The REM sleep behavior disorder (RBD) is a fascinating experiment of nature predicted by animal experiments nearly 40 years ago. Active paralysis of somatic muscles is one of the defining features of REM sleep. In the cat model of REM sleep behavior disorder, bilateral perlocus ceruleus lesions result in loss of the expected atonia of REM sleep, resulting in dream-enacting (oneiric) behaviors. In humans, REM sleep behavior disorder presents as complex behaviors arising from REM sleep, as the persistence of muscle tone during REM sleep permits the “acting out of dreams”, often with violent or injurious consequences to the patient or bed partner. These behaviors include talking, yelling, swearing, grabbing, punching, kicking, jumping, or running out of the bed and may result in lacerations, ecchymoses, or fractures. The acute, or transient, form is usually drug-induced (most commonly tricyclic antidepressants [TCAs] or serotonin-specific reuptake inhibitors [SSRIs]). REM sleep behavior disorder may also be a manifestation of narcolepsy. The chronic form is seen predominantly in men (80–90%) over 50 years of age. Initially felt to be “idiopathic”, it is now becoming apparent that spontaneous REM sleep behavior disorder is often a harbinger of degenerative neurological conditions, most commonly one of the synucleinopathies (Parkinson’s disease, multiple system atrophy, or dementia with Lewy body disease).

Interestingly, the symptoms of REM sleep behavior disorder precede any other manifestations of the underlying neurodegenerative disorders by an average of over 10 years. It is readily diagnosed by formal sleep studies which reveal persistence of muscle tone during REM sleep. Most cases of REM sleep behavior disorder respond dramatically to clonazepam administered at bedtime.

Keywords: parasomnia; REM sleep; REM sleep without atonia; clonazepam; REM sleep behavior disorder

Introduction

Parasomnias are undesirable experiential or motor phenomena arising from the sleep period, and can conveniently be divided into two major categories: those representing abnormalities of sleep states per se, and those due to abnormalities of various organ systems taking advantage of the sleep state to declare themselves. The primary sleep parasomnias can be divided into three categories: those arising from non-rapid eye movement (NREM) sleep such as disorders of arousal (confusional arousals, sleepwalking, or sleep terrors), those arising from REM sleep, and those not respecting sleep states such as head-banging, bruxism, or enuresis. The secondary sleep parasomnias may be classified by the organ system involved such as central nervous system (nocturnal seizures), cardio-pulmonary (sleep-related groaning), or gastro-esophageal (diffuse esophageal spasm) [1]. This review focuses on REM sleep behavior disorder.

Background

REM sleep behavior disorder is the most impressive of the REM sleep-related primary sleep parasomnias. This fascinating experiment in nature was
predicted by animal experiments in 1965. Cats with bilateral perilocus ceruleus lesions demonstrated prominent motor activity during REM sleep, termed “REM without atonia” [2]. The cat animal model has recently been extended to the rat [3]. In the 1970s, scattered reports of dream-enacting behaviors involving humans appeared; the polygraphic and behavioral condition was sometimes referred to as “stage 1REM with tonic electromyogram”. Recognition of REM sleep behavior disorder as a distinct clinical disorder followed the report in 1986 of a series of adult humans with this disorder [4, 5]. The overall prevalence of REM sleep behavior disorder is estimated to be between 0.38 and 0.5% [6, 7].

Case example

A 57-year-old male police officer (and avid recreational hunter) presented with a 5-year history of progressively severe and injurious dream-enacting behaviors. He would frequently shout obscenities, kick the wall, punch his pillow, and sometimes hit his wife in bed or grab her by the hair while dreaming that he was being confronted or attacked by unfamiliar people or animals. One night while dreaming of putting a wounded deer out its agonal misery, he nearly broke his wife’s wrist. As a result of her husband’s parasomnia, the wife developed a secondary insomnia, and would usually not feel rested upon arising in the morning. Overnight PSG study demonstrated classic REM sleep behavior disorder findings, with intermittent loss of REM atonia and increased phasic twitching during REM sleep of the submental, anterior tibialis, and extensor digitorum muscles. Treatment with clonazepam immediately controlled his dream-enacting behaviors and restored normal sleep continuity in his wife. This benefit has continuously been maintained during 15 years of nightly treatment, and at the original dose of 1 mg at bedtime. However, 18 years after the onset of REM sleep behavior disorder, he was diagnosed with recent-onset Parkinson’s disease, with bradykinesia, rigidity and resting tremor.

PSG sample

The typical PSG features are shown in figure 1.

Pathophysiology

Wakefulness, REM sleep, and NREM sleep are associated with a number of physiologic variables that usually occur in concert to produce a fully declared state. REM sleep contains two types of variables: tonic (occurring throughout the REM period), and phasic (occurring intermittently during a REM period). Tonic elements include a desynchronized EEG and somatic muscle atonia (sparing the diaphragm). Phasic REM elements...
include rapid eye movements, middle ear muscle activity, and extremity twitches. The tonic electromyogram suppression of REM sleep is the result of active inhibition of motor activity originating in the perilesus coeruleus region and terminating on the anterior horn cells via the medullary reticularis magnocellularis nucleus [8]. Multiple areas of the brainstem may influence muscle tone during REM sleep [9].

Loss of REM-atonia is alone insufficient to generate REM sleep behavior disorder. Presumably, there must also be disinhibition of motor pattern generators in the mesencephalic locomotor region to result in over-excitation of phasic motor activity with behavioral release during REM sleep. Recent studies in dogs by Lai and Siegel have revealed a co-localization of the atonia and locomotor systems of REM sleep in the pons, providing an anatomic basis for the simultaneous dysregulation of these two systems in REM sleep behavior disorder. In normal REM sleep, the motor system is highly activated at higher levels of the neuraxis, but paralyzed at the level of the spinal motoneurons. It is likely that REM-atonia may serve as a protective mechanism, preventing motor manifestations and accompaniments of the highly activated brain during REM sleep [10].

Approximately one-third to one-half the cases are still considered to be idiopathic without demonstrable neuroanatomic brainstem structural abnormalities, consistent with experimental animal data that indicate that the determination of REM-atonia is complex and may result from dysfunction of a number of neural networks. This is in contrast to the classic animal model of REM sleep behavior disorder involving the perilesus coeruleus regions. Recent neuroimaging studies have revealed dopaminergic abnormalities in the striatum: reduced dopamine transporters by SPECT scan, and decreased dopaminergic innervation by PET scan [11, 12].

Clinical Features

REM sleep behavior disorder is more common above age 50, and 80 to 90% of affected patients are men but the disorder may begin at any age [13–15]. It most frequently presents with the complaint of dramatic, violent, potentially injurious motor activity during sleep. These behaviors include talking, yelling, swearing, grabbing, punching, kicking, jumping, or running out of the bed. Injuries are not uncommon and include ecchymoses, lacerations, or fractures involving the individual or bed partner. The reported motor activity usually correlates with remembered dreammentation, leading to the complaint of “acting out my dreams”. In some cases, bruxism, somniloquy, or periodic limb movements of sleep may be the heralding or primary manifestation of this disorder. The duration of behaviors is brief, and upon awakening from an episode there is usually rapid return of alertness and orientation. Some patients adopt extraordinary measures to prevent injury during sleep: they may tether themselves to the bed with a rope or belt, sleep in sleeping bags, or sleep on a mattress on the floor in a room devoid of furniture.

The frequency of the episodes ranges from once every few weeks to multiple nightly episodes [16]. Despite the impressive behavioral and EMG motor activity, few patients with REM sleep behavior disorder complain of excessive sleep disruption and daytime fatigue. The multiple sleep latency testing rarely documents daytime somnolence, apart from cases in which REM sleep behavior disorder is associated with narcolepsy.

Acute REM sleep behavior disorder

Acute onset of REM sleep behavior disorder is almost always induced by medications (tricyclic antidepressants, monoamine oxidase inhibitors, serotonin-specific reuptake inhibitors, bisoprolol, selegiline, or cholinergic treatment for Alzheimer’s disease) or associated with their withdrawal (alcohol, barbiturate, or meprobamate) [17–22]. Caffeine and chocolate abuse has been implicated in causing or unmasking REM sleep behavior disorder [23]. REM sleep behavior disorder may be triggered by selegiline prescribed as treatment for Parkinson’s disease and by cholinergic agents prescribed for patients with Alzheimer’s disease [17, 19, 24]. Drug-induced (particularly SSRI medication) REM sleep behavior disorder is becoming increasingly common.

Chronic REM sleep behavior disorder

The chronic form of REM sleep behavior disorder is idiopathic in 25 to 60% of occurrences [13, 14, 25]. The remainder is associated with various degenerative neurologic disorders, most notably with the synucleinopathies (Parkinson’s disease [including juvenile Parkinson’s disease]), dementia with Lewy body disease, and multiple system atrophy (Shy-Drager syndrome, striatonigral degeneration, olivopontocerebellar degeneration) [26]. A recent study found that 40% of patients with Parkinson’s disease had either REM sleep
behavior disorder (16%) or polysomnographic evidence of REM sleep without atonia, and 90% of patients with multiple system atrophy had REM sleep without atonia [27–31]. In one series, over one third of males initially diagnosed with idiopathic REM sleep behavior disorder eventually developed symptoms of Parkinson’s disease [32]. With longer-term follow-up, this figure increased to 65% [33]. Interestingly, the mean interval between the onset of REM sleep behavior disorder symptoms and the first appearance of any other manifestation of Parkinson’s disease was over 13 years.

Since both REM sleep behavior disorder and narcolepsy may be considered conditions associated with abnormalities of state boundary control, it would stand to reason that REM sleep behavior disorder may be a manifestation of narcolepsy, and may be precipitated or worsened by the administration of tricyclic antidepressants or serotonin-specific reuptake inhibitors prescribed for the symptom of cataplexy [34]. REM sleep behavior disorder-like behaviors have been reported arising from episodes of cataplexy in a patient with narcolepsy [35].

Regardless of gender, age, or presence/absence of an underlying neurological disorder, the PSG and behavioral features of REM sleep behavior disorder are indistinguishable. This suggests the presence of a “final common pathway” in REM sleep behavior disorder that can be accessed by a wide variety of pathologic states.

**REM sleep behavior disorder variations**

**Parasomnia overlap syndrome**

There is a subgroup of parasomnia patients with both clinical and PSG features of both REM sleep behavior disorder and disorders of arousal (sleepwalking / sleep terrors). These cases demonstrate motor-behavioral dyscontrol extending across NREM and REM sleep. This condition often responds to clonazepam [36].

**Status dissociatus**

Status dissociatus, which may be the most extreme form of REM sleep behavior disorder, appears to represent the complete breakdown of state-determining boundaries, both clinically and polygraphically. Conditions associated with status dissociatus include protracted withdrawal from alcohol abuse, narcolepsy, olivopontocerebellar degeneration, and prior open heart surgery. One AIDS-related case with prominent brainstem involvement has been identified. The abnormal motor and verbal nocturnal behaviors of status dissociatus may respond to treatment with clonazepam [37, 38].

**Agrypnia excitata**

This recently described condition is characterized by generalized overactivity associated with loss of slow-wave sleep, mental oneiricism (inability to initiate and maintain sleep with wakeful dreaming), and marked motor and autonomic sympathetic activation seen in such diverse conditions as delirium tremens, Morvan’s fibrillary chorea, and fatal familial insomnia [39–41].

**Diagnostic workup**

The differential diagnosis of complex motor behaviors during sleep includes sleepwalking, obstructive sleep apnea, sleep terrors, nocturnal seizures, psychogenic dissociative states, post-traumatic stress disorder, nocturnal panic disorder, delirium, and malingering. A detailed review of the sleep-wake complaints should be followed by a medical, neurologic, and psychiatric history and examination. Information from a bed partner is most valuable. As it is often impossible to differentiate REM sleep behavior disorder from other parasomnias by history alone, formal polysomnographic study is mandatory. Such polysomnographic studies must be more extensive than those performed for many other sleep disorders, with an expanded EEG montage, monitors for movements of all four extremities, continuous technologist observation, and audiovisual recording.

**Minimum diagnostic criteria of REM sleep behavior disorder** [8]

1. PSG abnormality during REM sleep: elevated submental electromyographic (EMG) tone and/or excessive phasic submental and/or limb EMG twitching.
2. Documentation of abnormal REM sleep behaviors during PSG studies (prominent limb or truncal jerking; complex, vigorous, or violent behaviors), OR a history of injurious or disruptive sleep behaviors.
3. Absence of EEG epileptiform activity during REM sleep.
Some cases will have an identifiable underlying neurologic disorder, but many are idiopathic. Extensive neurologic evaluation (evoked potentials, CT, MRI, etc.) is warranted only if the history or neurologic examination is suggestive of structural CNS pathology.

**Treatment**

Clonazepam is a remarkably effective treatment in human REM sleep behavior disorder, in controlling both the behavioral and the dream-disordered components of this disorder. Treatment is usually immediately effective at a dose of 0.5–1.0 mg at bedtime (range: 0.25–4.0 mg). Despite the dramatic control of the clinical symptoms, clonazepam has little effect on the characteristic PSG REM sleep abnormalities. Nightly clonazepam is effective and safe, without tolerance over many years. If clonazepam is not effective or not tolerated, melatonin has been shown to be effective [42–44]. Adjunctive or alternative treatments, based on anecdotal reports, for the few REM sleep behavior disorder patients who do not respond fully to clonazepam or who develop daytime somnolence from this agent, include the following: desipramine or imipramine, carbamazepine, clonidine, carbidopa/L-dopa, L-tryptophan, melatonin or gabapentin [8, 45]. Despite the fact that anticholinergic medication has been implicated in triggering REM sleep behavior disorder, that medication has also been reported effective in the treatment of REM sleep behavior disorder [46]. In REM sleep behavior disorder associated with narcolepsy, the tricyclic antidepressants, serotonin-specific reuptake inhibitors, or monoamine oxidase inhibitors administered for cataplexy may be continued, and clonazepam added [47]. Underlying obstructive sleep apnea should be ruled out before prescribing clonazepam [48]. The treatment of Parkinson’s disease-associated REM sleep behavior disorder is the same as for idiopathic REM sleep behavior disorder [32].

**Future directions**

“Idiopathic” REM sleep behavior disorder is becoming progressively scarce (and may cease to exist) as more patients with REM sleep behavior disorder are being thoroughly evaluated and meticulously followed for prolonged periods. Drug-induced REM sleep behavior disorder is becoming increasingly common, and non-drug-induced REM sleep behavior disorder is very often a harbinger of degenerative neurologic conditions – particularly the synucleinopathies. Rigorous study of these relationships affords an exciting opportunity for basic scientists and sleep medicine clinicians working together to expand understanding of both sleep and neurological function.

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