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PARASOMNIAS (A AVIDAN, SECTION EDITOR)

Rapid Eye Movement Sleep Behavior Disorder: Overview and Current Perspective

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Abstract Rapid eye movement (REM) stage of sleep in normal circumstances is composed of vivid dream mentation associated with physiological skeletal muscle paralysis and thus, quiescence of motor activity. REM sleep behavior disorder (RBD) is a parasomnia characterized by disinhibition of motor control facilitating dream enactment behaviors. These nocturnal motoric behaviors due to lack of REM atonia range from benign limb movements to complex aggressive actions but are often manifested by violent, aggressive flailing, punching and kicking with vocalizations enacting action-filled hostile dreams. Polysomnographic evidence of increased electromyographic tone during REM with or without capturing clinical dream enactment together with careful history helps diagnose RBD. It is considered a prodromal feature of neurodegenerative alpha-synucleinopathies with high rate of eventual phenoconversion. The mainstay of treatment is to first ensure physical safety. When medications are necessary, options include either low-dose clonazepam, high-dose melatonin or both. Yearly surveillance with detailed neurological evaluation is vital for early detection and eventual management of neurodegenerative disorder.

Keywords REM sleep behavior disorder · Alpha-synucleinopathies · Dream enactment · REM sleep without atonia · REM parasomnia · Nocturnal motor activity · Oneirism

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Introduction

A patient with rapid eye movement (REM) sleep behavior disorder (RBD) is often brought to medical attention when there has been injurious nocturnal behavior to patient or bed partner as a result of violent enactment of dreams.

In the following chapter, we will give a brief overview of epidemiology, pathogenesis and etiological association with special emphasis on alpha-synucleinopathies. We will also discuss nomenclature, demographics, clinical manifestations, differential diagnosis, polysomnographic findings and management strategies. The goal of treatment is to ensure safety of patient and bed partner and to ensure careful longitudinal follow-up of these patients. They should be serially evaluated for the development of subtle neurological signs or symptoms suggestive of neurodegeneration.

Nomenclature

Rapid Eye Movement Sleep Without Atonia

REM sleep without atonia (RSWA) is the neurophysiological finding of increased electromyographic (EMG) tone in REM sleep confirmed by polysomnogram (PSG). Some have proposed designating the term "subclinical RBD" for this group

with implication that these patients will go on to develop dream enactment behavior, thus full spectrum of RBD but at this juncture, there is paucity of longitudinal follow-up of this population to arrive at this conclusion [1].

Rapid Eye Movement Sleep Behavior Disorder

RBD is a parasomnia characterized by recurrent dream enactment during REM sleep marked by neurophysiological substrate of increased EMG tone on PSG. For diagnosis of RBD, both clinical dream enactment and evidence of RSWA are required [2]. Some authors have used term clinically probable RBD if PSG testing for RSWA is not available but clinical history for dream enactment behavior is convincing.

Idiopathic Rapid Eye Movement Sleep Behavior Disorder

It refers to presence of RBD without any associated neurological disorder. While the term is still customarily used in literature, there has been growing opinion that RBD is a prodromal symptom in alpha-synucleinopathies, and hence it is not truly idiopathic [1, 3].

Symptomatic Rapid Eye Movement Sleep Behavior Disorder

This term denotes RBD in conjunction with a neurological disorder like an alpha-synuclein disorder [1, 3], narcolepsy [1, 4, 5], or paraneoplastic disorders [6, 7]. The expression secondary RBD is also used synonymously by other authors [1].

Alpha-Synucleinopathies

Disorders of neurodegeneration with alpha-synuclein pathology include Parkinson's disease, multiple system atrophy, dementia with Lewy bodies, and pure autonomic failure.

Epidemiology and Demographics

The estimated prevalence of RBD in general population is 0.5 % [2, 8] but significantly higher in elderly and specific neurodegenerative conditions. An elderly general population study cites PSG-proven RBD at frequency of 2 % while RWSA in absence of clinical dream enactment of 5 % [9].

In parkinsonian patients, the frequency of RBD is 30–54 % [10–13]. The prevalence is higher in other synucleinopathies, such as 50–80 % in dementia of Lewy body [14] and 80–95 % in multiple system atrophy [15, 16].

RBD in the young (less than 50 years old) is most commonly associated with narcolepsy or antidepressant use [1, 4, 17]. RBD is reported in 60 % of narcolepsy cases with a different phenotype, characterized by lack of the male preponderance that is seen in idiopathic RBD [8]. Of note, idiopathic RBD can also occur in young adulthood predating the clinical symptoms of neurodegeneration by decades [18].

Despite the reported male predominance (82–88 %) [1, 19, 20], RBD is common in women. It is frequently undiagnosed in women due to less injurious dream enactment and due to the frequent lack of a bed partner to witness nocturnal behaviors due to longer life span of women compared to men [20, 21]. Because of this, there has been some emerging evidence that RBD is more prevalent in females than is currently recognized [22].

Like Parkinson's disease, many cases of RBD are familial [8]. In addition, RBD is associated with various environmental, social, and behavioral factors. Patients with RBD are more likely to have a history of smoking, traumatic brain injury, pesticide exposure and fewer years of education [23].

Etiopathogenesis

Under normal circumstances, REM sleep motor atonia is the product of numerous brain pathways, most of which are localized to the pons. The critical structures in brain stem include "REM-on" region consisting of precoeruleus (PC) and sublaterodorsal nucleus (SLD), and extended part of the ventrolateral preoptic nucleus (eVLPO), locus coeruleus (LC), laterodorsal tegmental nucleus (LDTN), pedunculopontine nucleus (PPN), and raphe nucleus (RN). REM-off region consists of the ventrolateral part of the periaqueductal grey matter (vl-PAG) and lateral pontine tegmentum (LPT) [1]. The loss of REM sleep atonia in typical RBD appears to be due to dysfunction of this on/off switch for control of REM sleep [24]. The actual circuitry is complex and various processes such as other sleep disorders, drugs, and structural lesions have been demonstrated to lead to RBD. The basic pathophysiological mechanism of REM sleep-related atonia is illustrated in schematic diagram (Fig. 1). Axons originate from "REM-on region" (mainly PC and SLD) and synapse on nucleus magnocellularis of medial medulla. Neurotransmitters released from the originating axons cause postsynaptic inhibition resulting in skeletal muscle atonia.

In RBD associated with narcolepsy, altered/decreased function of hypocretin pathways projecting from the lateral hypothalamus to the brainstem plays a causative role [4, 25]. Orexin secreted by lateral hypothalamus promotes state stability, and thus its deficiency causes REM-wake instability leading to REM dream mentation with excess motor activity [5, 26].

RBD is associated with several neurological disorders, as summarized in Table 1. The disorders with the strongest RBD link are represented by superscript "a" [14, 15, 27].

Alpha-Synucleinopathies

The strong association between RBD and alpha-synucleinopathies has been well established. The term encompasses the neurodegenerative disorders characterized by

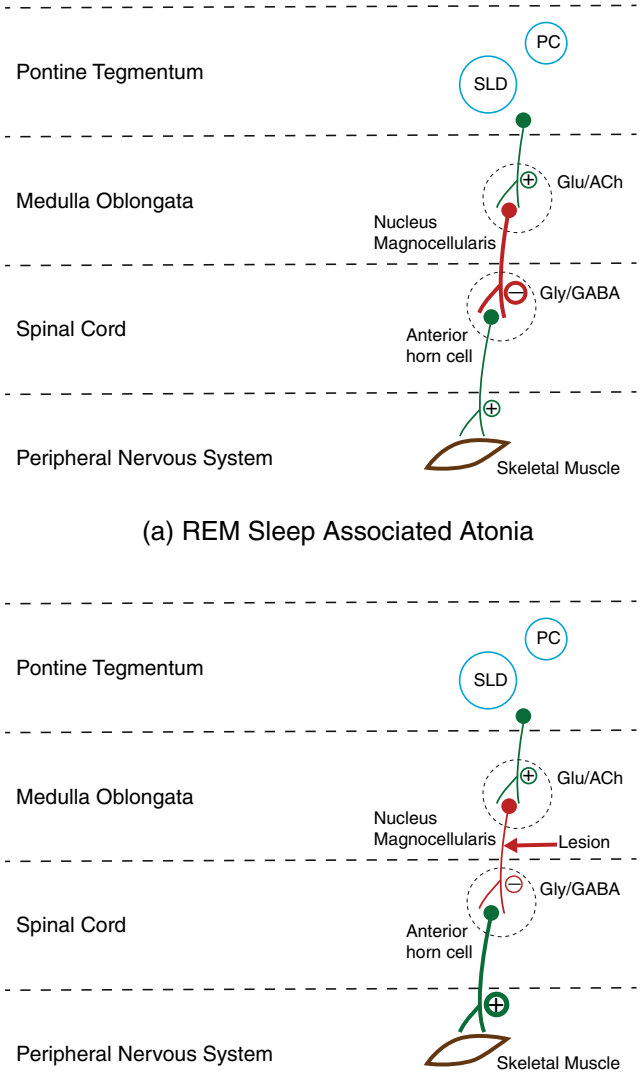

Fig. 1 **a** Schematic illustration of neural pathways mediating normal skeletal muscle atonia in REM sleep. **b** Disruption of this pathway leading to loss of REM-associated atonia and, thus, increasing tone. *Glu* glutamate, *Ach* acetylcholine, *Gly* glycine, *GABA* gamma aminobutyric acid, + excitatory neurotransmitter, − inhibitory neurotransmitter

pathologic alpha-synuclein deposits in central nervous system such as Parkinson's disease (PD), dementia of Lewy body (DLB), multiple system atrophy (MSA) and pure autonomic failure (PAF). These disorders are characterized by presence of Lewy bodies and aggregates of alpha synuclein and ubiquitin in neurons, which can be detected on autopsy [3, 28, 29]. Idiopathic RBD is a prodromal symptom of the disease, as it can predate the development of neurological disorder by decades [1, 18]. The brainstem nuclei involved in REM sleep atonia generation are affected early in the disease process, thus facilitating RBD emergence before cortical pathology [30–32].

Several neuroimaging techniques have shown changes indicative of ongoing pathologic process in RBD such as transcranial ultrasound which has demonstrated substantia nigra hyperechogenicity [33] and nuclear imaging which has revealed reduced striatal dopamine transporters [34], dopaminergic innervation [35], and altered nigrostriatal and nigrocortical connectivity [36, 37]. All of these results are consistent with a developing dopaminergic deficit seen in disorders of parkinsonism.

Investigations have demonstrated unique metabolic network abnormalities in RBD as measured by 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) and ethyl cysteinate dimer single positron emission tomography (ECD SPECT) which can predict ultimate conversion to clinical Parkinson's disease [38, 39].

MRI volumetric studies of RBD reveal grey matter reductions in the cerebellum, pons, and parahippocampus, similar to studies performed in DLB and MSA [40].

Evidence of wake and REM electroencephalographic (EEG) slowing has also been noted indicating cortical dysfunction [41, 42].

Other Neurological Disorders

RBD can also be associated with other neurodegenerative diseases in which disease pathology might topographically involve the pontine REM sleep generators. In contrast to alpha-synuclein disorders, it is not a precursor in these conditions but occurs either coincidental or subsequent to development of other neurological symptoms [43]. Table 1 enlists various disorders such as amyloidopathies, tauopathies, TDP-43 proteinopathies, tri/tetranucleotide repeat disorders, genetic, congenital, and developmental conditions which have been reported to occur with RBD although at a much lower frequency [3, 44–47]. The one exception is spinocerebellar ataxia type 3 (SCA3), a trinucleotide repeat disorder of cerebellar and brainstem degeneration. The majority of patients with SCA-3 develop RBD.

Narcolepsy and RBD both represent dysfunction of awake REM state boundary control. The association of RBD with this disease is strongest in narcolepsy type 1 (narcolepsy with cataplexy) [5]. As discussed above, it represents unique phenotype, with equal gender distribution and less aggressive dream enactment movements [48].

Medication-Associated Rapid Eye Movement Sleep Behavior Disorder

Medication-associated RBD may be the most common form of RBD, especially among the young [49, 50]. Approximately 10 % of depressed patients exhibit increase in REM sleep motor tone after treatment with sertraline compared to 3 % prior to treatment [51].

Several psychoactive drugs have been noted to precipitate or aggravate RSWA and RBD including tricyclic and tetracyclic antidepressants, monoamine oxidase (MAO) inhibitors, serotonin-specific reuptake inhibitors (SSRI) and

Table 1 Neurological disorders associated with RBD

ALPHA-SYNUCLEINOPATHY[a]
- Parkinson's disease [30–54 %]
- Dementia with Lewy bodies [50–80 %]
- Multiple system atrophy [80–95 %]
- Pure autonomic failure

AMYLOIDOPATHY
- Alzheimer's disease

TAUOPATHY
- Progressive supranuclear palsy
- Guadeloupean parkinsonism
- Frontotemporal dementia
- Amyotrophic lateral sclerosis

TRINUCLEOTIDE/TETRANUCLEOTIDE REPEAT DISORDERS
- Spinocerebellar ataxia-3[a]
- Huntington's disease
- Myotonic dystrophy type 2

OREXIN DEFICIENCY
- Narcolepsy

AUTOIMMUNE/INFLAMMATORY DISORDERS
- Voltage-gated K antibody limbic encephalitis
- Paraneoplastic cerebellar degeneration
- Ma2 encephalitis
- IgLON-5 parasomnia

GENETIC DISORDERS
- Wilsons disease
- Pantothenate kinase-associated neurodegeneration

CONGENITAL/DEVELOPMENTAL DISORDERS
- Moebius syndrome
- Smith-Magenis syndrome
- Autism
- Tourette syndrome

STRUCTURAL LESIONS
- Multiple sclerosis
- Astrocytoma
- Acoustic neuroma
- Vascular malformations
- CNS vasculitis
- Infarct

MEDICATION INDUCED[a]
- Tricyclic and tetracyclic antidepressants, monoamine oxidase inhibitors, selective serotonin inhibitors, serotonin norepinephrine reuptake inhibitors

MEDICATION WITHDRAWAL (acute)
- Alcohol, barbiturate, amphetamine, cocaine

[a] Disorders with the strongest RBD link [14, 15, 27, 75]

serotonin-norepinephrine reuptake inhibitors (SNRI), particularly venlafaxine, pentazocine, tramadol, and acetylcholinesterase inhibitors [50, 52, 53]. Drug-induced RBD cases tend to have high EMG tone predominantly in tibial leads [54].

Emerging evidence suggests that these medications may be unmasking a neurodegenerative disorder rather than causing de novo induction. According to one study, patients with antidepressant associated RBD also exhibited other prodromal symptoms like hyposmia, constipation, and subtle visual and motor findings [55]. Reduced striatal dopamine uptake as measured by (18) F-DOPA PET imaging has also been demonstrated in patients with medication-induced RBD [56]. These findings are intriguing and suggest that medication-induced RBD may also be a prodromal syndrome to alpha-synuclein degeneration; however, more studies are needed.

Lesional Rapid Eye Movement Sleep Behavior Disorder

A structural lesion localized to pontine centers governing REM sleep motor tone can also lead to RBD. Thus, cases of RBD caused by vascular, neoplastic, demyelinating, vasculitic and traumatic insults have been reported [57, 58]. In such cases, cranial imaging reveals the structural pathology and topographic involvement of pontine tegmentum in most cases.

Inflammatory/Autoimmune Rapid Eye Movement Sleep Behavior Disorder

RBD can also occur with certain autoimmune and inflammatory conditions without any identifiable structural lesion. The most common association is with voltage-gated potassium antibody encephalopathies such as limbic encephalitis and Morvan's syndrome [59]. It has also been reported in other encephalitides like Ma-2 enchephalitis and paraneoplastic cerebellar degeneration [6, 7]. Importantly, these conditions respond favorably to immunotherapy. In these cases, reciprocal anatomical connections between limbic system and brainstem regions are presumed to affect REM sleep muscle atonia [28].

Recently, a unique neurological syndrome has been described in eight patients in Europe with antibodies to IgLON-

5, a type of neuronal cell adhesion molecule, suggesting a novel inflammatory mechanism. It is a distinctive condition with both nonrapid eye movement (NREM) and REM parasomnias, sleep-related breathing dysfunction, dysautonomia, bulbar, neurological dysfunction, and pathological features suggesting a tauopathy. Clinical deterioration, lack of response to immunosuppressive agents, and mortality were noted in all the cases. The exact role of IgLON-5 antibody in tau pathogenesis is unclear, and further investigation is warranted [60].

Clinical Manifestations

Clinical phenomenology of RBD is characterized by abnormal vocalizations and motoric behavior representing dream enactment.

Abnormal vocalizations in RBD tend to be loud suggesting unpleasant dreams. Shouting, hollering, screaming and swearing are fairly common and are often contradictory to the typically soft-spoken nature of the person during wakefulness. This helps in distinguishing from NREM parasomnias, where vocalization is more often of a benign conversational nature [3].

In RBD, the motor activity ranges on a wide spectrum from subtle hand movements (often referred to as hand babbling) to more dramatic, violent and seemingly purposeful actions such as punching, flailing, running, jumping out of bed, etc. [2]. These behaviors can prove to be injurious to the patients and their bed partners. Unlike NREM parasomnias, the duration of behaviors in RBD is typically brief with a rapid return to alertness on arousal.

The dream content often involves animals or people chasing or attacking the patient or their loved ones with patient almost always assuming role of the defender. Many patients are able to recount the content of their dreams upon being awakened. Individuals with RBD can often recall vivid details of the nightmares for days and sometimes for weeks or years [3].

The frequency of dream enactment behaviors (DEB) also varies widely from several times every night to one night per month or less. Some appear to exhibit clustering without any known trigger.

Since REM sleep periods in latter half of the night are longer and with greater phasic REM activity, dream enactment is more pronounced in second part of the night [1].

Diagnostic Criteria (ICSD-3)

According to third edition of the International Classification of Sleep Disorders, the diagnosis of RBD requires fulfilling following criteria:

1. Recurrent nocturnal episodes of vocalizations and/or complex motoric behaviors consistent with dream enactment.
2. These behaviors are evidenced by in-laboratory PSG to occur in REM sleep or presumed to occur so based on clinical history.
3. Evidence of RSWA is obtained on in-laboratory PSG.
4. Sleep-related disturbance is not explained by another sleep or mental health disorder, medication or substance use

Polysomnographic Characteristics

According to the American Academy of Sleep Medicine, the polysomnographic features of RBD are characterized by excessive

1. Tonic activity in REM sleep in chin EMG
   and/or
2. Phasic activity during REM sleep in either chin or limb activity

> *Tonic activity* (sustained muscle activity) is demonstrated by an epoch of REM sleep with at least 50 % of the duration of the epoch having chin EMG amplitude greater than the minimum amplitude noted in NREM sleep.
> *Phasic activity* (excessive transient muscle activity) is demonstrated in submental or limb EMG when a 30-second epoch divided into ten sequential 3-second mini-epochs has at least five (50 %) mini-epochs of bursts of transient muscle activity. These bursts are 0.1–0.5 second in duration and at least four times greater in amplitude than background EMG activity [2]. Figure 2 demonstrates neurophysiologic findings of RBD on polysomnographic recording.

REM sleep atonia index (RAI) is a quantitative RSWA metric ranging from 0.0 to 1.0 (the lower the number, the greater the amount of REM sleep motor activity). It has been shown to demonstrate reasonable night-to-night consistency [61]. In order to standardize and objectively quantify excessive motor activity, computer-assisted scoring methods have been developed and an abnormal REM atonia index is defined as (<0.88) [54, 62, 63].

Diagnostic Tools

Several screening surveys are available to help identify RBD among general and disease populations. These tools share many similarities: they all inquire about the presence of dream enactment, and thus all have relatively similar sensitivities and specificities. A bed partner, if available, increases their yield and efforts should be made to include their observations as patients are often unaware of their behaviors. While an in-laboratory

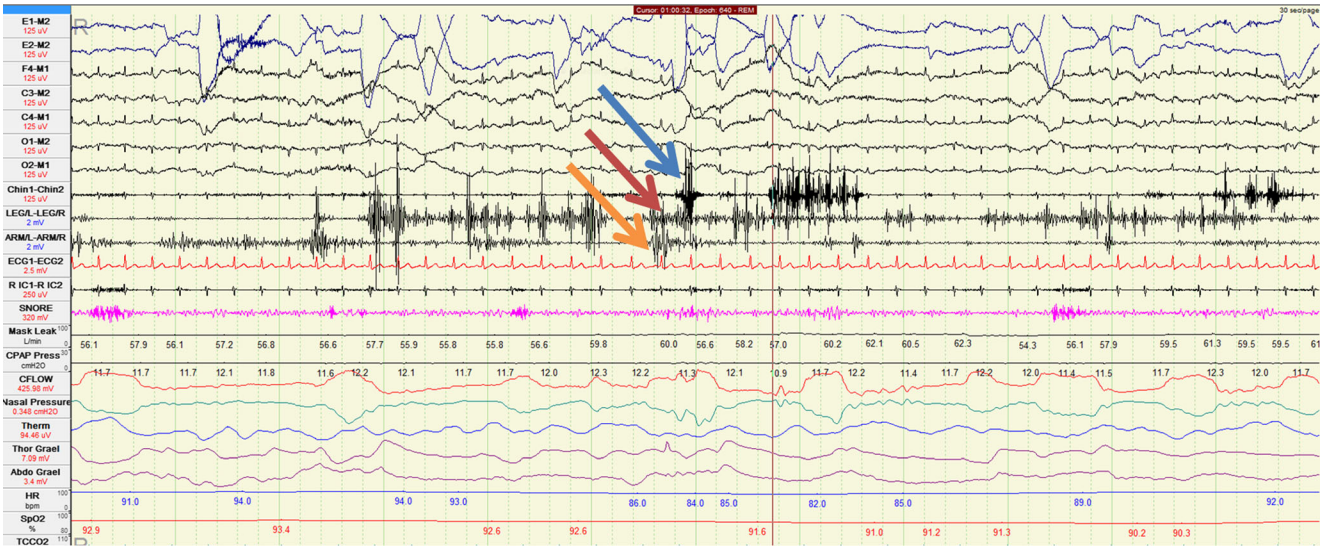

Fig. 2 Thirty-second epoch of polysomnogram showing increased electromyographic tone in submental (Chin1-chin2) denoted by *blue arrow*, in lower limb (left leg to right leg) denoted by *red arrow*, and in upper limb (left arm to right arm) derivations denoted by *orange arrow*

sleep study is needed for ICSD-3 diagnosis, initial PSG can miss up to 20 % of RBD cases [64] which could explain the relatively low specificity of the clinical tools noted below.

The RBD Questionnaire-Hong Kong (RBDQ-HK) is a validated 13-item measure with higher scores indicating greater severity. It has a positive predictive value of 86 % and a negative predictive value of 83 % [65].

The REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) is a ten-item screen, and a score greater than 4 has a sensitivity of 90 % and a specificity of 87 % [66].

Interestingly, a single RBD question-based Mayo Sleep Questionnaire (MSQ) demonstrated high diagnostic sensitivity and specificity of 98 and 74 % [67]. The referenced informant question is "Have you ever seen the patient appear to 'act out his/her dreams' while sleeping? (punched or flailed arms in the air, shouted, or screamed)."

Another survey, the RBD Single-Question Screen (RBD1Q) showed sensitivity of 94 % and specificity 87 % [68].

Innsbruck RBD inventory, a five-item-based questionnaire, has sensitivity and specificity of 91.4 and 86 %, respectively [69].

Differential Diagnosis

The other sleep-related conditions that can present like RBD include NREM parasomnias such as sleep walking, confusional arousals, and sleep terrors. These can be teased out by meticulous historical account. These disorders of arousal will occur in first half of the night, without any recollection of the event or dream mentation. Careful determination of nocturnal behaviors especially through collateral history by a caregiver or bed partner is crucial. Some of the factors differentiating RBD from a NREM parasomnia include initial presentation in middle age or the elderly, present in second half of the sleep period with eyes closed, dream recall, and low arousal threshold (the patients are easily woken up). Behaviors mostly occur in bed with jerky movements occurring in bursts with sudden jumping off the bed while enacting dreams. When sleep walking occurs, it is mostly in context of rushed movement of escape or rescue resulting in fall or throwing themselves against physical barriers [70]. Other conditions that lead to nocturnal arousals mimicking RBD are obstructive sleep apnea, periodic limb movements of sleep and gastroesophageal reflux [1, 3]. Pseudo-RBD comprises of RBD-like symptoms in patients who have obstructive sleep apnea. It is manifested by abnormal behavior occurring with arousal at the end of obstructive apneic event [71]. Nocturnal frontal lobe epilepsy is also in the differential which is marked by recurrent, stereotypical hypermotor seizures typically during NREM sleep. When seizures are suspected, an extended EEG montage should be employed during the in-laboratory PSG. Other conditions that can manifest as abnormal nocturnal behaviors included rhythmic movement disorder and psychogenic dissociative disorder.

On occasion, patients with RBD also demonstrate a NREM disorder of arousal as well such as sleepwalking. This is parasomnia overlap disorder, a subtype of RBD in the ICSD-3. Patients with parasomnia overlap disorder are often younger than patients with idiopathic RBD and typically respond well to conventional sleepwalking and RBD therapies [72, 73].

While polysomnography is often helpful in diagnosing other parasomnias, RBD is the only condition that requires polysomnography for ICSD-3 criteria [2]. Table 2 summarizes common sleep conditions mimicking RBD.

Table 2 Conditions included in differential diagnosis of RBD

Conditions mimicking RBD
Sleepwalking
Sleep terrors
Obstructive sleep apnea "pseudo-RBD"
Nocturnal seizures
Rhythmic movement disorder
Posttraumatic stress disorder
Complex nocturnal visual hallucinations
Periodic movements of sleep
Psychogenic dissociative disorder

Treatment

Foremost goal of management of RBD is ensuring safety of the patient and bed partner. There should be strong emphasis on making sleeping environment safe (level A evidence according to treatment guidelines [74]). Spouses and other bed partners should sleep separately. Firearms, as well as sharp potentially injurious objects, should be removed from the bedroom. Other options include the following: using a bed with padded rails, a mattress on the floor, and/or a sleeping bed to limit potential injury.

The next steps should include the elimination and substitution of aggravating drugs (if feasible) and treating any other exacerbating sleep-related conditions like OSA.

Pharmacological treatment options are discussed below.

1. Clonazepam

   It has been the most widely prescribed agent historically, which is used in 0.5–1-mg doses with response rate of approximately 90 % (level B) [25, 73, 74]. The mechanism of action is not clearly understood and has minimal effect on EMG tone in REM sleep.

   However, the results of longitudinal studies with clonazepam range from sustained benefit to incremental dose escalation and treatment failure [3, 27, 75, 76]. According to one study, 58 % of patients on clonazepam reported significant adverse effects, likely owed to its long half-life, leading to dose reduction or cessation in 50 % [76]. The adverse effects of confusion, sedation, respiratory depression, and cognitive and gait disturbances can be dangerous in RBD patients with alpha-synucleinopathies, and thus, careful monitoring is advised (level B) [74].
2. Melatonin

   It has been increasingly used in RBD as a first-line agent in a dose range from 3 to 15 mg (level B) [3, 74]. Although the mechanism of action is unclear, melatonin may restore RBD-related desynchronization of circadian rhythms. In contrast to clonazepam, it is also shown to decrease the number of REM epochs without atonia and decrease both phasic and tonic motor activities [77, 78]. Also, recent studies have shown favorability due to better side effect profile, with reduced falls and injuries when compared to clonazepam [74, 79]. This becomes especially relevant in RBD associated with neurodegeneration as these patients are vulnerable due to low cognitive reserve. Most common side effects include morning headaches, mild sleepiness and delusions/hallucinations. Ramelteon, a melatonin agonist, has also been reported to treat RBD in two cases [80].

   According to expert consensus, both clonazepam and melatonin are reasonable first-line therapies [74].
3. Pramipexole

   This dopamine agonist can also be used to treat RBD especially in cases associated with periodic limb movements (PLMS). A study of 14 patients demonstrated improvement in RBD in 80 % cases with reduction in REM density and PLM index but no change in RSWA [81].
4. Other agents

   There is some data suggesting use of acetylcholinesterase inhibitors like rivastigmine especially in RBD with associated cognitive impairment [Brunetti et al. 2014]. Other agents with efficacy based on limited case reports include imipramine, desipramine, carbamazepine, levodopa, Yi-Gan San, sodium oxybate, triazolam, zopiclone, quetiapine, clozapine, and cannabidiol [3, 74, 82].

Bed Alarm Therapy

Medication refractory RBD is a challenging and potentially life-threatening condition. Escaping the bed during dream enactment may result in serious trauma. Fortunately, the brain is responsive to auditory sound processing during REM sleep [83]. This principle applied through a customized pressure sensing bed alarm can deliver a calming message (usually from a family member) at the onset of dream enactment [84]. When the patient arises from the bed, the pressure pad triggers a voice recording such as "Bob you are having a dream. Lay back down." The patient then lies down, the recording shuts off and the patient returns to REM sleep.

Prognosis and Phenoconversion

Physically aggressive dream enactment behavior in RBD can pose a serious threat to the patient or bed partner. Trauma incurred can range from minor injuries to subdural hematoma, shoulder dislocation, cervical fracture, pelvic fracture, and lacerations severing arteries, tendons, and nerves. When a

bed partner is involved, injuries can have legal ramifications [3]. Environmental adaptation and timely pharmacotherapy can prevent these undesirable consequences.

As idiopathic RBD is a prodromal syndrome, a diagnosis dramatically increases a patient's risk of developing PD or other alpha-synuclein syndrome. Two longitudinal cohorts of RBD have shown approximately 50 % conversion rate in the first 10 years [30–32]. Ultimately, however, nearly all (81–91 %) surviving RBD patients demonstrate phenoconversion [18, 85].

RBD patients may be stratified by assessing other premotor symptoms and biomarkers of alpha-synucleinopathies, such as hyposmia and constipation which, when present, help identify individuals at high risk of disease conversion [32, 86]. Imaging modalities for dopamine dysfunction, such as dopamine transporter scan DaTscan and impaired autonomic regulation, such as MIBG cardiac scintigraphy, while useful in research studies, do not have established a role in clinical context [3].

While research on idiopathic RBD and predictive biomarkers continues to be an area of intense effort, the responsibility of discussion of the risk of phenoconversion lies with the treating physician. Also in current age, where most of the patients are computer savvy, they should receive counseling from appropriate medical sources rather than obtaining information from random social media. It is considered standard of practice to discuss the risk of conversion to neurodegenerative disorder with the patient at an appropriate time in a therapeutic relationship. The need for yearly surveillance with neurological exam should be discussed with the patient in attempt for early detection and symptomatic management. It also allows patient autonomy and provides them with an opportunity to make informed decision about their medical care and alleviate unnecessary distress to the family later on [1].

Conclusion

RBD is an intriguing disorder characterized by dream enactment and increased REM sleep motor tone on PSG. It's diagnosis has several clinical implications including sleep-related injury to patients and bed partners and predicting the development of alpha-synuclein neurodegenerative disorder sometimes decades into the future. Management includes environmental modification or pharmacotherapy with melatonin and/or clonazepam.

Clinically, it is important to frequently screen RBD patients for the development of subtle neurological symptoms, although at this time, disease-modifying therapies have not yet been proven. RBD detection is important as it allows clinicians to monitor and manage the patients' neurodegenerative process. Importantly, an international consortium of RBD investigators, the International RBD study Group (IRBDSG) has been established and is developing clinical trials for neuroprotection [87].

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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