Breakout H: Sleep in Neurology

April 16, 2015

Sleep in Neurology

• Moderator:
  - Carlos L. Rodriguez, MD

• Panel Members:
  - Charles Bae, MD
  - Nancy Foldvary-Schaefer, DO, MS
  - James Leverenz, MD
  - Jessica Vensel Rundo, MD, MS
  - Tina Waters, MD
Introduction

- Sleep is a function of the brain and brain alterations affect sleep by producing excessive sleep (hypersomnia), insufficient or disrupted sleep (insomnia), movement disorders and parasomias

- Sleep also effects neurologic disorders

Learning Objectives

- 1. Describe possible barriers to accurate diagnosis and optimal treatment of sleep-disordered breathing in stroke patients

- 2. Explain the importance of evaluating for underlying sleep disorders in epilepsy patients

- 3. Discuss causes of hypersomnia in patients with multiple sclerosis

- 4. Review the relationship between neurodegenerative disorders and sleep disorders
Case 1
Charles Bae, M.D.

• A 60 year old right-handed male with a past medical history of hypertension and hyperlipidemia presented with acute onset of aphasia and right hemiplegia
• NIHSS score : 14
• Diagnosis: left middle cerebral artery (MCA) occlusion
Case 1

- Treated with intravenous tissue plasminogen activator (tPA) which partially recanalized the left MCA occlusion
- Clinically he improved, but had residual deficits: Dysarthria and moderate right hemiparesis (face, arm and leg)

Case 1

- Overnight nurses told the primary team that the patient snored “like a chain saw” and kept his roommate awake all night long
- When his wife was available, she said that she had seen him stop breathing during sleep for years, but he would do nothing about it
- Snoring and apneas got worse after he gained 40 pounds 3 years ago
Case 1

- **STOP-BANG score: 6/8**
  - (+) snoring
  - (-) tired
  - (+) witnessed apneas
  - (+) hypertension
  - (+) BMI > 35 (his BMI was 41)
  - (+) age > 50
  - (-) neck circumference > 40cm (his NC 34 cm)
  - (+) male gender

Case 1

- While hospitalized he had a portable, four-channel polysomnogram (PSG) that showed an apnea–hypopnea index (AHI) of 32 with oxygen desaturations to 81%
**Discussion**

1. What is the risk of stroke in the setting of untreated sleep apnea?

2. How would you have evaluated this patient for sleep apnea?

3. What are some barriers to PAP adherence after a stroke?

4. What are the benefits of treating sleep apnea during acute rehab?

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**Who is eligible for a HST?**

Patients who:

1. Have a high pretest probability of moderate to severe OSA

2. Does not have comorbid medical disorders
   - CHF, moderate-severe CAD or pulmonary disease, neuromuscular disease, morbid obesity

3. Does not have comorbid sleep disorders
   - Central sleep apnea, PLMD, Insomnia, Parasomnias, Circadian rhythm disorders, Narcolepsy

Barriers to PAP adherence after stroke

- Hemiplegia
- Hemiparesis
- Cognitive deficits
- Facial weakness causing leak
- Lack of assistance at night

Treatment with CPAP and rehab outcomes

- Patients with AHI ≥ 15 treated with CPAP for 4 weeks while in rehab
  - Improvement in functional/motor outcomes (Canadian Neurological scale score)
  - No improvement neurocognitive outcomes (sustained attention response test, digit or spatial span-backward)
  
  Ryan et al. Stroke 2011

- Patients with AHI ≥ 5 treated with AutoPAP for 30 days
  - Greater median improvement in NIHSS (-3.0) of AutoPAP patients compared to non-PAP patients (-1.0, P=0.03)

Bravata et al. Sleep 2011
Questions?

Case 2
Tina Waters, M.D.
Case 2: Chief Complaint

• Ms. Smith is a 23-year-old female who presents to the sleep clinic with a complaint of excessive daytime sleepiness

Case 2: History of Present Illness

• Her sleepiness dates back to high school years when she would fall asleep in classes

• Her teachers sent home notes to her mother suggesting she was lazy

• She was scolded by her mother for not getting sufficient sleep at night
Case 2: HPI

- In college, she avoided early morning classes, although she fell asleep in afternoon classes

- She recently enrolled in graduate school and now works in a coffee shop

- She is attending classes in the evenings and works in the coffee shop during the day

Case 2: HPI

- Over the past couple of months, she has noticed acute worsening of daytime sleepiness, with drowsy driving

- She has been reprimanded for mood swings, falling asleep and poor customer service (spilling drinks, getting orders wrong, etc.) and for drinking too much coffee
Case 2: Sleep History

- Epworth Sleepiness Scale is 18/24

- During workdays:
  - Bedtime: 10 p.m.
  - Wake time: 7 a.m.
  - She has no trouble falling asleep but never wakes up feeling refreshed

- She works from 7:30 a.m. to 5 p.m. and attends classes 3 days a week from 7 p.m. to 9 p.m.

- On days without classes, she typically takes a 1 hr nap after work, which is not always refreshing

- During days off:
  - Bedtime: 1 a.m.
  - Wake time: 11 a.m.
  - She wakes up feeling slightly more refreshed on these days

- Caffeine intake:
  - While working, she drinks 3–5 espressos daily with limited improvement in her daytime sleepiness
Case 2: Sleep History

- At night she denies an urge to move her legs, nocturnal leg kicking, sleep paralysis, or cataplexy
- She has been told recently by her sleep partner that she has episodic snoring
- She admits to vivid dreams
- In the last month, her significant other has awakened her three times when she appeared to act out a dream with punching and kicking him

Case 2 continued

- PMH: At age 22, she was diagnosed with multiple sclerosis
- Medications:
  - Glatiramer
  - Multivitamin
  - Vitamin D
- She denies alcohol, tobacco, and recreational drug use
- ROS:
  - Feels cold
  - Intermittent tremor in hands
  - Fatigue
  - Numbness in left leg
  - Apathy
- Unremarkable PE except for slight dysarthria and brisk deep tendon reflexes bilaterally
Discussion Questions

• What is a comprehensive differential diagnosis based on the ICSD-3 for this patient?

• What diagnostic testing should be performed?

• How should testing be timed to help distinguish between delayed sleep-phase and other causes of hypersomnia?

MSLT Protocol Guidelines

• MSLT should be performed immediately after a PSG performed during patient's normal sleep period

• MSLT diagnosis of narcolepsy is suspect if TST is <6 hours on night prior to testing

• Stimulants and REM suppressing meds should ideally be stopped 2 weeks before MSLT

• Other sedating or stimulating meds should be minimized

Littner. AASM. SLEEP. 2005;28(1):113-121
Case 2 - PSG

- TST of 388 min., SE: 83%
- SL: 8 min, REM latency: 32 min
- AHI: 4 (REM AHI 8)
- PLM index: 23, PLM Ar index: <5
- Leg EMG recording revealed an augmentation of tone occurring in 40% of REM sleep and fragmented REM in the three episodes of REM recorded that night
Case 2 – MSLT

- MSL: 0.9, SOREMPs: 4/5

Discussion Questions

- How do you interpret the PSG and MSLT?
Case 2 - MRI

Brain MRI with and without contrast:

- How do you interpret the MRI?
- Does the MRI explain any of her symptoms?

RBD Pathophysiology

Pontine lesions cause reduced inhibition of the motor neurons and increased motor activity.
Discussion Questions

• What are common sleep disturbances in multiple sclerosis?

  - Insomnia
  - Circadian rhythm disorders
  - Drug induced sleep disturbances
  - Nocturnal movement disorders
  - Sleep related breathing disorders
  - Narcolepsy
  - REM behavior disorder

Sleep Disturbances in MS

• Cross sectional trial found sleep disorders in 74% of consecutive MS patients
  
  Veauthier C et al. Mult Scler 2011; 17(5):613-622

• To date, no exact data about prevalence of SRBDs in MS patients is known
  - Reports range from 11%- 80% with OSA
  
  Veauthier C et al. Mult Scler 2011; 17(5):613-622
  Kaminska et al. Mult Scler 2012;18:1159-69
  Kallweit et al. Mult Scler Int 2013;2013:2065581
  Braley et al. Mult Scler Int 2012:673936

  - Patients with brainstem involvement had higher AHI
  
Sleep Disturbances in MS

• Approx ¼ to ½ of MS patients suffer from insomnia

Brass et al 2014;10:1025-31
Leonavicius Psychiatr Danub 2014;26:249-55

• Prevalence of RLS is 4x higher in MS than general population

Manconi et al. SLEEP 2008;31:944-52

Inherited disorders causing secondary narcolepsy

• Prader-Willi Syndrome
  - Deletion of 15q11-q13 with paternal imprinting
  - Hyperphagia, short stature, hypogonadism, mild MR

• Niemann-Pick Type C
  - Sphingolipidosis, lysosomal accumulation of sphingomyelin; defect in esterification and transport

• Myotonic Dystrophy

• Norrie Disease
  - X linked disorder, mutation in gene encoding norrin
  - Blindness from degen changes of retina, MR, psychotic features

• Mobius Syndrome
  - Congenital facial paralysis with/without limb defects

• Coffin Lowry
  - X linked dominant, severe MR, growth restrictions, cardiac abnormalities, vision and auditory defects

**MS and Narcolepsy**

- 15 cases of patients suffering from narcolepsy and MS
  - CSF available in 5/15 patients and hypocretin 1 was reduced in all; 3/5 had bilateral hypothalamic lesions on MRI
    

- Both disorders share the same HLA-DR2 positivity, suggesting a similar autoimmune process
  
  Nishino, *Sleep Med Reviews* 2005

- 3 cases of narcolepsy within 4 families with familial MS
  
  Ekbom, *Arch of Neuro* 1966

- 7 narcolepsy patients with MS plaques in hypothalamus bilaterally with hypocretin deficiency - 3 were aquaporin 4 Ab positive, NMO
  
  Poirier, *Neurology* 1987

**Questions?**
Case 3

Nancy Foldvary-Schaefer,
D.O., M.S.

Case 3: GM 25 y.o. right handed male

- Normal birth & development
- First seizure - GTC age 15 y.o.
- Started on VPA after recurrence 2 months later
- Partial seizures 1/yr; self discontinued VPA age 20 yrs
- Partial - 4-7/wk; Generalized - 1/wk
- Several concussions, 2 with LOC as child
- Taking OXC 1200 mg bid, LEV 1000 mg bid
- Past AEDs: VPA, PHT, CBZ, LTG, TPM
- Exam: BMI 29.9 kg/m²; Neck 42 cm, Neuro normal, Friedman grade 3
Case 3: Noninvasive VEEG

- **Epilepsy Classification**: Left parieto-occipital epilepsy

- **Etiology**: Cryptogenic

- **Seizure Types**:
  - **Type 1**: Visual Aura -> Automotor (staring, lip smacking, unintelligible speech, unresponsiveness)
  - **Type 2**: Visual Aura -> Automotor -> Right Versive -> GTC

- **Related conditions**: Dysmorphic left hippocampus

Case 3: Noninvasive VEEG

- **EEG Classification (10-20, 10-10 bitemporal, sphenoidals)**

- **Interictal**:
  - Spike, Regional left parieto-occipital (max O1; 65%), temporal (max SP1, 30%)
  - Spike and Wave Complex, Generalized (max bifrontal, 5%)

- **Ictal**:
  - EEG Seizure, Generalized, Maximum left hemisphere (1 recorded)
  - EEG Seizure, Regional, Left parieto-occipital (2 recorded)
  - EEG: No EEG Change (1 recorded)
Case 3: Presurgical Evaluation

- **MRI:** Symmetrically small bilateral hippocampi, left hippocampal dysmorphism
- **FDG PET:** Left posterior parietal hypometabolism
- **Ictal SPECT:** Left temporo-parietal hyperperfusion (25 sec injection)
- **Invasive EEG:** (Subdural electrodes, left TPO, right occipital)
  - **Interictal:** Spike, left lateral occipital and temporal
  - **Ictal:** None recorded (20 days)
- **VNS implantation planned**

Case 3: Sleep History

- **Sleep Habits:**
  - Bedtime: 11 a.m.; Wake time: 9:30 a.m.
  - Sleep latency 30 min; 2 10-min night awakenings
  - Naps daily x 1 hour, refreshing
- **Nighttime Behaviors:**
  - Snoring but no witnessed apnea
- **Daytime Symptoms:**
  - Dozes in sedentary situations
  - Epworth Sleepiness Scale 16
  - Impaired concentration
- **Other:**
  - Tonsillectomy in childhood
  - Depressed mood, discontinued antidepressants
  - 14 kg weight gain over prior 6 mo since job loss
Discussion Questions

1. What treatment strategies would you consider given GM is considered to be a poor resective surgical candidate to improve seizure control?

2. What features regarding his history/exam support your strategy?

3. What further testing would you recommend?

Daytime Sleepiness is a Common Complaint of People with Epilepsy

- 33-45% of patients report EDS after starting AEDs
- Typically attributed to AEDs and seizures
- Sleepiness adversely impacts QOL, increases risk of occupational injury, MVAs and academic underachievement
- May contribute to cognitive complaints
- May provoke seizures in some patients with epilepsy
- ESS elevated in 18-28% of adults with epilepsy

Causes of Daytime Sleepiness in Epilepsy

- Seizures
- AED therapy
- Sleep disorders
  - Sleep apnea
  - Insomnia
  - CNS hypersomnia
  - Inadequate sleep hygiene
- Epilepsy

Prevalence of OSA by AHI Cutoff

Why are Epilepsy Patients at Risk for OSA?

- AED effects on upper airway physiology
- Vagus nerve stimulation
- Increased body weight
  - Reduced physical fitness
  - Direct drug effects
- Endocrinopathies
  - Polycystic ovarian syndrome
  - Hypothyroidism
- Seizure-induced changes on upper airway physiology
- Co-morbid neurologic disorders (stroke, tumor, degenerative disorders)

Does Treatment of OSA Improve Seizures?

- Seizure outcome at baseline (diagnostic PSG) and 1yr later in PAP-treated OSA (n=43), Untreated OSA (n=33) and No OSA (n=56)
  - Responder rate (≥50% reduction)
  - Successful outcomes (≥50% reduction or seizure-free at both baseline and follow up)
- All cases had standardized seizure documentation
- Documented PAP adherence in OSA cases (≥4 hr/night)

PAP-Treated group had 32.3 times odds of responding as Untreated OSA and 6.1 times as No OSA.

Case 3: Diagnostic In-lab VEEG-PSG

- Total sleep time 416 min
- Sleep efficiency 93%
- Sleep latency 6.4 min
- REM latency 197 min
- Supine sleep 46%
- Arousals/Arousal index 131/19.1
- Respiratory events 17 obs apnea, 103 hypopnea
- Apnea-hypopnea index 17.3 (supine 26.8; REM 14)
- SPO₂ Mean 93%; nadir 67%
- Periodic limb movements 0
- ECG SR; mean 62 bpm; rare PVCs
- EEG Spikes/slow, regional left PO
Case 3: CPAP Titration

- CPAP 8-16 cmH₂O tested
- CPAP 10 cmH₂O recommended
  - TST 56 min, REM 20 min
  - Supine 64%
  - Abolished snoring
  - AHI 0
  - Arousal index 3, lowest of recording
  - SPO₂ ≥94%
- Treatment reduced snoring, subjective sleepiness
- Seizures began to decline

Case 3: Follow Up

- VNS implanted & patient maintained CPAP adherence
- Patient became entirely seizure free (8yrs+) despite VNS lead fracture and battery failure
- Several years later, presented with worsening daytime sleepiness (ESS 18) prompting repeat titration
VNS Induced Respiratory Events

Sleep Strategies for Epilepsy Patients

- Always take a sleep history
- Consider PSG in all patients, especially those with OSA symptoms, older age, high AED burden
- PAP trial in all PSG+ patients
- Tailor AEDs with sleep in mind
  - Sleep hygiene education
  - Avoid drugs that decrease upper airway tone/cause weight gain in apneics and stimulating drugs in insomniacs
  - PSG pre/post VNS implantation
Questions?

Case 4

James Leverenz, M.D.
Case 4

- A 69 y.o. male presents to clinic with an eight year history of motor and memory complaints
  - First evaluated for memory loss 8 years ago, delirium after stent, “forgetfulness”
    - MMSE 29/30, normal brain CT
    - “…does not seem to be any significant cognitive decline…”

Case 4

- Five years ago
  - Exam consistent with essential tremor
  - Primary MD for “anxiety”

- Four years ago
  - Trouble with computation, crosswords, not trusting memory, hoarse voice
  - Otolaryngology
    - “Soft voice of PD”
  - Neurology
    - Not clearly PD
    - Problems balancing checkbook, MMSE 29/30, started Aricept (donepezil) 5 mg qhs
Case 4

- **Four years ago**
  - Nightmares/nausea – Aricept moved to a.m.
  - Then to Exelon (rivastigmine) patch
  - Subjectively better on f/u

- **Three years ago**
  - Constipation
  - Neurology
    - MoCA 28/30

- **Two years ago**
  - Neurology – “MCI”
  - Neurology – Back on Aricept at night for cost reasons

- **Two years ago**
  - Nausea – Aricept discontinued
  - Galantamine (Razadyne) started – weird dreams on higher dosing

- **One year ago**
  - Geriatrician
    - MoCA 20/30, increased tone
    - Not handling finances, help with computer
    - Hx of sleep disturbance
    - “Parkinson’s plus” (CBD, DLB)
  - Neuropsychology ordered
Case 4
Montreal Cognitive Assessment (MoCA)

Neuropsychological Testing Results
Case 4

- “Sleep Disturbance” 11 years previously
  • Neurologist
    • “acting out his dreams”
      • punched bedpost of bed injuring hand
    • “loud snoring”
  • Dx: likely OSAS, parasomnia
  • Sleep study
    • “no evidence of obstructive sleep apnea”
    • “High arousal index…”
    • “multiple muscle twitching during the REM period”

Case 4

- “Sleep Disturbance” 11 years previously
  • Neurologist
    • Clonazepam rx (0.5 mg qhs)
      • Reduced sleep movements
      • Increase to 1 mg associated with daytime fogginess
Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder


<table>
<thead>
<tr>
<th>Disease</th>
<th>All Cases (172)</th>
<th>PSG Confirmed (82)</th>
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<tbody>
<tr>
<td>LBD</td>
<td>45%</td>
<td>41%</td>
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<tr>
<td>AD/LBD</td>
<td>34%</td>
<td>30%</td>
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<tr>
<td>MSA</td>
<td>11%</td>
<td>20%</td>
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<tr>
<td>Combined</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>PSP &amp; other non LBD</td>
<td>7%</td>
<td>5%</td>
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</table>

Table 6
Clinicopathologic correlations based on the timing of the onset of RBD relative to the onset of other neurologic features among subjects with PSG-confirmed or probable RBD who underwent autopsy.

- **RBD preceded other features by > 5 y**
  - 83/87 = 95%
- **RBD preceded other features by > 10 y**
  - 53/53 = 100%
- **RBD preceded other features by > 15 y**
  - 30/30 = 100%
- **RBD preceded other features by > 20 y**
  - 16/16 = 100%
- **RBD occurred concurrently with other features**
  - 26/27 = 96%
- **RBD evolved after other features**
  - 51/57 = 90%

* Other features refers to cognitive impairment, parkinsonism and/or autonomic dysfunction.
Melatonin therapy for REM sleep behavior disorder: a critical review of evidence

Ian R. McGrane, Jonathan G. Leung, Erik K. St. Louis, Bradley F. Boeve

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Treatment</th>
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<td>McCarter et al</td>
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<td>Kunz et al</td>
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<tr>
<td>Kunz et al</td>
<td>6 open</td>
<td>label 3 mg qhs</td>
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Table 1: Medications associated with occurrence or worsening of RBD [19].

<table>
<thead>
<tr>
<th>Caused by acute administration</th>
<th>Caused by withdrawal</th>
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<tbody>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Selective serotonin/norepinephrine reuptake inhibitors</td>
<td>Benzodiazepines</td>
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<td>Tricyclic antidepressants</td>
<td>Barbiturates</td>
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<td>Monoamine oxidase inhibitors</td>
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<td>Mirtazapine</td>
<td>Pentazocine</td>
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<td>Cholinesterase inhibitors</td>
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<td>Beta-blockers</td>
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<td>Tramadol</td>
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<td>Caffeine</td>
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McGrane et al, Sleep Med, 16:19-26, 2015
REM sleep behavior disorder preceding other aspects of synucleinopathies by up to half a century

Classen DO et al, Neurology, 75:494-99, 2010

Abstract

Background: Idiopathic REM sleep behavior disorder (RBD) may be the initial manifestation of synucleinopathies, Parkinson disease (PD), multiple system atrophy (MSA), or dementia with Lewy bodies (DLB). Methods: We used the Mayo medical records linkage system to identify cases presenting from 2002 to 2008 meeting the criteria of idiopathic RBD at onset, plus at least 1.5 years between RBD and development of other neurodegenerative symptoms. All patients underwent evaluations by specialists in sleep medicine to confirm RBD, and behavioral neurology or movement disorders to confirm the subsequent neurodegenerative syndromes.

Results: Clinical characteristics were mostly 2.7 years between RBD and at least 15 years before meeting the criteria of PD, PD dementia (PDD), DLB, or MSA. The interval between RBD and subsequent neurologic symptoms ranged up to 65 years, with the median 25 years. At initial presentation, primary motor symptoms occurred in 13 patients; 3 with PD, 3 with MCI and 1 with PD/PDD, primary cognitive symptoms occurred in 13 patients; 1 with PD, 5 with PD/PDD, and 3 with MCI. One patient presented with primary autonomic symptoms, diagnosed as MSA. At most recent follow-up, 47% of patients progressed to develop dementia (PDD or DLB). Concomitant autonomic dysfunction was seen in 74% of all patients.

Conclusions: These cases illustrate that the synucleinopathies may start decades before the first symptoms of PD, DLB, or MSA. A long-duration prodromal phase has important implications for epidemiologic studies and future interventions designed to slow or halt the neurodegenerative processes. Neurology® 2010;75:344-349

Table

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Initial clinical diagnosis</th>
<th>First clinical diagnosis</th>
<th>Age at RBD symptom onset, y</th>
<th>Age at neurologic symptom onset, y</th>
<th>Interval from RBD to symptom onset, y</th>
<th>Age at PSL, y</th>
<th>Age at death, y</th>
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Classen DO et al, Neurology, 75:494-99, 2010
Discussion

1. What are the effects of cholinesterase inhibitor treatment on sleep?

2. What does the presence of REM sleep behavior disorder (RBD) tell us about diagnosis? What is the timing in relation to other symptoms in the Lewy body disorders?

3. What is an alternative treatment to clonazepam for RBD?

Questions?
Case 5

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History

- 39 year old right-handed male, presented from an outside hospital in transfer to the inpatient neurology service for myoclonus, progressive memory loss, and psychotic behaviors
History

• 4 months prior to admission, he began having intermittent whole body tremors, usually at onset of sleep

• 2 months prior to admission, he developed memory loss and confusion. Got lost while driving, forgot to proctor an exam, etc…
  - was relieved of teaching classes (teaching assistant) and moved in with parents due to the confusion and memory issues

History

• 1-2 months prior to admission, he was reportedly hypersexual towards fiancé, orally fixated, had perseverations

• Fiancé noted some difficulty with sleeping, waking up several times a night, noted to wander around the house

• Several weeks prior to admission, he developed visual hallucinations (talking to people who were not there, internally stimulated)

• Reportedly not sleeping much at all
**PMH/PSH/FH/SocHx**

- No prior medical issues, surgeries, or meds
- 40 lb unintentional weight loss in past 4 months
- No substance abuse, rare alcohol
- No significant family history for similar symptoms, dementia, psychosis, etc...
- PhD business graduate student
- Engaged, living with fiancé
- Travel to Brazil, Germany, Portugal, and Sweden within 1-2 years prior to presentation

**Psych History**

- 1 month prior to onset of symptoms, witnessed the choking death of a family friend
  - placed on Valium, Inderal, and Cymbalta for suspected anxiety, depression, and possible conversion reaction
  - did not have significant improvement in symptoms
Exam

• Exam upon admission:
  • General exam significant for hypertension (152/88) and tachycardia (113)
  • Neuro exam significant for orientation to self only, hyperreflexia diffusely (3/4), and intermittent myoclonus of all 4 extremities (not startle-sensitive)

Testing

• OSH testing was unremarkable including:
  - MRI/A brain and c-spine
  - CT chest, abdomen and pelvis
  - EEG
  - LP
  - Infectious workup, routine labs

  - Treated empirically for Lyme disease with doxycycline though testing was negative
Discussion

• What is your differential diagnosis?
• What other factors might be contributing to the patient’s clinical state?
• What further testing should be done?
• What medications should be considered to treat the altered mental status and insomnia?

Hospital Evaluation

• Labs – negative or normal
  - Metabolic: CMP, Mg, Phos, Amylase, lipase, Porphyrins, porphobilinogen, B12, folate, Vit E, B1, B6 Copper, ceruloplasmin, Calcium, calcitonin, Cortisol, GH, Prolactin, Organic acid, amino acids, acylcarnitine, sialic acid, oligosaccharides, ammonia, lactate, pyruvate, CEA, AFP
  - Infectious: HIV, Syphilis, Lyme, HBV/HAV/HCV, arbovirus, fungal battery (blasto, histo, asperg, coccidio), Whipple’s PCR (Tropheryma whippelii)
  - Paraneoplastic: Paraneoplastic panels, anti-NMDA receptor antibody
  - Autoimmune: CRP, WSR, ANA, C-ANCA, Anti-ENA, Celiac Ab, Anti gliadin, TSH, thyroglobulin ab, microsomal ab
  - Toxic: Heavy metal screen, 24hr urine toxin, GHB, Lithium
  - Vasculitis: Myeloperoxidase antibody – Churg-Strauss
  - Degenerative: Huntington’s disease, CLN gene (neuronal ceroid lipofuscinosis), POLG1 (mitochondrial diseases including cerebellar ataxia)
Hospital Evaluation

- Bedside EEG monitoring – continuous slow generalized

- CSF – negative or normal
  - Routine analysis, gram stain/cx, Tourtellotte, JC virus, HSV, EBV, CMV, enterovirus, West Nile, VZV, arbovirus, AFB, VDRL, Lyme, Toxoplasma, fungal, ACE, CJD - tau protein, 14-3-3, anti-NMDA and paraneoplastic panels

- MRI brain, c-spine w/wo – mild volume loss

MRI – Axial FLAIR

At admission 2 months later
Hospital Evaluation

- Psych evaluation – not felt to be primarily psychiatric

- Other Testing:
  - CT C/A/P – mild colitis
  - PET whole body – diffusely decreased uptake of FDG in brain; hypermetabolic L thyroid nodule
  - Cerebral angiogram - normal
  - Colonoscopy - negative for neoplasm, Whipple’s
  - Testicular u/s – normal
  - Skin biopsy r/o neoplasm - compound nevus
  - Sweat gland biopsy – possible mitochondrial disease – abnormal mitochondria
  - Thyroid FNA - hypercellular follicular nodule, cannot exclude origin from follicular neoplasm
  - Thyroidectomy with pathology negative for neoplasm

Hospital Course

- Intubated/sedated for 1 month in NICU for testing and complications during hospital stay
- Continued to have myoclonus & tachycardia
- Developed intermittent fevers

- Progressively agitated, not sleeping at night, not redirectable, seemingly internally stimulated, visually hallucinating, not eating
- Periods of lucidity, reading and speaking normally, memory intact to events prior to onset of symptoms.
- Periods of sleep up to 15 hours, then several days only sleeping 2 hours at a time
- Agitation and memory loss seemed to be linked to lack of sleep
Treatments

• Agitation/Hallucinations:
  - Zyprexa – not much benefit
  - Thorazine and Ativan – less agitation
  - Abilify and Haldol – provided some benefit

• Insomnia
  - Trazodone – for insomnia
  - Neurontin and Seroquel – some benefit

• Myoclonus
  - Klonopin – some benefit

• Underlying cause - ? paraneoplastic encephalitis
  - IVIG
  - IV methylprednisolone
  - PLEX - ? possibly some improvement

Discussion

• What is your primary diagnostic consideration?

• Are there any further tests that should be done?

• Are there any other treatment options to consider?
Diagnosis: Fatal Familial Insomnia

- Prion Protein Gene Testing result:
  
  D178N-129M gene mutation positive

Fatal Familial Insomnia

- A very rare autosomal dominant prion disease (transmissible spongiform encephalopathy) due to a mutation in the PRNP gene on the short arm of chromosome 20 which encodes for prion protein (PrP)

- D178N mutation in association with methionine at position 129 (D178N 129M)

- This mutation results in a progressive neurodegenerative illness with severe neuronal loss and atrophy of the anteroventral and mediodorsal thalamic nuclei

- Hallmark characteristics include insomnia and autonomic hyperactivity
Fatal Familial Insomnia – Clinical Characteristics

- Progressive, intractable insomnia
- Autonomic hyperactivity/instability (HTN, tachycardia, hyperthermia, hyperhydrosis)
- Tremor
- Ataxia
- Hyperreflexia
- Myoclonus
- Memory/concentration/attention deficits
- Confusion/disorientation
- Hallucinations
- Oneiric (O-ny-ric) stupor – dream enactment behaviors

Diagnostic Studies

- Labs - loss of circadian rhythm of secretion of melatonin, prolactin, GH; ↓ACTH, ↑cortisol and catecholamines
- CSF – nl or elevated 14-3-3, tau, NSE
- Imaging
  - MRI brain - diffuse atrophy, may be more prominent in thalamus, inferior olives
  - PET – hypometabolism of thalamus, inferior olives
  - MR SPECT – decreased transport of 5HT
- EEG – nonspecific CSG, may have periodic sharp waves
- Brain biopsy - PrP נ may just be in thalamus or temporal lobes; focal gliosis of thalamus, inferior olives, cerebellum; vacuolation (spongiosis) in the cortex

Fatal Familial Insomnia – PSG findings

• Reduced TST
• Sleep fragmentation, fluctuations between wake and theta activity
• Loss of K complexes and spindles
• Reduction or loss of SWS
• Decreased REM
• Loss of REM atonia

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Case Presentation - Outcome

• Patient discharged to nursing facility 6 days prior to reporting of genetic testing for FFI
• Family informed on same day as result known
• Family discussion next day included possibility of PSG: Family declined
• Patient developed respiratory distress – presumptively due to aspiration – expired 7 days after FFI diagnosis confirmed
Case Presentation - Outcome

• Autopsy
  - Western blot analysis positive for PrPres
  - Astrogliosis present in thalamus and inferior olives
  - No spongiosis

• The mother had been tested for FFI and is negative
  - Father was tested and results unknown
  - Sister has declined testing

Questions?
Conclusion

- Obstructive sleep apnea (OSAS) is assoc with increased risk for stroke, stroke can interfere with management of OSAS and treatment of OSAS can improve recovery from stroke.

- Multiple sclerosis can cause a wide variety of different sleep disorders.

- Complex relationship between epilepsy and sleep disorders and how management of either condition can have positive and negative repercussions.

- Two different neurodegenerative disorders presenting with sleep disorders which were clues to the diagnosis of the underlying condition.