Disclosures

• All medications discussed are off-label
• I will mention a test available at the Mayo Clinic, where I used to work.
Outline/Objectives

• Learn about our understanding of the multiple causes of sleep fragmentation in Parkinson’s Disease
• Get an update on our current understanding of and implications of REM-Sleep Behavior Disorder
• Learn about a newly-described antibody associated with unusual parasomnias and sleep abnormalities
Sleep Disorders in Parkinson’s Disease

There are a lot of them
Sleep in PD: It’s Terrible

• Up to 90% of PD patients have a sleep disorder
  • Insomnia
  • Parasomnias [particularly REM sleep behavior disorder (RBD)]
  • Excessive daytime sleepiness (50% have ESS >10)
  • Periodic limb movements of sleep
  • Restless leg syndrome (RLS) in 15-30%
  • Obstructive sleep apnea (OSA)
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Mechanisms of Sleep Disruption in PD

- Symptoms of the disease:
  - Pain
  - Depression/anxiety
  - Motor: tremor, trouble turning in bed
  - Autonomic: nocturia

- Medications:
  - Wearing off of PD meds
  - Side effects: amantadine, levodopa
  - Downstream effects from EDS from dopamine agonists
  - RBD from antidepressants
Mechanisms of Sleep Disruption in PD

• Direct effects from pathophysiology
  • **Neurodegeneration** of centers involved in sleep: locus coeruleus, hypothalamus, amygdala, thalamus, pedunculopontine nucleus
  • **Melatonin**: Studies have shown reduced melatonin in PD patients versus controls, with some correlation with decreased volume of the hypothalamus.
  • **Hypocretin/orexin**, which maintains wakefulness: A small pathology study in late-stage PD patients found an almost 50% reduction in total hypocretin neurons in the prefrontal cortex and hypothalamus as well as reduced hypocretin concentration in the CSF
  • **Circadian rhythm malfunction** from degeneration of dopaminergic retinal ganglion cells and the suprachiasmatic nucleus
The Washing Cycle of Sleep

• The glymphatic system: CSF, interstitial fluid and water transport (facilitated by aquaporin 4 channels) may clear toxic proteins from the brain during sleep.

• Studies have shown a 30% increase in CSF β-amyloid and 36% increase in α-synuclein following 1 night of sleep deprivation in humans.
Could poor sleep lead to PD? Jury’s still out

A recent study showed that individuals with sleep fragmentation as per 1-week actigraphy had a higher presence of Lewy body pathology and substantia nigra cell loss on post-mortem examination at a median of 1.4 years later.

It is unknown how powerful a risk factor fragmented sleep is at this time.
Therapies being explored for insomnia in PD

• Light therapy
  • Study 1: Timed light therapy (3000–4000 lx) for a 1-h period 1–4 h before sleep may reduce insomnia and nocturnal movement
  • Study 2: 10000 lux twice daily for 1 hour may improve EDS in PD (Epworth Sleepiness Scale improved from 16 to 11 after 2 weeks)
  • Study 3: A table-top device emitting blue/green narrow bandwidth LED light (λ = 450 – 570 nm, 950 Lux) might improve motor, nonmotor, and sleepiness in PD; Phase 3 trial underway
Therapies being explored for insomnia in PD

- Cognitive Behavioral Therapy (over the internet; apps)
- Dual orexin receptor antagonist suvorexant under study for insomnia in PD
- Lots of marijuana research of course
- DBS of GPi for...insomnia?
REM Sleep Behavior Disorder

A common affliction in Parkinson’s Disease
A Series of Implications

History
Dream Enactment Behavior

Implies
REM Sleep Behavior Disorder (RBD)

Implies
Neurodegenerative Disease (Alpha-synucleinopathies)
“Dream Enactment Behavior”

• “Do you ever act out your dreams: scream, thrash around, throw off your covers, or fall out of bed?”

• Multiple causes:
  • Untreated obstructive sleep apnea
  • Sleepwalking and sleep terrors
  • Epilepsy
  • Post-traumatic stress disorder
  • Alcohol or drug administration or withdrawal: ANTIDEPRESSANTS
  • Autoimmune conditions like vasculitis

• RBD needs polysomnography to confirm
  • RBD = DEB plus REM Sleep Without Atonia on PSG
Typical Patient at Home
REM Sleep Behavior Disorder

- Abnormal vocalizations – talking, yelling, swearing, screaming
- Abnormal motor behavior – limb flailing, punching, kicking, lurching out of bed
- Altered dream mentation – typically involve a chasing/attacking theme
- Motor behavior matches dream content
- Occurs in latter half of sleep
“Have you ever been told, or suspected yourself, that you seem to ‘act out your dreams’ while asleep (for example, punching, flailing your arms in the air, making running movements, etc.)?”

- 242 idiopathic RBD patients and 242 controls
- Sensitivity of 93.8% and a specificity of 87.2%

HOWEVER,

- Isolated REM sleep atonia loss without dream enactment is relatively common in the general population
- A study of 203 patients in 2016 suggested that up to 44% of idiopathic RBD cases may be unaware of their sleep behaviors.
- Many cases may be detected first with polysomnography

PMID: 22729987 --Ronald Postuma et al.
RBD: Interesting Facts

- Present in between 5% and 13% of adults aged 60 to 99 years, mostly men (10:1 men:women)
- 5-fold more likely to develop in patients receiving antidepressants and 10-fold more likely to develop in those with a psychiatric diagnosis
- Risk factors for RBD are similar to Parkinson disease (PD)
  - Lower educational level, previous head injury, occupational pesticide exposure, and farming
- Risk factors that differ from PD:
  - Smoking, ischemic heart disease, inhaled corticosteroids
  - Coffee & smoking are not protective
A study of 171 RBD patients (Barber et al, Sleep 2017) found that 74% (95% CI 66-80%) met Movement Disorders Society criteria for a diagnosis of prodromal Parkinson’s disease.

Rate of diagnosis of a neurodegenerative disease over 2 to 5 years after RBD onset is approximately 15% to 35%, becoming 90% after 25 years.

Highly variable duration of RBD before phenotypic conversion (up to 50 yrs).

Up to 82% of older men diagnosed with RBD develop parkinsonism or dementia.

One study: Almost half of PD patients, at least 88% of MSA patients, and about 80% of DLB patients have RBD.

Associated symptoms may give clues to underlying disease:
- Autonomic → Multiple Systems Atrophy or Pure Autonomic Failure
- Cognitive → Lewy Body Dementia
- Motor → Parkinson’s
Other Causes of RBD

• Secondary RBD more often seen in young people
• Antidepressant Use: Revealing early what lies underneath?
• RBD can be seen in 36% to 50% of those with narcolepsy
• Brainstem lesions caused by inflammatory, neoplastic, or cerebrovascular disorders (especially in the dorsomedial pons)

Most nuclei involved are in dorsomedial pons
New Insights on Alternative Underpinnings of RBD

- Seen in other neurodegenerative diseases:
  - Huntington’s, Alzheimer’s, PSP (13%), ALS (?c9orf72), Vascular dementia (25-75%)
  - However, synucleinopathy was the underlying pathology in 94% of autopsied patients in the largest multicenter autopsy series of RBD
- The insight into the presence of cholinergic abnormalities may explain why in PD those with RBD have more dementia, autonomic dysfunction, and more severe gait abnormalities.

PMID: 32257544
New Insights on Alternative Underpinnings of RBD

• Autoimmune/Paraneoplastic Diseases:
  • Anti-voltage-gated potassium channel antibody complex syndrome (including the CASPR-2 and LGI-1 epitopes)
  • IgLON-5 disease

PMID: 32257544
RBD: Treatment (none are FDA-approved)

- Mirtazapine, Beta-blockers, cholinesterase inhibitors, tramadol, and alcohol may worsen; consider switching an SSRI or SNRI to bupropion
- Melatonin qhs (3-12 mg)
- Clonazepam up to 2 mg qhs
  - Caution in sleep apnea, cognitive impairment, ataxia
- The reality:
  - > 30% of patients may not achieve adequate symptom control.
  - 30% to 40% objective symptom reduction only
- Alternative therapies under consideration:
  - Pramipexole (mixed efficacy reported)
  - Melatonin agonists (ramelteon)
  - Phytocannabinoids (Cannabidiol (CBD))
  - Rivastigmine (mixed results)
IgLON-5 Disease

Are some neurodegenerative diseases actually autoimmune?
IgLON-5 Disease

• First Reported in the Lancet in 2014

A novel NREM and REM parasomnia with sleep breathing disorder associated with antibodies against IgLON5: a case series, pathological features, and characterization of the antigen

Lidia Sabater, PhD1,*, Carles Gaig, MD1,2,3,*, Ellen Geli, MD1,4,*, Luis Bataller, MD5,7, Jan Lewerenz, MD6, Estefania Torres-Vega, BSc7, Angeles Contreras, MD8, Bruno Giometto, MD9, Yaroslau Compa, MD2, Cristina Embid, MD3,10, Isabel Vilaseca, MD3,11, Alex Iranzo, MD1,2,3, Joan Santamaría, MD1,2,3, Josep Dalmau, MD1,12,13, and Francesc Graus, MD1,2
**IgLON-5**

**Disease: Clinical features**

**4 clinical profiles**

1. Predominant sleep disorder
2. A bulbar syndrome (dysphagia, sialorrhea, resp failure, stridor)
3. A PSP-like syndrome (gaze palsy, gait disorder)
4. Cognitive impairment with or without chorea

The sleep disorder may appear later in the course.

**PMID:** 28381508
The sleep disorder of anti-IgLON5 disease presents as a complex sleep pattern characterized by abnormal sleep initiation with undifferentiated NREM sleep, RBD, periods of normal NREM sleep, stridor, and obstructive apnea.

To characterize it, the original authors made new definitions of sleep abnormalities:

1. **UN-NREM**: “undifferentiated NREM sleep”
   - Irregular slow theta EEG activity, clearly different from the awake alpha rhythm, lacking vertex sharp waves, K complexes, sleep spindles or delta slowing, and without definite and recurrent rapid eye movements

2. **P-SN2**: “Poorly structured stage N2” P-SN2
   - Scant but definite K complexes or spindles at 12–14 Hz, associated with either excessive EMG activity, movements or occasional bursts of rapid eye movements of lower amplitude than those typical seen in REM sleep in the same patient.
In a subsequent study of 27 patients, NREM sleep onset and sleep re-entering after an awakening occurred as UN-NREM (median: 29.8% of total sleep time [TST]) and P-SN2 sleep (14.5% TST) associated with vocalizations and simple and quasi-purposeful movements.

In all patients, if sleep continued uninterrupted, there was a progressive normalization with normal N2 (11.7% TST) and N3 (22.3% TST) sleep but stridor and obstructive apnea emerged. REM sleep behavior disorder (RBD) occurred in four patients.

Actigraphy showed a 10-fold increase of nocturnal activity compared with controls.

IgLON-5 Sleep Study from original Lancet paper, Sabater *et al.*
IgLON-5 Disease: Physiology

- HLA-DRB1*10:01 and HLA-DQB1*05:01 were positive in 13/15 (87%) patients.
- The DRB1*10:01 allele was 36 times more prevalent than in the general population.
- All patients had IgLON-5 antibodies in their serum, and most of these were also positive in CSF.
- Mayo tests for this now in their Serum Autoimmune Movement Disorder Evaluation, **Test ID: MDS2**
IgLON-5 Disease: Pathophysiology

• Neuropathological examination showed neuronal loss and gliosis associated with an atypical tauopathy, mainly involving the tegmentum of brainstem and hypothalamus.
• This is similar path to PSP and CBD
• The absence of glial pathology, grains, or globular glial inclusions makes this atypical for the above disorders
• Response to immunotherapy is partial or absent
• BIG QUESTION: IgLON-5: cause or effect of a neurodegenerative tauopathy?
Take-Home Points

• People with Parkinson’s have a rough time sleeping
• Motor and non-motor symptoms, medication wearing-off and side effects, and structural brain changes all play a role in fractured sleep in PD patients
• RBD’s strong association with an underlying synucleinopathy may help us cure PD someday
• IgLON-5 antibodies are associated with movement disorders, dementia, and multiple sleep abnormalities
• We don’t yet have satisfactory treatments for any of these problems
Thank You!