

REM SLEEP WITHOUT ATONIA – FROM CATS TO HUMANS

M.W. MAHOWALD¹ AND C.H. SCHENCK

Minnesota Regional Sleep Disorders Center and the Departments of Neurology (MWM) and Psychiatry (CHS), Hennepin County Medical Center and the University of Minnesota Medical School, Minneapolis, MN, USA

REM SLEEP WITHOUT ATONIA – REM SLEEP BEHAVIOR DISORDER (RBD)

Animal Models of RBD.

In experiments conducted by Dr. Michel Jouvet in 1965, bilateral lesions of pontine regions adjacent to the locus coeruleus in cats caused absence of the expected atonia associated with REM sleep, allowing the cats to demonstrate prominent motor behaviors during REM sleep (oneiric behaviors) (18). The cat model has recently been extended to the rat (42).

Loss of REM-atonia is alone insufficient to generate RBD. 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 (34). Recent studies in dogs by Lai and Siegel have revealed a colocalization 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 RBD (22). Ongoing animal experiments in a number of basic science laboratories studying the state-dependent nature of motor control continue to produce interesting and important data. Interestingly, spontaneous cases have occurred in dogs and cats (16).

Human RBD.

In the 1960s, scattered reports of dream-enacting behaviors by European, Japanese, and American investigators involving humans appeared; the polygraphic and behavioral condition was sometimes referred to as "stage 1-REM with tonic electromyogram". RBD was formally recognized and named in the mid-1980s, and it was incorporated within the International Classification of Sleep Disorders in 1990 (43, 50, 60).

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),

¹ Corresponding Author: Dr. M.W. Mahowald, 701 Park Avenue South, Minneapolis, MN 55415, USA - Tel. 612 873 6201 - Fax 612-904-4207 - E-mail: mahow002@tc.umn.edu

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 perilocus coeruleus region and terminating on the anterior horn cells via the medullary reticularis magnocellularis nucleus (29). Multiple areas of the brainstem may influence muscle tone during REM sleep (31).

In REM sleep behavior disorder, the REM sleep state is incomplete: all elements are present except the atonia, permitting motor activity to occur that parallels dream mentation generated by the activated REM sleep state. The observed motor activity may result from either impairment of tonic REM muscle atonia, or from increased phasic locomotor drive during REM sleep. Although the original animal model was produced with lesions of the locus coeruleus region, it is clear from later animal studies that the atonia of REM sleep is determined or influenced by a number of brainstem regions (23, 51).

Neuroimaging Studies.

Neuroimaging studies indicate dopaminergic abnormalities in RBD. SPECT studies have found reduced striatal dopamine transporters (9, 10), and decreased striatal dopaminergic innervation has been reported (1). Decreased blood flow in the upper portion of the frontal lobe and pons has been reported (55), as has functional impairment of brainstem neurons (32). PET and SPECT studies have revealed decreased nigrostriatal dopaminergic projections in patients with multiple system atrophy and RBD (15).

Epidemiology.

A recent phone survey of over 4900 individuals between the ages of 15 and 100 years of age indicated an overall prevalence of violent behaviors in general during sleep of 2%, one quarter of which were likely due to REM sleep behavior disorder, giving an overall prevalence of REM sleep behavior disorder at 0.5% (37).

Clinical Manifestations.

REM sleep behavior disorder has two striking demographic characteristics: it is more common above age 50 years, and 80% to 90% of affected patients are men. However, the disorder affects both sexes, and may begin at any age (38, 46, 54). 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 violence of the sleep-related behavior is often discordant with the waking personality. The reported motor activity usually correlates with remembered dream mentation, leading to the patient's complaint of "acting out my dreams". Infrequently, the primary complaint is one of sleep interruption. The dura-

tion 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 (26).

Etiology.

There are two forms of RBD: acute and chronic. The acute form is almost always induced by medications (tricyclic antidepressants, monoamine oxidase inhibitors, serotonin-specific reuptake inhibitors, bisoprolol, selegiline, or cholinergic treatment for Alzheimer disease) or associated with their withdrawal (alcohol, barbiturate, or meprobamate) (6, 17, 24, 48, 52, 56). Caffeine and chocolate abuse has been implicated in causing or unmasking REM sleep behavior disorder (57, 63).

The chronic form of REM sleep behavior disorder is idiopathic in 25% to 60% of occurrences (38, 46, 53). Initially, almost all cases of RBD were felt to be idiopathic in origin. Systematic long term follow-up has indicated that the majority will eventually manifest other symptoms of a number of neurodegenerative disorders.

RELATIONSHIP OF RBD TO UNDERLYING NEUROLOGICAL DISORDERS

Synucleinopathies.

The most common underlying neurological degenerative disorders associated with RBD are the synucleinopathies (Parkinson disease (including juvenile Parkinson disease), dementia with Lewy body disease, and multiple system atrophy (Shy-Drager syndrome, striatonigral degeneration, olivopontocerebellar degeneration) (4, 5). Surveys indicate a very high prevalence of REM sleep behavior disorder or RWA in patients with Parkinson disease (up to 40%) or multiple system atrophy (up to 90%) (8, 13, 14, 36, 39, 65, 66).

In one series, over two thirds of males initially diagnosed with idiopathic REM sleep behavior disorder eventually developed symptoms one of the synucleinopathies (44, 45). Amazingly, the average interval between the onset of REM sleep behavior disorder and the first other symptom of the underlying neurodegenerative disease is over ten years.

Narcolepsy.

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 (48).

Agrypnia Excitata.

Oneiric symptoms reminiscent of REM sleep behavior disorder are present in all three conditions (fatal familial insomnia, Morvan's fibrillary chorea, and delirium tremens) included in the recently described condition "agrypnia excitata," and should lead to closer scrutiny of sleep in other neurologic conditions (7, 25, 33, 41). Agrypnia excitata shares some clinical features with "status dissociatus," a condition which possibly represents a total breakdown of state boundaries (27, 28).

Miscellaneous Conditions.

Other conditions reportedly associated with RBD or RWA include: mitochondrial encephalo-myopathy, normal pressure hydrocephalus, Tourette's syndrome, Machado-Joseph disease (spinocerebellar ataxia type 3), cerebellopontine angle tumors, group A xeroderma, multiple sclerosis, ischemic or hemorrhagic cerebrovascular disease, brainstem neoplasms, autism, and Guillain-Barré syndrome (2, 11, 12, 19, 20, 35, 40, 58, 59, 61, 62, 67).

Differential Diagnosis.

The differential diagnosis includes sleepwalking, sleep terrors, nocturnal seizures, psychogenic dissociative states, posttraumatic stress disorder, nocturnal panic disorder, delirium, and malingering.

Diagnostic Evaluation.

A detailed review of the sleep-wake complaints should be followed by a medical, neurological, and psychiatric history and examination. Information from a bed partner is most valuable. Polysomnographic study usually reveals excessive tonic and/or phasic muscle activity during REM sleep (29).

The Figure 1 shows the typical polysomnographic features of venlafaxine-induced RWA.

Management.

The acute form is self-limited following discontinuation of the offending medication or completion of withdrawal. About 90% of patients with chronic REM sleep behavior disorder respond well to clonazepam administered one-half hour prior to sleep time. The dose ranges from 0.5 mg to 2.0 mg, and there has been little, if any, tendency to develop tolerance, dependence, abuse, or adverse side effects despite years of continuous administration and efficacy (47, 49). Interestingly, polygraphically there is little change in the muscle tone during REM sleep following effective treatment (64). Melatonin at doses up to 12 mg at bedtime may also be effective (3, 21).

PERSPECTIVES AND IMPLICATIONS

RBD is a fascinating experiment of nature. Dr. Jouvet's astute observation of "oneiric" behaviors in the cat by 1965 has led to greater understanding of sleep and

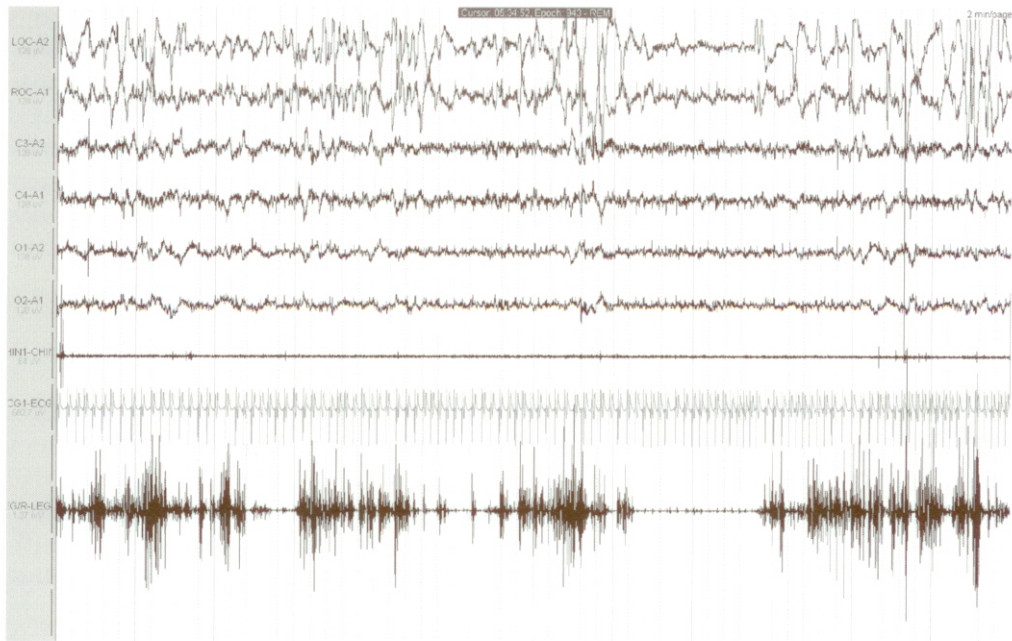


Fig. 1. REM sleep without atonia in a patient receiving chronic oral venlafaxine. This two minute epoch of REM sleep in a 20 year-old man without symptoms of RBD demonstrates dramatic release of anterior tibialis muscles activity.

LOC = left outer canthus, ROC = right outer canthus, A1 = left ear, A2 = right ear, C3 = left central, C4 = right central, O1 = left occipital, O2 = right occipital, Chin1-Chin2 = submental EMG, ECG1-ECG = electrocardiogram, Leg/R-Leg/L = left and right anterior tibialis EMG.

wakefulness in humans. His important discovery of the animal model of RBD led to the fascinating relationship between RBD and numerous degenerative neurological conditions. It also buttressed the concept of state dissociation, which has served to explain many previously unexplainable human phenomena including narcolepsy, disorders of arousal, waking hallucinations, lucid dreaming, and out-of-body experiences (30). The concept of state dissociation in humans was made possible only by applying information obtained from basic science animal research studies to the human condition – without which these often dramatic, and treatable conditions would have remained in the mystical, supra-natural, or psychiatric arenas, without appropriate or effective treatment options. Sleep or wakefulness occurring asynchronously in bits and pieces of the brain is a most useful concept. From our standpoint, the basic science work in the function and mechanism of sleep is pertinent, not only adding to our knowledge in these important areas for the sake of knowledge, but also in providing clinicians with important information that is of immense clinical importance. The payoff of such research has been great, and demands that it should be ongoing. The field of sleep research and sleep medicine is in a unique position to foster close interactions between basic scientists and clinicians, the result

being basic science answers to clinical questions, and unanswered clinical questions guiding the direction of and reinforcing the basic science research. The clinical conditions discussed above underscore the value of close cooperation among those working at all levels: molecular, cellular, multi-cellular, and clinical. Continued study of state dissociation by both basic scientists and clinicians will undoubtedly identify and explain even more of these fascinating conditions, with important therapeutic implications. The reciprocal benefits of close collaboration between basic scientists and clinicians will continue to be realized.

SUMMARY

Basic science research observations often lead to unexpected surprises. It is likely that in 1965 when Dr. Michel Jouvet placed bilateral peri-locus coeruleus lesions in cats and observed REM sleep without atonia (RWA) and "oneiric" behavior that could only be explained by "acting out dreams" (or "dreaming out acts"), he recognized that it was an important observation, but had little inkling of its true significance. Nor could he even imagine that it would lead to such greater understanding of wake/sleep phenomena in humans.

Likely also, the first observation of REM sleep behavior disorder (RBD) in humans was felt to be interesting and novel – again with no true appreciation of what this seemingly simple observation would lead to important clinical relationships with numerous neurodegenerative disorders. The identification of RBD in humans also buttressed the concept of state dissociation, which has served to explain many previously unexplainable human behavioral phenomena.

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