sleep in iRBD participants with a decrease in its instability. Moreover, we also show that a complex modification of sleep chin atonia exists in these participants, which also involves NREM sleep; for iRBD more complex neuropathologic models encompassing REM sleep and NREM sleep mechanisms are needed.

1. Introduction

Bedtime clonazepam has been the longstanding first-line therapy for rapid eye movement sleep behavior disorder (RBD), due to its effectiveness in controlling the clinical hallmarks of RBD such as abnormal dream-enacting behaviors and disturbed dream content. The clinical benefits of clonazepam in RBD have been confirmed by several large case series that have reported a response rate to clonazepam therapy of approximately 90% [1], and its use is relatively safe, without apparent dosage tolerance despite years of nightly therapy [2]. However, no double-blind, placebo-controlled, randomized trials for the treatment of RBD with clonazepam are available [3,4]. Additionally, it is difficult to devise a study in an ethically feasible manner, given the risk for recurrent injuries usually associated with RBD (eg, major morbidity, potential lethality) [5].

To contribute to a better knowledge of the possible mechanisms by which clonazepam exerts its beneficial effects on RBD, we reported the results of the analysis of the modifications induced by this substance on sleep structure and motor activity during sleep

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in drug-free idiopathic RBD (iRBD) participants and in participants under long-term therapy [6]. Unlike a previous small short-term study in which clonazepam appeared to suppress the excessive phasic motor-behavioral activity [7], we were unable to identify any modification involving rapid eye movement (REM) sleep. However, we found significant changes in nonrapid eye movement (NREM) sleep parameters (moderately increased total sleep time [TST], sleep efficiency, NREM sleep stage 2, and slow-wave sleep [SWS]). We found decreased wakefulness after sleep onset and NREM sleep stage 1 sleep [6]. This result was not completely surprising, as well-known effects of benzodiazepines on sleep [8,9] and the different NREM sleep changes also have been previously reported in RBD [10] and in another REM sleep–related disorder such as narcolepsy [11,12].

For these reasons, we decided to analyze the characteristics of NREM sleep in drug-free patients with iRBD, in comparison to both normal controls and patients with narcolepsy/RBD. We also decided to evaluate the changes following the long-term use of bedtime clonazepam in iRBD patients. For these purposes, we did not limit our evaluation to the classical sleep stages but extended the analysis to NREM sleep instability [13,14] and to the chin tone during REM and NREM sleep [15–17].

2. Participants and methods

2.1. Participants

Patients with iRBD attending the Sleep Disorders Center of the San Raffaele hospital, Milan, Italy, were retrospectively and consecutively recruited for our study. The diagnosis of iRBD was based on the International Classification of Sleep Disorders, 2nd Edition (ICSD-2) criteria [18] for RBD, including presence of REM sleep without atonia; sleep-related injurious-disruptive behaviors by history; or abnormal sleep behaviors documented during video-polysomnographic (vPSG) monitoring, absence of electroencephalographic (EEG)* epileptiform activity during REM sleep, and sleep disturbance not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance-use disorder. Secondary forms of RBD were excluded on the basis of historical data, neurologic examination, and encephalic magnetic resonance imaging findings. All iRBD patients with at least one subtentorial vascular lesion or at least two vascular supratentorial lesions greater than 0.5 cm were excluded. A careful history was collected from all patients to evaluate the age at onset of their symptoms, and patients who underwent at least one vPSG when they had never been treated before with clonazepam and another vPSG after a period of at least one year of regular treatment with clonazepam (0.5–1 mg at bedtime) were identified and recruited for our study.

Additionally, patients with narcolepsy/cataplexy and RBD were retrospectively and consecutively recruited for our study. A diagnosis of narcolepsy with cataplexy was based on the ICSD-2 criteria [18]. All patients had at least two sleep onset REM sleep episodes on the multiple sleep latency test, cataplexy, and excessive daytime sleepiness, reflected by a mean sleep latency at the multiple sleep latency test of 8 minutes or less, and all patients carried the HLA DQB1*0602 antigen. A diagnosis of RBD also was based on the ICSD-2 criteria [18], as reported above. All patients had not used drugs for at least three weeks at the time of the vPSG recording.

None of the controls recruited had any physical, neurological, or psychiatric disorders, or history of sleep concerns. None of these subjects were taking medication at the time of recording. Exclusion criteria included a sleep disorder diagnosis (ie, sleep apnea), a major mental illness, notable history of cognitive difficulties, prior (within one year) or current use of a neuroleptic agent or selective serotonin reuptake inhibitors (eg, venlafaxine), or history of alcohol or other substance abuse.

Our study was approved by the local ethics committee and all participants provided informed consent according to the Declaration of Helsinki.

2.2. Nocturnal polysomnography

Nocturnal vPSG was held in a standard sound-attenuated (noise level to a maximum of 30 dB nHL) sleep laboratory room. Participants were not allowed to drink caffeinated beverages the afternoon preceding the recording and were allowed to sleep in until their spontaneous awakening in the morning. Lights-out time was based on individual habitual bedtime and ranged between 21.30 and 23.30 hours. The following signals were recorded: EEG (at least two channels, one central and one occipital, referred to the contralateral earlobe); electrooculogram (electrodes placed 1 cm above the right outer canthus and 1 cm below the left outer canthus and referred to A1); electromyogram (EMG) of the submentalis muscle (bipolar derivations with two electrodes placed 3 cm apart and affixed using a collodion-soaked gauze pad, impedance was kept less than 10 KΩ [typically <5 KΩ]); EMG of the right and left tibialis anterior muscles; and electrocardiogram (one derivation). Sleep signals were sampled at 200 Hz or 256 Hz and stored on a hard disk for further analysis. The sleep respiratory pattern of each patient was monitored by the use of oral and nasal airflow thermistors and/or nasal pressure cannula, thoracic and abdominal respiratory effort strain gauge, and by monitoring oxygen saturation (pulse oximetry). This monitoring was performed in all participants in a previous recording (within 1 week) or during the study recording; participants with an apnea–hypopnea index of higher than 5 were not included. Sleep stages were scored following standard criteria [19] on 30-second epochs. Because muscle atonia can be absent in RBD, REM sleep was scored without submental EMG atonia using EEG and electrooculogram only. According to a method specifically developed for RBD [7,20], onset of a REM sleep period was defined as the occurrence of the first REM in the presence of an EEG signal characteristic of REM sleep (low amplitude mixed frequencies, absence of sleep spindles and K complexes). Offset of a REM sleep period was determined by the occurrence of a specific EEG feature indicative of another stage (K complex, sleep spindle, or EEG signs of arousal) or absence of REMs during 3 consecutive minutes. Epochs containing technical artifacts or extremely elevated muscle activity causing saturation of amplifiers were carefully detected and marked for exclusion from the subsequent quantitative EMG analysis.

2.3. REM sleep behavior disorder severity scale

To classify the severity of RBD episodes in iRBD patients we evaluated motor behavior events during REM sleep on vPSG recordings and graded them visually and polysomnographically on an event-to-event basis, using the recently proposed REM sleep behavior disorder severity scale (RBDSS) [21]. According to this scale, the location of movements was categorized as follows: 0, no visible movement; 1, slight movements or jerks 2, movements involving proximal extremities, including violent behavior; and 3, axial involvement including bed falls. Vocalizations were rated as 1 for present or 0 for absent. The final RBDSS score was determined by the highest score obtained in each vPSG recording, (the grading of the most violent episode observed during the recording session). To statistically treat these results, we slightly modified the final score (RBDSSmod) by adding to the movement location category (0–3) the value of 0 in the absence of vocalizations or 0.5 in their presence; in this way we obtained a 8-level grading for RBDSSmod