REM-BEHAVOR DISORDER

Background

Rapid eye movement (REM) sleep behavior disorder (RBD) is a sleep disorder characterized by loss of normal voluntary muscle atonia during REM sleep associated with complex motor behavior while dreaming.[1,2,3,4]

The International Classification of Sleep Disorders requires the following criteria for the clinical diagnosis of RBD:[5]
Presence of REM sleep without atonia (RSWA) on polysomnography (PSG)
At least one of the following conditions:
Sleep-related, injurious, potentially injurious, or disruptive behaviors by history (eg, dream enactment behavior)
Abnormal REM sleep behavior documented during PSG monitoring
Absence of EEG epileptiform activity during REM sleep (unless RBD can be clearly distinguished from any concurrent REM sleep-related seizure disorder)
Sleep disorder not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder
Therefore, RSWA is an electrophysiological finding, sought on PSG in evaluation for suspected RBD.

Pathophysiology

The precise pathophysiology and neural structures involved in RBD are unknown. Based on recent animal (cats, rats), lesional, and neuropathological studies, sleep-regulating nuclei, particularly the pontine tegmentum, are thought to be involved in the pathogenesis of RBD. Also, a complex interplay of various neurochemical systems, such as noradrenergic, cholinergic, and serotonergic systems, seems to exist in the pathogenesis of RBD.[1,6]

Normally, generalized atonia of skeletal muscles occurs during REM sleep. This atonia results from active inhibition of the final common pathway of spinal motor neurons via the medullary magnocellular reticular formation (MCRF); this suppresses anterior horn cell activity via projections of the ventral lateral reticulospinal tract. Various pontine nuclei are known to influence the REM and non-REM sleep circuits, including locus coeruleus(LC), pedunculopontine nucleus (PPN), and laterodorsal tegmental nucleus (LDTN).[7] In addition, forebrain cortical and subcortical structures, substancia nigra, thalamus, hypothalamus, basal forebrain, and frontal cortex are also involved. However, their precise roles are unknown.
Several studies over the past few years suggested that RBD is frequently associated with neurodegenerative disorders characterized by alpha synuclein deposition, including Parkinson disease (PD), multiple system atrophy (MSA), and Lewy body dementia (LBD); RBD is less frequently associated with nonsynucleinopathies.[8,9,1,2,10]
Studies have suggested that RBD may be associated with alpha-synuclein – mediated degeneration of sleep-regulating nuclei in the brain stem, particularly the pontine tegmentum.

Studies by Eisensehr et al using iodine 123 (^{123}I) immunoperoxidase technique (IPT) single photon-emission computed tomography (SPECT) demonstrated that striatal presynaptic dopamine transporters are reduced in idiopathic RBD.[11] Studies by Fantini et al demonstrated impairment of cortical activity in idiopathic RBD, particularly in the occipital region during both wakefulness and REM sleep compared with controls.[12] Results were similar to the functional studies such as perfusion and metabolic impairment pattern observed in diffuse Lewy body (DLB) disease and in Parkinson disease. Similar cortical activity in the frontal and temporal regions was impaired only during wakefulness.

In essence, RBD may be the prodrome of neurodegenerative disease, such as DLB or Parkinson disease.[1] In experimental studies in cats, bilateral pontine lesions resulted in a persistent absence of REM atonia associated with prominent motor activity during REM sleep similar to that observed in RBD in humans.

Frequency

United States

The exact incidence and prevalence of RBD are unknown because of inadequate reporting and misdiagnosis. However, a telephone survey indicated a 2% overall prevalence of violent behaviors during sleep, 25% of which were likely to be due to RBD. This gives a prevalence of 0.5% of RBD in the general population.

International

No difference in the frequency of RBD exists internationally.

Mortality/Morbidity

The morbidity and mortality rates of RBD depend on the etiology.

No death has been reported in idiopathic cases; however, patients and bed partners may experience serious injury.[13] In the reported cases, 32% of patients had injured themselves and 64% had assaulted their spouses.[4] Subdural hematomas occurred in 2 patients.[4]

In secondary cases, the morbidity and mortality rates depend on the specific underlying disease itself.

Race

Racial differences in incidence and prevalence of RBD have not been reported.

Sex

RBD occurs predominantly in males.[14] In a recent report by Olson et al, of 93 patients with RBD, only 12 (13%) were females.[4]

Age

Typically, RBD is a disease of elderly persons.[8] The risk increases after the sixth decade, although the disease may occur at all ages, including childhood.[14]

Clinical

History

The presenting complaint is violent dream-enacting behaviors during REM sleep, often causing self-injury or injury to the bed partner.[15] The dream-enacting behaviors are usually nondirected and may include punching, kicking, leaping, crying out, or running from bed while still in REM sleep.[16]

Directed behavior, such as homicide, has not been reported.

The patient may be wakened or may wake spontaneously during the attack and recall vividly the dream that corresponds to the physical action.

In some cases, an extended prodrome of prominent limb and body movements occurs before the development of RBD.

Physical

The neurologic examination findings are unremarkable in idiopathic cases; in secondary cases, the physical findings depend on the underlying disorder.

Causes

In a recent study, Nightingale et al suggested that 36% of persons with narcolepsy experience symptoms of RBD.[17] This link has lead to the identification of a strong association of RBD with HLA class II genes.[18]

RBD may be idiopathic. However, several studies have suggested that idiopathic RBD is a potential marker for the later development of neurodegenerative disorders, particularly Parkinson disease (PD) and Lewy body dementia (LBD).[8,19,9,1,2,20,10,21,22] The risk varies among different studies. Therefore, evidence suggest that many cases of idiopathic RBD may not be truly idiopathic, leading some to suggest the term cryptogenic rather than idiopathic.[23]

RBD may occur in association with various neurological conditions (ie, secondary RBD), including vascular lesions, brainstem neoplasm, demyelinating disease, autoimmune/inflammatory disorders, and neurodegenerative

disorders. Recent studies suggested that RBD is more frequently associated with synucleinopathies, including PD, LBD, multiple system atrophy (MSA), and pure autonomic failure (PAF), than with nonsynucleinopathies.

Workup

Laboratory Studies

- Routine medical history should include questions that screen for abnormal sleep movements and altered dreams. Routine laboratory tests are usually not helpful.

Imaging Studies

- Imaging studies are not indicated in idiopathic cases.[1] They are indicated if neurological dysfunction is suggested by history and neurologic examination.[4] However, a recent study demonstrated that IPT-SPECT might be a useful tool in the diagnosis of REM sleep behavior disorder (RBD).

Other Tests

- The most important diagnostic studies include the following:
    - Polysomnographic (PSG) video recording: This is the most important diagnostic test in RBD.[24] On PSG, at least some tonic or phasic abnormalities of muscle tone are observed during REM sleep accompanying the attack, though usually patients have both.
    - Monitoring electro-oculogram (EOG)
    - EEG[3,10]
    - ECG
    - Nasal flow
    - Multiple electromyography (EMG) channels using chin, bilateral extensor digitorum, and tibialis anterior muscles

Treatment

Medical Care

REM sleep behavior disorder (RBD) is treated symptomatically by various medications; however, the response varies in individual cases. Therefore, all available medications should be tried before considering the patient's RBD as intractable.

The other important aspect of management of patients with RBD is environmental safety. Potentially dangerous objects should be removed from the bedroom, and the mattress should be placed on the floor or a cushion should be put around the bed.

Consultations

The neurologist may consult a sleep specialist for proper diagnosis and treatment of RBD.

Diet

No special recommendations or restrictions of diet exist for RBD.

Medication

The treatment of REM sleep behavior disorder (RBD) can be challenging in some patients with underlying neurodegenerative conditions. Clonazepam is highly effective in the treatment of RBD.[25,13,4] It is effective in

nearly 90% of patients (complete benefit in 79% of patients and partial benefit in another 11% of patients), with little evidence of tolerance or abuse. The response usually begins within the first week, often on the first night. The initial dose is 0.5 mg at bedtime. If this is ineffective, doses can be increased to 1-2 mg. With continued treatment for years, moderate limb twitching with sleep talking and more complex behaviors may re-emerge. Nevertheless, control of the violent behaviors persists. The treatment should be continued indefinitely, as violent behaviors and nightmares relapse promptly with discontinuation of medications in almost all patients. The specific mechanism of action of clonazepam in RBD is unknown but may reflect in part its serotonergic properties. In a minority of patients, particularly in elderly persons, clonazepam may increase the risk of confusion or falls and may worsen obstructive sleep apnea.[13] Clonazepam is ineffective in approximately 10% of patients.

Several studies demonstrated the beneficial effect of melatonin on RBD.[26,16] The effective dose of melatonin was 3-6 mg PO qhs; only 36% of patients experienced adverse effects, which resolved with decreased dosing. The dosage may be increased every 5-7 days to 12 mg/d in some cases, if tolerated. The mechanism of melatonin is unclear;[16] Kunz and Bes suggested that melatonin restored RBD-related desynchronization of the circadian rhythms.[27] Polysomnography (PSG) studies showed possible direct restoration of the mechanisms producing REM sleep muscle atonia.

Other medications, such as tricyclic antidepressants, may be effective in some patients. However, tricyclics are known to precipitate RBD.[13] The newer generations of antidepressants, particularly venlafaxine and mirtazapine, are frequent precipitators or aggravators of RBD.[28]

Levodopa may be very effective in patients in whom RBD is the harbinger of Parkinson disease.

In addition, anecdotal reports exist of responses to carbamazepine, clonidine, and L-tryptophan.

Benzodiazepines

By binding to specific receptor sites, these agents appear to potentiate the effects of GABA and facilitate inhibitory GABA neurotransmission and other inhibitory transmitters.

Clonazepam (Klonopin)

Very effective in treatment of RBD in small doses. Exact mechanism of action unknown. Little evidence of tolerance or abuse with such small doses.

Adult

Initial dose: 0.5 mg PO qhs; may be increased rapidly to 1 -2 mg/d in some cases

Pediatric

Not established

Tricyclic antidepressants

This is a complex group of drugs that have central and peripheral anticholinergic effects, as well as sedative effects.

Amitriptyline (Elavil)

Although known to precipitate RBD, effective in individual cases.

Adult

10 mg PO qhs initially; may be increased gradually to 75 mg/d

Pediatric

Not established

Antiparkinsonian agents

These agents often are indicated for patients with Parkinson disease.

Levodopa/carbidopa (Sinemet)

May be very effective in patients in whom RBD is harbinger of Parkinson disease.

Comes in different strengths of 25/100 mg, 25/250 mg, and 10/100 mg.