Diagnosis, Treatment, and Monitoring of the Patient With Rapid Eye Movement Sleep Behavior Disorder

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Often associated with neurodegenerative disorders, rapid eye movement sleep behavior disorder is a complex sleep disorder that can be difficult to diagnose and treat. Patients with the disorder must be closely monitored.

Rapid eye movement (REM) sleep behavior disorder (RBD) is a complex, difficult condition that occurs with dreaming during the REM sleep stage. Other disorders may mimic RBD, making its diagnosis difficult. Additionally, an association with neurodegenerative disorders may exist, which requires monitoring of patients with RBD who may have or develop 1 of these conditions. Our review of the literature about RBD focuses on recommendations for its monitoring and treatment.

RBD has a relatively short history as a sleep disorder. Although initially studied in cats during the 1960s, in the 1980s, work with neurodegenerative disorders and with patients going through alcohol withdrawal allowed for description and definition of RBD in humans. The disorder is characterized by the loss of normal voluntary atonia of the muscles during REM sleep combined with complex movements when the patient is dreaming.[1,2] The current minimal diagnostic criteria include body or limb movements associated with dreaming and 1 or more of the following: dreams that appear to be acted out during sleep, sleep behavior that disrupts sleep continuity, and potentially harmful behavior during sleep.[2]

People usually seek medical attention for RBD after some sleep-related injury has occurred to themselves or a bed partner. Rarely do they seek help because of sleep disruption alone. The behaviors described by history or found during polysomnography (PSG) include talking, laughing, shouting, gesturing, swearing, grabbing, arm flailing, slapping, kicking, punching, sitting up, leaping from bed, crawling, and even running. Walking is actually uncommon in RBD, and leaving the room is especially rare and usually accidental. The eyes typically are closed in RBD, which is a major reason for injury during sleep, as the person is not attuned to the actual environment. Chewing, eating, drinking, defecation, and urination have not been documented to occur during REM sleep, so these activities would not indicate RBD.[3]

PARASOMNIAS AND DISORDERS THAT CAN MIMIC RBD

There are other sleep disorders besides RBD that can manifest as complex, injurious, and have violent sleep or dream-related behaviors in adults. Some of the disorders mimicking RBD in both children and adults are sleep terrors, sleepwalking, obstructive sleep apnea (OSA), nocturnal seizures, rhythmic movement disorder, paroxysmal dystonia, frightening hypnopompic hallucinations, sleep-related dissociative disorder, and posttraumatic stress disorder (PTSD). Malingering can also mimic RBD and can be considered as a differential diagnosis in some cases.[3]

Parasomnias can occur independently or with another sleep disorder. One of the most well known is sleepwalking, a disorder of arousal in which the person arises from a deep sleep and may display long, complex behavior followed by memory impairment of the event. Unlike RBD, sleepwalking tends to occur during stages 3 to 4 of non-REM sleep (now called stage N3), and electroencephalography (EEG) changes typically demonstrate a change in the delta rhythm just before arousal. The eyes are usually open, but motor behavior is usually clumsy and purposeless with slowed speech and mentation as well as poor response to stimulation. On occasion, potentially injurious behavior has occurred during sleepwalking.[4]

Other parasomnias include disorders of arousal, nocturnal seizures,

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psychogenic dissociative disorders, malingering, and Munchausen by proxy syndrome, which mimics parasomnias. Violent or potentially injurious behavior can occur with parasomnias because of factors such as the activation of central pattern generators, sleep/wake state dissociation, and sleep inertia. Nocturnal seizures are rarely violent and typically difficult to diagnose.[5]

RBD is also considered to be a parasomnia. Typical behaviors described in RBD include grasping, punching, screaming, kicking, and occasionally, jumping out of bed. Injuries most often reported include bruising, lacerations, bone fractures, and occasionally, subdural hematomas. Arousal from the episode is usually rapid and accompanied by a recall of a dream that will coincide with the observed behavior.[6] One study reported a patient with RBD who constructed a plywood barrier to protect his wife from him during sleep.[1]

NORMAL SLEEP

Normal sleep consists of 2 broad stages, non-REM (NREM) and REM sleep. The NREM stage is further divided into substages called N1, N2, and N3, according to the latest classification system. The stages differ by not only the presence or absence of eye movement, but also the types of brain waves seen during each stage. There is also variance in muscle activity during the different stages.[7,8] REM sleep is characterized by the rapid eye movements, low chin electromyography (EMG) tone, sawtooth waves, and transient muscle activity. The EEG demonstrates low amplitude with mixed frequency.[7,8]

DEFINITION OF RBD

The International Classification of Sleep Disorders (ICSD) set the following minimal diagnostic criteria:

A. Presence of REM sleep without atonia, defined as sustained or intermittent elevation of submental EMG tone or excessive phasic muscle activity in the limb EMG.
B. At least 1 of the following:
   1. Sleep-related injurious or potentially injurious disruptive behaviors by history; or
   2. Abnormal REM behaviors documented on PSG.
C. Absence of epileptiform activity during REM sleep unless RBD can be clearly distinguished from any concurrent REM sleep-related seizure disorder.
D. Sleep disturbance not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.[8]

To diagnose RBD, clinicians recommend an overnight sleep study, adding video monitoring and an extended EMG montage. In a typical PSG, the chin EMG is recorded as well as an EMG of the lower limbs. In RBD, characteristic findings consist of the absence of muscle atonia and the presence of increased EMG activity in the upper and lower extremities. Therefore, recording the EMGs from both upper and lower limbs, (an extended EMG montage) is important for a diagnosis. In some patients with RBD, EMG activity will occur in the upper extremities and not in the lower limbs.[9] Figure 1 contains an example of PSG fragments in a patient with RBD.[10]

Recent studies of cerebral blood flow and EEG readings have shown that RBD is more than just a parasomnia. In addition to the above diagnostic criteria, PSG will show 1 or more of the following: chin EMG tone will be excessively augmented and irrespective of the EMG chin activity, there will be excessive chin and limb phasic EMG twitching. Additionally, 1 or more of the following clinical features will occur: excessive body or limb jerking; vigorous, complex, or violent behavior; and an absence of epileptic activity associated with the disorder.[2]

These symptoms are not associated with mental disorders but can be associated with neurologic disorders, including supranuclear palsy, Alzheimer dementia (AD), Lewy body dementia (LBD), neoplasm of the brain stem, multiple sclerosis (MS) with brain stem involvement, and others. A complex relationship exists between RBD and Parkinson disease (PD). Although not all patients with RBD develop PD and vice versa, RBD may precede the development of PD by several years. Patients with idiopathic RBD are considered to be at higher risk for 1 of the neurodegenerative disorders.[2]

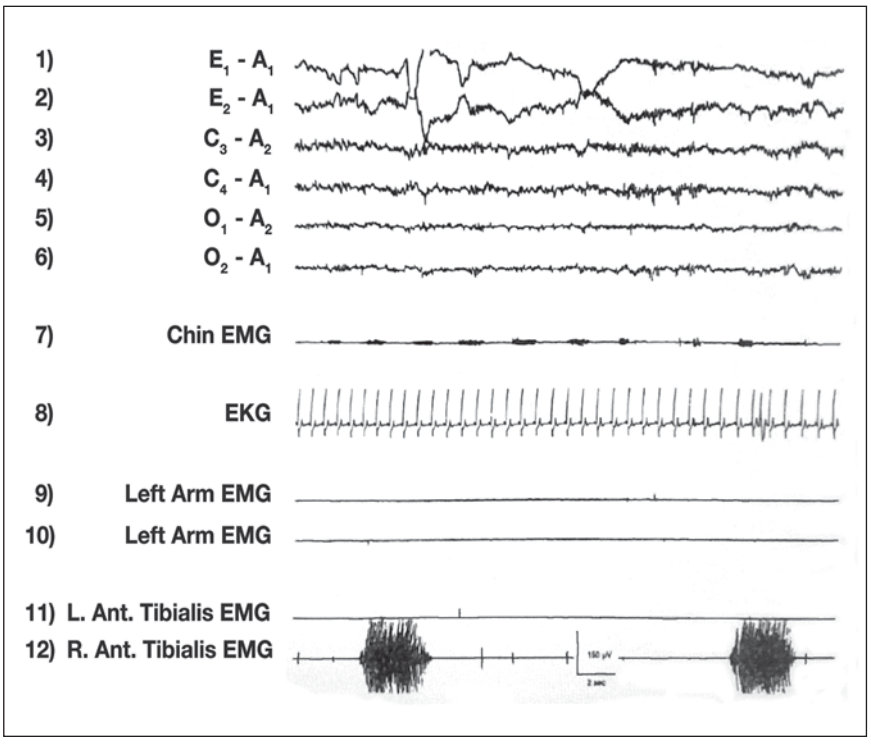

Figure 1. Nocturnal PSG of a dissociated state in a 58-year-old man with multiple sclerosis. A pathologic process usually confined to NREM sleep—periodic leg movements (12)—has intruded into REM sleep, which has typical rapid eye movements (1-2) and a desynchronized EEG (3-6). Chin EMG atonia alternates every 3 seconds with augmented tone (7).[10]

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Clinical Forms of RBD

RBD can be acute or chronic. Acute RBD has been noted in cases of drug abuse or intoxication (especially involving the abuse of tricyclic antidepressants, monoamine oxidase inhibitors, or serotonin selective reuptake inhibitors [SSRIs]).[7] Withdrawal from alcohol and sedative hypnotic agents; the use of certain medications, including venlafaxine and mirtazapine; SSRI medications, such as paroxetine and fluoxetine; and other antidepressants can result in a rebound increase in REM and cause RBD.[9,11] Bupropion is 1 antidepressant that is not considered to be a precipitating factor for acute RBD. Except for some cases of PTSD, psychiatric disorders are not usually predisposing factors in the development of RBD.[3]

RBD is described as either idiopathic or secondary to a neurologic disorder. Any lesion that involves the region of the brain, mainly in the brain stem, responsible for REM sleep atonia can trigger secondary RBD. It has been found in association with brain stem tumors, cerebrovascular lesions, Guillain-Barré syndrome, and recently in 2 disorders not associated with the brain stem, Morvan's syndrome and limbic encephalitis. Most often, however, RBD is associated with neurodegenerative disorders, including PD, LBD, and multiple system atrophy (MSA). RBD has been added to the diagnostic criteria for LBD as it is a suggestive feature of that disorder. In patients with MSA, RBD is estimated to be present in about 90% of these patients. Muscle tone abnormalities during REM sleep have been reported in up to 58% of PD patients.[6] RBD has been noted to sometimes subside considerably during late stages of an underlying neurodegenerative disorder.[3]

Chronic idiopathic RBD is diagnosed when there are no associated neurologic signs or lesions of the central nervous system. Up to 60% of RBD patients are estimated to have the idiopathic form. Some researchers believe that idiopathic RBD is a pre-

cursor to the development of a neurodegenerative disease. Studies are ongoing regarding this theory. Finally, some authors are recommending the term *cryptogenic* be used instead of *idiopathic* to describe this chronic form of RBD.[6] Idiopathic RBD is considered to be uncommon in both women and children.[3]

There is also a subclinical form of RBD, sometimes called "REM without atonia," which consists of abnormalities of RBD found on a PSG but without any clinical history of RBD. Some minor behaviors are reported, such as limb twitching, jerking, and talking, but no complex behaviors may be reported. In cases of subclinical RBD, about 25% will have the eventual emergence of clinical RBD. "Virtually all of the neurodegenerative disorders" associated with clinical RBD are also associated with the subclinical form.[3]

Typical Behaviors in RBD

Elaborate motor activity during REM sleep together with dream mentation characterizes the parasomnia known as RBD. Behaviors typical to this disorder include punching, kicking, screaming, grasping, and may even include jumping out of bed. Injuries related to this behavior have been reported by more than 75% of respondents in some studies. These injuries include ecchymoses, lacerations, bone fractures, and even subdural hematomas. The arousal from the episode is usually rapid and often the recalled dream is consistent with the observed behavior. The PSG data in RBD will reveal intermittent or complete loss of physiologic muscle atonia and excessive EMG phasic activity during the REM sleep period.[6]

Dreams and Daytime Temperament in Patients With RBD

Typically, a patient with RBD reports unpleasant, vivid, action-filled dreams that are usually congruent with the behaviors during sleep. It is commonly assumed that the lack of motor inhibition allows these patients to enact the imagery in their dreams. Patients will report fighting back animals or people who are attacking them or trying to flee such an attack occurring during their dream. The aggressiveness and violence during sleep is often in sharp contrast to the daytime temperament. Most often, the patient with RBD is mild mannered and sometimes placid when awake. A study of dream characteristics in patients with RBD found an increased occurrence of animals in the dreams as well as aggression themes, similar to the content of children's dreams. In children, the frequency of this content decreases with age, and experts hypothesize that a neurodegenerative process underlying RBD may release the archaic dream pattern in patients with RBD. However, the dream content and excessive EMG activity during REM sleep in RBD may instead reflect the hyperactivity of a common neuronal generator.[12]

Epidemiology of RBD

Men are primarily affected by RBD with the male:female ratio approximately 8:1. The reason for male predominance is still unclear. Female subjects may have the disorder but with less aggressive activity that does not result in medical attention.[6] Possibly sex hormones play a role in mediating violent and aggressive behavior, and that might explain the gender difference. However, 2 recent studies did not find sex hormone alterations or abnormalities as the probable cause of RBD in patients with PD or in idiopathic RBD.[13,14] In addition, RBD typically affects men older than 50 years of age.[6]

The prevalence of RBD is unknown. One study using a telephone survey to assess the incidence of violent behavior during sleep suggested a prevalence of 0.5% in the general population. Another study of Hong Kong residents (N = 1034) older than 70 years of age estimated a prevalence of 0.04%.[6] The American Academy of Sleep Medicine in its diagnostic and coding manual (2005) stated that a prevalence of 0.38% in the general population with a prevalence of 0.5% in the elderly population had been reported. They reported that one-third of people with newly diagnosed PD had RBD, whereas 90% of those with MSA had RBD.[3]

PATHOPHYSIOLOGY OF RBD

Although RBD can be idiopathic, the parasomnia may be associated with neurologic conditions. These include neurodegenerative disorders that can be subdivided into synucleinopathies, tauopathies, and other neurologic disorders. Synucleinopathies include LBD, PD, MSA, and pure autonomic failure (PAF). The tauopathies include AD, progressive supranuclear palsy, olivopontocerebellar atrophy, and corticobasal degeneration. Other neurologic disorders that are associated with RBD are amyotrophic lateral sclerosis, epilepsy, MS, Machado-Joseph disease, limbic encephalitis, and vascular lesions.[2] The concept of idiopathic RBD has been challenged, and at least in a certain number of cases, RBD may represent the early manifestation of an impending neurodegenerative disorder.[12]

In 2000, Olson et al reported their study of 93 patients with RBD.[1] Fifty-three patients (57%) had known or suspected neurologic disorders other than RBD. These patients underwent either a CT scan or an MRI. Among the 25 patients diagnosed with PD, symptoms of RBD preceded the PD symptoms by a median of 3 years (range 1-30 years) in 52%, or 13 of

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the 25 patients. Five of 7 patients with dementia alone had symptoms of RBD a median of 3 years before the dementia diagnosis. Fourteen patients had MSA. In 5 of these 14 patients, RBD symptoms preceded the MSA by a median of 4 years (range 1-11 years). When gender differences of patients with RBD and a neurologic disorder were compared, 67% of the females (8 of 12 females with RBD) and 54% of the males (44 of 81 males with RBD) had both disorders.[1]

All 93 patients in this study underwent PSG, 68 with the full-night diagnostic study and 25 with the split-night protocol (the second half of the night is devoted to a trial of positive airway pressure treatment for sleep disordered breathing). Additionally, 8 patients had a Multiple Sleep Latency Test (MSLT) performed following their PSG study. Ninety of the PSGs demonstrated increased EMG activity (phasic or tonic) during REM sleep. The other 3 PSGs did not show sustained REM sleep and were considered to be ambiguous sleep with REMs intruding into NREM sleep without atonia. Of the 8 MSLTs, shortened mean sleep latency was found in 2 patients with narcolepsy and 1 with PD. Sleep onset REM sleep was found in 3 patients, 1 believed to be the result of a medication withdrawal (imipramine) and 2 with narcolepsy.[1]

In the Olson et al (2000) study, patients were videotaped during the PSG. Of the 93 patients studied, 42 exhibited gross abnormal motor behavior during sleep. Ten patients had a prior history of sleepwalking in addition to reports of abnormal motor activity during sleep. Of these ten, 5 had recorded gross abnormal motor activity that occurred only during REM sleep. Five of these 10 patients had underlying neurodegenerative disorders.[1]

Brain scans using positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies of patients with idiopathic RBD have found changes in the brain stem. This area is involved with parkinsonism. The scans have found decreased binding to the presynaptic dopamine transporters, but it is unknown if this dysfunction is an epiphenomenon or the primary cause of RBD.[3]

TREATMENT OF RBD

The treatment of RBD is generally 2-fold. First, establishing and maintaining a safe sleep environment is paramount. Bed tables and harmful objects need to be removed from the bedroom and replaced with pillows.[6] In our sleep clinic, patients with RBD are advised to remove sharp objects from the bedroom and to be sure that all guns are in a locked safe or cabinet. Patients who also sleepwalk, especially out of the bedroom, are given additional safety tips.

These safety tips include locking doors to the outside, putting a chair or large piece of furniture in front of doors exiting the home, unplugging stoves if there is a history of cooking or even eating during sleep, blocking stair entries to prevent a fall, padding the floor near the bed, and sometimes putting the mattress on the floor. Advising the spouse or significant other to sleep in a separate bedroom is most important, until the patient is diagnosed and adequately treated. These safety tips are individualized after talking to the patient (and spouse or family if available) about their specific history and needs.

Second, pharmacologic treatment can control the symptoms of RBD. Clonazepam, administered at bedtime, has been found to significantly control both the abnormal behavior manifestations and the dream content of RBD. Therefore clonazepam is considered the drug of choice for treatment. Dosing range is from 0.5 mg to 2.0 mg. As a benzodiazepine, clonazepam has the potential to worsen sleep-disordered breathing, which may also be present in a patient with RBD.[6] Caution is advised with its use in patients with OSA, neurodegenerative disorders, and chronic liver disease.

About 90% of patients respond to clonazepam treatment without experiencing undesirable adverse effects (AEs). Some undesirable AEs are daytime sleepiness, prominent sedation, and confusion. When AEs are intolerable or a patient is not responding to clonazepam treatment, health care providers should consider another pharmacologic agent.

One retrospective study reviewed records from 1994 to 2006. The records revealed 39 patients with a diagnosis of RBD. The investigators analyzed 36 patients out of the original 39 who had used clonazepam as treatment for RBD. Of those thirty-six, 21 (58%) had adverse reactions to clonazepam, with 50% of those either having the dose reduced or discontinuing the medication altogether. The investigators analyzed long-term treatment (mean of 20 months) and found that 21 (54%) patients still used clonazepam, 8 (21%) used another medication, while 4 (10%) used a combination of medications to adequately control their symptoms.[15]

Other medications that have been investigated for use in patients with RBD include melatonin (level B), pramipexole, and levodopa (level C).[16]A persistent benefit with the use of melatonin was found beyond 1 year in 8 of 14 patients who had not tolerated clonazepam.[17] Quetiapine and clozapine are also considered effective in treating RBD but have not been systematically studied.

Table 1. Treatment recommendations for REM behavior disorder[16]

Recommendation levels[a]	Non-pharmaceutical	Pharmaceutical	Efficacy (benefit)	Adverse effects (AEs)
Level A	Environmental safety or self-protection measures[b]	None		
Level B		a. Clonazepam b. Melatonin c. Pramipexole	a. 90% estimated toleration[12] b. Eight of 14 found persistent benefit over 1 year[13] c. Mixed results, possible benefit in patients with no diagnosis of neurodegenerative disease[14]	a. 58% (N = 21) had AEs with 50% of those needing a lower dose or discontinuing b. Few AEs[14] c. Caution in patients with LBD, may exacerbate symptoms[14]
Level C		Levodopa	Possible benefit in small study (N = 3 with Parkinson disease)[14]	Drug may worsen or even trigger RBD[14]

[a]The following 3 levels are based on the American Academy of Sleep Medicine's classification of evidence 1 to 4, depending on the study design (1 = most rigorous; 4 = least rigorous). Level A is supported by a substantial amount of high-quality evidence (levels 1 or 2) or based on a consensus of clinical judgment. Level B is supported by a sparse amount of high-grade data (levels 1 or 2), a substantial amount of low-grade data (levels 3 or 4), or clinical consensus by the task force. Level C is supported by low-grade data (levels 3 or 4) without the volume of data to recommend more highly and is likely subject to revision with further studies.

[b]These measures include placing a mattress on the floor, bed partner sleeping in separate bed or room, barricades of pillows or screens, restraint devices (potential for skin breakdown with these), or padded waterbeds.[14] At our clinic, patients are also advised to keep guns in a safe or locked cabinet and to keep no sharp objects in the bedroom. Additional safety tips are given if the patient also sleepwalks.

Other studies have found that some medications can either improve or worsen RBD symptoms. These medications include dopamine agonists and cholinesterase inhibitors. Tricyclic antidepressants can induce RBD. SSRIs and noradrenergic and serotonergic activities have also been found to induce symptoms.[2] Acetylcholinesterase inhibitors such as donepezil; benzodiazepines, such as temazepam, triazolam, and alprazolam; other drugs, including desipramine and clozapine; and carbamazepine, sodium oxybate, and yi-gan san have been reported with varying success in small-case series and reports. However, larger studies to validate the findings are lacking in the literature.[16] Table 1 shows the more common treatments for RBD along with the recommendation level for the treatment.

FUTURE POSSIBILITIES

A recent Japanese study has found a reduction of olfactory function in patients with idiopathic RBD (IRBD) at the same magnitude as found in patients with PD and LBD. This brief test was determined to be useful as a clinical indicator or screening tool for IRBD with Lewy body formation and appropriate to use with elderly Japanese patients.[18]

Another study of Japanese patients validated the use of the REM Sleep Behavior Screening Questionnaire. The study compared 52 patients with known IRBD and 55 patients with known OSA without RBD. The researchers determined that this questionnaire was a good screening tool for IRBD in elderly Japanese patients.[19]

CONCLUSION

RBD is a complex disorder characterized by grossly abnormal and sometimes violent behavior during sleep. It will often precede an underlying neurodegenerative disorder by a few years or more. Thus, patients diagnosed with RBD who do not yet have a neurologic diagnosis should be monitored for the potential onset of 1 of these disorders. To accurately diagnose RBD, clinicians recommend an overnight sleep study using an extended EMG montage with video monitoring.

Treatment is 2-fold. The safety of the patient and others needs to be addressed. An article on the best practices for the treatment of RBD rated

modification of the sleep environment for self-protection as a level A recommendation (highest recommendation). Pharmacologic treatment is usually effective and was rated a level B recommendation.[16] Clonazepam, a benzodiazepine, is considered to be the first-line pharmacologic treatment for RBD. AEs can occur with this medication, and if the patient is unable to tolerate clonazepam, health care professionals should consider other pharmacologic treatment.

Author disclosures

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