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Original Article

Rapid eye movement sleep behavior disorder and rapid eye movement sleep without atonia in narcolepsy

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ABSTRACT

Narcolepsy is a rare disabling hypersomnia disorder that may include cataplexy, sleep paralysis, hypnagogic hallucinations, and sleep-onset rapid eye movement (REM) periods, but also disrupted nighttime sleep by nocturnal awakenings, and REM sleep behavior disorder (RBD). RBD is characterized by dream-enacting behavior and impaired motor inhibition during REM sleep (REM sleep without atonia, RSWA). RBD is commonly associated with neurodegenerative disorders including Parkinsonisms, but is also reported in narcolepsy in up to 60% of patients. RBD in patients with narcolepsy is, however, a distinct phenotype with respect to other RBD patients and characterized also by absence of gender predominance, elementary rather than complex movements, less violent behavior and earlier age at onset of motor events, and strong association to narcolepsy with cataplexy/hypocretin deficiency. Patients with narcolepsy often present dissociated sleep features including RSWA, increased density of phasic chin EMG and frequent shift from REM to NREM sleep, with or without associated clinical RBD. Most patients with narcolepsy with cataplexy lack the hypocretin neurons in the lateral hypothalamus. Tonic and phasic motor activities in REM sleep and dream-enacting behavior are mostly reported in presence of cataplexy. Narcolepsy without cataplexy is a condition rarely associated with hypocretin deficiency. We proposed that hypocretin neurons are centrally involved in motor control during wakefulness and sleep in humans, and that hypocretin deficiency causes a functional defect in the motor control involved in the development of cataplexy during wakefulness and RBD/RSWA/phasic motor activity during REM sleep.

1. Introduction

Narcolepsy is a rare and disabling disorder characterized by excessive daytime sleepiness (EDS) and abnormal rapid eye movement (REM) sleep manifestations that may include cataplexy (sudden loss of muscle tone triggered by strong emotions), sleep paralysis, hypnagogic hallucinations, and sleep-onset REM periods [1]. Nighttime sleep is frequently interrupted by several and long awakenings, and abnormal movements or behaviors during REM and NREM sleep [2]. REM sleep parasomnias include REM sleep behavior disorder (RBD), recurrent sleep paralysis, and nightmares, being all frequently reported in narcolepsy [2]. In addition, NREM sleep parasomnias with confusional arousals, sleep terrors and sleepwalking, and some other parasomnias without clear related-sleep stage, such as sleep-related eating disorder (SRED), were also frequently reported in narcolepsy [3]. However, only few studies have focused on frequency, natural history of age of onset, time of night of the events, characteristics of the behavior, memory for the events, and family history of NREM and REM parasomnias in narcolepsy [4,5].

According to ICSD-2, RBD is characterized by a loss of REM sleep muscle atonia (RSWA) together with prominent motor behavioral manifestations associated with dreaming during REM sleep [1]. These sleep behaviors mostly produce injuries to the patient and/or bed partner, being the main reason for consultation. Analysis of remembered dreams contents reported an increased proportion of aggressive contents without any problem of daytime aggressiveness [6], but a recent study contrasted these aggressive dream contents [7].

RBD may occur alone and is then called "idiopathic" RBD, but RBD is also often associated with neurological diseases such as,

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neurodegenerative disease especially synucleinopathies, but also brainstem lesion, Guillain–Barré syndrome, alcohol withdrawal syndrome and narcolepsy [5,8–21]. However, most of the clinical RBD characteristics detailed above, were reported in the idiopathic form of RBD, with only poor data suggesting their relevance for its description in narcolepsy. In addition, motor sleep disturbances with dissociated sleep including the presence of RSWA required for the full diagnosis of RBD were intrinsic features of narcolepsy in association or not with clinical RBD [1]. Hence, the clinical and polysomnographic features for the diagnosis of RBD as proposed in ICSD-2 [1], may then be discussed and revised in the context of narcolepsy. This paper addresses these points with special emphasis on the relations between RBD, RSWA and narcolepsy.

2. Definition and frequency of REM sleep behavior disorder in narcolepsy

RBD is characterized by intense motor or verbal paroxysmal dream-enacting episodes arising in REM sleep during loss of muscle atonia [1]. According to the ICSD-2 [1], the diagnosis of RBD is based on the following criteria: (a) presence of REM sleep without atonia with excessive amounts of sustained or intermittent elevation of submental EMG tone or excessive phasic submental or (upper or lower) limb EMG twitching; (b) at least one of the following: (i) sleep related injurious, potentially injurious, or disruptive behaviors by history, (ii) abnormal REM sleep behaviors documented during polysomnographic monitoring; (c) absence of EEG epileptiform activity during REM sleep unless RBD can be clearly distinguished from any concurrent REM sleep related seizure disorder; (d) the sleep disturbance is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder. However, this definition referred mostly to the idiopathic form of RBD and appeared not fully relevant for the diagnosis of RBD associated with narcolepsy as detailed below.

The prevalence of clinical RBD remains largely unknown in the general population. A large telephone survey in the general population assessing violent behaviors during sleep suggested a prevalence around 1.6% with a male predominance [22]. However, mild nocturnal agitations including forms of RBD with less aggressive behaviors certainly exist with less clinical consultation requested that may also involve a larger percentage of women [22]. Narcolepsy represents the second most frequent cause of RBD after the neurodegenerative diseases, which correspond to 10–15% of patients affected with RBD [21].

The occurrence of RBD in narcolepsy was reported since the earlier descriptions [2,16,17]. The frequency of RBD in narcolepsy with cataplexy seems to be fairly high, clinically evident in 45–61%, polysomnographically detectable in 36–43% of them, but without any controlled studies available [4,5,15–19]. Some discrepancies existed between these frequencies in relationship with the small number of patients studied, differences in the diagnostic criteria of RBD (clinical versus clinical plus polysomnography, diagnostic criteria), presence of sleep-related injury or not, inclusion of patients with and without cataplexy, patients treated with anticataplectic medications or other drugs known to influence sleep or motor activity, but also recruitment bias in favor of those presenting parasomnias. In addition, most of the frequency studies on RBD are made by questionnaire surveys or semistructured clinical interviews based on the clinical criteria that do not account for the gold standard tool for RBD including the video-PSG. PSG with quantified analysis of surface EMG from chin muscle, and right and left tibialis anterior in REM sleep are indeed crucial to fully confirm the diagnosis [4,5,14,15,23]. However, there is no cutoff proposed regarding the percentage of REM sleep without atonia for the diagnosis of RBD in the context of narcolepsy. In narcolepsy, the typical RBD acting-out dream is more frequently disclosed by questionnaires or by clinical interview than by video-PSG. Even in absence of clinical complaint of RBD, video-PSG may reveal an excessive increase in chin EMG tone or excessive limb or chin EMG twitching during REM sleep associated with infrequent and simple motor behavior without any history of injurious or disruptive sleep behaviors in narcolepsy [5,14]. The latter milder form of RBD may have remained undetected with final underestimation of RBD in narcolepsy [5]. Current criteria to diagnose RBD in narcolepsy remained questionable with some clinical and PSG uncertainties in the recognition of the RBD condition itself in narcolepsy. Similar discrepancies on frequency of RBD were also reported in patients with Parkinsonism disclosed by clinical versus PSG studies with underestimate of the frequency of RBD in this population using the clinical data alone.

3. Phenotype of REM sleep behavior disorder in narcolepsy

Case reports of traumatic/violent behavior have been reported during RBD in the context of narcolepsy with and without cataplexy; however, generally the behavior is less violent to bed partners/themselves than in idiopathic RBD and RBD associated with Parkinsonism [17,18,24–27]. Clinical RBD manifestations in narcolepsy ranged from increased muscle twitchings and jerks to complex, organized and finalistic motor and verbal activities leading to an enacted dream behavior [5,27]. A recent study showed higher occurrence of elementary movements during REM sleep in patients with narcolepsy and RBD compared to narcoleptics without RBD, but the occurrence of complex movements did not differ significantly [4]. RBD is rarely an every night phenomenon in patients and narcolepsy with frequencies range from one or a few attacks per month to one or more every night [4], but usually increase over the years, particularly with psychoactive medications. Due to the physiological increase in REM sleep in the last third of the night, RBD episodes in general, are often more intense during the early morning hours, and are accompanied by the recall of vivid, fearful dreams [21]. However, as nighttime and daytime REM sleep dysregulation with low REM sleep latency at night were the neurophysiologic hallmarks of narcolepsy, we may expect different findings. Hence, a recent narcolepsy study show that RBD episodes occurred with comparable frequency in REM sleep periods of the first and second halves of the night, regardless of the length of REM periods, patients' age or disease duration [4]. However, aggressive-violent movements were significantly more frequent in RBD episodes of the second half of the night without any differences in sleep parameter in patients with RBD occurring in the first half versus second of the night [4].

In addition to the low frequency of injuries and the rare number of clinically relevant episodes, RBD in narcolepsy also differed from the idiopathic form on its different sex ratio (affecting mostly men in the idiopathic form) and its much earlier age at onset, which precede narcolepsy in one-third of the patients [16–19,21]. Hence, RBD may be an early symptom in narcolepsy childhood, but mostly RBD increased in severity and frequency with the aging process [28]. Patients with narcolepsy with cataplexy seemed to be more frequently affected by RBD than those without cataplexy [19]. However, in many patients with cataplexy, RBD can be induced or aggravated by anti-cataplectic treatment, for example antidepressants including serotoninergic, noradrenergic/serotoninergic and tricyclic drugs [29].

The presence of other REM and NREM parasomnias is also frequently reported in the medical history of narcoleptics with RBD when compared to narcoleptic without RBD [17]. Like other REM sleep-parasomnias, autonomic activation is not dramatic during