Sleep and Degenerative brain disorders: Dementia

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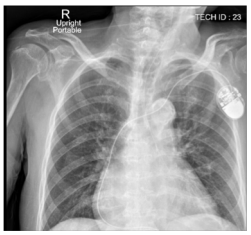
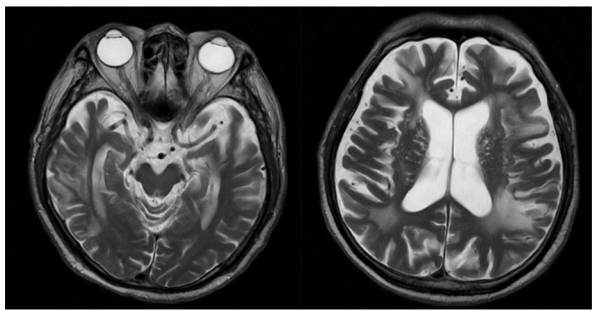
Case: Sleep disorder in AD



- M 90 yrs old, Hx of advance stage of AD, HTN, CKD, PAD, chronic AF on pace maker, CVD-multi-infraction
- Had a poor short term memory, un-inhibitory behavior, sleep disorder-sleep wake cycle disturbance, agitation and frequently apathy



Case: Sleep disorder in AD

16 เมษายน
ช่วงหัวค่ำหลัง 3 ทุ่มหลับแต่ไม่สนิท นอน 5 Hrs 30 min, 3.28-06.00 มี Delirium ผุดลุกผุดนั่ง พูดคนเดียวเสียงดัง เรียกหาคุณแม่ น่าจะเป็นเพราะสิ่งที่แม่พูดตอนบ่าย

17 เมษายน
นอนได้ 2 ช่วง เพราะปวดถ่าย กลางดึก และไอ ช่วงหัวค่ำประมาณ 4 ชม ช่วงกลางดึก ประมาณ 4 ชม รวมเป็น 8 ชม ทำให้การนอนหลับไม่ค่อยจะดี เช้านี้ ตอนทำกายภาพ เช้า เดินได้ดีแต่ช่วงสายนั่งหลับ ไม่ยอมทำกิจกรรม

18 เมษายน
ทั้งคืนนอนหลับสนิทได้ประมาณ 3 ชั่วโมง ตื่นช่วง 9 โมง มาทำกายภาพเช้า ตามปกติดีแต่ตลอดวันไม่ค่อยยอมลืมตา ทำกายภาพได้ดี ช่วง Sundown ซึม พาไปนั่งรถเข็นก้อไม่ยอมลืมตา เพิ่งจะมาตาโต ตอนหลังทานนม ช่วง 1 ทุ่มครึ่ง

22 พฤษภาคม 2019 สรุปโดยรวม
มีพูดคนเดียวบ้าง ช่วง00.40กับช่วงเช้าจับใจความไม่ได้ หลับๆตื่นๆ พูดคนเดียว โดยรวมเวลา 1ชม พูดแล้วก็หลับต่อ หลับสนิท ประมาณ10ชม
ในช่วงเช้าออกกำลังกายกับทีมNeuro ให้ความร่วมมือดี ชวนพูดคุยถามตอบตรงคำถาม ก่อนเดินยืดกล้ามเนื้อ ออกกำลังกายบนเตียง ทำให้การเดินในตอนเช้าดี ไม่เดินเขย่งเท้า

INTRODUCTION: Sleep and Degenerative brain disorders

- Sleep disturbances are common in neurodegenerative disease and impair quality of life
- People with Alzheimer's disease (AD) develop daytime hypersomnia and nighttime insomnia
  - These symptoms likely result from circadian rhythm disruption due to
    - Reduced external or environmental cue that entrains or synchronizes an organism's biological rhythms input
    - Suprachiasmatic nucleus dysfunction
    - Melatonin alterations

Sleep disorders in Alzheimer's Disease

- Sleep disturbances are quite common in dementia, particularly Alzheimer's disease (AD)
- These and secondary agitation, the primary impetus in institutionalizing older individuals with cognitive decline, as family members are unable to take care of them at night.
- Nocturnal exacerbation of delirium or sun-downing is a well-recognized entity in dementia and is often associated with sleep disturbances.

Sleep disorders in Alzheimer's Disease

- Sundowning is characterized by agitation, confusion, and irritability as natural lights begin to fade in the evening and at night
- Daytime hypersomnia and nighttime insomnia are the most common sleep complaints with dementia
- Association between disturbed sleep and cognitive decline is bidirectional and complex

Sleep disorders in Alzheimer's Disease

- Circadian rhythm sleep disorders (CRSD) are common in this cohort and can manifest with both the excessive daytime sleepiness and poor sleep continuity at night
- Most common circadian rhythm sleep-wake disorder to affect this group is irregular sleep-wake disorder
- Most disabling of sleep disorders in AD

Circadian rhythm disorders in degenerative brain disorders

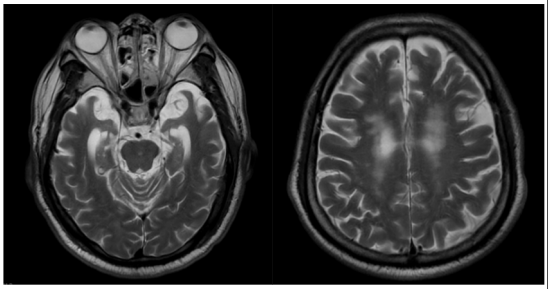
- The circadian sleep-wake rhythms controlled by suprachiasmatic nucleus (SCN), master clock or pacemaker resides in hypothalamus
- Even with normal aging, SCN degenerates resulting in earlier awakenings and less consolidation of nocturnal sleep
- Disturbances of circadian rhythms, as well as fragmentation of sleep at night, more pronounced in AD.

Circadian rhythm disorders in degenerative brain disorders

- CSF melatonin levels decrease with normal aging
  - Become even lower in AD; onset is earlier, and its peak becomes irregular, presumably due to SCN degeneration
- Dysfunction of the SCN and related retino-hypothalamic tract, alteration of melatonin levels, and significantly reduced exposure to zeitgebers lead to CRSD in dementia and AD,
  - Can cause both excessive daytime sleepiness and nighttime insomnia
- In animal models, β-amyloid increases during wakefulness and is cleared from the brain during sleep through the lymphatic system
  - With sleep deprivation, a further increase in β-amyloid levels

Case

- M 77 yrs, HX DM, CAD, S/P PCI, HTN, gall stone and recently had cholangitis and Alzheimer's dementia, admit for ERCP
- Had Hx of sleep disorder, insomnia, snoring, sleep apnea, patient had frequently stop breathing during asleep
- Patient's son shows home video documented that the patient had frequently
  - OSA
  - CSA
- Also, the patient had daytime hypersomnolence, frequent fragmented sleep, cognitive decline rapidly recently

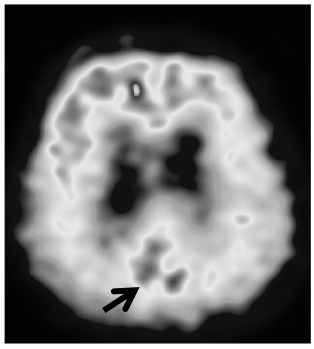


Case: CPAP use home for monitoring and therapy

Compliance Summary	
Date Range	1/5/2562 - 14/5/2562 (14 days)
Days with Device Usage	14 days
Days without Device Usage	0 days
Percent Days with Device Usage	100.0%
Cumulative Usage	4 days 9 hrs. 36 mins. 8 secs.
Maximum Usage (1 Day)	11 hrs. 48 mins. 30 secs.
Average Usage (All Days)	7 hrs. 32 mins. 34 secs.
Average Usage (Days Used)	7 hrs. 32 mins. 34 secs.
Minimum Usage (1 Day)	2 hrs. 13 mins. 20 secs.
Percent of Days with Usage >= 4 Hours	78.6%
Percent of Days with Usage < 4 Hours	21.4%
Total Blower Time	4 days 11 hrs. 3 mins. 15 secs.
Auto CPAP Summary	
Auto CPAP Mean Pressure	7.8 cmH2O
Auto CPAP Peak Average Pressure	9.4 cmH2O
Average Device Pressure <= 90% of Time	9.9 cmH2O
Average Time in Large Leak Per Day	14 mins. 51 secs.
Average AHI	17.6

Obstructive sleep apnea linked to higher Alzheimer's risk

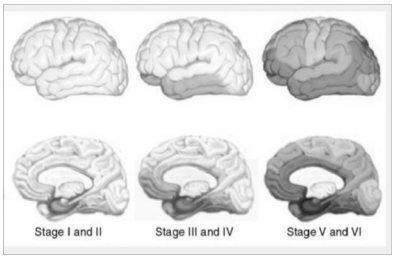
- A study[1] of 208 participants, aged 55-90 yrs
  - 50 % participants had obstructive sleep apnea
  - 36.5 % had a mild form of the disorder, and 16.8 % had a severe form
  - 104 participants took part in a longitudinal study 2 years revealed a link between severity of sleep apnea and the concentration of amyloid beta



1. Ram A. Sharma et. All., AJRCCM Issues Vol. 197, No. 7 | Apr 01, 2018

Obstructive sleep apnea linked to higher Alzheimer's risk

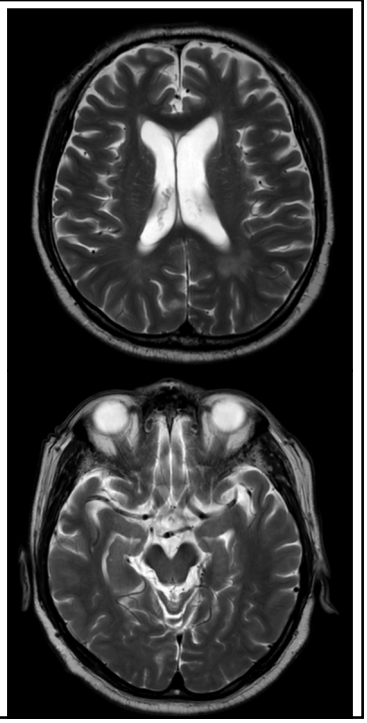
- Recent evidence has supported an association between sleep disruption, particularly obstructive sleep apnea (OSA), and increased risk for dementia
  - Mayo Clinic Study of Aging, in 288 elderly aged >=65 years with both Tau-PET and Amyloid-PET scans and whose bedpartners had completed a questionnaire that assessed whether participants had witnessed apneas during sleep
  - 15% had witnessed apneas during sleep
    - Witnessed apneas significantly associated with tau in Entorhinal cortex



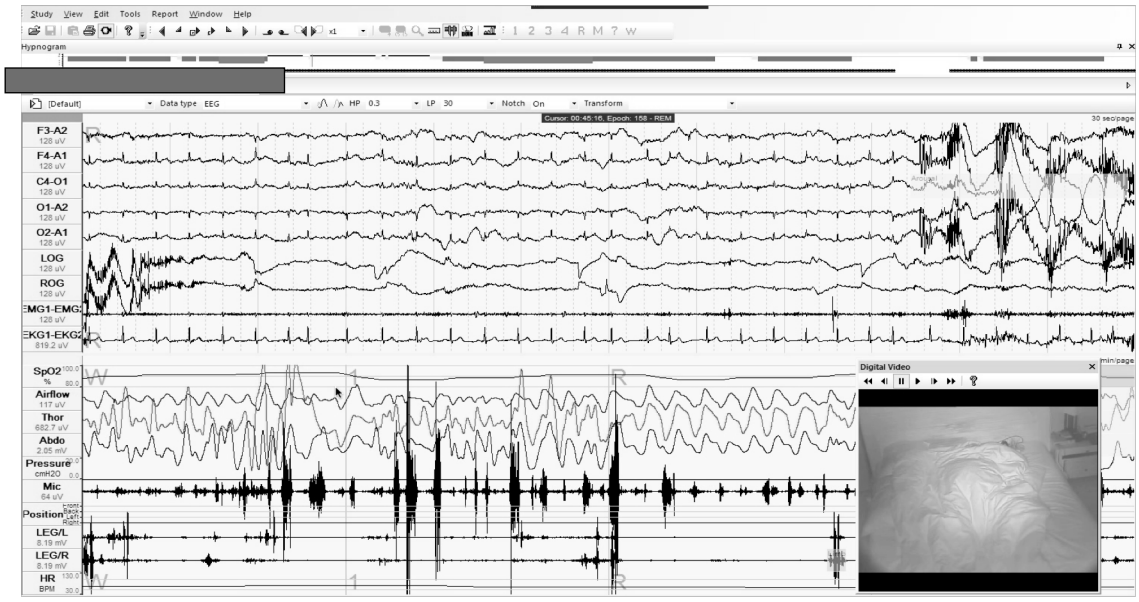
1. Diego Z. Carvalho et. al., preliminary study presented at American Academy of Neurology's 71st Annual Meeting in Philadelphia, May 4 to 10, 2019.

Case: Sleep disorder in Dementia

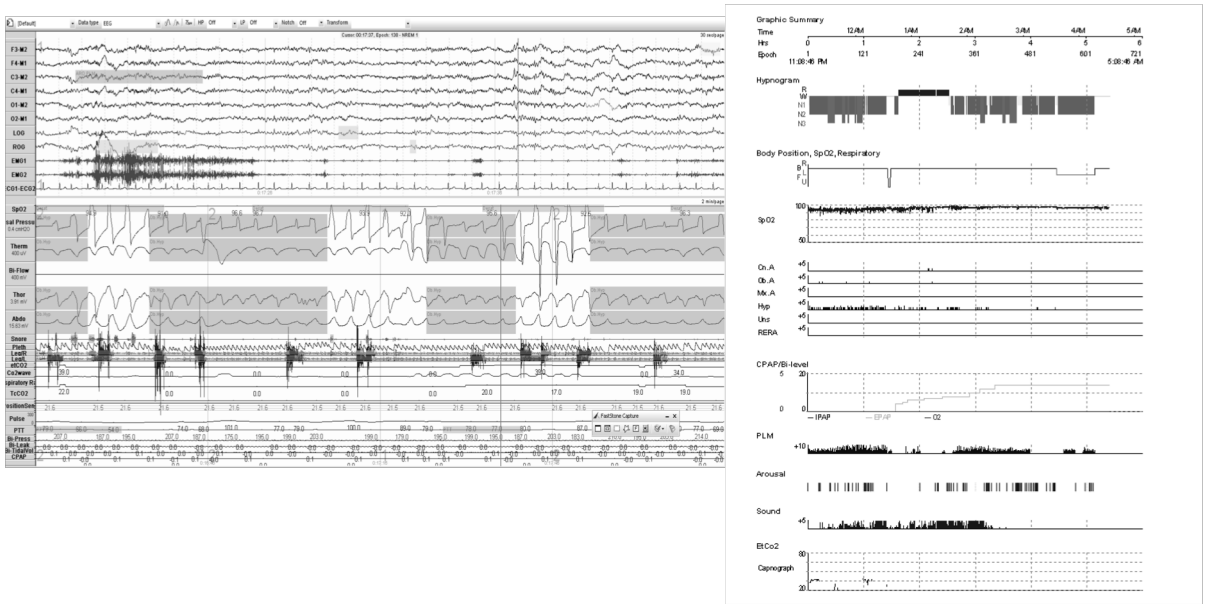
- M 76 yrs (1st visit May 2011)
- Present with Hx of bad dream, abnormal movement during asleep, cognitive decline, PH of HTN and DM
- Had PSG study, MRI brain, FDG-PET
- TMSE 26/30, MoCA 26/30



Case: Sleep disorder in Dementia

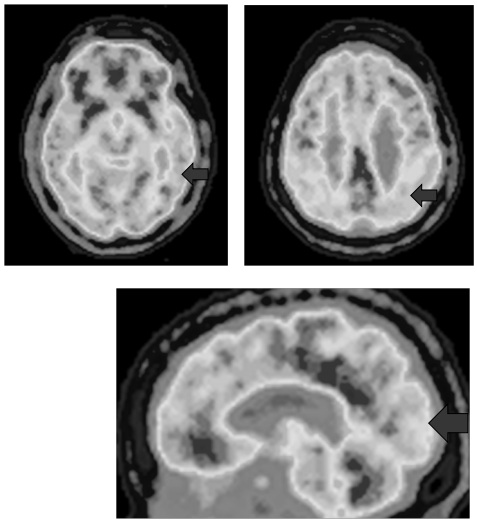


Case: Sleep disorder in Dementia



Case: Sleep disorder in Dementia

- Diagnosis
  - RBD, Mild OSA, PLM
  - Dementia: LWD, Parkinson's disease



F18-FDG PET

Parasomnias in degenerative brain disorders

- Parasomnias, such as rapid eye movement (REM) sleep behavior disorder (RBD)
  - Rarely been reported in AD but have a more significant association with α-synucleinopathies
- Parasomnias are undesirable sensorimotor events that appear exclusively during sleep
- Parasomnias are disorders of arousal, partial arousal, and sleep stage transition
- These disorders do not primarily cause a complaint of insomnia or excessive sleepiness, but frequently involve abnormal behaviors during sleep

Parasomnias in degenerative brain disorders

- Many of the disorders common in children, but some are also present in adults
- Parasomnias subdivided into the following groups:
  - Disorders of arousal from non-REM sleep: confusional arousal, sleep walking, and sleep terror
  - Parasomnias usually associated with REM sleep: REM sleep behavior disorder (RBD), recurrent isolated sleep paralysis, and nightmare disorder
  - Other parasomnias, such as enuresis, sleep-related groaning (catathrenia), exploding head syndrome, sleep-related hallucinations, and eating disorders
- RBD has particular relationship to neurodegenerative diseases

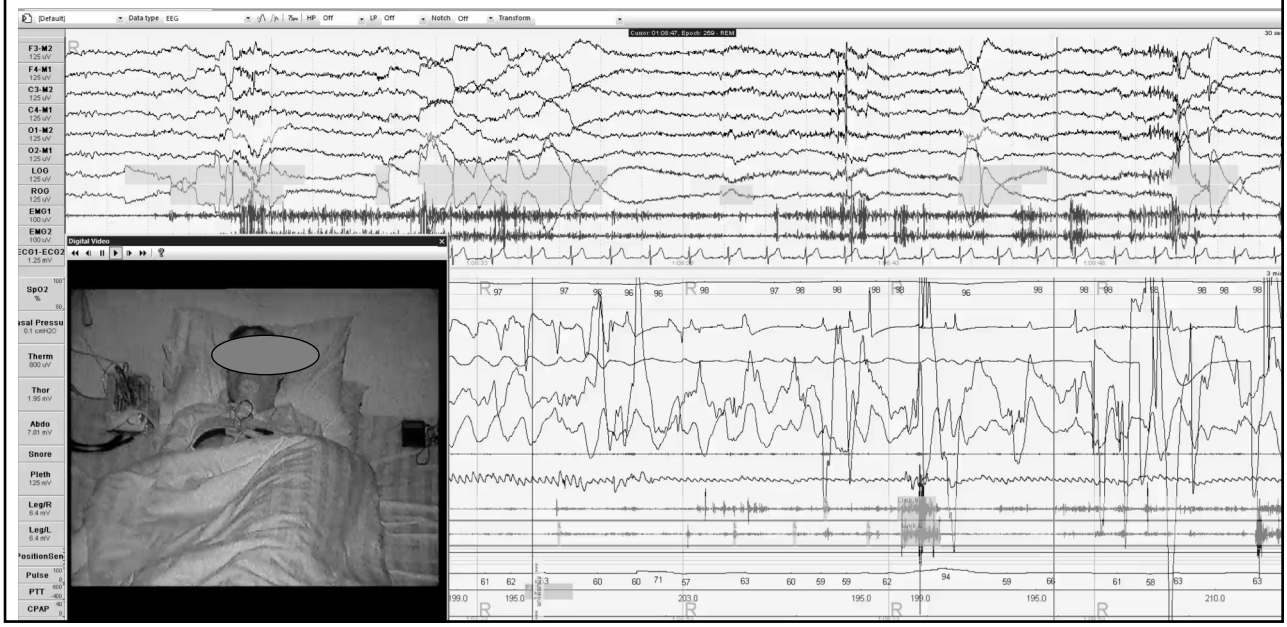
REM sleep behavior disorder (RBD) in degenerative brain disorders

- Characterized by vigorous movements occurring during REM sleep associated with an abnormal absence of the physiological muscle atonia and with increased phasic electromyographic (EMG) activity during REM sleep
- Diagnostic criteria are:
  - Presence of REM sleep without atonia
  - EMG finding of excessive amounts of sustained or intermittent elevation of fragmented EMG tone, or excessive phasic submental or (upper or lower extremity) EMG twitching

REM sleep behavior disorder (RBD) in degenerative brain disorders

- Diagnostic criteria are
  - One or both of the following:
    - Sleep-related injuries, potentially injurious or disruptive behaviors in history
    - Abnormal REM sleep behaviors document edduring polysomnography (PSG) monitoring
  - Absence of epileptiform activity during REM sleep unless RBD can be clearly distinguished from any concurrent REM sleep- related seizure disorder
  - Sleep disturbance not being better explained by another sleep disorder,

REM behaviour disorder



REM sleep behavior disorder (RBD) in degenerative brain disorders

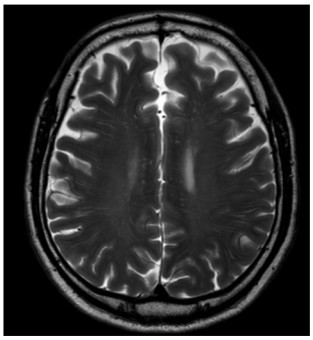
- The patient and those sharing bed can be injured
- RBD is observed in majority of patients with MSA, in DLB, and in a significant proportion of patients with Parkinson's disease
- RBD is also commonly observed in diffuse Lewy body (DLB) and Machado–Joseph disease

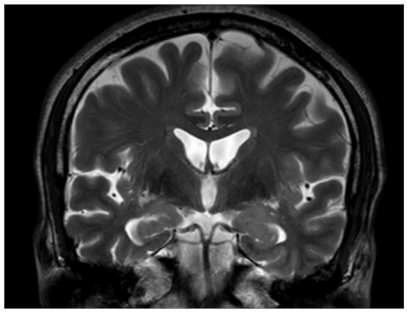
REM sleep behavior disorder (RBD) in degenerative brain disorders

- Patients with isolated RBD have significant risk of developing Parkinson's disease, DLB, or MSA
  - Especially if other brainstem manifestations such as changes reduced smell, depression, mild cognitive impairment, or incontinence are present
- The occurrence of hallucinations in Parkinson's disease related to presence of RBD
- Reduced striatal dopamine trans- porters observed in these patients

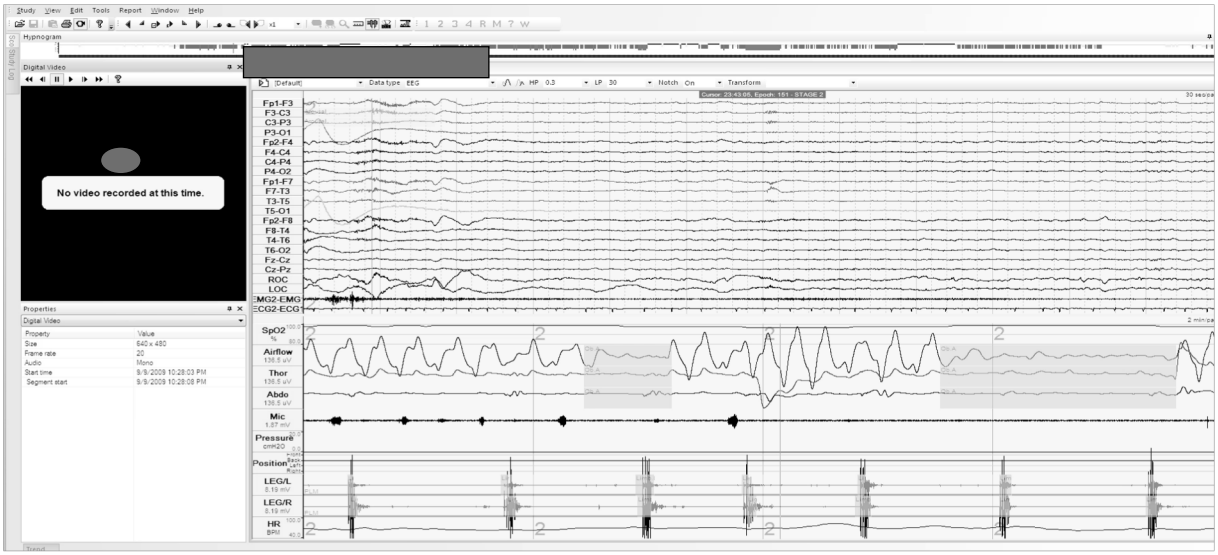
Case

- M 63 yrs old, HX HT, present with feeling hot over body, legs and hands cramp (Nov 2008), have to closed his eyes, then he walked to the restroom and had amnesia during in the restroom
- Had frequently cramp of both hands and feet during asleep lasting 1-2 minutes, sometime witness said patient had snoring and sometime had non-verbal vocalization
- PH: paroxysmal AF, Cervical disc C5-6 radiculopathy, cognitive impairment, behavioral change: Obsessive compulsive
- Investigations: MRI brain, PSG study

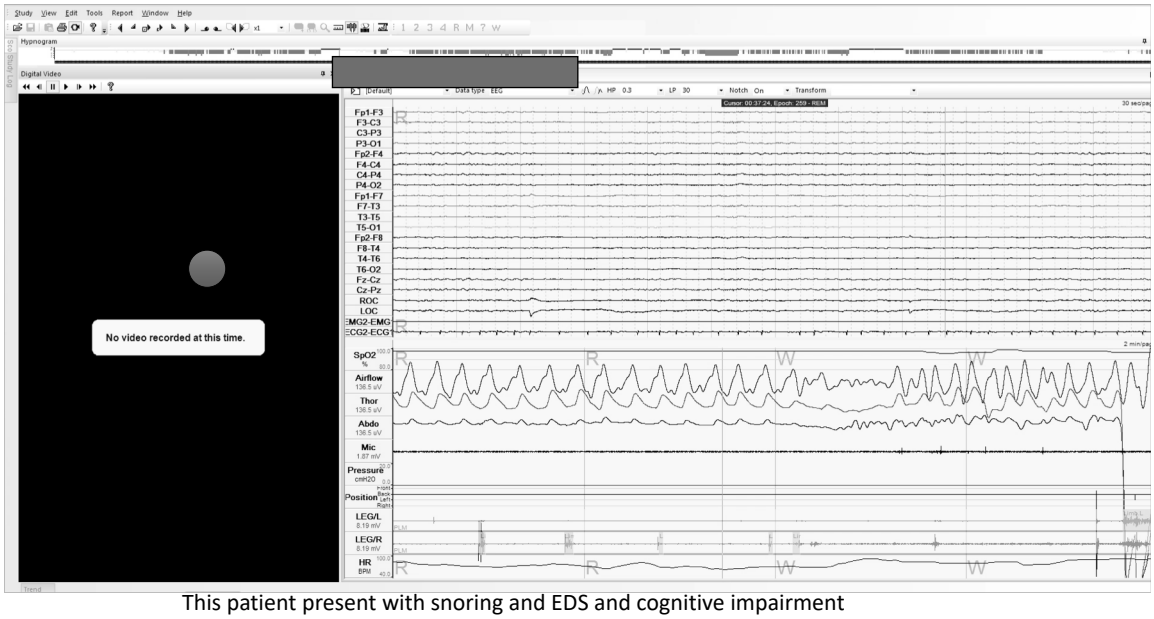




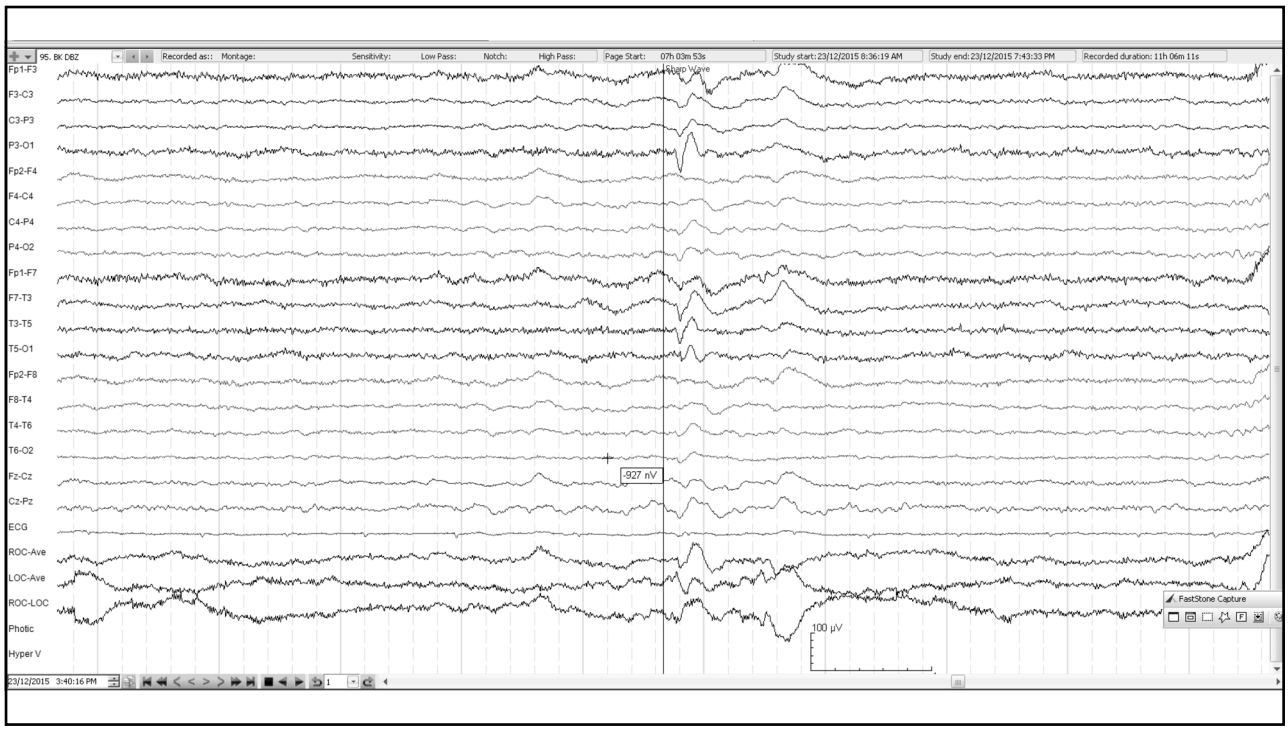
Case: Periodic Limb Movement in degenerative brain disorders



Case: Nocturnal seizure in dementia



This patient present with snoring and EDS and cognitive impairment



Periodic Limb Movement Disorder in Sleep/Restless Legs Syndrome in degenerative brain disorders

- RLS and PLM commonly found in patients with neurodegenerative disorders
- PLM characterized by clusters of repetitive leg movements during sleep, typically accompanied by nighttime arousals and sleep fragmentation
  - Occur typically every 20 to 40 seconds, and may recur several hundred times
- Patients with PLMS may complain of EDS and/or insomnia
- Clinically, diagnosis of PLMS requires a PLM greater than or equal to 5

Periodic Limb Movement Disorder in Sleep/Restless Legs Syndrome in degenerative brain disorders

- In adults, prevalence of PLMS 9% - 20% [1], Women affected twice as often as men
  - This rate increases dramatically with age
  - With reported prevalence rates of up to 45% in community dwelling elderly > 65 yrs old
  - Restless leg syndrome (RLS) strongly linked to PLMS
- Diagnosis of RLS made on basis of history alone
  - Often with one question: "When you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by walking or movement?"
- Treatment typically required to manage RLS/PLMS
  - Dopamine agonists are effective in both reducing the number of kicks and associated arousals
  - Both ropinirole and pramipexole currently FDA approved for treatment of RLS

1 Allen et al. 2003

Sleep disorders associated with neurological disease: Tauopathies

- Patients with progressive supranuclear palsy, Alzheimer's disease, and corticobasal degeneration may complain of significant sleep-related circadian disturbances, as well as sleep–wake and daytime problems
- Sleep/wake disturbances and disruption commonly observed in Alzheimer's disease, with daytime sleep, sleep attack and episodes of microsleep
- Insomnia (sleep fragmentation and difficulties main- taining sleep) common, as nocturnal wandering, nocturnal confusion, 'sundowning' psychosis, and nocturia

Sleep disorders associated with neurological disease: Tauopathies

- EDS, sleep attacks, and episodes of microsleep during the daytime may be associated with cognitive problems
- Sleep-related disorders such as RBD, RLS, PLMS, nocturnal complex and dystonic movements, and cramps may occur in progressive supranuclear palsy and cortico-basal degeneration, but rare in Alzheimer's disease
- Sleep breathing disorders common in Alzheimer's disease and associated with disease progression and poor prognosis;
  - However, clinical significance of diagnosing and treating is questionable

Sleep disorders associated with neurological disease: Synucleinopathies

- **Parkinson's disease, MSA, and DLB** often associated with major sleep–wake disorders
- Parkinson's disease-related motor symptoms including nocturnal akinesia, early-morning dystonia, painful cramps, tremor, and difficulties turning in bed
- Treatment-related nocturnal disturbances (e.g. insomnia, confusion, hallucinations, and motor disturbances)

Sleep disorders associated with neurological disease: Synucleinopathies

- Sleep-related symptoms such as hallucinations and vivid dreams (nightmares), insomnia (sleep fragmentation and difficulties maintaining sleep), nocturia, psychosis, and panic attacks
- EDS, sleep attacks, and episodes of microsleep during waking hours

Sleep disorders associated with neurological disease: Synucleinopathies

- Sleep-related disorders including RBD, RLS, PLMS, nocturnal dystonic movements, cramps, and SDB
- Presence of RBD in Parkinson's disease is associated with cognitive and autonomic changes
- Laryngeal stridor and obstructive sleep apnoea, commonly observed in patients with MSA and are associated with poorer prognosis
  - CPAP may improve respiration and prognosis

Sleep disorders associated with neurological disease: Treatment

- Treatment of Parkinson's disease-related motor symptoms can be treated with long-acting DA agonists to obtain continuous DA receptor stimulation during the night
- Some sleep disorders, such as RLS and PLMS, may be controlled by DA agents
- Clonazepam or donepezil, possibly prescribed with melatonin, has been suggested based on case series for treatment of RBD

Sleep disorders associated with neurological disease: Treatment

- Patients with dementias often present circadian disturbances that may be relieved by melatonin and light therapy

- A combined treatment of sleep hygiene, daytime exercise and nighttime environment modification has been shown effective in improving sleep-wake cycles both in AD patients and cognitively normal elderly population
  - Daily exercise, 30 min in duration, preferably outdoors
  - Decreasing time spent in bed during the day and limiting naps 30 min before 1 P.M
  - In selected cases, Rx with hypnotics might be useful, but evidence is limited and care about risk of falls, daytime sedation, confusion, and worsening of SDB in elderly