Rapid Eye Movement Sleep Behavior Disorder and Other Rapid Eye Movement Sleep Parasomnias

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ABSTRACT

Purpose of Review: The most common rapid eye movement (REM) parasomnia encountered by neurologists is REM sleep behavior disorder (RBD), and nightmares are so frequent that every neurologist should be able to differentiate them from the dream enactment of RBD. Isolated sleep paralysis is relatively common and is often mistaken for other neurologic disorders. This article summarizes the current state of the art in the diagnosis of RBD, discusses the role of specific questionnaires and polysomnography in the diagnosis of RBD, and reviews recent studies on idiopathic RBD as an early feature of a synucleinopathy, secondary RBD, and its management. Recent diagnostic criteria and implications of nightmares and isolated sleep paralysis are also reviewed.

Recent Findings: Idiopathic RBD can now be considered as part of the prodromal stage of a synucleinopathy. Therefore, an accurate diagnosis is mandatory, and this implies detection of REM sleep without atonia. The polysomnography montage, including EMG of the submentalis and flexor digitorum superficialis muscles, provides a high sensitivity and specificity for the diagnosis. The exact diagnosis is important for patient counseling and for future neuroprotective trials.

Summary: REM parasomnias include RBD, sleep paralysis, and nightmares, which have distinct clinical characteristics and different implications regarding diagnostic procedures, management, and prognosis.

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INTRODUCTION

Rapid eye movement (REM) sleep behavior disorder (RBD), nightmares, and sleep paralysis are categorized among parasomnias occurring specifically during REM sleep. In the past few years, important advances in research into these disorders have enriched the field, particularly in RBD, which has been linked to neurodegeneration.

RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER

RBD has a low prevalence in young adults, but is a more frequent parasomnia among the elderly, with an estimated prevalence of probable RBD of up to 7.7%.[1–3] The recent interest in RBD by neurologists is because, beyond its classification as a parasomnia, it has been recognized to be an early form of a synuclein disease.

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KEY POINT

- Although rapid eye movement sleep behavior disorder can be suspected by the patient's history, polysomnography is required for a definite diagnosis.

Diagnostic Criteria

The current diagnostic criteria for RBD were published in the 2014 *International Classification of Sleep Disorders, Third Edition (ICSD-3)* by the American Academy of Sleep Medicine (AASM) (**Table 5-1**).[4] These criteria require that sleep-related vocalizations or complex motor behaviors plus pathologically increased muscle tone during REM sleep on the polysomnogram (REM sleep without atonia) are present. Although RBD can be suspected by history, for a definite diagnosis of RBD, polysomnography is required.

While former *ICSD* criteria only required ''excessive'' submental or (upper or lower) limb EMG activity during polysomnography for the diagnosis of RBD, the current *ICSD-3* criteria list exact polysomnography measures for scoring guidelines and are established on evidence-based data for detecting REM sleep without atonia in the evaluation of RBD.[5,6]

Typical clinical characteristics of RBD include sleep-related complex motor behaviors and vocalizations that are associated with dreaming. Observers have the impression that apparent dream enactment is occurring (the behaviors seem to mimic dream content). Dream content is often elaborate, typical for REM-sleep dreaming, in contrast to the more static imagery and ruminations of non-REM dreamlike experiences. In RBD, patients can be awakened easily and are usually quickly oriented. The vocalizations and behaviors show a very large intraindividual and interindividual variability in RBD. This can be of some clinical help to differentiate the dream enactment behaviors of RBD from the lower variability of vocalizations in somniloquy and non-REM parasomnia or behaviors observed with periodic leg movements or sleep-related epilepsy. If subjects are not awakened immediately after the RBD episode or do not wake up spontaneously because of injury during an episode, dream content is frequently no longer remembered. The easy ability for awakening and reorientation in idiopathic RBD can help to clinically differentiate RBD from non-REM parasomnias and nocturnal wandering in dementia.

Because REM sleep is more likely to occur and REM episodes last longer in later parts of the night, RBD episodes often occur in the second half of the

TABLE 5-1 ***International Classification of Sleep Disorders, Third Edition*, Diagnostic Criteria for Rapid Eye Movement Sleep Behavior Disorder**[a]

All criteria of the following must be met for a diagnosis of rapid eye movement (REM) sleep behavior disorder

A. Repeated episodes of sleep-related vocalization and/or complex motor behaviors

B. These behaviors are documented by polysomnography to occur during REM sleep or, based on clinical history of dream enactment, are presumed to occur during REM sleep

C. Polysomnographic recording demonstrates REM sleep without atonia

D. The disturbance is not better explained by another sleep disorder, mental disorder, medication, or substance use

[a] Reprinted with permission from the American Academy of Sleep Medicine.[4]

night (whereas non-REM sleep parasomnias often occur in the first hours of sleep).

Clinical History Taking

Mild RBD probably often goes undiagnosed, as patients may be unaware of their nighttime behaviors or may ignore that dream-associated behaviors reflect a pathology that should be reported to their physician.[7,8] Specific history taking for RBD should include the bed partner whenever possible. Useful screening questions for a partner can help determine if the patient seems to ''dream a lot'' or if the partner can observe what their partner dreams about. If a partner is not available, questions to the patient should relate to whether they have been told about such behaviors or if injuries or falls out of bed have occurred during sleep (with or without remembered dreaming). Specific history taking is necessary because RBD symptoms are often not spontaneously reported,[9] and, specifically in idiopathic RBD, only patients with more severe symptoms tend to be sent to the sleep laboratory.[10]

A history of dream enactment behavior alone is insufficient to diagnose RBD, as this occurs frequently in the general population and may point to non-REM parasomnia (eg, somnambulism, sleep terrors, hypnagogic hallucinations), other sleep disorders where abnormal behaviors may occur (eg, nocturnal epilepsy, vigorous periodic limb movements, severe obstructive sleep apnea), or may be confused with nightmares or visual hallucinations.

Polysomnographic Diagnosis

Clinical diagnosis is always required in RBD, in addition to confirmatory polysomnographic features, along with recorded dream enactment behavior or complex behavior, according to current *ICSD-3* diagnostic standards. In other words, polysomnographic features of REM sleep without atonia alone are not diagnostic of RBD.

Polysomnography is mandatory for a definite and reliable diagnosis of RBD because other conditions may mimic its symptoms. Standardized protocols and normative values exist for making an exact quantitative diagnosis of RBD. The hallmark of RBD is abnormally increased activity on the surface EMG of chin (mental and submental) and upper or lower extremity surface EMG recordings during REM sleep on polysomnography. Usually, this abnormally increased EMG activity is subdivided into tonic and phasic or *any* EMG activity. Tonic EMG activity is characterized by a longer-lasting increase in the tone of the EMG (lasting longer than one-half of a 30-second epoch). Phasic EMG activity is characterized by shorter, often twitchlike increases in EMG tone, lasting 0.1 to 5 seconds.[11] While tonic EMG activity is usually only found in the mental/submental EMG, phasic activity is present in mental/submental as well as extremity muscles. Although different pathophysiologic pathways are thought to underlie tonic and phasic EMG activity in RBD, the term *any* EMG activity has been introduced for clinical reasons of quantification.[6]

Early during the course of the development of polysomnographic methods for the evaluation of RBD, Mahowald and Schenck[12] suggested that arm EMG should be recorded to accurately diagnose RBD. Because some patients have RBD behaviors mostly in the arms, and because EMG activity and movements during REM sleep in leg muscles are less specific, it is highly recommended to perform an EMG recording from the upper extremities in combination with the chin EMG to diagnose RBD (**Supplemental Digital**

KEY POINT

- Standardized protocols and normative values exist for making an exact quantitative diagnosis of rapid eye movement sleep behavior disorder.

Content 5-1, *links.lww.com/CONT/A221*) (**Figure 5-1**).[13]

Normative values for EMG activity that help to discriminate between RBD and controls have been published for 11 striated muscles (surface EMG),[6] and the most sensitive and specific, yet simple, EMG combination was of the mental/submental and flexor digitorum superficialis muscles in the upper limbs.[6] For accurate diagnosis of RBD, the polysomnography EMG montage, therefore, should include the mentalis or submentalis muscle and both upper extremities (right and left flexor digitorum superficialis). Other published values refer to the chin alone, and recent work has demonstrated that a quantitative diagnosis of RBD with highly similar EMG values can also be feasible in polysomnography with tibialis anterior EMG recordings only, and even in split-night polysomnography including

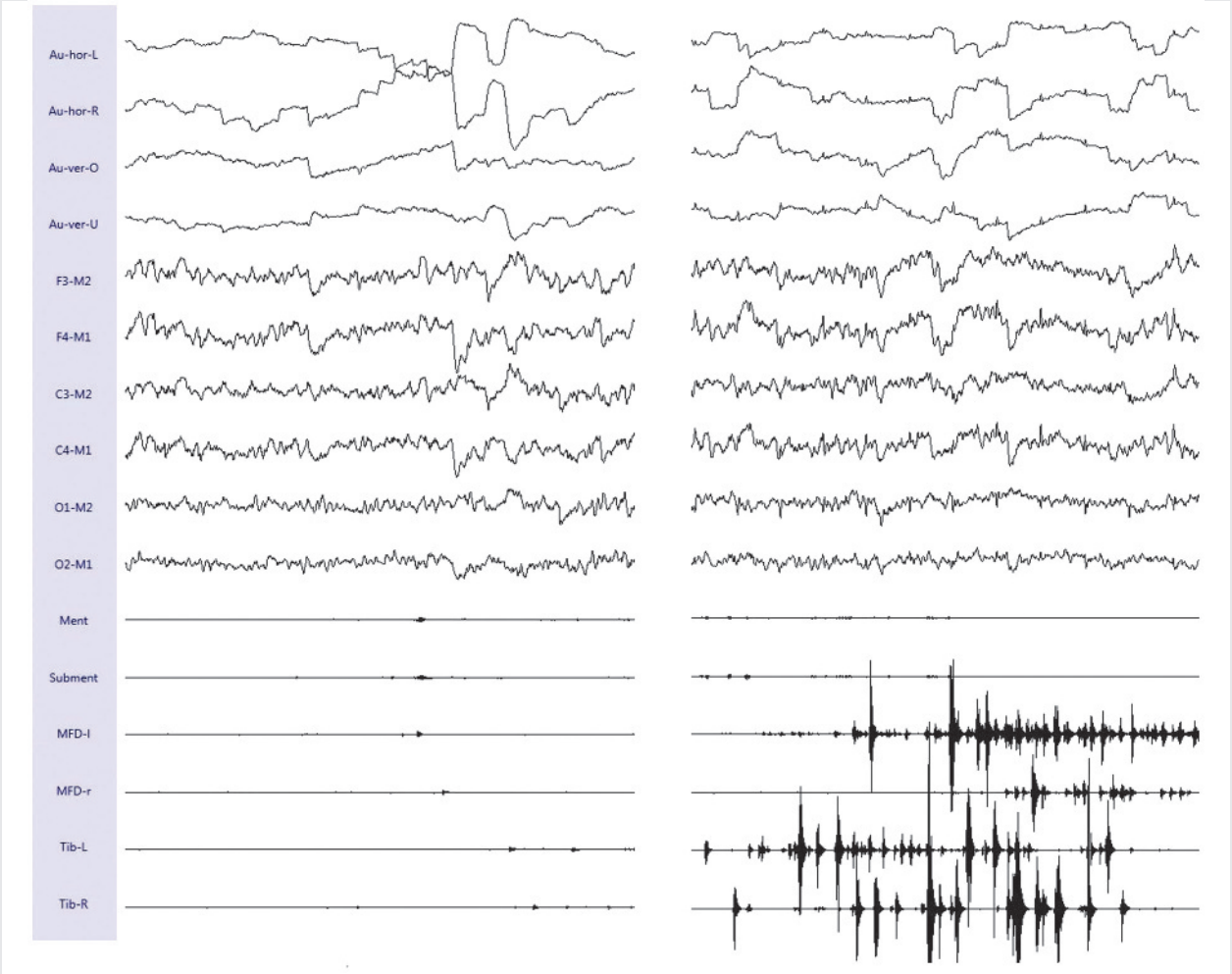

FIGURE 5-1 Examples from polysomnographic records (each panel is 10 seconds) from normal rapid eye movement (REM) sleep (left tracings) and REM sleep in a patient with REM sleep behavior disorder (RBD) (right tracings). The top four channels are horizontal and vertical electrooculography, the central six channels are EEG according to the American Academy of Sleep Medicine, and the bottom six channels represent mental and submental, left and right flexor digitorum superficialis, and left and right tibialis anterior muscles. Whereas in normal REM sleep, almost complete atonia is seen in all recorded muscle channels, in RBD, excessive phasic EMG activity is seen in both upper and lower extremity muscles. Note that in this epoch, the excessive muscle activity would not have been seen if chin EMG would have been recorded alone.

continuous positive airway pressure (CPAP) titration.[14,15] However, it is preferable, whenever possible, to have either full-night diagnostic or CPAP treatment studies rather than split-night studies, especially for research purposes.[7] The normative values require that any EMG activity (tonic, phasic, or other) in the combined recording of mentalis and right and left arm (flexor digitorum superficialis) during REM sleep should be at least 27% in 30-second epochs for RBD and 32% when a 3-second mini-epoch scoring approach is applied.[16]

Because visual quantification of increased EMG activity during REM sleep requires highly specific knowledge and is time consuming, several attempts have been made to develop computerized methods for automatic detection and quantification of EMG activity during REM sleep. A series of different approaches and techniques have been validated and published.[17–20] Some of them require separate software and analysis after polysomnography, while others can be run together with a regular polysomnographic analysis. Some rely on EMG activity analysis for the chin only.[21,22] Only one automatic analysis software designed to quantify EMG activity during REM sleep includes other additional muscles.[19]

Nevertheless, with either automated or visual scoring approaches, high technical quality of polysomnogram recordings and complete elimination of artifacts that can confound EMG activity analysis (such as snoring artifacts) are necessary, and a visual plausibility check of all calculated values with a cross-check of the original polysomnogram is necessary to ensure the quality of the diagnosis of RBD.[23]

One night of polysomnography recording is usually sufficient to make a diagnosis of RBD.[24,25] A second night is sometimes necessary in patients who do not have enough minutes of REM sleep during the first night of polysomnography or when REM sleep is markedly interrupted by apneas. In some clinical settings, the diagnosis of RBD may still have to be determined purely on clinical grounds, such as in developing regions with scarce resources, in large-scale epidemiologic studies where polysomnography is infeasible or unaffordable, or when REM sleep cannot be recorded or overall sleep architecture is so disturbed that recognition of REM sleep is impossible. Sleep architecture is often highly disturbed in advanced parkinsonism with underlying synucleinopathy, or sometimes in the setting of autoimmunity, as in the recently described IgLON5 autoimmunity syndrome,[26,27] which is now called anti-IgLON5 disease.[28] However, polysomnographic confirmation of RBD diagnosis should be considered the standard of practice.

KEY POINT

- For accurate polysomnographic diagnosis of rapid eye movement sleep behavior disorder, polysomnography should include an EMG montage using the mentalis or submentalis muscle and both upper extremities (right and left flexor digitorum superficialis).

Questionnaires for Diagnosis

Because polysomnography is sometimes not readily available, several questionnaire-based instruments have been developed to screen for RBD, namely, the REM Sleep Behavior Disorder Screening Questionnaire, the REM Sleep Behavior Disorder Questionnaire Hong Kong,[29] the Mayo Sleep Questionnaire,[30] the Innsbruck REM Sleep Behavior Disorder Inventory,[31] and the International REM Sleep Behavior Disorder Study Group's REM Sleep Behavior Disorder Single-Question Screen.[32] All of these have been validated with a reasonable sensitivity and specificity in the context of the respective validation studies. Nevertheless, some recent work has shown that the sensitivity and specificity of diagnostic RBD questionnaires strongly depend on the settings[33]; false positives are very frequent if patients

KEY POINTS

- Patients with idiopathic rapid eye movement sleep behavior disorder have no motor or cognitive symptoms.
- Most individuals initially diagnosed with idiopathic rapid eye movement sleep behavior disorder are eventually diagnosed with Parkinson disease, dementia with Lewy bodies, and, less frequently, with multiple system atrophy.

have to complete the questionnaire themselves, and false negatives occur in patients who are unaware of their nocturnal behaviors.[19]

Therefore, it should be kept in mind that questionnaires are appropriate to make a diagnosis of probable RBD only, and their usefulness and outcomes rely on the intervention of a trained interviewer. For screening purposes, a multistep strategy including confirmatory polysomnography has therefore been recommended.[34]

Video-polysomnography is recommended to diagnose RBD, but in contrast to EMG, where published cutoff values exist, no cutoff values exist for video analysis.[35] Overall, the majority of motor events, even in severe RBD, are simple elementary movements,[36] and complex or violent behaviors are much more rare and initiated during REM sleep with rapid eye movements in the majority of patients (compared to REM sleep without rapid eye movements).[37] While minor jerks during REM sleep exist in the healthy population,[35] it has been suggested that apparently intentional behaviors (so-called REM sleep behavioral events) at night could indicate the future development of RBD in patients with early Parkinson disease (PD).[38–40]

Idiopathic Rapid Eye Movement Sleep Behavior Disorder

RBD can be divided into a primary (idiopathic form) or secondary form when the parasomnia is linked to a second condition or situation.

Idiopathic rapid eye movement behavior disorder as an early feature of synucleinopathies. Patients with idiopathic RBD have no daytime motor or cognitive symptoms. However, three lines of evidence indicate that idiopathic RBD is not an innocent sleep abnormality, but represents, at least in most older adult cases presenting to sleep centers, the prodromal stage of a neurodegenerative disease characterized by neuronal cell loss and abnormal deposits of α-synuclein in surviving cells. These diseases are termed synucleinopathies and include PD, dementia with Lewy bodies (DLB), and multiple system atrophy (MSA), with disease subtypes defined by specific motor, cognitive, or autonomic impairments at presentation. Longitudinal follow-up in patients with idiopathic RBD diagnosed in sleep centers shows that most individuals initially diagnosed with idiopathic RBD are eventually diagnosed with PD, DLB, and, less frequently, with MSA.

Schenck and colleagues[41] first showed that parkinsonism developed in 11 of 29 (38%) subjects with idiopathic RBD 4 years after the diagnosis of the sleep disorder and 13 years after the estimated onset of RBD symptoms. After 16 additional years, 21 (81%) patients from this cohort were diagnosed with PD, DLB, or MSA.[42] Iranzo and colleagues[43] found that 20 of 44 (45%) patients with idiopathic RBD developed a defined neurodegenerative syndrome after a mean follow-up of 5 years. Clinical diagnoses were PD (n = 9), DLB (n = 6), MSA (n = 1), and mild cognitive impairment (n = 4). After 7 years of additional follow-up, 36 (82%) developed PD (n = 16), DLB (n = 14), MSA (n = 1), and mild cognitive impairment (n = 5). The rates of phenoconversion from idiopathic RBD diagnosis were 35% at 5 years, 73% at 10 years, and 92.5% at 14 years.[44] Similar results have been found in a large international multicenter cohort involving 279 subjects.[45]

Overall, these observations indicate that RBD is usually not idiopathic per se, but perhaps most properly termed a cryptogenic disorder that

represents an early stage of PD and DLB before the clinical onset of overt parkinsonism and cognitive impairment. Interestingly, in the setting of RBD, the coexistence of mild cognitive impairment indicates the progression to dementia in less than 5 years.[46] Thus, in patients with RBD and comorbid cognitive impairment, the disease should not be considered idiopathic. Another important aspect is that the coexistence of RBD in subjects with cognitive impairment (either mild cognitive impairment or dementia) indicates that the underlying process is a synucleinopathy (DLB or PD) and not Alzheimer disease or frontotemporal dementia.

Patients with idiopathic RBD show often subtle subjective or objective clinical abnormalities that are typical features of the synucleinopathies. Patients with idiopathic RBD may show abnormalities typical of PD such as hyposmia, depression, constipation, and decreased dopaminergic uptake in the putamen on functional imaging (**Case 5-1**).

Patients' perceived time of onset of RBD and nonmotor symptoms such as hyposmia, constipation, and depression are highly variable. Clinical examination may reveal facial akinesia, reduced arm swing, and other forms of subtle bradykinesia that still are not sufficient to disclose frank parkinsonism. Asymptomatic cognitive deficits in the executive, memory, and visuospatial domains are shown by neuropsychological tests, while electroencephalography may demonstrate subtle cortical slowing. Neuroimaging may show a number of abnormalities, including decreased metaiodobenzylguanidine uptake in cardiac scintigraphy; decreased putaminal dopamine uptake in dopamine transporter imaging; hyperechogenicity of the substantia nigra and hypoechogenicity on the brainstem raphe on transcranial sonography; loss of intensity in the substantia nigra and

KEY POINT

- Patients with idiopathic rapid eye movement sleep behavior disorder show abnormalities typical of Parkinson disease such as hyposmia, depression, constipation, and decreased dopaminergic uptake in the putamen on functional imaging.

Case 5-1

A 69-year-old man presented with a 4-year history of abnormal behaviors during sleep, which were described by his wife. Upon awakening, he would not recall these behaviors, which consisted of violent activities such as punching, kicking, knocking over the nightstand, and grabbing his wife by the neck. These behaviors were performed with his eyes closed and mainly during the second half of the night. If awakened during one of the episodes, he reported dreaming that unknown intruders were attacking him or chasing him. One night he jumped out of bed while dreaming that he was fighting against a lion. Another night he hit the wall and broke his right arm. He had no symptoms of insomnia, excessive daytime sleepiness, snoring, restless legs syndrome, or seizures. He reported no cognitive or motor problems. The patient had a history of depression and was treated with venlafaxine.

On examination, he had facial akinesia and reduced right arm swing, but limb bradykinesia, tremor, rigidity, and postural imbalance were absent. Video-polysomnography showed increased electromyographic activity during rapid eye movement (REM) sleep in all four limbs, but not in the mentalis, associated with jerks and raising the arms. Obstructive sleep apnea and periodic limb movements were absent. The patient was diagnosed with idiopathic REM sleep behavior disorder (idiopathic RBD), and clonazepam was started (1 mg at bedtime), which led to a dramatic decrease in dream-enacting behaviors.

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KEY POINT

- Dysfunction in idiopathic rapid eye movement sleep behavior disorder is widespread and involves the olfactory system, the limbic system, the autonomic system, the nigrostriatal system, the hippocampus, and the cortex. These abnormalities do not occur in all subjects with idiopathic rapid eye movement sleep behavior disorder, and some individuals show only a few abnormalities, while others have many.

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During 5 years of follow-up, he developed constipation and loss of the sense of smell. Cognitive symptoms were still absent, but neuropsychological testing showed executive dysfunction. After 6 years of follow-up, he first reported motor slowness. Neurologic examination revealed shuffling gait, bilateral asymmetric bradykinesia, and rigidity, and he was diagnosed with Parkinson disease (PD). Dopamine transporter imaging showed decreased bilateral putaminal uptake. The patient started levodopa (750 mg/d), and motor examination showed improvement in bradykinesia and rigidity.

Comment. This case illustrates that idiopathic RBD may be the first feature of PD. It also shows that patients with idiopathic RBD have no motor or cognitive symptoms and may be unaware of their symptoms as reported by the bed partner; these symptoms, which may result in injuries, respond to clonazepam. Additionally, patients with idiopathic RBD have asymptomatic, usually covert prodromal historical features of PD (eg, depression, constipation, hyposmia), and their baseline examinations may show subtle parkinsonian signs and asymptomatic neuropsychological dysfunction. In this patient, the mentalis muscle was atonic on video-polysomnography, but diagnostic REM sleep atonia loss (REM sleep without atonia) was apparent only in the limbs, demonstrating the importance of recording EMG in the limbs, especially in the arms, where isolated REM atonia loss may be seen in the flexor digitorum superficialis muscles. Typically arising from idiopathic RBD, PD was characterized in this patient by the akinetic-rigid motor subtype that responded to conventional dopaminergic therapy.

locus coeruleus/subcoeruleus area on 3T MRI; abnormal metabolic network characterized by increased activity in the pons and hippocampus and decreased activity in occipital and temporal areas by positron emission tomography (PET); decreased fractional anisotropy and increased mean diffusivity in the midbrain and pontine nuclei that regulate REM in sleep diffusion-tensor imaging; and increased gray matter density in both hippocampi revealed by voxel-based morphometry.

These findings indicate that dysfunction in idiopathic RBD is widespread and involves the olfactory system, the limbic system, the autonomic system, the nigrostriatal system, the hippocampus, and the cortex. These abnormalities do not occur in all subjects with idiopathic RBD, and some individuals show only a few abnormalities, while others have many. This indicates that some patients with idiopathic RBD are close to manifesting parkinsonism or cognitive decline, while others are not. Researchers have sought to establish which abnormalities identify those subjects with idiopathic RBD with a short-term risk for being diagnosed with PD, DLB, or MSA. They found that decreased dopaminergic putaminal uptake and hyposmia identify those subjects with idiopathic RBD who have an increased short-term risk (2.5 to 5 years) of being diagnosed with a synucleinopathy.[47,48] Patients with cortical electroencephalographic slowing tend to develop mild cognitive impairment and subsequent dementia. Hyperechogenicity of the substantia nigra alone and autonomic abnormalities do not seem to identify the risk for short-term conversion. Researchers have also evaluated if these abnormalities change with time, reflecting an active neurodegenerative process during the prodromal stage of the synucleinopathies. While dopamine

transporter imaging demonstrates progressive decline in putaminal uptake,[49] and tests show progressive cognitive deficits,[50] smell impairment, dysautonomic abnormalities, and the echogenic size of the substantia nigra by transcranial sonography remain unchanged with time. Abnormal deposits of phosphorylated α-synuclein are detected in peripheral organs outside the brain in patients with idiopathic RBD.

The Sleep Innsbruck Barcelona (SINBAR) group[51] reported that colonic biopsies detected phosphorylated α-synuclein aggregates in the submucosal nerve fibers or ganglia in four out of 17 patients with idiopathic RBD and in none of the 14 controls. In a second study, biopsy of the submandibular gland detected phosphorylated α-synuclein deposits in greater than 85% of the subjects with idiopathic RBD, and in none of the controls, in whom glandular parenchyma was obtained by the procedure.[52]

Secondary Rapid Eye Movement Sleep Behavior Disorder

Aside from the idiopathic form of RBD, the parasomnia can be found in association with other medical conditions or with the introduction of some medications and is referred to as secondary RBD.

Diagnosis. Confirmation with videopolysomnography is mandatory to establish the association between RBD and other conditions. RBD may be secondary to established neurodegenerative diseases (eg, PD, spinocerebellar ataxias), autoimmune diseases (eg, anti-IgLON5 disease, narcolepsy, paraneoplastic syndromes), focal brainstem lesions (eg, ischemic infarct, tumors), or induced by medications (eg, antidepressants) (**Table 5-2**).[53]

The link is established when the underlying condition impairs the brainstem (pons and medulla), limbic structures (amygdala), and pathways that modulate REM sleep atonia. Therefore, RBD is frequent in patients with neurodegenerative diseases (eg, PD, DLB, MSA) that affect these regions, but is rare in Alzheimer disease or frontotemporal dementia. For some conditions (eg, PD and MSA), RBD has been well characterized in a number of publications, while for other conditions (eg, Huntington disease, Machado-Joseph disease, PD with parkin2 mutations, myotonic dystrophy, Wilson disease), RBD has been reported in single or a few small case series involving small numbers of patients or in anecdotal reports (eg, attention deficit hyperactivity disorder). In some instances, RBD may be an important clinical feature, while in others it is not significant and is overlooked by other features (eg, dementia, parkinsonism, confusion, seizures). When RBD is associated with a neurodegenerative disease, the parasomnia may occur before or after the onset of the classic symptoms of the disease (eg, dementia, parkinsonism). In idiopathic PD, RBD is linked to a specific phenotype where male sex, the rigid-akinetic motor subtype, dysautonomia, and cognitive impairment predominate.[54] RBD occurs in the majority of patients with MSA, if not all, but only about one-half of them are aware of their vigorous dream-enacting behaviors. RBD in DLB (and in all dementias) should be distinguished from visual hallucinations resembling nightmares, and both confusional awakenings and episodes of nocturnal agitation can mimic the dream-enacting behaviors seen in RBD. Denervation of the amygdala and the brainstem by hypocretin/orexin deficiency explains why RBD may occur in narcolepsy. However, in narcolepsy, RBD is not very common and is usually not a bothersome symptom compared with

KEY POINTS

- In patients with idiopathic rapid eye movement sleep behavior disorder, abnormal deposits of phosphorylated α-synuclein are detected in peripheral organs outside the brain.
- Rapid eye movement sleep behavior disorder may be secondary to established neurodegenerative diseases (eg, Parkinson disease, spinocerebellar ataxias), autoimmune diseases (anti-IgLON5 disease, narcolepsy, paraneoplastic syndromes), focal brainstem lesions (ischemic infarct, tumors), and may be induced by medications (antidepressants).

TABLE 5-2 Conditions Associated With Rapid Eye Movement Sleep Behavior Disorder

- ▶ **Neurodegenerative Diseases**
  - Idiopathic Parkinson disease (25%–58% of the cases)
  - Parkinson disease with LRRK2 mutation (15%)
  - Parkinson disease with parkin2 mutation (a few descriptions)
  - Dementia with Lewy bodies (50%–70% of the cases)
  - Multiple system atrophy (90%–100% of the cases)
  - Mild cognitive impairment (a few descriptions)
  - Pure autonomic failure (a few descriptions)
  - Alzheimer disease (anecdotal cases)
  - Progressive supranuclear palsy (a few descriptions)
  - Guadeloupean parkinsonism (a few descriptions)
  - Frontotemporal dementia (anecdotal descriptions)
  - Corticobasal syndrome (anecdotal descriptions)
  - DJ1 mutations and parkinsonism-dementia–amyotrophic lateral sclerosis complex (anecdotal descriptions)
  - Amyotrophic lateral sclerosis (a few descriptions)
  - Neurodegeneration with brain accumulation type 1 (anecdotal descriptions)
  - Wilson disease (a few descriptions)
  - Huntington disease (a few descriptions)
  - Spinocerebellar ataxia type 3 (a few descriptions)
  - Spinocerebellar ataxia type 2 (a few descriptions)
- ▶ **Autoimmune Disorders**
  - Narcolepsy (30% of the cases)
  - Limbic encephalitis associated with antibodies to voltage-gated potassium channels/LIG1 (a few descriptions)
  - Anti–*N*-methyl-D-aspartate (NMDA) encephalitis (anecdotal descriptions)
  - Anti-Ma1 and anti-Ma2 encephalitis (anecdotal descriptions)
  - Anti-IgLON5 disease (100%)
  - Guillain-Barré syndrome (anecdotal descriptions)
- ▶ **Other Neurologic Conditions**
  - Myotonic dystrophy type 2 (anecdotal descriptions)
  - Autism (anecdotal descriptions)
  - Tourette syndrome (anecdotal descriptions)
  - Chiari malformations (anecdotal description)
  - Smith-Magenis syndrome (anecdotal description)
  - Möbius syndrome (anecdotal description)
  - Attention deficit hyperactivity disorder (anecdotal description)
  - Posttraumatic stress disorder (a few descriptions)

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TABLE 5-2 Conditions Associated With Rapid Eye Movement Sleep Behavior Disorder *Continued from page 1026*

▶ **Structural Brain Lesions (Anecdotal Descriptions)**
Ischemic infarct
Hemorrhage from cavernoma
Tumors (astrocytoma, neurinoma, lymphoma)
Demyelinating plaques in multiple sclerosis
Limbic encephalitis
Autosomal dominant leukodystrophy
▶ **Drugs That Can Cause or Worsen Rapid Eye Movement Sleep Behavior Disorder**
Antidepressants (especially selective serotonin reuptake inhibitors [SSRIs] and serotonin norepinephrine reuptake inhibitors [SNRIs])
Beta-blockers

hypersomnia, cataplexy, and sleep fragmentation. RBD occurs in autoimmune disorders, paraneoplastic syndromes, tumors, strokes, and multiple sclerosis when the structures that regulate REM sleep atonia (medial magnocellular nucleus, subcoeruleus nucleus, amygdala) are damaged.

Antidepressants including tricyclics, selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) can induce RBD. Lipophilic beta-blockers such as bisoprolol may also trigger RBD. Discontinuation of the offending drug is usually associated with the elimination of the clinical and video-polysomnographic features of RBD, suggesting that the parasomnia was simply a side effect of these drugs. However, in other cases, RBD persists, suggesting that the antidepressant may have unmasked an otherwise latent neurodegenerative process.

RBD has been described in the new entity, anti-IgLON5 disease.[26,27] This neurologic disorder is characterized by the presence of autoantibodies against IgLON5 (a neuronal cell adhesion protein) and the haplotypes DQB1*0501 and DRB1*1001, and postmortem examination shows a tauopathy involving the brainstem and hypothalamus. From a clinical point of view, there are a variety of neurologic (eg, gait instability, dysphagia, chorea, dementia, tiredness, hoarseness, dystonia, upward gaze palsy) and sleep (eg, insomnia, stridor, dream-enacting behaviors, hypersialorrhea during sleep, hypersomnia) abnormalities. Video-polysomnography shows a very complex sleep pattern characterized by sleep-breathing abnormalities (obstructive sleep apnea and inspiratory stridor secondary to vocal cord palsy) and by abnormal sleep architecture. Abnormal sleep architecture includes infrequent normal N1 and N2 sleep, normal N3 sleep with delta waves only in the second half of the night, periods of diffuse delta activity typical of normal N3 sleep mixed with spindles, poorly structured stage N2 sleep with spindles and K complexes, vocalizations and apparently intentional behaviors in non-REM sleep, and RBD of mild intensity characterized by very frequent limb and body jerks, but no vocalizations and no complex or finalistic (apparently goal-directed) behaviors. This entity affects people of both sexes older than

KEY POINTS

- Antidepressants including tricyclics, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors can induce rapid eye movement sleep behavior disorder. Lipophilic beta-blockers such as bisoprolol may also trigger rapid eye movement sleep behavior disorder.
- Rapid eye movement sleep behavior disorder has been described in the new entity, anti-IgLON5 disease, characterized by the presence of autoantibodies against IgLON5 (a neuronal cell adhesion protein), and postmortem examination shows a tauopathy involving the brainstem and hypothalamus.

KEY POINTS

- First-line drug treatment of rapid eye movement sleep behavior disorder symptoms are clonazepam or melatonin at bedtime.
- Patients with idiopathic rapid eye movement sleep behavior disorder are candidates for enrollment in neuroprotective trials.
- Nightmares are usually benign when isolated, but may be one of the features of several conditions such as rapid eye movement sleep behavior disorder, narcolepsy, sleep terrors, depression, posttraumatic stress disorder, and the effect of some medications.

the age of 50 and does not respond to immunotherapy.

Management. To minimize the risk of injury, protection measures are recommended to improve the safety of the sleep environment, such as sleeping in separate beds or bedrooms, removing dangerous objects from the bedroom, installing bed rails, or placing cushions on the floor next to the bed. First-line drug treatments of RBD symptoms are clonazepam and melatonin at bedtime, and either is effective in reducing dream-enacting intensity and frequency, but they do not impact, in idiopathic RBD cases, the risk for developing PD and DLB. The typical effective doses are clonazepam 0.25 mg to 2 mg and melatonin 3 mg to 12 mg at bedtime. Dopaminergic agents are not effective.[55]

It is debatable if physicians should inform the patient with idiopathic RBD that the parasomnia is associated with a risk for developing parkinsonism and dementia. The issue raises ethical and practical considerations. It is important to remark that (1) patients with idiopathic RBD feel well and have no motor or cognitive problems, (2) no interventions exist to stop the neurodegenerative process, and (3) the risk for conversion is not absolute and not imminent. For these reasons, some physicians argue against disclosing information that would lead to years of worry. If physicians are reluctant to disclose information, it is very likely that newly diagnosed patients with idiopathic RBD or their relatives will search on the Internet and find out the strong link between their parasomnia and a neurodegenerative disease. Patients may then think that their physician withheld important information regarding their health. The authors believe that early disclosure of the risk is an optimal approach to provide accurate counseling. Physicians should inform patients with caution but with a determined attitude. The conversation should focus on the goals of good medical care, commitment, and encouraging periodic follow-up visits. Patients should learn that these routine visits will allow the earliest identification of parkinsonism and cognitive impairment and will enable appropriate management for enhancing quality of life. Also, patients should be informed that clinicians and researchers aim to design disease-modifying drug trials in the idiopathic RBD population, and patients with idiopathic RBD are candidates to be considered for enrollment in neuroprotective trials.

Of course, physicians do not need to give all this information at the initial visit, but can provide it on subsequent follow-up visits, depending on each individual patient.

NIGHTMARES

Contrary to popular belief, dreams occur not only during REM sleep but also during all stages of non-REM sleep. Thus, nightmares (repeated occurrences of extended, dysphoric, and well-remembered dreams that usually involve threats to survival, security, or physical integrity) may occur in all sleep stages. An important feature of nightmares is that, upon waking, the person remembers the unpleasant dream and is fully oriented and alert. Particularly in children, nightmares are isolated, transient, and benign. In these cases, education and reassurance that nightmares are harmless conditions are sufficient. See **Table 5-3** for the *ICSD-3* diagnostic criteria for nightmares.

Nightmares are usually benign when isolated but may be one of the features of several conditions such as RBD, narcolepsy, sleep terrors, depression, posttraumatic stress disorder, and the effect of some medications.

TABLE 5-3 ***International Classification of Sleep Disorders, Third Edition*, Diagnostic Criteria for Nightmares**[a]

Criteria A through C must be met for a diagnosis of nightmares

A. Repeated occurrences of extended, extremely dysphoric, and well-remembered dreams that usually involve threats to survival, security, or physical integrity

B. On awakening from the dysphoric dreams, the person rapidly becomes oriented and alert

C. The dream experience, or the sleep disturbance produced by awakening from it, causes clinically significant distress or impairment in social, occupational, or other important areas of functioning as indicated by the report of at least one of the following:

1. Mood disturbance (eg, persistence of nightmare affect, anxiety, dysphoria)
2. Sleep resistance (eg, bedtime anxiety, fear of sleep/subsequent nightmares)
3. Cognitive impairments (eg, intrusive nightmare imagery, impaired concentration, or memory)
4. Negative impact on caregiver or family functioning (eg, nighttime disruption)
5. Behavioral problems (eg, bedtime avoidance, fear of the dark)
6. Daytime sleepiness
7. Fatigue or low energy
8. Impaired occupational or educational function
9. Impaired interpersonal/social function

[a] Reprinted with permission from the American Academy of Sleep Medicine.[4]

Nightmares can be the side effect of medications (eg, beta-blockers, antidepressants, nicotine, or varenicline patches) or the effect of substance withdrawal (eg, alcohol). In RBD, dream content consists of situations where the patient is attacked or chased. The same content may occur in subjects with severe obstructive sleep apnea (**Case 5-2**) and periodic limb movement disorder, although they usually occur in N2 sleep. Nightmares in sleep terrors occur in N2 and N3 sleep and involve threats and the need to escape from something like a fire or a small room. Depression and obstructive sleep apnea are associated with nightmares consisting of frustration (eg, not finding the car in a parking lot or not finishing tasks at work) or, in the case of sleep apnea, sometimes suffocation or drowning.

Therapy is warranted when recurrent nightmares cause significant stress and impairment in social, occupational, and other areas of functioning (eg, anxiety, fear of sleep, fatigue). For nightmares associated with posttraumatic stress disorder, prazosin 1 mg to 3 mg nightly has been shown to be beneficial, leading to its adoption for treatment of nightmares more broadly, although evidence for treatment of nightmares unassociated with posttraumatic stress is not established.[55] A mindfulness-based intervention known as dream image rehearsal therapy has also been reported to be successful in

KEY POINTS

- Isolated sleep paralysis is a benign condition but can be a highly frightening situation when it first occurs. Secondary sleep paralysis is a feature of narcolepsy. Relevant neurologic and medical differential diagnoses must be ruled out.
- Sleep paralysis is termed hypnagogic when it occurs upon falling asleep and hypnopompic when it occurs upon awakening.

Case 5-2

A 66-year-old man presented to a sleep center with a 3-year history of dream-enacting behaviors. He had been diagnosed with Parkinson disease 7 years earlier and was taking 2 carbidopa/levodopa 25 mg/100 mg tablets 3 times daily (total levodopa dosage of 600 mg/d) and the rotigotine patch (8 mg). Behaviors witnessed by his wife while the patient slept included gesturing, pointing out, smacking, kicking, talking, and shouting. He recalled having disturbing dreams such as fighting someone or having trouble finding his car keys. These abnormal behaviors and nightmares did not change after being treated with clonazepam (3 mg at bedtime) for 6 months. He was a habitual loud snorer and admitted to dozing off while watching television and reading magazines. He denied cognitive impairment. Neurologic examination was unremarkable.

Video-polysomnography showed an apnea-hypopnea index of 57 per hour, an arousal index of 65, minimal oxyhemoglobin saturation of 64%, and a decrease in slow-wave sleep percentage. Videotape analysis disclosed abnormal behaviors that appeared to be acting out a dream (ie, gesturing, kicking, talking) that only occurred during arousals at the end of most obstructive sleep apneic events. Behaviors displayed from arousals in rapid eye movement (REM) sleep were indistinguishable clinically from those occurring in non-REM sleep. REM sleep was characterized by muscle atonia. No increased tonic or phasic EMG activity occurred in the mentalis and four limb muscles. Epileptiform activity was not detected. The patient accepted treatment with continuous positive airway pressure (CPAP). A second polysomnographic study showed that CPAP titration eliminated snoring, apneic events, arousals, and oxyhemoglobin desaturations with an optimal pressure of 9 cm of H_20. A second video-polysomnography study also found normal REM sleep atonia. During follow-up visits, the patient reported good CPAP compliance, using the machine every night, with complete cessation of his abnormal sleep behaviors, unpleasant dreams, snoring, and daytime hypersomnolence.

Comment. Severe obstructive sleep apnea can mimic the characteristic symptoms of RBD. Video-polysomnography should be performed in subjects with suspected RBD to confirm or to exclude the presence of this parasomnia.

the management of nightmare disorder. Image rehearsal therapy involves "rewriting" the storyline, theme, or conclusions of a typical distressing nightmare to a more positive conclusion during wakefulness for 10 to 20 minutes daily, with hopes that this strategy improves the nightmarish dream content.[55]

RECURRENT ISOLATED SLEEP PARALYSIS

Whereas in RBD, persisting muscle tone during REM sleep permits the occurrence of RBD behaviors, in recurrent isolated sleep paralysis, it is assumed that REM sleep muscle atonia, otherwise a hallmark of physiologic REM sleep, persists and extends into wakefulness. Isolated sleep paralysis is a benign condition but can be experienced as a highly frightening situation when it first occurs. Secondary sleep paralysis is a feature of narcolepsy, and relevant neurologic and medical differential diagnoses (eg, hypokalemic periodic paralysis) must be ruled out.

Sleep paralysis is termed hypnagogic when it occurs upon falling asleep and hypnopompic when it occurs upon awakening. The characteristic clinical feature of sleep paralysis is

the complete inability to move (not only heaviness) in the presence of full wakefulness. Ancillary respiratory muscles are also affected from REM sleep atonia, and the diaphragm is the only respiratory muscle continuing to function during REM sleep. A sensation of difficulty breathing, sometimes associated with hallucinatory experiences, have contributed to the fact that sleep paralysis is recognized in different popular cultures.[56] Extrinsic eye muscles are unaffected. While no specific medical treatment beyond reassurance as to its ultimately physiologic and benign nature is recommended for recurrent isolated sleep paralysis, frequent triggers (eg, sleep deprivation, jet lag, comorbid obstructive sleep apnea triggering arousal) should be recognized and corrected or avoided. Differential diagnosis may include hypokalemic periodic paralysis, complex nocturnal visual hallucinosis, panic attacks, obstructive or central sleep apnea, and transient ischemic attack. However, the characteristic features of recurrent, short-lived, symmetrical paralysis with rapid recovery and a benign clinical course experienced only upon awakening from sleep are diagnostic historical features for recurrent isolated sleep paralysis. While sleep paralysis is listed among the REM-related parasomnias in the *ICSD-3*, it should be also noted that even in healthy persons, sleep paralysis may sometimes go along with hallucinatory experiences, namely, visual, acoustic, or tactile hallucinations of the perception of a person's presence. However, hypnagogic hallucinations are listed among the other parasomnias. In some cases, rudimentary low-volume vocalizations are also uttered during sleep paralysis.

CONCLUSION

RBD is clinically characterized by dream-enacting behaviors and nightmares. Video-polysomnography is needed to establish its diagnosis, showing abnormal behaviors and REM sleep without atonia. An optimal video-polysomnographic montage should include audio and EMG recording of the mental/submental and flexor digitorum superficialis muscles in the upper limbs. Correct diagnosis is important because other conditions may mimic RBD symptoms, and the idiopathic form may herald PD and DLB. Patients with idiopathic RBD are candidates for testing neuroprotective medications to halt the degenerative process and prevent the onset of parkinsonism and dementia. Recurrent sleep paralysis and nightmares are usually benign conditions, but, in some cases, are components of sleep disorders such as in narcolepsy, sleep terrors, and RBD.

VIDEO LEGEND Supplemental Digital Content 5-1

Rapid eye movement sleep behavior disorder. A 63-year-old man with idiopathic rapid eye movement (REM) sleep behavior disorder showing typical prominent jerks during REM sleep.

links.lww.com/CONT/A221

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KEY POINTS

- Ancillary respiratory muscles are also affected from rapid eye movement sleep atonia, and the diaphragm is the only respiratory muscle continuing to function during rapid eye movement sleep.
- The differential diagnosis for recurrent isolated sleep paralysis may include hypokalemic periodic paralysis, complex nocturnal visual hallucinosis, panic attacks, obstructive or central sleep apnea, and transient ischemic attack. However, the characteristic features of recurrent, short-lived, symmetrical paralysis with rapid recovery and a benign clinical course experienced only upon awakening from sleep are diagnostic historical features for recurrent isolated sleep paralysis.

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