5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 2

Treatment of adult and pediatric primary sleep disorders (Level 2)

Parasomnia's - video session & treatment

Stine Knudsen
Oslo, Norway

Email: stine.knudsen@dadlnet.dk

Parasomnias

Stine Knudsen, MD, Expert in Sleep Medicine, Ph.D
Nevsom - Norwegian Centre of Expertise for
Neurodevelopmental Disorders and Hypersomnias,
Oslo University Hospital, Norway

Norwegian National Advisory Unit on RARE DISORDERS

NevSom – Norwegian Centre of Expertise for Neurodevelopmental disorders and Hypersomnias

Oslo University Hospital

Conflict of Interest Disclosures for Speakers

[X] I have the following relationships with entities **producing**, **marketing, re-selling, or distributing** health care goods or services consumed by, or used on, patients:

Type of Potential Conflict	Details of Potential Conflict
Grant/Research Support	none
Consultant	none
Speakers' Bureaus	UCB Pharma, AOP Orphan, Jazz Pharmaceuticals
Financial support	none
Other	none

[X] The material presented in this lecture has no relationship with any of these potential conflicts

Norwegian National Advisory Unit on RARE DISORDERS

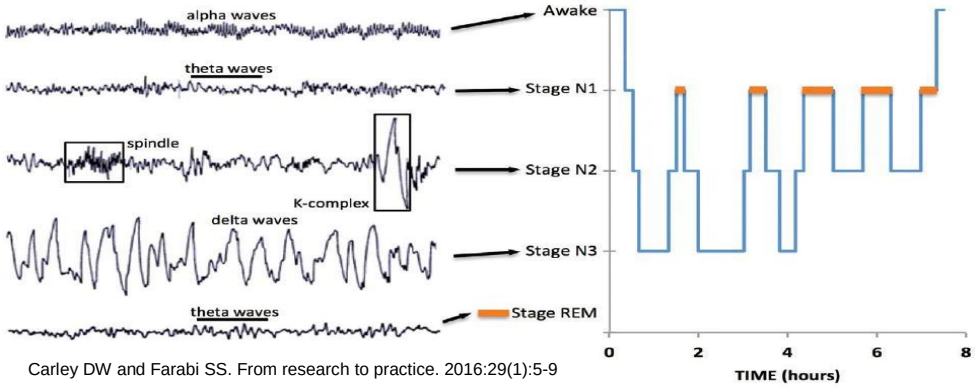
NevSom – Norwegian Centre of Expertise for Neurodevelopmental disorders and Hypersomnias

Oslo University Hospital

What is a parasomnia?

- Brain dysfunctions=neurological disorders.
- Abnormal behaviours, experiences and autonomic responses during sleep/emerging from sleep.
- Dissociative states: abnormal mixture of features from sleep and wake states
- Categorized according to the sleep stage they emerge from:
- Rapid eye movement (REM) sleep parasomnias
- Non-REM sleep parasomnias
- State-independent parasomnias (overlap parasomnia disorders)

Sleep/wake stages and characteristics

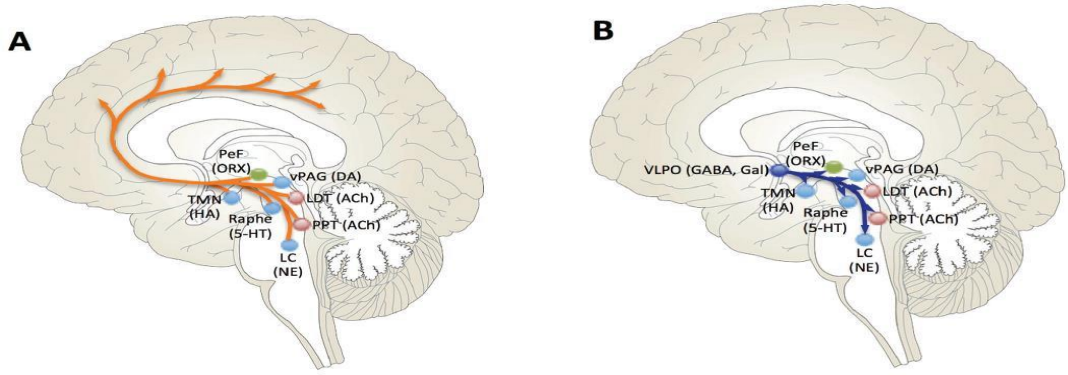


Carley DW and Farabi SS. From research to practice. 2016:29(1):5-9

Wake:EEG is desyncronized, you are conscious, can move, no dreaming.
REM sleep: EEG is desynchronized, you are unconscious, you are paralysed, you dream.
NREM sleep: EEG is increasingly synchronized, you are unconscious, you can move, you *can* dream.

Note!: At night: there is most NREM sleep in the beginning, most REM sleep in the end.

Neurobiological regulation of sleep and wake states

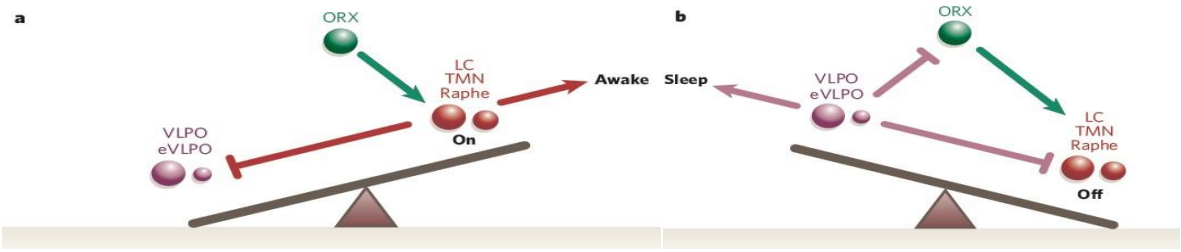


VLPO = Ventrolateral preoptic nucleus; TMN = Tuberomammillary nucleus; LDT = laterodorsal tegmental nucleus; PPT = pedunculopontine tegmental nucleus; LC = locus coeruleus; ORX=orexin/hypocretin; Ach = acetylcholine; NA = noradrenaline; 5-HT = serotonin; HIST = histamine; Gal = galanine

A: The reticulary ascending activating system (wake), B: the descending inhibiting system (sleep)

Carley DW and Farabi SS. From research to practice. 2016:29(1):5-9

Sleep wake regulation – neuronal flip-flop switch



eVLPO, extended ventrolateral preoptic nucleus; ORX, orexin; LC, locus coeruleus; TMN, tuberomammillary nucleus.

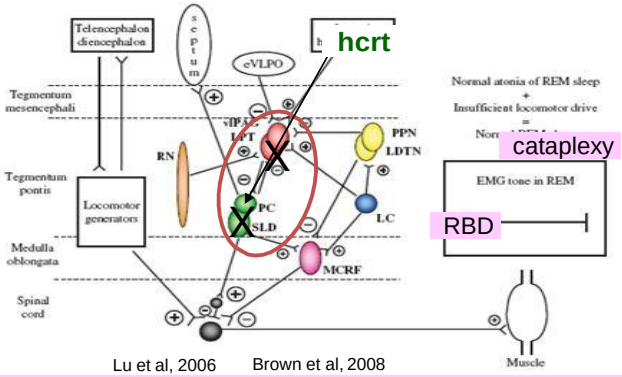
Saper CB, et al. Nature. 2005;437:1257-63

Hypocretin (orexin) projections from the hypothalamus stabilizes the major neural networks (flip-flops) in the brainstem controlling sleep/wake and tonus.

If there is a normal neuronal flip-flop regulation: we are mostly either asleep or awake. And have intact tonus during wake and NREM sleep, but atonic during REM sleep.

Not much "in-between states" (partly awake/asleep, dissociated tonus/REM symptoms).

Another neuronal flip-flip switch: REM sleep and muscle tone regulation



Lu et al, 2006 Brown et al, 2008

Hypocretin neurons are also the main stabilizers of REM sleep/tonus.

If there is normal function of the REM/tonus flip-flop neuronal switch:
- REM and NREM sleep/features do not occur at the same time.
- REM sleep features (muscle atonia, dreaming) do not occur during wakefulness.
- During REM sleep you are atonic/paralysed (cannot act out/move during dreams).

Dissociative states (bad neuronal flip-flops ☺): parasomnia disorders

- **Intermediate/mixed states, contains features from more than one state (wake and sleep; REM and NREM):**
- **NREM sleep with dissociated wake features:** arousal disorders (confusional arousals, sleep walking, sleep/night terror).
- **REM sleep with dissociated wake features:** REM sleep behaviour disorder (RBD), lucid dreaming.
- **Wake with dissociated REM sleep features:** hypnagogic hallucinations, sleep paralysis, cataplexy.
- **State independent/mixed REM and NREM sleep features**: Parasomnia overlap disorder.
  Completely disintegrated sleep/wake features: status dissociatus. Not possible to distinguish stages of wake, NREM, REM sleep (prion diseases, fatal familial insomnia, end stage neurodegenerative diseases PD, ALZ etc).

Antelmi et al. Sleep Med. Reviews 2016;28:5-17

NREM sleep parasomnias

- **Somnambulism (Sleep walking)**
  (ICD-10-CM-code:F51.3)
- **Confusional arousals**
  (ICD-10-CM-code:G47.51)
- **Night/sleep terrors (pavor nocturnus)**
  (ICD-10-CM-code:F51.4)
- Sleep related eating disorder
  (ICD-10-CM-code:G47.59)
- Sexsomnia

International Classification of Sleep disorders (ICSD-3)

NREM parasomnias- pathophysiology

- Recurrent episodes of incomplete awakening from sleep
- Presumed pathology: sleep-wake boundary dysregulation, resulting in impaired complete cortical arousal from sleep state.
- Occur mostly during deep slow (NREM sleep stage 3/sometimes stage 2).
- Characteristics: Simple to complex movements (not stereotypical), eyes open, amnesia afterwards.

- Higher prevalence in children, suggest that developmental immaturity plays a role.
- Genetic predisposition: a higher prevalence of HLA-DQB1*05:01 and HLA-DQB1*04 alleles. Also an autosomal dominalt trait for chromosome 20q12-q13.12 locus in sleep walking.

- Priming/precipitating factors : anything that can cause 1) sleep fragmentation (increased sleep-wake transitions where “things can go wrong” (pain, restless legs, OSAS, noise, stress) or 2) decreased ability to wake up/increased sleep drive (sleep deprivation, sedating drugs (hypnotics)).

Irfan et al. Continuum (Minneap. Minn.) 2017;23(4):1035-50

Confusional arousals

- Partial/incomplete awakenings from slow wave sleep (NREM stage 2 or 3).
- Prevalent in children (17%) and 3-4% of adults.

- Episodes: sits up in bed, confused and disorientated with automatic behaviour (mumbling, low vocalisation, confused motor movements).
- No “terror” or getting out of bed.

- Impaired responsiveness to external stimuli. Complete/partial amnesia for episodes (maybe a vague recollection).

- Episodes can happen rarely or many times pr night. Normally brief (few minutes), but can be prolonged if due to sedative hypnotic drugs.

Irfan et al. Continuum (Minneap. Minn.) 2017;23(4):1035-50

Confusional arousal - video

By kind courtesy of Dr. Rune Markhus
National Centre for Epilepsy, Norway

Norwegian National Advisory Unit on RARE DISORDERS
NevSom – Norwegian Centre of Expertise for Neurodevelopmental disorders and Hypersomnias
Oslo University Hospital

Sleep walking (somnambulism)

- Present in 29.1% of children (peak age 10 years), 1-4% of adults.
- Hereditary: a child has a 47% risk if one parent sleep walked, 62% risk if both parents sleep walked.
- Nocturnal episodes range from aimless wandering to complex protracted acts, like urinating in a closet, leaving the house, leaving the house unclothed etc.
- Impaired response to redirection guidance, and can be risky (can lapse out).
- Potentially injurious, falling of a balcony, going into traffic…
- Emerges from N3 slow wave sleep.

- In adults often associated with other sleep disorders, OSAS, RLS, sedative drugs. Especially benzodiazepines like zolpidem.
- Also precipitated by other drugs, antidepressants etc.
- Importantly: if RLSi s misinterpreted as insomnia, hypnotics can induce sleep walking (e.g. complication of hypnotic treatment).

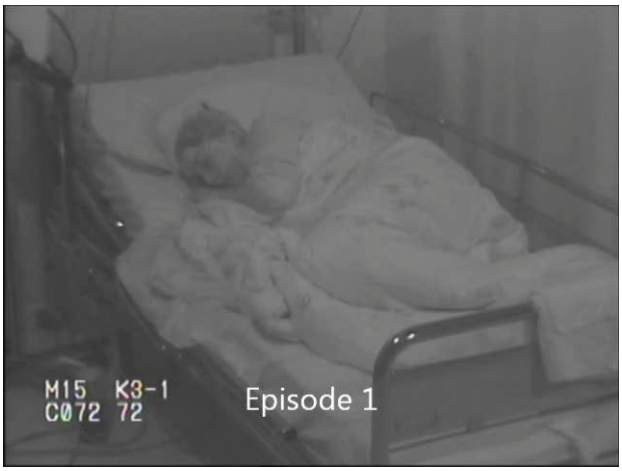
Irfan et al. Continuum (Minneap. Minn.) 2017;23(4):1035-50

Somnambulism - video

By kind courtesy of Dr. Rune Markhus
National Centre for Epilepsy, Norway

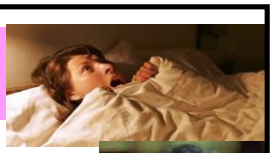
Norwegian National Advisory Unit on RARE DISORDERS
NevSom – Norwegian Centre of Expertise for Neurodevelopmental disorders and Hypersomnias
Oslo University Hospital

"Confusional arousal (with a little pavor nocturnus)" - video



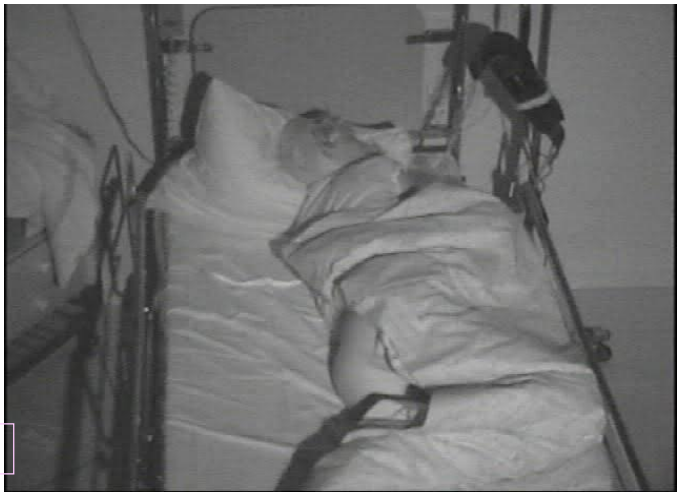
By kind courtesy of Dr. Rune Markhus
National Centre for Epilepsy, Norway

Sleep/night terror – pavor nocturnus



- Dramatic arousal disorder: abrupt arousal episodes starts with a scream/crying and intense fear and autonome and behavioral hyperactivity.
- Can leap out of bed, run around in fright. Intense autonome activation (mydriasis, tackycardia etc).
- Attemts to stop the patient can lead to aggression.
- Amnesia for the episodes (sometimes vague recollection of a dream of fire in the house, ceiling coming down etc).
- Common in children (14.7-56%), but rare in adults (2.5%), very rare in the elderly (1%).
- Can be nessary to take precations so injury is avoided (door locks/alarms etc) .

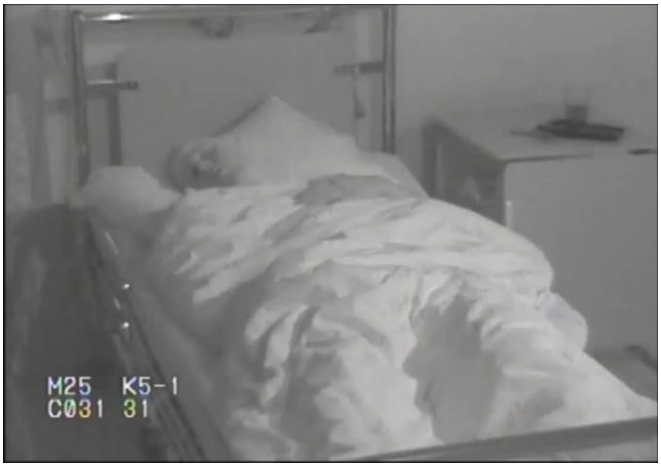
Pavor nocturnus - video



By kind courtesy of Dr. Rune Markhus
National Centre for Epilepsy, Norway

NREM parasomnias - differencial diagnosis

Video epilepsy(?)



By kind courtesy of Dr. Rune Markhus
National Centre for Epilepsy, Norway

NREM parasomnias - evaluation

- Comprehensive history from patient and family/bed partner: age of onset (since childhood?), what happens (stay in bed or not), stereotypical or not, is early/late at night. Home video-recordings?
- Signs of autonome activations/fright may differentiate between different NREM parasomnias (sleep walking or night terrors for example).

- If needed: Video polysomnography to diff. diagnose NREM vs. REM parasomnia (RBD), OSAS with confusion, psychogenic/malingering.
- Possibly combined polysomnography with full EEG measurement (if stereotypical/epilepsy is suspected as diff diagnosis).

NREM parasomnias - management

- Primary goal: safety for patient and bed partner.
- Removing sharp/potential harmful objects, secure windows and doors, install door alarms.
- Evaluation of predisposing/precipitating factors: removal of sedatives, treatment of comorbidities (RLS, OSAS)

- In children: mild/moderate NREM parasomnias like confusional arousals and sleep terrors: often effective with anticipatory awakening 15-20 min before typical night terror time.

- In adults with persistent moderate/severe episodes; try pharmacological treatment.
- No RCTs, but In case series: benzodiazepines like clonazepam have shown sustained effect in 86% with sleep walking and night terrors; various case reports of benefit from SSRI, TCA on night terrors. Schenck CH, Mahowald MW 1996; Am J Med 100(3):333-37
- Hypnotherapy has shown 27-87% effect in NREM parasomnia case series.

Parasomnia differencial diagnoses

Time at night	Age	Parasomnia	Sleep Stage	Non–Rapid Eye Movement (REM) Instability	REM Sleep Atonia	Other Features
Beginning	young	Confusional arousal	Non-REM	Present	Present	Hypersynchronous EEG delta activity
Beginning	young	Sleepwalking	Non-REM	Present	Present	Restless legs syndrome
Beginning	young	Sleep terrors	Non-REM	Present	Present	Increased heart rate
Beginning	young	Sleep-related eating disorder	Non-REM	Present	Present	Restless legs syndrome, periodic limb movements, rhythmic masticatory muscle activity
All night	young	Sleep enuresis	Non-REM/REM	Present	Present	
Beginning	young	Sexsomnia	Non-REM	Present	Present	
End	elderly	REM sleep behavior disorder	REM	Absent	Absent	Periodic limb movements, irregular heart and respiratory rate
Beginning	young	Epilepsy (frontal)	Non-REM	Present	Present	Stereotyphic, +/- paraxysmal activity
All night	young	Psychogenic	wake	absent	present	occur from wake, possibly daytime anxiety

Edited version of Irfan et al. Continuum (Minneap. Minn.) 2017;23(4):1035-50

Norwegian National Advisory Unit on RARE DISORDERS

NevSom – Norwegian Centre of Expertise for Neurodevelopmental disorders and Hypersomnias

Oslo University Hospital

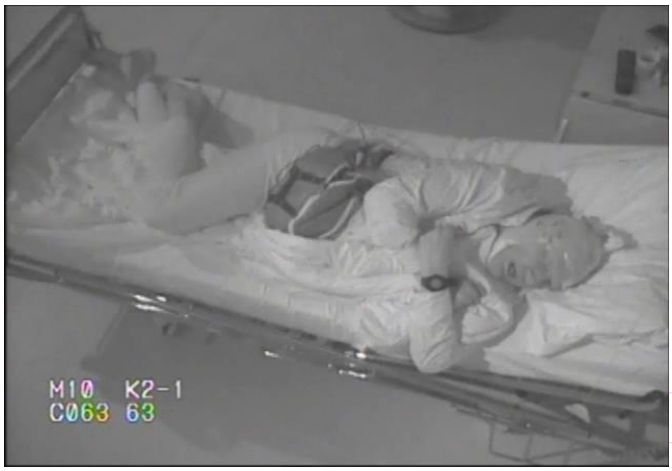
REM sleep parasomnias

- **REM sleep behaviour disorder (RBD)**
  (ICD-10-CM-code:G47.52)
- Nightmare disorder
  (ICD-10-CM-code:F51.5)
- Sleep paralysis
  (ICD-10-CM-code:G47.53)
- Hypnagogic hallucinations
  (ICD-10-CM-code:H53.16)
- Lucid dreaming

International Classification of Sleep disorders (ICSD-3)

for Neurodevelopmental disorders and Hypersomnias

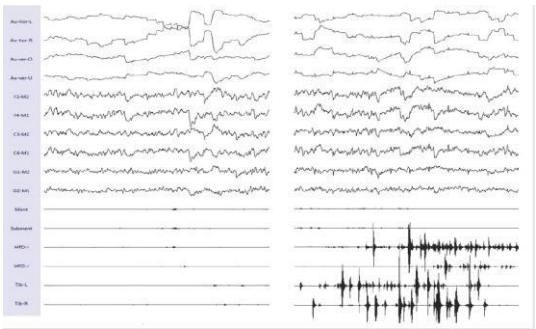
REM sleep behaviour disorder - video



By kind courtesy of Dr. Rune Markhus
National Centre for Epilepsy, Norway

REM sleep behaviour disorder - diagnosis

+



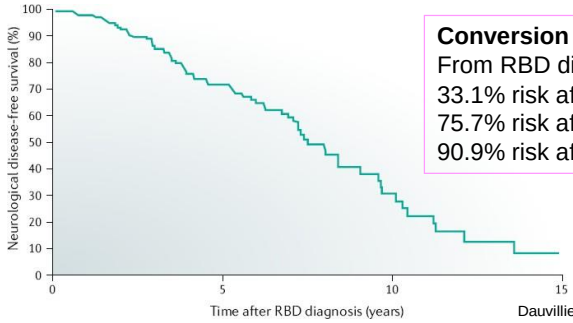
Högl B, Iranzo A. Continuum (Minneap. Minn.) 2017;23(4):2017-34

Clinical history of repeated episodes
of dream enactment (vocalization and/or complex motor behaviours related to dreams)
Violent behaviours sometimes, but necessarily.

Video-PSG showing:
lack of REM muscle atonia in EMG
(tonic and/or phasic activity in chin and/or limb channels)

iREM sleep behaviour disorder (iRBD)

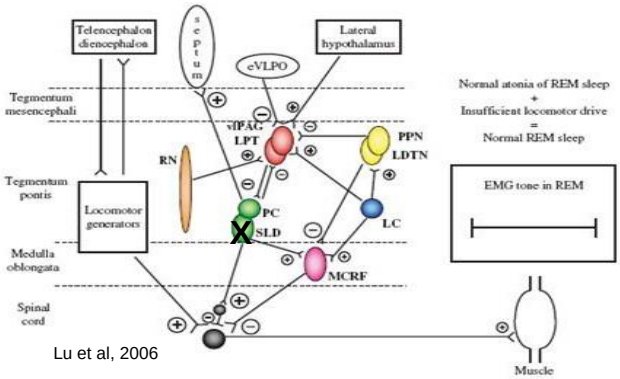
- Formally identified/described as a human neurological disease in 1986. (Schenck C et al. Sleep. 1986;9:293-308)
- Notably: the majority of patients with the "idiopathic" RBD form is now recognized as having the earliest form of a synuclein brain disease (PD, DLB, MSA). Can also be part of narcolepsytype 1 (which does not progress to synucleinopathy).



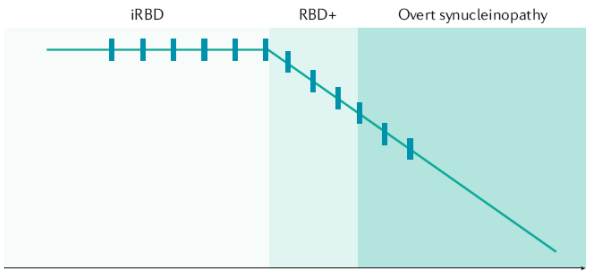
Conversion rate of iRBD to synucleinopathy:
From RBD diagnosis time:
33.1% risk after 5 years
75.7% risk after 10 years
90.9% risk after 14 years

Dauvilliers Y, Schenck CH et al. Nature Reviews - Disease Primers. 2018;4:19

RBD – disease model



Lu et al, 2006



Dauvilliers Y, Schenck CH et al. Nature Reviews - Disease Primers. 2018;4:19

RBD – early stage of synuclein deposits/neurodegeneration. Gradual destruction of the REM-on nuclei (SLD nucleus) results in early loss of muscle atonia during REM sleep.

Gradial development from iRBD to RBD+ and further to a full synucleinopathy

iRBD - pathology

- Primary form (idiopathic form) – **not** an innocent sleep abnormality - it is linked to development of synucleinopathies.
- iRBD patients have no daytime motor or cognitive symptoms (yet), but can have hyposmia, depression, constipation or decreased dopamine uptake in the putamen on functional imaging. Can also have asymptomatic cognitive deficits revealed on neuropsychological testing.
- RBD is the best prodromal marker for PD (positive likelihood ratio:130) compared to the other known markers: depression, constipation, hyposmia (positive likelihood ratio: 2-4).
- RBD: a unique marker for dementia subclassification: mild cognitive impairment combined with RBD, indicates that a synucleinopathy dementia (PD or DLB) but not Alzheimers or Frontotemporal dementia will emerge within 5 years. Ferrini-Strampi L et al. Neurology 2004:62(1):41-45

RBD management

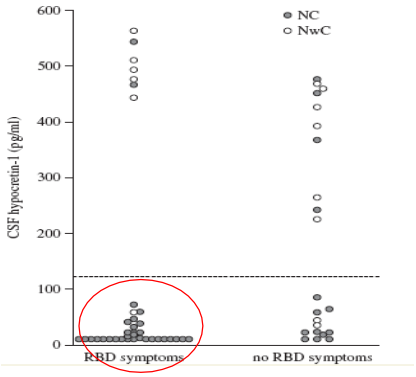
- **Be really sure of the diagnosis (a serious disease marker; the patient will google it).**
- So rule out differential diagnoses like NREM parasomnias (sleep/night terror, sleep walking, hypnagogic hallucinations), other REM parasomnias (nightmares), other nocturnal pathology (epilepsy, severe OSAS, severe PLMs), and secondary RBD.
- Inform about the disease, but do it with caution. Focus on good medical care, follow-ups etc.
- Improve safety in the bedroom, minimize risk of injury (sleep in separate beds/rooms, remove dangerous objects, bed rails, cushions on the floor).
- First-line drugs (usual effective doses): Clonazepam 0.25-2 mg (not if co-existing cognitive/balance problems), or melatonin 3-12 mg at bedtime.
- **Follow-up the patient for development of PD, DLB, MSA – 9/10 (10/10?) will progress.**

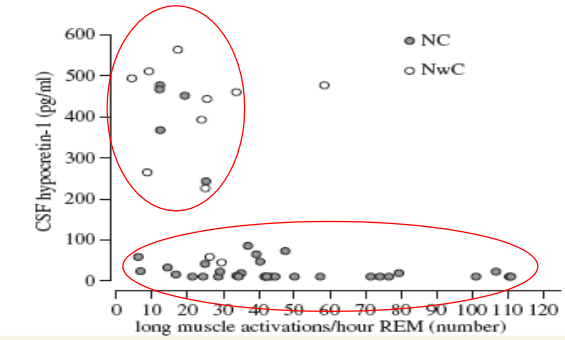
Secondary RBD

- RBD in association with other diseases or medications.
- RBD secondary to neurodegenerative disorders like PD, DLB (not so often MSA), just meaning that RBD occurs after the development of overt synucleinopathy in come cases.
- RBD secondary to other autoimmune brain disorders like narcolepsy, autoimmune encephalitis, paraneoplastic syndromes), focal structural brainstem lesions.
- RBD secondary to drugs, especially antidepressants, lipophilic B-blockers. Discontinuation of these drugs eliminates RBD. So perhaps just a side effect.
- But an open question if it in reality means that the drugs have unmasked a latent neurodegenerative process (especially if RBD persists after the drug has been stopped)

Högl B, Iranzo A. Continuum (Minneap. Minn.) 2017;23(4):2017-34

Secondary RBD: Narcolepsy 24 hour REM dissociation (RBD and cataplexy)





Knudsen et al, Brain 2010

Hypocretin deficiency is associated with 24 hour tonus dysregulation:
cataplexy and REM sleep behaviour disorder in human narcolepsy.
Probably due to abnormal REM-sleep "flip-flopping", due to loss of upstream hcrt stabilisation.
neuronal brainstem destruction like in iRBD, will not get PD, DLB, MSA.

Parasomnias – reading suggestions

- International Classification of Sleep Disorders (3. edition)

- Irfan M, Schenck CH, Howell MJ. Non-rapid Eye Movement Sleep and Overlap Parasomnias. Continuum (Minneap. Minn) 2017;23(4):1035-50
- Högl B, Iranzo A. Rapid Eye movement Sleep Behaviour Disorder and Other REM Movement Sleep Disorders. Continuum (Minneap. Minn) 2017;23(4):1017-34
- Dauvilliers Y et al. REM sleep behaviour disorder. Nature Reviews - Disease Primers. 2018;4:19

Thanks for sharing your wakefulness

Various other parasomnias

- **Other parasomnias:**
- Exploding head syndrome
- Sleep-related hallucinations
- Sleep enuresis
- Parasomnias due to a medical disorder
- Parasomnias due to a medication or substance

- Isolated symptoms: sleep talking

- Parasomnia overlap disorder: status dissociatus

International Classification of Sleep disorders (ICSD-3)

Sleep related violence and sexsomnia

- Wide spectrum of behaviours ranging from simple or semi-purposeful behaviours to more complex, inappropriate acts.
- About 1.6% of the general population report to have violent behaviours during sleep (running away from bed, punching, kicking etc).
- Violent behaviours can occur during both NREM and REM parasomnias (confusional arousals, sleep walking, sleep terrors, RBD, overlap parasomnia disorder) and during nocturnal epileptic seizures.
- Sexsomnia ranges from sexual vocalisations, genital brushing and masturbation to fondling another person and complex/violent sexual acts.
- Sexomnia is primarily classified amongst the NREM parasomnias (confusional arousals and sleep walking), but have also been reported in RBD, parasomnia overlap disorder, OSAS, sleep-related seizues.
- **Both conditions are challenging medical-legal issues…**

Ingravallo F et al, J Clin Sleep Med. 2014;10(8):927-35

Sleep related violence

Authors	Description	Charge	Defense	Forensic evaluation and expert's conclusion	Verdict
Howard and D'Orbán, 1987 (case B)	A 34-year-old salesman strangled his wife while dreaming of being chased by two armed Japanese soldiers. They were sleeping together in their bed.	Murder	NT	Psychiatric and neurological evaluation; psychological tests; EEG. Conclusion: NT.	Acquittal
Broughton et al., 1994	A 23-year-old recently unemployed man drove 23 km to the home of his wife's parents, where he beat and stabbed his mother-in-law, who died, and strangled his father-in-law, who survived.	First degree murder, and attempted murder	SW	Clinical assessment*; EEGs; brain CT; 2 PSGs. Conclusion: SW.	Acquittal
Nofzinger and Wettstein, 1995	A 37-year-old male laborer, possibly dreaming about deer hunting, shot and killed his wife (unclear if they were sleeping together).	First degree murder	OSA	Pulmonary examinations; video-PSG. Conclusion: severe OSA that could be associated with confusion and memory loss.	Conviction
Kayumov et al., 2000	26-year-old unemployed man was accused of first-degree murder of his girlfriend's 2-year-old daughter after he awoke to find her covered in blood and not breathing.	First degree murder	SW	Mental status examination; hypnotic interview; 2 video-PSGs Conclusion: parasomnia diagnosis not supported.	Conviction
Cartwright, 2004	A 42-year-old electrical engineer stabbed and killed his wife, leaving her body outside near the pool.	First degree murder	SW	Forensic workup as in the case reported by Broughton et al. plus 4 night PSGs (including a night with sound-induced arousals). Conclusion: SW followed by sleep terror.	Conviction
Poyares et al., 2005	A 26-year-old Hispanic, recently married man threw his son out of a 3rd floor window and then ran into the street.	Attempted murder	SW	Psychiatric evaluation; EEG; brain CT; video-PSG. Conclusion: SW.	Case dropped
Ebrahim and Fenwick, 2008	A 22-year-old man beat his father to death after going to sleep after a night of drinking.	Murder	SW	Mental and cognitive state assessment; neuropsychological tests; brain MRI; EEG; 5 night video-PSGs (including a night with verbal and tactile provocation, a night with alcohol challenge, and a PSG after 36h of sleep deprivation). Conclusion: confusional arousal into what was a SW episode.	Acquittal

Ingravallo F et al, J Clin Sleep Med. 2014;10(8):927-35

Sexsomnia

Authors	Description	Charge	Defense	Forensic evaluation and expert's conclusion	Verdict
Thomas, 1996	38-year-old male mechanic with a long-term partner was found drinking a beer while naked in a major urban thoroughfare.	Indecent exposure	SW	Psychiatric evaluation of the defendant and telephone interview of the partner. Conclusion: SW.	Acquittal
Borum and Appelbaum, 1996	31-year-old single man loudly knocked on door of communal bathroom while yelling; when the female occupant opened the door, he pushed and struggled with her, and his hand touched her breast.	Indecent assault/ battery, assault with intent to rape	Not explicitly stated	Neurological evaluation. Conclusion: nocturnal complex partial seizure.	Acquittal
Schenck and Mahowald, 1998	26-year-old man, with partner, engaged in sexual behavior with his friend's 4-year-old daughter, who had crawled into bed with him during the night.	Sexual misconduct	SW	Interviews of defendant, his mother, his sister and his current partner. Conclusion: parasomnia.	Acquittal
Rosenfeld and Elhajjar, 1998	45-year-old married businessman fondled his 14-year-old daughter's female friend, who was sleeping downstairs in the living room of his house.	Sexual battery	SW	Neurologic and psychiatric evaluation. Conclusion: SW.	NR
Guilleminault et al., 2002	18-year-old single student placed his finger into the vagina of a young woman who was sleeping in the vicinity.	Sexual assault	SW	Clinical assessment*; 2 urine drug tests; EEG in regular and sleep-deprived conditions; video-PSG; MSLT. Conclusion: NREM parasomnia.	Acquittal

Ingravallo F et al, J Clin Sleep Med. 2014;10(8):927-35

Norwegian National Advisory Unit on RARE DISORDERS
NevSom – Norwegian Centre of Expertise for Neurodevelopmental disorders and Hypersomnias
Oslo University Hospital