Proceedings of UCLA Healthcare
-VOLUME 17 (2013)-

CLINICAL VIGNETTE

The Slumbering Giant-Slayer: a modern day Jekyll and Hyde

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A patient presents with a complaint of abnormal movements during sleep. He is a 54-year-old male without significant past medical or surgical history who is not taking any medications. He presents with at least 2 years of movements during sleep, which can at times be violent. He describes vivid dreams, often with violent events. He will often awaken from these dreams and recall specific episodes. He gives an example of a dream in which his nephew was fighting on the beach and sought his help, and when he arrived at the beach he had to fight monstrous giants. His bed partner reports that he will sometimes punch at the air or make violent gestures in his sleep. These episodes usually occur in the latter 3rd of the night. sHe has never had any personal injuries or injured anyone else during his sleep. He is alert and oriented when awakening from these dreams.

He denies episodes of awakening screaming or confused. He denies sleep walking, but occasionally talks in his sleep. There are no other reported abnormal behaviors during sleep.

The patient usually goes to bed at about 11 pm and falls asleep within 15 to 20 minutes. He denies uncomfortable sensations in the legs or arms that interfere with falling asleep. He reports occasional nocturia, typically once nightly. He reports occasional dry mouth upon awakening, but denies morning headaches. He denies having sore muscles in the morning. He has not been known to snore or have witnessed apnea. He does not have a history of sleep paralysis, hypnagogic or hypnopompic hallucinations, or cataplexy. He has never used any medications or herbal remedies for insomnia or depression. He reports some daytime sleepiness, but generally does not feel that sleepiness limits his activities during the day. He has not been in any motor vehicle collisions due to sleepiness, but recalls infrequent episodes of missing freeway exits and not realizing until several exits later. The Epworth Sleepiness Scale is 8 out of a possible 24 (signifying a normal propensity to fall asleep).

He works as an architect and denies any job limitations due to fatigue. He never smoked and is a social drinker. He occasionally drinks caffeinated beverages, but never more than 2 in a day. He has a family history of dementia, presumed Alzheimer's type, in his father. His BMI is 23 (normal) and his neck circumference is 15.5 inches. He has a Mallampati class 1 view, a long narrow uvula and a torus on the hard palate. Lungs are clear and heart sounds are normal.

The patient was scheduled for a polysomnogram with 4-limb montage. He was recommended to abstain from alcohol and to avoid driving if sleepy.

The sleep study showed a sleep latency of 7 minutes and sleep efficiency of 91%. He had 84 minutes of REM sleep, accounting for 23% of the total sleep time. His apnea-hypopnea index was 0 events per hour and his minimum SpO2 was 95%. He had a periodic limb movement of sleep (PLMS) index of 13 events per hour and an associated arousal index of 4 events per hour. He had significant movement recorded in all 4 limbs and the chin EMG during REM sleep, a finding referred to as "REM without atonia" (figure 1). The EEG tracing showed no sign of epileptiform activity.

The polysomnogram showed definitive evidence of muscle movements during REM sleep. This finding, coupled with the clinical history of violent behaviors that lead to sleep disruption and potential for injury, makes the diagnosis of REM Sleep Behavior Disorder (RBD).

REM Sleep Behavior Disorder

RBD is predominantly present in males and usually is diagnosed after age 50. The prevalence is believed to be about 0.4% of the general population. The common features are punching, kicking, talking, and leaping from bed in what has been termed dream enactment, known as oneirism, with recall of violent dreams. The eyes are closed during an RBD episode, but patients wake to consciousness rapidly without

confusion. Sleep phenomena that are rarely seen in RBD include sleep-walking, eating, sexual behaviors, urination and defecation. There is generally no history of violent behavior during wakefulness and many patients are actually described as calm and docile individuals.

Clinical features that may be noted for years prior to manifesting RBD include sleep talking, yelling, limb twitching and jerking during sleep that may or may not be dream related. Another commonly associated feature is periodic limb movements during sleep, documented to occur in 75% of patients with RBD. These repetitive movements are generally not associated with cortical arousals.

RBD has been associated with neurodegenerative disorders, specifically, the synucleinopathies. These disorders are united by a common pathologic lesion in which aggregates of alpha-synuclein protein accumulate in select neurons and glial cells. The most common manifestations of this disease process include Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. In newly diagnosed Parkinson's disease about one third of patients have RBD and in multiple system atrophy, RBD is present in 90% of subjects[1].

Other predisposing factors include narcolepsy, stroke and medication use. Antidepressant medications including the tricyclic antidepressant clomipramine, the MAO inhibitors selegiline and phenelzine[2], the selective serotonin reuptake inhibitors (venlafaxine, fluoxetine[3], and paroxetine[4] in particular), mirtazapine and other antidepressants (except bupropion due to its dopaminergic effect) may elicit RBD.

The pathophysiology of RBD is complex, but has been identified with clarity over the last 3 decades. The key aspect is rapid eye movement sleep, maintaining all of the usual features of REM, but without the usual atonia of most skeletal muscles. Normally, REM sleep is notable for an EEG pattern that shows low voltage, mixed frequency activity similar to wakefulness. Although the brain is active in REM, the muscles are normally quiet due to neurologic inhibition. This is mediated via a pathway from the locus coeruleus and pontine tegmentum to an area in the medulla known as the nucleus reticularis magnocellularis that in turn inhibits the spinal alpha motoneurons via the ventrolateral reticulospinal tract. In RBD, this pathway is inhibited, allowing for muscle activity. In addition, RBD generally has an increase in "phasic" activity leading to bursts of neurologic impulses that are transmitted to the muscles. The rapid eye movements are examples of this phasic activity, although those occur normally during REM as the ocular muscles are not normally inhibited during REM sleep[5].

Brain imaging techniques have been utilized to attempt to categorize anatomic or functional areas of pathology, but SPECT imaging has shown conflicting results[6] with both increased and decreased pontine blood flow. SPECT has shown reduced uptake by the presynaptic dopamine transporter in the striatum, a finding that may be related to an early preclinical stage of an alpha-synucleinopathy such as Parkinson's Disease. Likewise, transcranial sonography has identified hyperechogenicity in the substantia nigra in patients with "idiopathic" RBD (iRBD), a finding that is present in 90% of Parkinson's patients. Diffusion tensor imaging with MRI technology has characterized microstructural changes in brainstem, olfactory region, substantia nigra, and other white matter areas of iRBD patients. This finding suggests that neuroimaging may be useful in the future for diagnosis and/or prognosis[7]. Another study investigated olfactory function combined with transcranial sonography, showing similar deficits in Parkinson's Disease patients and subjects with iRBD, again demonstrating an association[8].

Holding a peculiar place in medicine as a type of long-range warning system, RBD portends an increased risk of developing the neurodegenerative conditions known as synucleinopathies. Men who are over 50 years old and are diagnosed with RBD have a two-thirds probability of developing a parkinsonian disorder in the next 13 years[1].

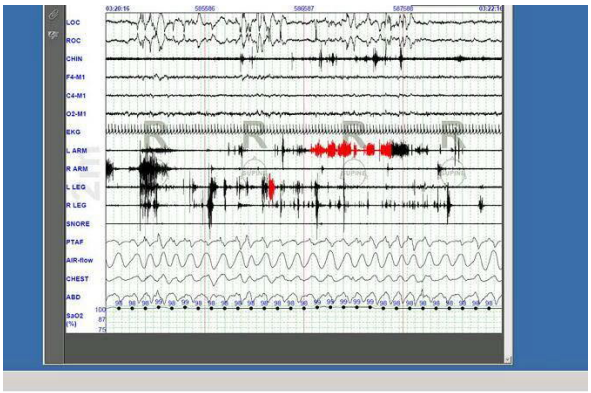
RBD has been associated with cardiac abnormalities, chiefly via the autonomic nervous system. A retrospective case control study of 10 patients showed that the usual changes in heart rate variability noted during REM sleep do not occur in patients with RBD[9]. Evidence also exists for impaired heart rate response to arousals and leg movements[10], and cardiac sympathetic neuronal damage as measured by cardiac MIBG scintigraphy[11]. This finding appears to be present in patients with Parkinson's disease and Lewy body dementia, but not other neurologic conditions related to RBD[12].

The treatment of RBD was first attempted using tricyclic anti-depressant medication, as these are potent suppressors of EEG evidence of REM sleep. These trials were not successful. Due to the frequency of patients exhibiting Periodic Limb Movements of Sleep (PLMS), which was effectively

treated with benzodiazepines, clonazepam was also used to treat RBD. The efficacy was profound, with immediate resolution of both dream enactment behavior as well as eliminating the disturbing dreams that plagued patients[5]. Clonazepam remains the mainstay of treatment for RBD. Studies have shown a reduction in REM sleep phasic activity[13]. A large case series of 96 patients reported 79% complete benefit and 11% with partial response[14] and another study of 93 patients reported an 87% response rate with clonazepam at a dosage between 0.5 to 2 mg nightly[15]. A recent study evaluated 39 patients and found that many patients derived benefit from clonazepam (54%), but a significant number (58%) had side effects as well, including sedation, confusion, and cognitive impairment. Other medications with anecdotal success reported by patients in this review included melatonin, zopiclone, and alprazolam[16]. A Mayo Clinic review of 45 RBD patients noted that melatonin users (n=25) and clonazepam users (n=18) experienced comparative reductions in symptoms, but complete suppression was only attained in 3 patients in each group[17]. There have been contradictory results for the use of other medications; so the current recommendation is treatment with clonazepam (provided there are no limiting co-morbidities) with melatonin as an alternative option for monotherapy or as an adjunct to clonazepam[18].

Summary

The patient met the criteria for a diagnosis of REM sleep behavior disorder. Although he had no clear family history of this disease process, one could speculate that his father's dementia may have been linked to a synucleinopathy. The patient was started on clonazepam therapy and has not experienced any vivid dreams in 2 months. His bed partner reports no violent actions during sleep since starting clonazepam. The patient has noted no side effects to date and no increase in daytime hypersomnolence.



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Submitted on May 30, 2013