REM Sleep Behavior Disorder: Dancing in my sleep

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No disclosures
Parasomnia

- Undesirable physical events or experiences

- Occur during
  - Entry into sleep
  - Within sleep
  - During arousal from sleep

- NREM

- REM

- Sleep/wake transition
RSBD Outline

- Definition
- Epidemiology
- Pathogenesis
- Etiology
- Clinical Features
- Diagnosis and Differential
- Treatment
- Prognosis and Counseling
REM sleep behavior disorder

“...he was thrusting his sword in all directions, speaking out loud as if he were actually fighting a giant. And the strange thing was that he did not have his eyes open, because he was asleep and dreaming that he was battling the giant... He had stabbed the wine skins so many times, believing that he was stabbing the giant, that the entire room was filled with wine...”

—Miguel de Cervantes, Don Quixote de La Mancha (1605), page 364, Editorial Juventud, S.A., Barcelona, 1995 edition (author’s translation)
REM sleep behavior disorder

- First reported in 1965 that bilateral lesions of the pontine regions adjacent to the locus coeruleus caused absence of REM atonia (cats, rats)

- Phenomenon first recorded in humans in 1985 (University of Minnesota)
  - 90% male, age mid 50’s, youngest 9 yo

- Schenck et al published seminal paper in June 1986 that established RSBD as a bona fide sleep disorder

REM sleep behavior disorder

- REM related parasomnia
- Hallmark: Loss of REM sleep atonia
- Characterized by dream-enactment behaviors
  - Benign to violent/oneiric/injurious
  - Less aggressive behavior in younger population/women
- Acute/ Iatrogenic
- Spontaneous or “idiopathic”/ Chronic
- Precursor to CNS pathology
Epidemiology

- 0.5% general population and 2% older adults
- Estimated 35 million worldwide
  - Vast majority of cases go unrecognized
- Adults
  - Strong male predominance (9:1)
  - Middle aged adults (>50y)
  - Younger adults (<40y)
    - Medication related
    - Comorbid narcolepsy
    - Parasomnia overlap
Epidemiology

• Spontaneous RBD is a prodromal syndrome of alpha-synuclein neuropathology
  • Parkinson disease (33-50%)
  • Multiple system atrophy (80-95%)
  • Dementia with Lewy bodies (80%)

• Environmental and behavioral risk factors
  • Smoking
  • Education
  • Traumatic brain injury
  • Pesticide exposure
Epidemiology

- Rare in children
- Virtually never idiopathic
- Associated with:
  - Narcolepsy
    - RBD precedes narcoleptic features
  - Brainstem tumors
  - Medications
  - Neurodevelopmental disorders
    - Autism

ICSD 2014
# Sleep/Wake Neurotransmitters

<table>
<thead>
<tr>
<th>WAKE</th>
<th>NREM</th>
<th>REM</th>
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</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>GABA</td>
<td>REM ON</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>Adenosine</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Serotonin</td>
<td>REM OFF</td>
</tr>
</tbody>
</table>

- **REM ON**: Relatively high levels of neurotransmitters during REM sleep.
- **REM OFF**: Relatively low levels of neurotransmitters during REM sleep.
Pathophysiology of REM sleep behavior disorder

Lesion

- Pons
- Medulla

Excite

Medullary Inhibitory Area

Lack of Excitation

Lack of Inhibition

Motor Neurons

Muscles

Net effect

Muscle Atonia

Inhibit

Medullary Inhibitory Area

* Via magnocellularis neurons

* Via the lateral tegmentoreticular tract

Lack of Muscle Atonia
RSBD Predominance

Timing of sleep-related movements and behaviors throughout the sleep period

- **Sleep-wake transition movements**: Examples include hypnic jerks, hypnagogic foot tremor, periodic limb movements, and sleep-related rhythmic movement disorder.
- **Disorders of arousal**: Disorders of arousal from non-REM sleep include confusional arousals, sleep-related abnormal sexual behavior, sleep terrors, sleepwalking, and sleep-related eating disorder.
- **REM sleep behavior disorder, nightmares, and sleep paralysis**: REM: rapid eye movement.

* Time through the sleep period

Wake → REM → Stage N1 → Stage N2 → Stage N3
## Pathogenesis

### Normal REM
- Pons
- Skeletal muscle atonia
- Dream mentation
- Sleep related memory consolidation
- Recall

### RSBD
- Pons
- Dysfunction of pontine REM-on and REM-off nuclei
- Loss of skeletal muscle atonia
- Dream enactment
  - Attacked/chased/threatened
- Recall
Etiology

- CNS pathologies that result in failure to inhibit spinal motoneurons
  - Alpha synuclein neuropathology
  - Non-synuclein neurologic disorders
  - Narcolepsy and state boundary control
    - Almost always with cataplexy
    - Distinct phenotype of RBD
    - Less complex, no sex predominance, earlier onset, orexin deficiency
  - Pontine lesions
Etiology:
Alpha-synuclein neurodegeneration

- Most common
  - Parkinson disease
  - Multiple system atrophy
  - Dementia with Lewy bodies

- Spontaneous/“idiopathic”

- RBD can PRECEDE onset of neurodegenerative disease by months to decades (average 10y)
Table 1
Demographic and clinical findings of 231 RBD patients with MSA, DLB, PD and the idiopathic form seen at our sleep center. RBD was confirmed by VPSG in all subjects.

<table>
<thead>
<tr>
<th>Male (%)</th>
<th>MSA (n = 67)</th>
<th>DLB (n = 17)</th>
<th>PD (n = 65)</th>
<th>IRBD (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>56.7</td>
<td>94.1</td>
<td>70.8</td>
<td>86.3</td>
</tr>
<tr>
<td>Age at diagnosis of RBD (years)</td>
<td>61.5 ± 7.9</td>
<td>74.2 ± 6.5</td>
<td>65.8 ± 7.5</td>
<td>68.4 ± 6.7</td>
</tr>
<tr>
<td>Age at RBD onset (years)</td>
<td>54.7 ± 10.2</td>
<td>65.3 ± 11.8</td>
<td>61.0 ± 7.7</td>
<td>61.0 ± 8.8</td>
</tr>
<tr>
<td>RBD duration (years)</td>
<td>7.3 ± 6.9</td>
<td>8.9 ± 10.4</td>
<td>4.6 ± 4.0</td>
<td>7.2 ± 7.2</td>
</tr>
<tr>
<td>Age at disease onset (years)</td>
<td>57.1 ± 8.2</td>
<td>71.7 ± 8.4</td>
<td>56.2 ± 9.7</td>
<td>N/A</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>4.4 ± 2.7</td>
<td>3.2 ± 4.4</td>
<td>9.6 ± 6.0</td>
<td>N/A</td>
</tr>
<tr>
<td>RBD preceding disease onset (%)</td>
<td>52.2</td>
<td>100</td>
<td>18.5</td>
<td>N/A</td>
</tr>
</tbody>
</table>

n: number of subjects, RBD: Rapid eye movement sleep behavior disorder, MSA: Multiple system atrophy, DLB: Dementia with Lewy bodies, PD: Parkinson’s disease, IRBD: idiopathic RBD, N/A: not applicable, VPSG: video-polysomnography.
REM Sleep Behavior Disorder Associated with Neurodegenerative Disease

**Synucleinopathy**
- Lewy body disease (LBD)
  - Incidental LBD
  - Parkinson’s disease (PD)
  - PD with dementia (PDD)
  - Dementia with Lewy bodies (DLB)
  - Pure autonomic failure (PAF)
  - Multiple system atrophy (MSA)

**Tauopathy**
- Pick’s disease
- Corticobasal degeneration (CBD)
- Progressive supranuclear palsy (PSP)
- Argyrophilic grain disease (AGD)
- Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17MAPT)
- Guadeloupean parkinsonism

**Trinucleotide Repeat Disorders**
- Spinocerebellar Atrophy-3 (SCA-3)
- Huntington’s Disease (HD)

**Prionopathy**
- Creutzfeldt-Jakob disease (CJD)
- Fatal familial insomnia (FFI)
- Gerstmann-Straussler-Scheinker (GSS)

**Amyloidopathy**
- Alzheimer’s disease (AD)

**TDP-43opathy**
- Frontotemporal lobar degeneration (FTLD) with TDP-43-positive inclusions
- FTLD with motor neuron disease (FTLD-MND)
- Hippocampal sclerosis (HS)
- Amyotrophic lateral sclerosis (ALS)
- Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17PGRN)

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Etiology:

- Other neurologic disorders
  - Cerebrovascular disease
  - Multiple sclerosis
  - CNS neoplasm
  - Progressive supranuclear palsy
  - Normal pressure hydrocephalus
- Medications
  - TCA, MAOI, SSRI, SNRI
  - Beta blockers
  - Withdrawal from alcohol
- ?Autoimmune disease
Clinical Features

- Abnormal behavior arising from REM
  - Action filled
  - Unpleasant/violent
- Sleep related injury
- Sleepwalking or leaving the room is extremely RARE
- PLM’s in NREM common
- EDS/fatigue uncommon
- No history of aggression

- Family History
- Dream Enactment
  - Kicking
  - Punching
  - Flailing
  - Talking/shouting
  - Gesturing
  - Slapping
  - Mimic eating/drinking
  - Laughing
  - Leaping from the bed
Clinical Subtypes

- Parasomnia overlap disorder
  - Disorder of arousal
  - Sleep related eating disorder
  - Rhythmic movement disorder
  - Male predominant/all age groups
  - Begin in childhood/adolescence

- Status dissociatus
  - Extreme form of state dissociation with RBD features
  - Underlying neurologic/medical condition usually present
Clinical Subtypes

• Agrypnia excitata
  • Dream enactment
    • REM related or related to dissociated REM sleep-wakefulness state
  • Generalized motor overactivity
• Impaired ability to initiate and maintain sleep
• Loss of slow wave sleep
• Marked motor and autonomic sympathetic activation
Diagnosis

- Clinical history/evaluation
  - Neuroimaging to rule out other causes

- Video PSG
  - Increased phasic/tonic EMG activity
  - Dream enactment
  - Exclude other disorders (OSA, Epilepsy, PLMD)

- Absence of epileptiform activity

- Subtle motor and cognitive features of early neurodegeneration
ICSD Diagnostic Criteria

- Repeated episodes of sleep related vocalization and/or complex motor behaviors
- These behaviors are documented by PSG to occur during REM sleep or based on clinical history of dream enactment, are presumed to occur during REM sleep
- PSG recording demonstrates REM sleep without atonia
- The disturbance is not better explained by another sleep disorder, mental disorder, or substance use
- Absence of epileptiform activity during REM sleep unless RSBD can be clearly distinguished from any concurrent REM sleep related disorder
Table 1
Proposed Minor Changes to the Definitions and Diagnostic Criteria for REM Sleep Without Atonia and and REM Sleep Behavior Disorder

**REM sleep without atonia (RSWA)**

*Abnormal EMG tone during REM sleep*

- the electrophysiologic finding of excessive amounts of sustained or intermittent elevation of submental EMG tone and/or excessive transient muscle activity on the submental or limb derivations

**Probable RBD**

*Abnormal behaviors during REM sleep*

- a history of recurrent abnormal and disruptive sleep behavior with injuries or the potential for injury
  - the behaviors are usually (but not necessarily) associated with dream mentation
  - the behaviors are usually (but not necessarily) associated with dreams involving a chasing or attacking theme

**Definite RBD**

*Abnormal sleep behavior and abnormal EMG tone during REM sleep. Items A + B + C must be present for the diagnosis of definite RBD*

A. Presence of RSWA

- the electrophysiologic finding of excessive amounts of sustained or intermittent elevation of submental EMG tone and/or excessive transient muscle activity on the submental or limb derivations (the specifics of which require further study)

B. Presence of abnormal REM sleep behavior by history and/or on PSG

- a history of recurrent abnormal and disruptive sleep behavior with injuries or the potential for injury (fulfills criteria for probable RBD) and/or
- documentation of abnormal REM sleep behaviors during polysomnographic monitoring (i.e. prominent limb or truncal jerking; complex, vigorous, or violent behaviors)

C. Absence of EEG epileptiform activity during REM sleep

- unless RBD can be clearly distinguished from any concurrent REM sleep-related seizure disorder
Fig. 2. A) Excessive phasic electromyographic activity and intermittent increased tonic electromyographic activity in the chin with normal atonia in the limbs during REM sleep in a patient with RBD. B) Abnormal phasic electromyographic burst of all the muscles recorded associated with a sudden body jerk during REM sleep in a patient with RBD. (Abbreviations as in Fig. 1).
Evaluation of Biomarkers in Patients with iRBD
Synucleinopathies

Hypothesis - Among those with iRBD, abnormalities on the following measures would predict the associated evolving phenotype within the synucleinopathy spectrum:

<table>
<thead>
<tr>
<th>Phenotype/Disorder</th>
<th>Cog</th>
<th>Motor</th>
<th>Smell</th>
<th>Aut</th>
<th>MRI/MRS</th>
<th>DaT</th>
<th>PET</th>
<th>MIBG</th>
</tr>
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<tbody>
<tr>
<td>iLBD</td>
<td>NI</td>
<td>NI</td>
<td>+/-</td>
<td>+/-</td>
<td>NI</td>
<td>+/-</td>
<td>NI</td>
<td>Abnl</td>
</tr>
<tr>
<td>PD</td>
<td>NI</td>
<td>Abnl*</td>
<td>Abnl</td>
<td>Abnl</td>
<td>NI</td>
<td>Abnl</td>
<td>NI</td>
<td>Abnl</td>
</tr>
<tr>
<td>DLB</td>
<td>Abnl*</td>
<td>Abnl*</td>
<td>Abnl</td>
<td>Abnl</td>
<td>Abnl*</td>
<td>Abnl</td>
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</tr>
<tr>
<td>MSA</td>
<td>NI</td>
<td>Abnl*</td>
<td>NI</td>
<td>Abnl</td>
<td>NI</td>
<td>Abnl</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>PAF</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>Abnl</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
</tr>
</tbody>
</table>

Boeve 2010
Differential Diagnosis

- Nightmares
  - No motor activity/injury
- PLMD
- Epilepsy
  - Nocturnal frontal lobe epilepsy
  - Nocturnal complex partial seizure
- OSA
- Narcolepsy
- Dissociative psychiatric disorders
- NREM parasomnias
  - Age, timing, response upon awakening, vocalizations
  - Confusional arousals
  - Sleep terrors
  - Sleepwalking
- Rhythmic movement disorder
- PTSD
- Malingering
Treatment

• Goals
  • Decrease intensity of dream enactment behavior
  • Prevent injury (self and bed partner)
  • Identify cause (iatrogenic, neurodegenerative)

• Clonazepam
  • Mean effective dose 1mg po hs (0.25mg-4mg)
  • GABAergic activity depressing motor reflexes
  • Side effects can limit use
  • Other benzodiazepines not as effective
Treatment

• Melatonin
  • 3-12 mg po hs, well tolerated
  • Uncertain mechanism for RSBD
  • Decreases tonic (not phasic) REM activity
  • Restoration of REM circadian rhythm
  • In place of or co-administer with clonazepam

• ? cholinesterase inhibitor, pramipexole, dopaminergic agents, clozapine, triazolam,quietiapine, sodium oxybate
Treatment

- Discontinue medications that can cause RSBD
- Neurological evaluation
  - Neurodegenerative disease
    - RSBD is part of the process, not so much a predisposing factor
  - Not just once, but at least yearly
Treatment

- Safety measures
  - Place mattress on floor
  - Keep sharp objects away from bed
  - Remove extraneous furniture from bedroom
  - Bed “alarm” designed to deliver calming message
Treatment

Since most patients with RBD are male, it may be the “male pride” that keeps them from using barriers designed for infants, and other techniques have been used. Some have constructed plywood barriers placed along side the bed and on the bed in between the patient and spouse, with padding affixed to the sides of the plywood facing the patient. Others use a small mattress and place it on its side adjacent to the bed, with chairs leaning against the mattress to keep it in place. Some sleep in a sleeping bag in the bed in a cocoon-like fashion, with the open end of the sleeping bag toward the head tied as snuggly as possible. Some go to bed with oven mits on their hands, with shoestrings tied around the wrists to keep the mits in place. One man has used a rope with one end tied around him and the other end tied around the bedpost to alter his tendency to lurch and run out of bed. These and other colorful examples of safety ingenuity are described in other informative and entertaining sources\(^1\) – Carlos Schenck’s text on parasomnias is a must-read for anyone interested in the RBD field.\(^2\)
Prognosis

- Depends on underlying cause
- Most patients (80-90%) will eventually develop a neurodegenerative disorder
  - Conversion rate is about 50% every 10 years
- Strongest risk factors for conversion
  - Motor dysfunction
  - Abnormal color vision
  - Olfactory dysfunction
  - Cognitive dysfunction
Counseling

Googling your symptoms when you don’t feel well is the most efficient way to convince yourself you are dying.
Future Directions

• Ongoing clinical research/trials
  • Biomarkers
  • Pathophysiology of RSBD
  • Treatment medications

• Video PSG criteria
  • RSBD v REM sleep without atonia

• Early intervention strategies for neurodegenerative diseases
Take Home Points

• RSBD is associated with neurodegenerative disease
  • Clinical s/sx of RSBD can precede neurologic disease by months to decades
  • Yearly neurologic exam in all RSBD patients essential

• Question all patients regarding abnormal sleep behaviors

• Safety is important
Figure 1—A patient with chronic RBD demonstrates his homemade restraint apparatus that he used every night for five years to prevent himself from leaving the bed and injuring himself during dream-enacting episodes.
References

- International Classification of Sleep Disorders 2014
- Uptodate
- Schenck, C. et al. REM Sleep Behavior Disorder: Clinical, Developmental, and Neuroscience Perspectives 16 years after its Formal Identification in SLEEP. Sleep 2001 25(2): 120-38
References


- Kim, YE and Joen, BS. Clinical Implication of REM Sleep Behavior Disorder in Parkinson’s Disease. Journal of Parkinson’s Disease. 2014. 4: 237-44