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REM-Behavior Disorder

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Abstract

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia exclusively occurring during REM sleep. Viewing this disorder through a neurologic lens can provide longitudinal context for patients and their treating physicians, given the well-known association of RBD with a specific group of neurodegenerative disorders: the alpha synucleinopathies. It is important to have a high degree of clinical suspicion, the ability to make an accurate diagnosis, manage the symptoms, and more importantly monitor the patient for evolution of possible underlying neurological pathology. This chapter will discuss aspects of the clinical history, physical examination, ancillary testing, and diagnostic criteria.

Keywords: rapid eye movement (REM), REM sleep behavior disorder (RBD), Parkinson's disease (PD), alpha synucleinopathies, dementia with Lewy bodies (LBD)

1. Introduction

There are a variety of disorders that can manifest complex movements and behaviors that happen during sleep. REM behavior disorder (RBD) is one such disorder characterized by loss of physiologic REM muscle atonia and dream enactment. Motor activity consists of highly complex, vigorous or violent dream enacting behaviors that are noticed when they result in injuries of the patient or their bed partner. Some behaviors include punching, kicking, jumping out of bed, and talking. If the patient is awoken they may recall an unpleasant dream of falling, being attacked or chased by either another person or an animal. The latter are common dream contents associated with RBD.

A disorder of the elderly, RBD onset occurs between the sixth and seventh decades [1], with an estimated prevalence of between 1 and 7.7% of the population [2]. The true extent of this disorder is largely unknown [3]. The disease is male predominant [4]. Symptoms are thought to arise from underlying dysfunction of the brainstem structures that regulate REM sleep atonia, mostly located in the dorsal mesopontine tegmentum and ventromedial medulla [4]. Injury to these areas can occur in the setting of structural lesions (such as stroke or multiple sclerosis), medication side effects (seen with certain antidepressants and beta blockers), or neuronal loss from neurodegenerative disease. There is a known association between RBD and the group of neurodegenerative conditions classified as alpha synucleinopathies. RBD is considered a prodrome of these conditions and can be present years before other neurological symptoms become apparent, thus the importance of early diagnosis and subsequent monitoring [5].

2. Diagnosis

Often RBD is a missed diagnosis, likely due to under reporting. While some patients have no recollection of their nighttime behaviors, others may simply not view these as abnormal. Obtaining an accurate clinical history then depends on corroborative information gathered from the patient's bed partner, as they may witness the dream enactment behavior. Of note, spouses may comment on the patient's night time behaviors being out of character as compared to how they behave during the daytime. For patients who do not have a regular bed partner, questions regarding vivid dreams (specifically of being attacked or engaged in combat) and unexplained night time injuries such as falling out of bed should be explored.

Differential diagnoses for complex nocturnal behaviors can be divided into several categories (see **Table 1**) including: partial arousal parasomnias, nightmare disorder, sleep related respiratory disorders, sleep related movement disorders, seizure disorders, and psychiatric disease. *Partial arousal parasomnias* occur mostly from slow wave sleep (happening during the first half of the night as noted in **Table 2**) and pathophysiology is presumed to be an incomplete transition from sleep to wakefulness [6]. These episodes consist of an arousal with associated disorientation and amnesia. Behaviors are quite primitive such as walking and eating. Episodes may be exacerbated by factors that increase the threshold for arousal (e.g. sleep deprivation, sedating medications). *Confusional arousals* are part of this category; however, these are rare in adults. As opposed to sleep walking and sleep related eating disorder,

Partial arousal parasomnias (arising from slow wave sleep):

- Sleep talking/somniloquy
- Sleep walking/somnambulism
- Night terrors
- Confusional arousals
- Sleep related eating disorder

Nightmares

Obstructive sleep apnea

Periodic limb movements of sleep

Nocturnal frontal lobe epilepsy

Nocturnal panic attacks

Sleep-related groaning (Catathrenia)

Table 1.
Differential diagnoses of RBD.

NREM parasomnias	RBD
Occur in the first part of the night	Occur in the second part of the night
Patient is amnesic of event	Patient recalls the event
Variable duration (minutes or longer)	Last seconds to minutes
Patient is difficult to arouse	Patient easily arousable
Male predominance	Male predominance
Provoked by sleep deprivation, stress	Unprovoked
Higher prevalence among children	Higher prevalence among older adults

Table 2.
SWS parasomnias vs RBD.

NFLE	RBD
Stereotyped asymmetric hypermotor behaviors of trunk or proximal extremities	Variable dream enacting behaviors in a self-defense manner including vocalizations
Short duration 5–60 s	Duration is seconds to 2 min
Patient is amnesic to the event	Patient recalls the event
Occurs from NREM stages	Occurs during REM sleep
May have nightly clusters	Rare, sporadic events
Age of onset first or second decade	Age of onset fifth decade

Table 3.
Nocturnal frontal lobe epilepsy vs RBD.

confusional arousals are associated with poor responsiveness and amnesia but during confusional arousals there is no ambulation. *Nightmare disorder* consists of recurrent awakenings during which the patient is able to recall a disturbing dream and experiences associated intense emotions such as fear, anxiety, or sadness. It is important to note that in nightmares there is preservation of REM atonia, therefore body movement is rare and the patient is fully alert after awakening (as opposed to a confusional arousal). *Obstructive sleep apnea* should be investigated if patient has a history notable for excessive daytime sleepiness. *Periodic limb movements of sleep* and other *sleep fragmenting conditions* may precipitate partial arousal parasomnias, which can be misinterpreted as RBD. Lastly, while parasomnias are largely a disorder of childhood, primary RBD (as described below) almost exclusively occurs in older adults.

Nocturnal frontal lobe epilepsy (NFLE) is one of the most important differential diagnosis for complex nocturnal behaviors that may mimic RBD (see **Table 3**) [7]. NFLE also presents with complex, exclusively nocturnal, bizarre behaviors; the hallmark of this disorder is that each episode is stereotyped (like with all epilepsies), where actions occurring during parasomnias or RBD are varied. The “classic” example is bicycling of the legs at night time out of sleep. Unlike RBD or parasomnias, there is no particular predilection for a time of night for these seizures to occur. Similar to parasomnias (but unlike RBD), the patient will be amnesic to the events themselves. Preferred treatment for nocturnal frontal lobe epilepsy includes anticonvulsant agents such as carbamazepine, oxcarbazepine, and lamotrigine.

Once suspicion for RBD is raised, confirmatory polysomnogram (PSG) should be pursued as this will provide a definite diagnosis. A full attended polysomnogram set up includes: abbreviated electroencephalography leads, eye movement monitoring, nasal airflow monitoring, oronasal thermistor, mental/submental EMG, snore sensor, single ECG lead, chest/abdomen respiratory effort belts, pulse oximetry, and bilateral tibialis anterior EMG monitoring. When testing for RBD additional monitoring includes surface electromyography (EMG) preferably of the upper extremities as lower extremity movements are less specific [8]. The most sensitive information is obtained from monitoring of the chin (mental/submental electrodes) and flexor digitorum superficialis. Diagnostic features on PSG include increased muscle activity on surface EMG, specifically of both the chin and upper extremities. Activity on EMG is categorized as tonic or phasic. Tonic activity lasts longer than 15 s, while phasic activity is much shorter lasting less than 5 s. Typically, tonic activity is observed in the chin, while phasic activity is observed in both the chin and upper extremity EMG. Additionally, combined chin/arm activity should be present for at least 27% of a 30 s epoch (as per the International Classification of Sleep Disorders Guidelines). This is a highly specialized test and its interpretation relies on visual quantification, therefore technical quality is of the utmost importance [9]. Performing a full

18 channel EEG montage during routine diagnostic PSG can help rule out NFLE, especially if a complex behavior is captured on the PSG study night.

Diagnostic criteria as established by the International Classification of Sleep Disorders, Third Edition include [10]:

- Repeated episodes of sleep related vocalization and/or complex motor behaviors
- Behaviors are documented by polysomnogram to occur during REM sleep or based on clinical history of dream enacting behavior, are presumed to occur during REM sleep
- Polysomnogram demonstrates REM sleep without atonia
- Disturbance is not better explained by another sleep disorder, mental disorder, medication, or substance abuse.

3. Primary rapid eye movement sleep behavior disorder (synucleinopathies)

Once diagnosed, RBD can be classified as primary (idiopathic) or secondary. *Idiopathic RBD* can be considered an early symptom of alpha synucleinopathies which include: Parkinson's disease, Lewy Body Dementia and Multiple System Atrophy. The diagnosis of RBD can be made years before any other neurologic symptoms are identified. In 80% of cases RBD preceded the diagnosis of neurodegenerative disease (more easily recognized motor features), by a mean of 14 years [11]. There is evidence to suggest that patients with RBD and mild cognitive impairment will develop dementia in an interval of 5 years or less [9]. Other subtle potentially predictive biomarkers of RBD (see **Table 4**) include: olfactory loss/anosmia, autonomic dysfunction (ranging from sexual dysfunction to cardiovascular symptoms), color vision deficit, cognitive impairment, excessive daytime sleepiness, psychiatric disorders (such as anxiety, depression, psychosis, impulse control disorders), personality changes, dopamine dysfunction, and excessive EMG activity [11]. The pathophysiology and temporal relation between these symptoms and motor symptom onset is highly variable. Subsequent neurological examination may show subtle signs of Parkinsonism such as mild bradykinesia, while neurocognitive testing can show evidence of memory and executive dysfunction. Neuroimaging is useful if dopamine transporter scan shows evidence of decreased dopamine uptake in the putamen. Electroencephalogram can show cortical slowing as well [9]. Biopsy of the colon and submandibular gland in patients with idiopathic RBD has shown evidence of phosphorylated alpha synuclein deposits.

Anosmia
Autonomic dysfunction
Color vision deficit
Cognitive impairment
Excessive daytime sleepiness
Psychiatric disorders
Personality changes
Dopamine dysfunction
Excessive EMG activity

Table 4.
Potential biomarkers of RBD.

4. Secondary rapid eye movement sleep behavior disorder (non-synucleinopathy)

Other causes of RBD include neurologic disorders stemming from structural lesions such as pontine stroke or multiple sclerosis plaques. This can also rarely occur in the setting of progressive supranuclear palsy, Alzheimer's disease, and Huntington disease among others. RBD can coexist with narcolepsy in 50% of patients. Medications that can precipitate RBD include antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclics, and monoamine oxidase inhibitors (MAOi). Some beta blockers have also been identified as culprits.

5. Treatment

Symptomatic management of RBD should be approached from multiple angles. First, maintaining a safe sleep environment for the patient by removing objects that can inflict harm or lowering the bed closer to the floor. Bed partners may also opt for sleeping in separate bed for their own safety. Co-sleeping is an important part of intimacy, however, and this can continue by advising the patient to sleep in a sleeping bag on top of the bed shared with their loved one. Bed alarms to warn loved ones about the patient exiting the bed can also be helpful in reducing night time injuries associated with RBD.

Medical management with melatonin or low dose benzodiazepines such as clonazepam has been shown to reduce the dream enacting behaviors. Benzodiazepines are thought to work by suppressing REM sleep. Theoretically, other REM suppressant medications (including SSRIs, TCAs, selective SNRIs) may also help, given their mechanism of action. However there are no trials supporting or refuting their efficacy and some may precipitate RBD as previously mentioned. These medications do, however, have lower tolerance and abuse potential than benzodiazepines. These treatments do not modify the risk of progression to PD, MSA, or LBD. Dopaminergic agents have not been shown to reduce dream enactment behaviors but may help comorbid periodic limb movements if present. In RBD cases refractory to conventional treatment, cholinesterase inhibitors such as rivastigmine (studied in one trial) and donepezil (several cases) have been noted to reduce the number of dream enactment episodes as reported by bed partners.

6. Ethical considerations

As stated previously, development of RBD can herald a diagnosis of potentially disabling neurological disorders by over a decade. While not every patient with primary RBD will go on to develop one of these conditions, we believe that patients should be informed of the association between RBD and the alpha synucleinopathies and therefore their risk of developing one of these disorders. The discussion should be geared towards ensuring periodic follow up and reducing anxiety by answering any questions the patient may have on the subject. Serial neurologic exams, either comprehensive or focused on Parkinsonian features like tremor, rigidity, and bradykinesia should be performed. This can ensure early, effective treatment of motor and other non-motor symptoms that can positively impact patients' quality of life.

7. Conclusion

RBD is a complex night time behavior consisting of dream enactment due to the loss of physiologic REM muscle atonia. It can be classified as idiopathic, which is in many cases a non-motor symptom of the alpha synucleinopathies. This group of neurodegenerative illnesses includes Parkinson's disease, Lewy body dementia, and multiple system atrophy. The importance of understanding REM sleep behavior disorder and its implications cannot be overstated. Clinical suspicion and appropriate history taking, supports an early diagnosis and symptomatic management. More importantly, treating physicians are able to educate and monitor patients for the development motor symptoms suggestive of neurodegenerative disease. This window of opportunity allows for enrollment in clinical trials and emerging therapies. Secondary RBD related to structural lesions or medications is important to recognize in order to discontinue the offending agent and decrease the risk of night time injury. Medical management with melatonin or clonazepam can reduce the episodes of dream enactment. Non-medical interventions such as ensuring a safe sleeping environment can help prevent injury.

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