Review

Rapid Eye Movement Sleep Behavior Disorder and Neurodegenerative Disease

Michael Joseph Howell, MD; Carlos Hugh Schenck, MD

IMPORTANCE The dream enactment of rapid eye movement sleep behavior disorder (RBD) is often the first indication of an impending α-synuclein disorder, such as Parkinson disease, multiple-system atrophy, or dementia with Lewy bodies.

OBJECTIVE To provide an overview of RBD from the onset of dream enactment through the emergence of a parkinsonian disorder.

EVIDENCE REVIEW Peer-reviewed articles, including case reports, case series, retrospective reviews, prospective randomized trials, and basic science investigations, were identified in a PubMed search of articles on RBD from January 1, 1986, through July 31, 2014.

FINDINGS Under normal conditions, vivid dream mentation combined with skeletal muscle paralysis characterizes rapid eye movement sleep. In RBD, α-synuclein abnormalities in the brainstem disinhibit rapid eye movement sleep motor activity, leading to dream enactment. The behaviors of RBD are often theatrical, with complexity, aggression, and violence; fighting and fleeing actions can be injurious to patients as well as bed partners. Rapid eye movement sleep behavior disorder is distinguished from other parasomnias by clinical features and the demonstration of rapid eye movement sleep without atonia on polysomnography. Consistent with early neurodegeneration, patients with RBD demonstrate subtle motor, cognitive, and autonomic impairments. Approximately 50% of patients with spontaneous RBD will convert to a parkinsonian disorder within a decade. Ultimately, nearly all (81%-90%) patients with RBD develop a neurodegenerative disorder. Among patients with Parkinson disease, RBD predicts a non–tremor-predominant subtype, gait freezing, and an aggressive clinical course. The most commonly cited RBD treatments include low-dose clonazepam or high-dose melatonin taken orally at bedtime.

CONCLUSIONS AND RELEVANCE Treatment of RBD can prevent injury to patients and bed partners. Because RBD is a prodromal syndrome of Parkinson disease (or related disorder), it represents a unique opportunity for developing and testing disease-modifying therapies.

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Author Affiliations: Department of Neurology, University of Minnesota, Minneapolis (Howell); Department of Psychiatry, University of Minnesota, Minneapolis (Schenck).

Corresponding Author: Michael Joseph Howell, MD, Department of Neurology, University of Minnesota, 717 Delaware St SE, Room 510, Minneapolis, MN 55414 (howell@umn.edu).

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Advent of Dream Enactment

Long before the onset of bradykinesia and tremor in Parkinson disease (PD), a constellation of seemingly unrelated symptoms may arise, including difficulty with smell (hyposmia) and constipation. These symptoms are often subtle and not disclosed to health care professionals. Patients will describe these phenomena as having been present for decades but of little significance. A more dramatic manifestation of neurodegeneration will arise in the form of violent, often injurious, sleep behaviors. This condition is rapid eye movement (REM) sleep behavior disorder (RBD) (**Box**). It emerges as the result of brainstem abnormalities in regions that control REM sleep years before the α-synuclein degeneration of dopamine-producing neurons in the substantia nigra of the midbrain produce the classic PD symptoms.[1]

The customary suppression of motor activity during normal REM sleep is the result of multiple interacting pathways that terminate on spinal motor neurons. Discrete areas of the brainstem influence REM-related muscle tone, including REM-on nuclei (precoeruleus and sublateral dorsal) and REM-off nuclei (ventral lateral portion of the periaqueductal gray matter and lateral pontine tegmentum). Patients with RBD demonstrate abnormalities in these pontine regions.[2]

Rapid eye movement sleep behavior disorder movements appear purposeful because the individual is acting out an internal dream plot; when awoken, patients frequently describe vivid dreams. The spectrum of dream enactment behavior (DEB) ranges from small hand movements to violent actions, such as punching, kicking, or leaping out of bed. Rapid eye movement sleep behavior disorder typically arises during the fifth or sixth decade of life in a patient without a history of sleepwalking; the frequency of DEB varies from

nightly to weekly or monthly, and actions tend to become more brazen over time.[2,3] Discordant from their waking personality, patients often have sleep-related vocalizations that are loud and laden with expletives.[1]

Potential sleep-related injuries include fractures, dislocations, lacerations, and hematomas. Patients will take various measures to prevent sleep-related injury, such as sleeping on a floor in a room devoid of furniture, and often have DEB for years before seeking medical attention. As bed partners are frequently the target of violent dream enactment, RBD occasionally has forensic implications.[1]

The prevalence of RBD in the general population is approximately 0.5% (35 million patients worldwide), with higher frequencies among patients with neurodegenerative diseases, the elderly, or individuals who are taking antidepressant medications.[2,3] Overall, most patients with RBD are men; however, female patients with RBD are underreported. Women have less injurious behaviors and thus are less likely to receive medical attention. Furthermore, because of the sex differences in life expectancy, elderly women are more likely to sleep without a bed partner and thus have unwitnessed parasomnia behaviors.[1]

Methods

Peer-reviewed articles, including case reports, case series, retrospective reviews, prospective randomized trials, and basic science investigations, were identified in a PubMed search of articles on RBD from January 1, 1986, through July 31, 2014. The PubMed search was performed on September 1, 2014, and resulted in 505 publications.

Transition to Neurodegenerative Disease

The interval between the onset of RBD and the parkinsonian triad of resting tremor, bradykinesia, and cogwheel rigidity varies, but on average, 50% of patients will convert to parkinsonism within 10 years.[4,5] Ultimately, 81% to 90% of otherwise idiopathic cases of RBD develop into a neurodegenerative disorder.[4,5] Even among the rare cases of apparently persistent idiopathic RBD, neuroimaging biomarkers are abnormal, and the results of postmortem examination reveal α-synuclein abnormalities.[2]

Before the onset of parkinsonism, patients with RBD have subtle yet progressive motor and gait abnormalities that are consistent with its subclinical pathologic features.[1,2] While attempting to stand, motionless patients have postural instability when distracted.[6] During gait initiation, they show abnormal force generation consistent with freezing of gait, and there is a measurable decline in velocity and cadence while walking, with an increase in stride and swing variability.[7,8]

Findings from neuropsychological testing reveal mild but progressive deficits in visuoconstructional skills, facial expression recognition, and color identification, similar to the impairments observed in patients with PD and dementia with Lewy bodies (DLB).[2,9] The combination of RBD, hyposmia, and impaired color identification predicts a more rapid conversion to PD.[9]

Comorbid autonomic dysfunction is consistent with RBD as part of an evolving neurodegenerative disorder. Enteric neuron pathologic features manifest as constipation and symptoms similar to hyposmia; when combined with RBD and impaired color vision, these symptoms predict progression to PD. Findings from cardiac scintography have demonstrated sympathetic denervation in patients with RBD, and heart rate orthostatic responses in RBD are blunted compared with controls and intermediate compared with individuals with PD.[2]

By the time PD motor abnormalities develop, up to 90% of dopaminergic cells in the substantia nigra are dysfunctional. Findings from neuroimaging have demonstrated progressive dopaminergic abnormalities in RBD before the onset of parkinsonian motor features.[10] Cholinergic denervation has been reported in RBD and, like cholinergic impairment in PD, these findings are correlated with cognitive decline.[11] Findings from magnetic resonance imaging, functional magnetic resonance imaging, and electroencephalography have demonstrated cortical abnormalities in RBD similar to those in patients with PD and DLB.[12-14]

Dream enactment behavior with RBD may emerge with antidepressant medication therapy and, like spontaneous cases of RBD, appears to indicate early α-synuclein disorders that are unmasked by these medications. Medication-associated dream enactment may be the most prevalent form of RBD among young adults.[1,15] An intriguing recent study demonstrated that patients with antidepressant-associated RBD have other prodromal markers of α-synuclein neurodegeneration, such as hyposmia, constipation, and visual and subtle motor impairments. These findings imply that antidepressants may expose, instead of induce, RBD in individuals who are at risk for neurodegeneration.[16]

RBD Comorbid With Neurodegenerative Disease

The prevalence of RBD varies among α-synuclein disorders: 30% to 50% in PD, 50% to 80% in DLB, and 80% to 95% in multiple-system atrophy.[2,17,18] The presence of RBD predicts the non–tremor-predominant subtype of PD and a more rapid decline in motor and cognitive function, with greater disease burden.[1,2,17,18] Patients with RBD also have higher Hoehn and Yahr stages (increased severity) and greater motor fluctuations.[1,2,17,18] Orthostatic hypotension and constipation are more common in PD with RBD compared with PD alone.[17,19] In DLB, the presence of DEB is associated with earlier onset of parkinsonism and visual hallucinations.[20]

Freezing of gait is disabling and unresponsive to current medical and surgical PD therapy. It is characterized by transient episodes of absent forward movement during ambulation, gait initia-

Box. International Classification of Sleep Disorders Criteria, 3rd Revision

REM Sleep Behavior Disorder

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

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

C. Polysomnographic recording demonstrates REM sleep without atonia.

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

Abbreviation: REM, rapid eye movement.

Table. James Parkinson's Description of RBD and FOG in Case VI

Symptoms	Description
RBD	"His attendants observed, that of late the trembling would sometimes begin in his sleep, and increase until it awakened him: when he always was in a state of agitation and alarm…" "…when exhausted nature seizures a small portion of sleep, the motion becomes so violent as not only to shake the bed-hangings, but even the floor and sashes of the room…"
FOG	"…whilst walking he felt much apprehension from the difficulty of raising his feet, if he saw a rising pebble in his path? He avowed, in a strong manner, his alarm on such occasions; and it was observed by his wife, that she believed that in walking across the room, he would consider as a difficulty the having to step over a pin."

Abbreviations: FOG, freezing of gait; RBD, rapid eye movement sleep behavior disorder.

tion, or turning. Many of the same pontine regions implicated in the pathogenesis of RBD also mediate the pathophysiologic conditions of freezing of gait. Patients with PD and RBD are most likely to have freezing of gait and a higher frequency of falls.[19]

Interestingly, in his original 1817 monograph[21] titled, "An Essay on the Shaking Palsy," Parkinson not only described the condition that would later bear his name but also appeared to link RBD and freezing of gait. He described a patient (case VI) with the combination of a violent parasomnia and transient gait interruption (**Table**).

The presence of RBD also predicts cognitive dysfunction. Among patients with PD and RBD, 73% have mild cognitive impairment compared with only 11% of patients with PD alone.[11] In a prospective study,[22] 4 years after an initial baseline evaluation, 48% of patients with PD and RBD had converted to dementia compared with 0% of patients with PD without RBD. Conversely, among patients with dementia, the presence of RBD helps distinguish DLB from Alzheimer pathologic conditions.[2]

Rapid eye movement sleep behavior disorder occurs, albeit rarely, in the setting of other neurodegenerative disorders, including tauopathy-related parkinsonian syndromes (progressive supranuclear palsy and Guadeloupean parkinsonism), TDP-43opathies (frontotemporal dementia and amyotrophic lateral sclerosis), trinucleotide repeat disorders (spinocerebellar ataxia type 3 and Huntington disease), and amyloidopathies (Alzheimer disease). With the exception of spinocerebellar ataxia type 3, the prevalence of RBD is relatively low in these conditions, and RBD does not typically precede, but instead follows, the other neurological deficits.[2]

Investigation

Whether DEB presents in isolation (premorbid) or in combination with a neurodegenerative disease, the first step in clinical management is to discern RBD from other parasomnias. These superficially similar disorders include the non-REM parasomnias (disorders of arousal, such as sleepwalking and night terrors), other REM parasomnias (nightmare disorder, sleep-related hallucinations, and sleep paralysis), and sleep-related epilepsy.

A detailed review of a patient's nocturnal episodes, preferably with the assistance of a bed partner, can help distinguish RBD from other sleep-related disorders. Rapid eye movement sleep behavior disorder consists of brief recurrent dream enactment, mainly during the second half of the night (owing to the predominance of REM sleep at that time), in contrast to the disorders of arousal (non-REM parasomnias) in which there is often a lifelong history of prolonged complex behaviors without dream mentation that more often occur in the first half of the night. Dream content is often confrontational and aggressive in RBD, and punching and kicking actions are common. Furthermore, owing to the low arousal threshold of REM sleep, episodes are readily reversible with external stimulation (such as the voice of a bed partner), and patients typically orient within moments of arousal. This feature differs from non-REM parasomnias (in particular, night terrors), in which attempts to calm an individual can paradoxically exacerbate behavior. Other REM sleep parasomnias (nightmares, sleep-related hallucinations, and sleep paralysis) are distinguished from RBD by the absence of dream enactment. Abnormal behaviors in nocturnal epilepsy are stereotyped and recurrent. Scalp electroencephalography may demonstrate ictal epileptic activity, and thus a low threshold for treatment is necessary.[1,3]

Rapid eye movement sleep behavior disorder is associated with various environmental exposures and behavioral risk factors. In particular, patients with RBD are more likely to have a history of traumatic brain injury, farming, pesticide exposure, and fewer years of education.[23] These risk factors are not surprising because they are similar to those associated with PD.[23]

Polysomnography with time-synchronized video is necessary for establishing an RBD diagnosis and to exclude reversible conditions, such as obstructive sleep apnea, that can fragment REM sleep and precipitate dream enactment. Even when abnormal behaviors do not occur overnight, polysomnography can establish the diagnosis by demonstrating increased REM sleep motor tone and/or increased phasic motor activity (**Figure 1** and **Figure 2**). The combination of REM sleep motor activity with a history of DEB and the absence of a separate, clinically significant sleep disorder establishes the diagnosis.[1,3]

Once RBD has been identified, it is important to screen patients for parkinsonian features and ancillary symptoms. When chronic unexplained hyposmia and constipation coexist with RBD, the triad is highly suggestive of impending neurodegeneration. Furthermore, it is useful to probe for early bradykinetic features of non–tremor-predominant PD. These phenomena are often perceptible but so slight that they are dismissed as routine aging. Does the patient have difficulty with turning over in bed? Is there bradykinesia while eating or dressing? Are these difficulties unilateral (highly suggestive of PD)? Has the patient's handwriting changed and speech volume diminished? Finally, freezing of gait may be screened with the question, "Do your feet ever feel as if they are stuck to the floor?"

On examination, careful scrutiny for subtle parkinsonism is essential. It should be noted that the non–tremor-predominant form of PD is easily misdiagnosed, especially in the early stages of the disease. Documentation should contain the patient's affect, voice volume, speed of articulation, blink rate, and motor tone, using distracting maneuvers to elicit subtle cogwheeling rigidity. Important features of gait testing include stride length, arm swing, number of steps to turn, and any freezing of movement. Furthermore, postural instability (loss of righting reflex with sudden retropulsion) is a risk factor for falling and commonly noted in patients with PD and RBD. The Unified Parkinson Disease Rating Scale includes these examination features and can be used to prospectively quantify the burden of PD. Baseline cognitive screening should be conducted by administering a Mini-Mental State Examination or Montreal Cognitive Assessment.[1]

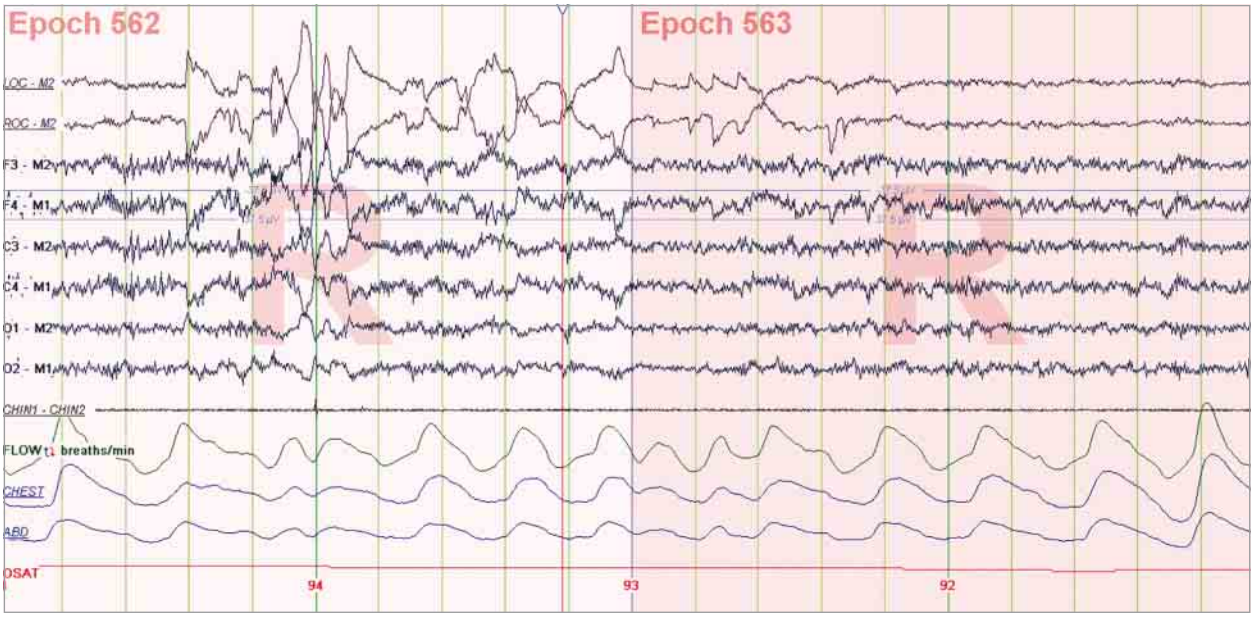
Therapy

Efforts to protect the patient and bed partner by modifying the sleeping environment are the initial steps in RBD treatment. Bed partners should sleep separately until DEB is brought under control; the bed should be placed far from a window; and potentially injurious bedside objects, including a night table, lamp, and any firearms, should be removed.[1]

Comorbid sleep disorders should be treated, and aggravating medications, if possible, should be eliminated. Most medication-induced RBD cases are self-limited following discontinuation of the offending agent, and DEB typically resolves when any underlying sleep-disordered breathing is treated.[1]

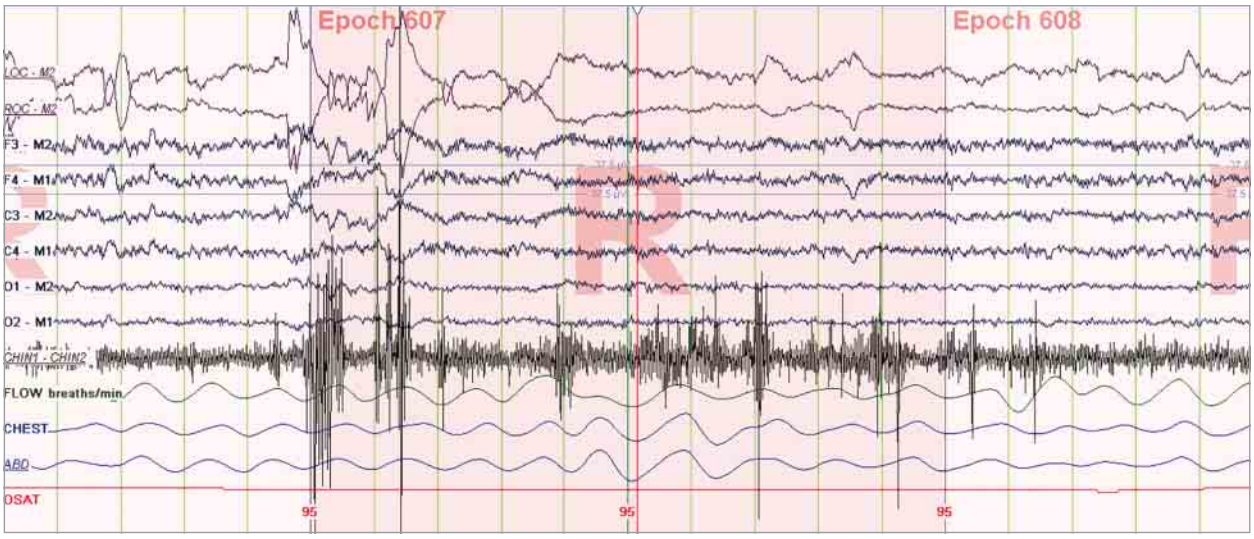
When violent DEB persists or in situations with a high probability of injury, pharmacotherapy is appropriate. The most effective medications include clonazepam and/or melatonin.[1,2] Because a sizable, randomized, placebo-controlled therapeutic study in RBD has

Figure 1. Normal Rapid Eye Movement Sleep Atonia



This 60-second polysomnographic recording demonstrates normal rapid eye movement sleep atonia. The sharp rapid eye movements can be recognized in the extraocular leads (left outer canthus–M2 and right outer canthus–M2) along with an absence of motor activity measured by chin electromyography (CHIN1-CHIN2).

Figure 2. Rapid Eye Movement Sleep Without Atonia



This 60-second polysomnographic recording demonstrates an elevation of rapid eye movement motor activity as measured by chin electromyography (CHIN1-CHIN2). Notice that the motor activity is often temporally associated with the phasic eye movements of rapid eye movement sleep (left outer canthus–M2 and right outer canthus–M2). In addition, the respiratory leads do not demonstrate evidence of sleep-disordered breathing but instead show normal respiratory effort (CHEST and ABD), airflow (FLOW), and oxygenation saturation (OSAT).

not yet been performed, to our knowledge, treatment strategies have largely arisen as a consensus based on case series and small clinical trials.

In the original RBD case series, 7 of the first 10 patients had rapid and sustained improvement of symptoms with oral clonazepam taken at bedtime.[24] Subsequently, clonazepam has been a first-line therapy, with reports suggesting that up to 90% of patients initially respond well to low doses (0.5-1.0 mg).[1,2] However, clonazepam's therapeutic mechanism in RBD is not fully understood, and subsequent trials have had mixed results. Although most patients respond at first, some patients develop drug tolerance and treatment failure.[1] Furthermore, clonazepam may be problematic among elderly persons and in patients with parkinsonism because its prolonged duration of action may result in morning sedation and gait impairment.

More recent studies have suggested that melatonin is a safe and effective therapy for isolated cases of RBD and those associated with PD and related disorders. A recent retrospective study[25] of melatonin and clonazepam noted equal efficacy; however, melatonin had a superior adverse effect profile, with fewer participants reporting falls and injuries. Melatonin is an endogenous pineal gland hormone that is secreted in response to evening darkness and helps entrain circadian rhythms. The hormone, when given exogenously in high doses (6-15 mg), substantially reestablishes normal REM atonia.[2,26] In the setting of advanced PD, melatonin is a particularly intriguing option because it is only mildly sedating.

Other medical therapies are further limited by weak evidence; however, cholinergic and dopaminergic agents may be useful in some cases. One small placebo-controlled crossover trial noted reduced dream enactment with the cholinesterase inhibitor rivastigmine.[27] In patients with RBD who have frequent, comorbid, periodic limb movements identified on polysomnography, pramipexole dihydrochloride, a dopamine agonist, has been reported to decrease nocturnal behaviors.[28] Similar to treating obstructive sleep apnea in the setting of behaviors that mimic RBD, pramipexole likely works by reversing a sleep-fragmenting condition (periodic limb movements).

Deep brain stimulation of the subthalamic nucleus does not improve RBD in patients with PD. Patients with PD and RBD who underwent subthalamic nucleus deep brain stimulation noted improvements in subjective sleep quality but little to no improvement in reestablishing REM atonia or decreasing DEB.[29] These findings were not unexpected because the subthalamic nucleus has no known effect on REM sleep.

Occasionally, RBD will be refractory to medication, with persisting violent injurious behaviors. Exiting the bed during dream enactment is a particularly high-risk behavior. However, because REM sleep is characterized by a low arousal threshold, patients are readily responsive to complex auditory processing. This phenomenon is often noted by bed partners who can calm a patient down with a simple phrase, such as, "David, you are having a dream; lay back down." A customized bed alarm that delivers a calming message at the onset of dream enactment can prevent the patient from leaving the bed and avert sleep-related injury.[1]

RBD in Neuroprotective Trials

Nearly all (81%-90%) surviving patients with spontaneously developing RBD will develop a neurodegenerative disorder.[4,5] This sobering statistic is often difficult for patients to comprehend and for physicians to explain. For patients who are understandably distressed about the likelihood of an impending neurological disorder, it should be explained that conversion often takes decades, PD is a treatable condition, and there are growing opportunities to participate in clinical trials.

At this time, it is uncertain what measures may be taken to prevent the progression of α-synuclein neurodegeneration. Because RBD is a consistent prodrome of PD, RBD provides a therapeutic window for the development of disease-modifying therapies. Furthermore, numerous readily identifiable biomarkers have already been demonstrated to predict disease progression from the advent of dream enactment to the emergence of parkinsonism.[1] These biomarkers could lead to the development of specific neuroprotective therapies.

A consortium of multinational investigators, the International Rapid Eye Movement Sleep Behavior Disorder Study Group, assembles annually to promote the development of collaborative clinical trials. One aim of this group is to identify neuroprotective strategies that can impede the progression of neuropathologic features in PD and other α-synuclein disorders.[1]

Conclusions

Rapid eye movement sleep behavior disorder is a condition characterized by dream enactment and sleep-related injury. It is caused by early α-synuclien neurodegeneration to brainstem structures that control REM sleep and predates the onset of PD, multiple-system atrophy, or DLB. Patients with RBD are diagnosed with in-laboratory video polysomnography and typically respond to either high doses of melatonin or low doses of clonazepam. As a prodromal syndrome of PD, RBD provides a unique opportunity for the development of neuroprotective therapies.

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