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

CHRISTIANA CARE HEALTH SYSTEM

RSBD Outline

- Definition
- Epidemiology
- Pathogenesis
- Etiology
- Clinical Features
- Diagnosis and Differential
- Treatment
- Prognosis and Counseling

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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

Schenck, et al. Sleep 1986. 9(2): 293-308

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

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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

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Epidemiology

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

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Lloyd, R. et al J Clin Sleep Med 2012. 8(2): 127-31

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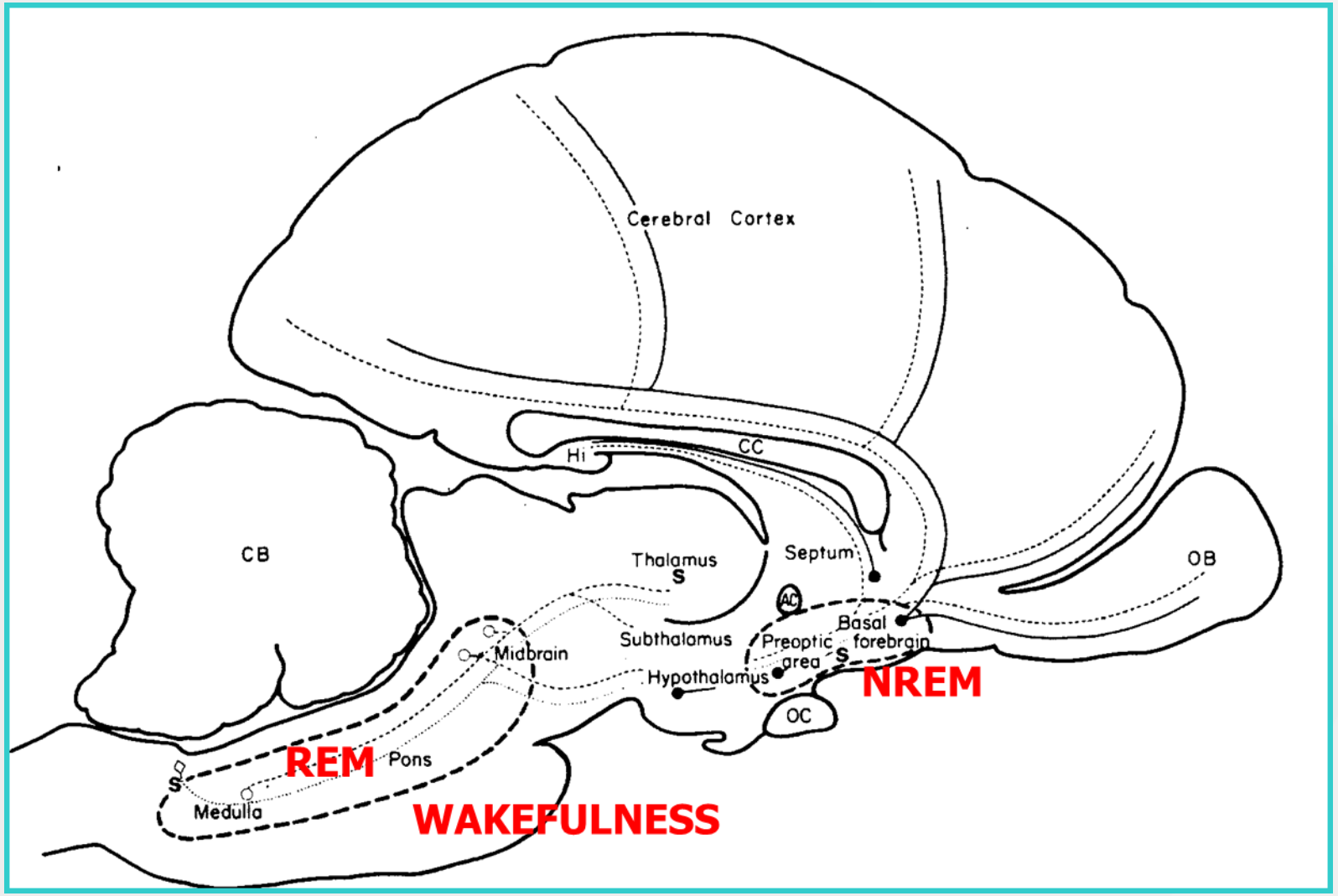

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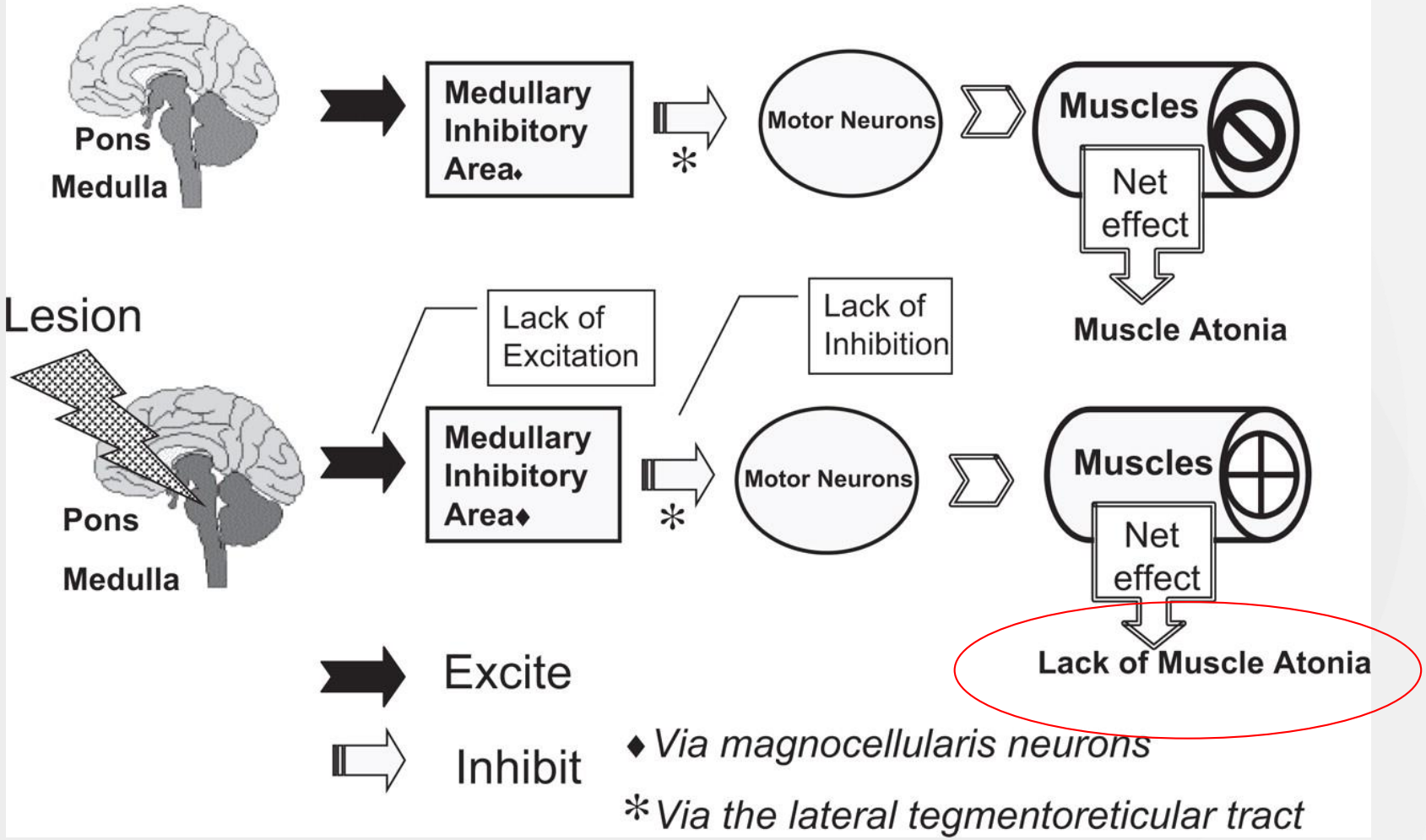
Sleep/Wake Neurotransmitters

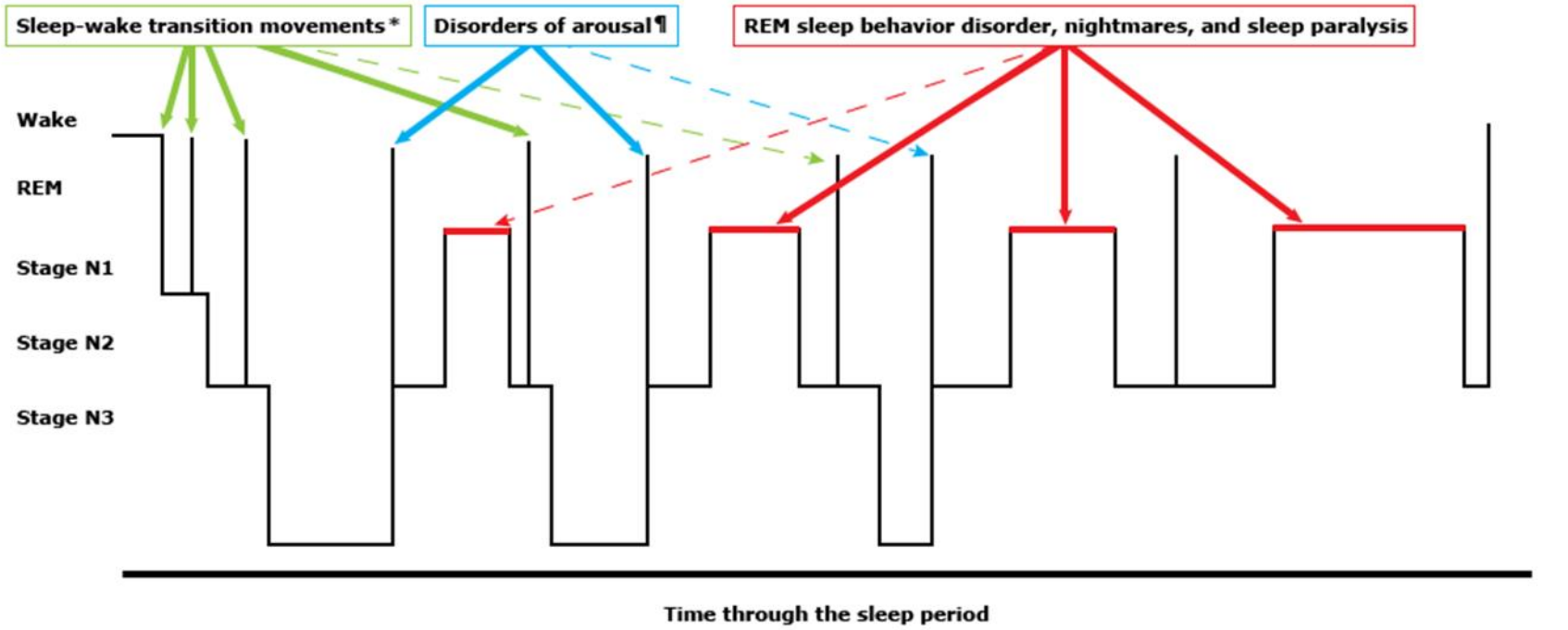
WAKE	NREM	REM
Dopamine	GABA	REM ON
Acetylcholine	Adenosine	Acetylcholine
Norepinephrine	Serotonin	REM OFF
		Serotonin
		Norepinephrine

Pathophysiology of REM sleep behavior disorder



RSBD Predominance

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



* Examples include hypnic jerks, hypnagogic foot tremor, periodic limb movements, and sleep-related rhythmic movement disorder.
¶ Disorders of arousal from non-REM sleep include confusional arousals, sleep-related abnormal sexual behavior, sleep terrors, sleepwalking, and sleep-related eating disorder.

REM: rapid eye movement.

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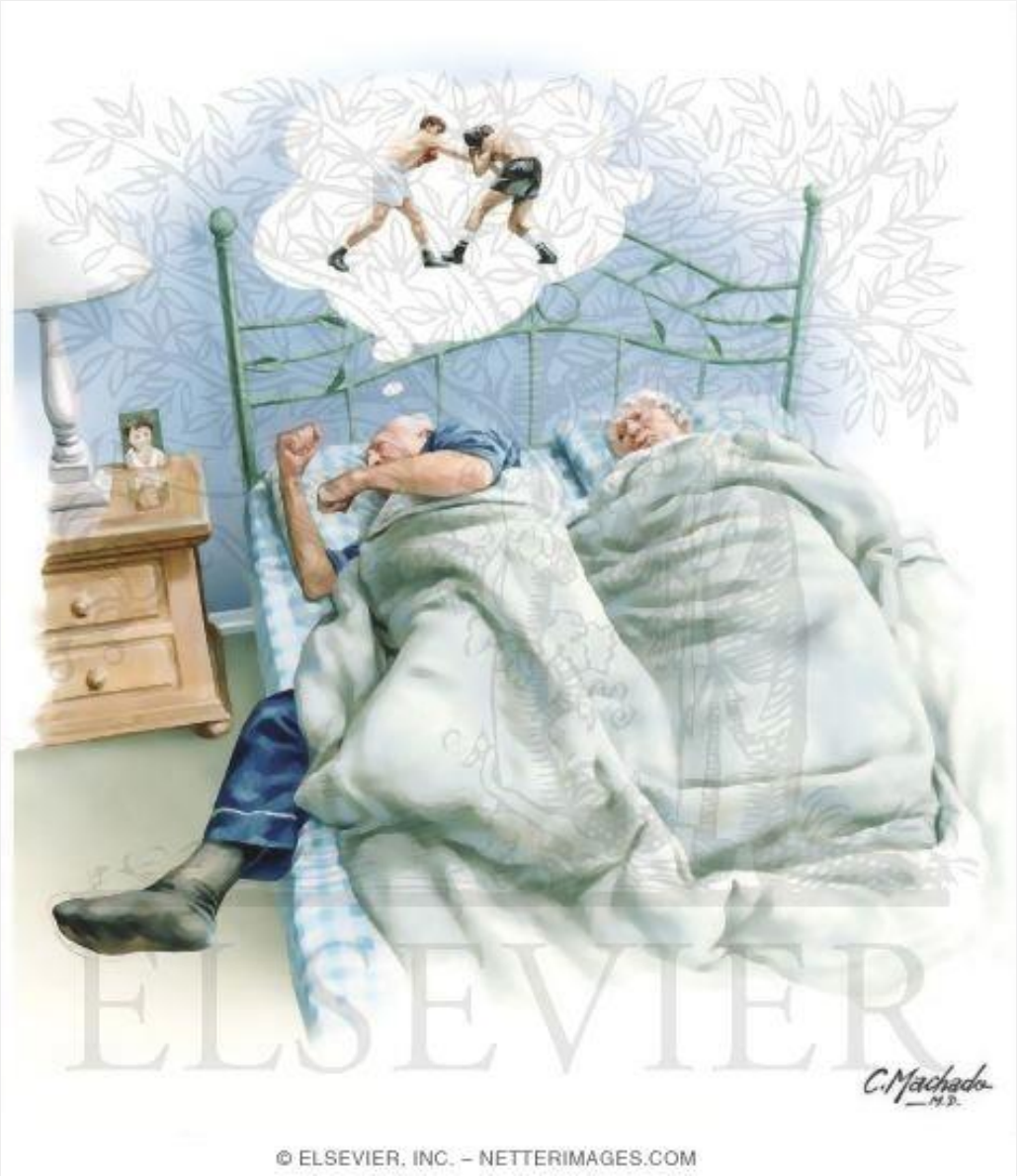
Pathogenesis

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



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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.

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

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.

Iranzo, et.al.

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)

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)

Tauopathy

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

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-17*PGRN*)

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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

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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

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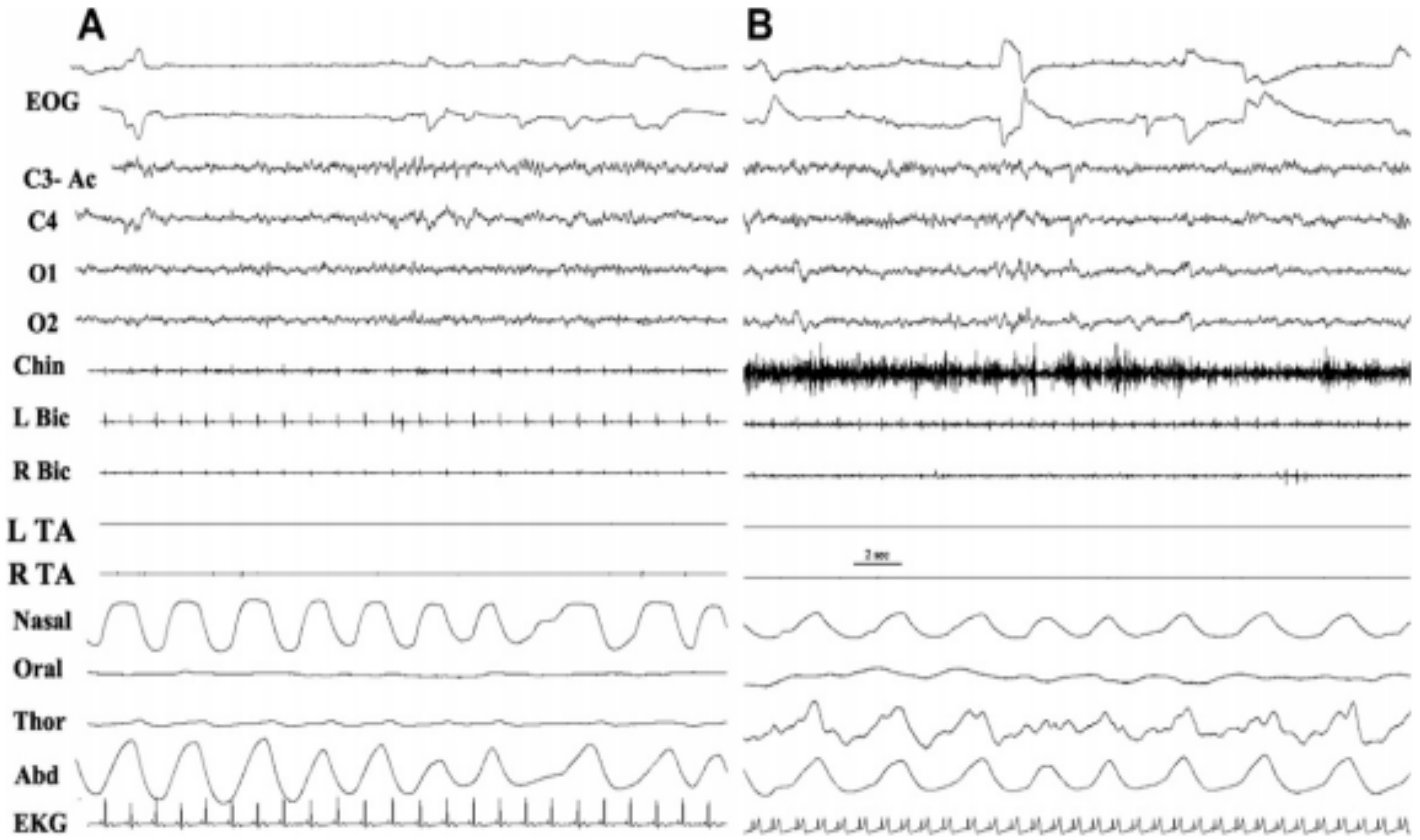

Fig. 1. A) A normal REM sleep episode in a healthy subject showing muscle atonia in the chin, upper and lower limbs. B) Sustained tonic electromyographic activity in the chin with normal atonia in the limbs during REM sleep in a patient with RBD. EOG: electrooculogram. C3, C4, O1, O2: electrode positions according to the 10/20 International system, referenced to combined ears (Ac). Chin: electromyography of the mentalis muscle. L and R Bic: electromyography of the left and right biceps brachii. L and R TA: electromyography of the left and right tibialis anterior. Nasal: nasal air flow. Oral: oral air flow. Tho: thoracic respiratory movements. Abd: abdominal respiratory movements. EKG: electrocardiogram. Note the time calibration mark.

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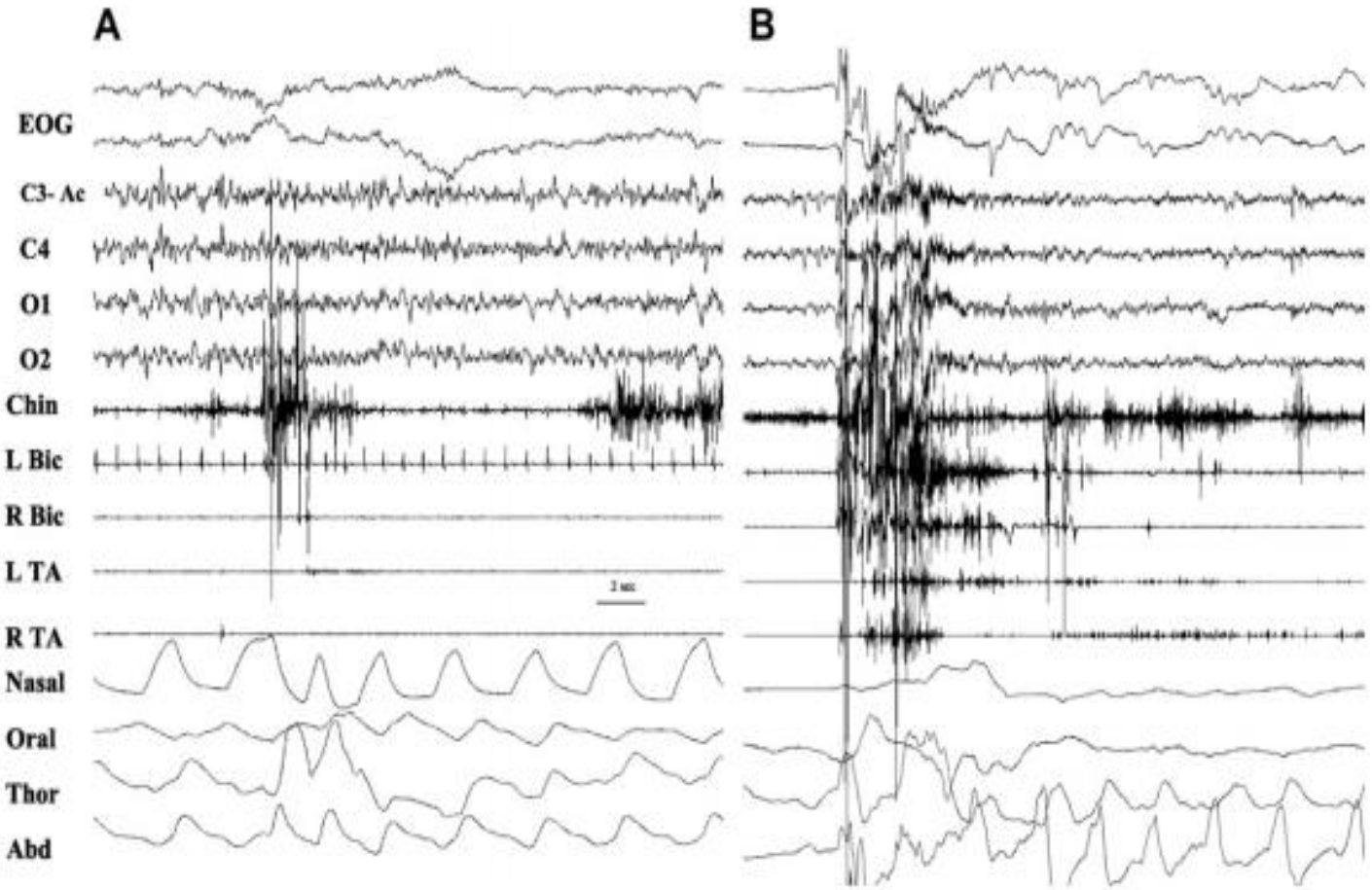

Fig. 2. A) Excessive phasic electromyographic activity and intermittent increased tonic electromyographic activity in the chin with normal atonia in the limbs during REM sleep in a patient with RBD. B) Abnormal phasic electromyographic burst of all the muscles recorded associated with a sudden body jerk during REM sleep in a patient with RBD. (Abbreviations as in Fig. 1).

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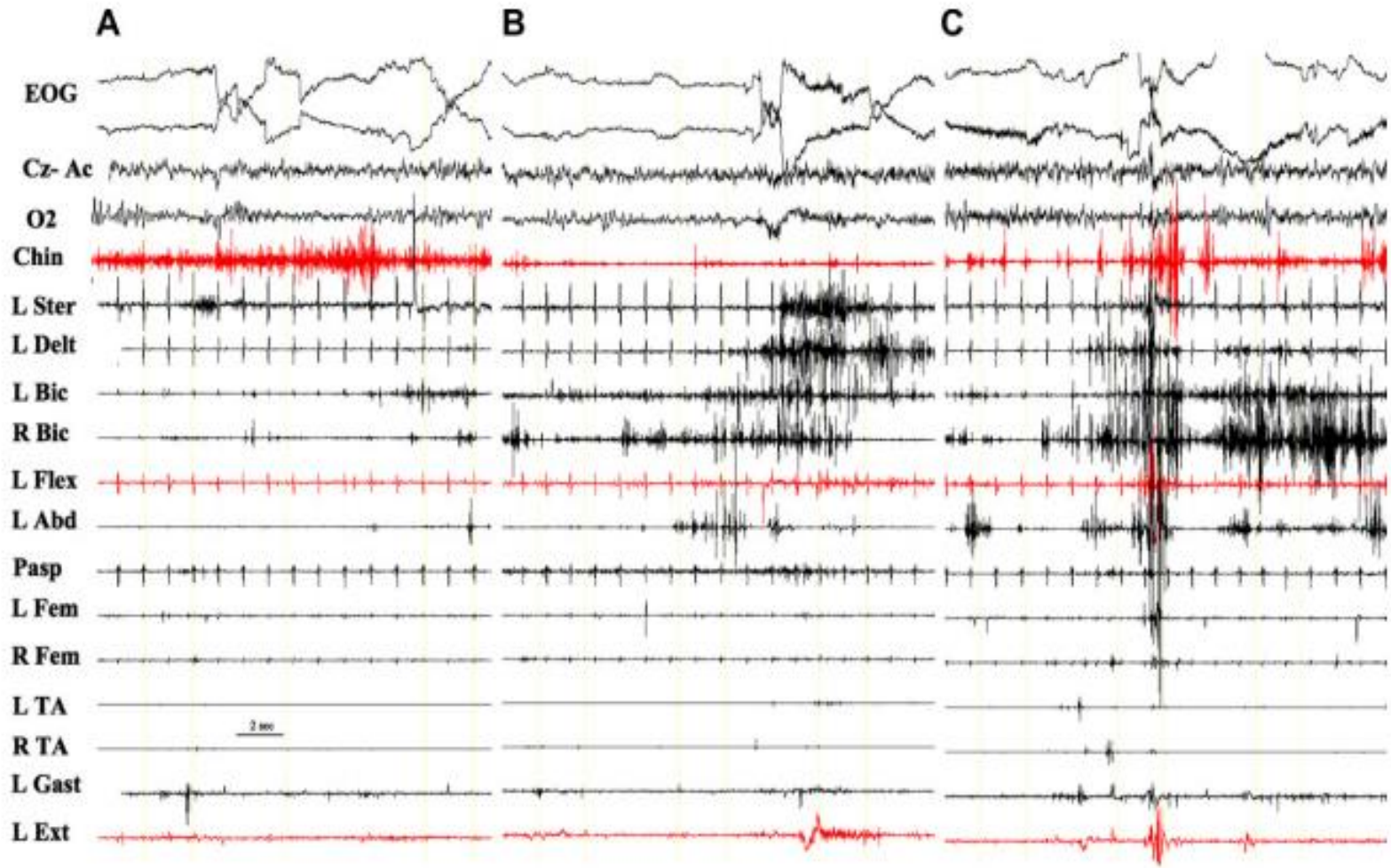

Fig. 4. Electromyographic activity from multiple muscles during REM sleep in a patient with RBD. A) Lack of atonia only in the chin. B) Atonia in the chin and increased phasic electromyographic activity in the upper limbs starting in both biceps brachii and spreading to the deltoid and sternocleidomastoid. C) Increased phasic electromyographic activity mainly in the upper limbs. EOG: electrooculogram. Cz, O2: electrode position according to the 10/20 International system, referenced to combined ears (Ac). Chin: electromyography of the mentalis muscle. Ster: sternocleidomastoid. Delt: deltoides. Bic: biceps brachii. Flex: flexor digitorum superficialis. Abd: abductor pollicis brevis. Pasp: thoracolumbar paraspinal. Fem: rectus femoris. TA: tibialis anterior. Gast: gastrocnemius; Ext: extensor digitorum brevis. L: left, R: Right.

Iranzo et al.

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:

Phenotype/ Disorder	Cog	Motor	Smell	Aut	MRI/MRS	DaT	PET	MIBG
iLBD	Nl	Nl	+/-	+/-	Nl	+/-	Nl	Abnl
PD	Nl	Abnl*	Abnl	Abnl	Nl	Abnl	Nl	Abnl
DLB	Abnl*	Abnl*	Abnl	Abnl	Abnl*	Abnl	Abnl*	Abnl
MSA	Nl	Abnl*	Nl	Abnl	Nl	Abnl	Nl	Nl
PAF	Nl	Nl	Nl	Abnl	Nl	Nl	Nl	Nl

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, pramiprexole, 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

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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

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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.

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