Restless Legs Syndrome (RLS) (Willis Ekbom Disease)

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Picture courtesy FOAMed
Financial Disclosures

• No financial disclosures to declare
Objectives

• Review the definition and clinical features of Restless Legs Syndrome (RLS) and periodic limb movements (PLMS)
• Evaluate epidemiology, etiology and psychiatric comorbidities
• Understand pharmacological and non pharmacological treatment options
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Restless Legs Syndrome – DSM-5

- “URGE” Unpleasant sensation
  U – urge to move legs
  R – est – symptoms worsened at rest
  G – ets better with movement
  E – vening – symptoms worse in evening
- ≥ 3x/week, ≥ 3months
- Significant distress
- Not due to medical condition, substance
MR. D., A 45 YEAR OLD MALE WITH A COMPLAINT OF INSOMNIA AND LEG DISCOMFORT
### These are not RLS

<table>
<thead>
<tr>
<th>Condition</th>
<th>How many criteria met?</th>
<th>Differentiate from RLS</th>
<th>Co-exist With RLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg cramps</td>
<td>4 of 4</td>
<td>Muscle spasm easily identified</td>
<td>+</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>1 of 4</td>
<td>Numbness, burning, and tingling without an urge to move</td>
<td>+++</td>
</tr>
<tr>
<td>Arthritis</td>
<td>2-3 of 4</td>
<td>Discomfort in joints, at rest, improves with movement</td>
<td>++</td>
</tr>
<tr>
<td>Vascular</td>
<td>2-3 of 4</td>
<td>Varicosities and PVD. +/- relief with movement; rub helps more. Walking is worse.</td>
<td>++</td>
</tr>
<tr>
<td>Positional discomfort</td>
<td>1-2 of 4</td>
<td>Foot or leg “asleep” from compression. Shift and its gone.</td>
<td>--</td>
</tr>
<tr>
<td>Akathisia</td>
<td>3-4 of 4</td>
<td>Urge to move, all over, caused by dopamine antagonists</td>
<td>+</td>
</tr>
</tbody>
</table>


Slide courtesy of Dr. Winkelman.
Periodic Limb Movements (PLMs)

• Repetitive leg (limb) movements **DURING SLEEP**
• Typically 20-40 seconds apart
• Cause awakenings and fragmentation
• Patient often unaware. Bedpartner reports “kicking”
• c/o frequent awakenings, light sleep
• aka Nocturnal Myoclonus
Restless Leg Syndrome (RLS) 80%

Periodic Limb Movement Disorder (PLMD)
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Epidemiology/Etiology - RLS

• 5-10% of the population affected (♀/♂ = 2/1)
• The leading hypothesis is brain dopamine dysfunction
• Involves a circadian fluctuations in dopamine
• Deficiencies in other substances, especially iron, likely play a role. Others? – Mg, opioids, Vit B12
• Key diagnostic question: Do your legs ever bother you at night?

RLS and Psychiatric Comorbidity

Winkelman and Colleagues—
238 pts with RLS – evaluated for psychiatric disorders vs controls (12 m prevalence):

<table>
<thead>
<tr>
<th>Disorder</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panic Disorder</td>
<td>4.65</td>
</tr>
<tr>
<td>Generalized Anxiety Disorder</td>
<td>3.52</td>
</tr>
<tr>
<td>Major Depressive Disorder</td>
<td>2.55</td>
</tr>
</tbody>
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Address Exacerbating Factors

• Caffeine
• Tobacco
• Alcohol
• Medications
  - dopamine blockers (antipsychotics, GI motility agents)
  - antidepressants (SSRI’s)
  - mirtazapine*
Exacerbating Influence of Psychotropics on RLS/PLMS

- **Neuroleptics**\(^1,2\)
- **Lithium**\(^3,4\)
- **Antidepressants (PLMS)**\(^5,6\)
  - Consider bupropion\(^7,8\)

Check Iron (Ferritin)!

• Intake – food?
• Absorption - GI difficulties
• Blood loss?
  - Anemia – Cough? Poop?
  - Menstrual Periods/Pregnancy
  - Blood donations
• Target ferritin > 75 μg/L
• May replace e.g. FeSO₄ with vitamin C tid 2 hours before or after meals
Dopaminergic Agents

• Intermittent (<3x/week)
  Levodopa (Sinemet)
  (Sinemet CR 25/100,
   1 tab po qhs prn)
  take as abortive therapy
  when symptoms arise

• Daily or almost daily
  (>3x/week)
  - Pramipexole (Mirapex)
  - Ropinirole (Requip)

  eg Pramipexole 0.25-0.5
  mg po q2h before bed
  take 2 hours before
  symptoms are worst

Side Effects – Pramipexole

- Nausea
- Nasal stuffiness
- Constipation
- Leg swelling
- Insomnia
- *Sleepiness (caution driving)
- *Pathological gambling and impulsive behaviors
Side Effects – with longer use

- Augmentation

  Symptoms begin earlier in the day (may add earlier or change med)

- Rebound

  Symptoms return in the middle of the night (change med)
Second and Third Line Agents

- Gabapentin (Neurontin)
- Pregabalin (Lyrica)
- Benzodiazepines (sedative hypnotics)
  - Clonazepam (rivoltir / klonopin)
  - Lorazepam (ativan)
- Opioids
  - Codeine
  - Hydrocodone
  - Methadone*
- (Quinine obsolete)
Summary

• RLS is very common (~10%)
• Symptoms are difficult to describe
• Use URGE criteria to diagnose
• Dopaminergic drugs are the first line of treatment and are very effective
• RLS is very treatable, but often unrecognized, and significantly impacts quality of life as a result
Primary Disorders of Hypersomnolence

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Objectives

• Understand differential diagnosis of excessive daytime sleepiness and primary disorders of hypersomnolence

• Recognize narcolepsy with cataplexy:
  - definition and clinical features
  - epidemiology and etiology, diagnosis
  - therapeutic options
    - non pharmacological
    - pharmacological
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Excessive Daytime Sleepiness

• Lack of sleep (Inadequate quantity of sleep)
  – Insufficient time in bed

• Inadequate quality of sleep
  – Sleep Apnea, PLMD, environment

• Intrinsic sleepiness
  – Hypersomnolence disorders (Narcolepsy; Idiopathic Hypersomnia)

• Medical/psychiatric disorder
  – Mood disorder
  – Medications, medical – thyroid, anemia etc.

• Circadian Rhythm Disturbance
  – Shift work, delayed sleep phase, etc.
Hypersomnolence Disorders

- Hypersomolence disorder
  - Idiopathic hypersomnia
  - Kleine Levin Syndrome
  - Kluver Bucy Syndrome

- Narcolepsy
  - with cataplexy*
  - without cataplexy
    (+/- hypocretin)
Hypersomnolence disorder

• Self reported sleepiness despite a main sleep period lasting 7 hours, with ≥1 of
  - recurrent lapses to sleep in the day
  - a prolonged episode >9 hrs unrefreshing sleep
  - difficulty being awake after abrupt awakening

• >3x/wk, >3months

• Significant distress

• Not due to substance, medical condition
Narcolepsy - DSM-5

• Recurrent periods of irrepresible need to sleep, ≥ 3x/wk, ≥3 months
• Cataplexy*
• Hypocretin deficiency (CSF Hcrt-1 < 110pg/mL)
• PSG – REM latency ≤ 15 min, or MSLT with - SL ≤ 8 min and ≥ 2 SOREMPs
REBECCA, A 19 YEAR OLD FEMALE WITH A COMPLAINT OF EXCESSIVE DAYTIME SLEEPINESS
Narcolepsy “Pentad”

- **Excessive Daytime Sleepiness**
  - May fall asleep without warning, unusual situations

- **Cataplexy (75%)**
  - Flaccid muscle paralysis; eyes and diaphragm OK; pt. remains awake but paralyzed.

- **Hypnagogic / pompic hallucinations (50-60%)**
  - “Multimodal”. Often highly emotional, sexual, frightening

- **Sleep Paralysis (50-66%)**
  - Awakes unable to move anything but eyes. Can’t breathe voluntarily or talk. HH often occur.

- **Disturbed nocturnal sleep**
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Narcolepsy: Prevalence

• Approximately 1/2000 US patients suffer from narcolepsy
• Estimated 15-30% are currently diagnosed
• Under –DX!

Undiagnosed 70%
Diagnosed 30%

Silber MH et al. Sleep, 2002; 25(2): 197-205
Figure 7.4 Age of onset of narcolepsy. This graph demonstrates that narcolepsy most commonly commences in the second decade followed by the third and then the first and fourth decades.
Markers of Narcolepsy

- **Hypocretin/Orexin**
  90-95% of narcolepsy with cataplexy – are CSF hypocretin deficient
- **HLA DQB1*0602** – strongly associated with hypocretin deficiency (95%)
- **Recent association - H1N1, + Pandemrix flu vaccine**
- **HLA DQA1*0102**
- **HLA DRB1*1503**
Hypocretin/Orexin Projections
Excessive Daytime Sleepiness (EDS)

- **Multiple Sleep Latency Test (MSLT)**
  - Following an NPSG
  - 4 or 5 X 20 minutes naps at 2 hour intervals
  - Example: 9am, 11am, 1pm, 3pm
  - Check for: 1) Avg. SOL & 2) REM sleep x2

- Pathological Sleepiness = fall asleep < 8 mins + 2 or more SOREMPS
Narcolepsy: A Missed Diagnosis?

- Epilepsy
- Schizophrenia
- Depression, Bipolar
- Personality Disorder
- “Neurotic” Disorder
- Adjustment Reaction
- Substance abuse

Correct Diagnosis? Study of Physician Narcolepsy recognition

- Neurologists %?
- Family Med %?
- Internists %?
- Pediatricians %?
- Psychiatrists %?

Kryger MH et al, Sleep. 2002; 25(2): 36-41
Douglass AB, CNS Spectr; 2003; 8(2): 120-6
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Narcolepsy Treatment

- Education
  - Not their fault
  - Not “lazy”
- Prophylactic naps
- Avoid activities/jobs where sleeping is an issue (e.g. shift work)
Narcolepsy Treatment

• Rx: Stimulant medication
  - Modafinil (Alertec)
  - Methylphenidate (Ritalin)
  - Dexedrine

• REM suppressant medications for cataplexy
  - SSRI – e.g. Fluoxetine, Venlafaxine
  - TCA – e.g. Clomipramine

• Strongest anticataplectic = Sodium oxybate
  (Xyrem, GHB) – powerful amnestic
Sodium Oxybate (Xyrem)

• Used for sleepiness and cataplexy
• Given hs and again 2.5-4 hours later
• Start – 3-4.5 g/day, increase by 1.5 g/day every 2 weeks until max of 9 g/day
• Side-effects: dizziness, nausea, sleepwalking, confusion, resp depression
• Do not use with CNS depressants (including BZD, alcohol), untreated OSA, COPD, obesity-hypoventilation syndrome
Summary

- Narcolepsy is a disorder of excessive daytime sleepiness, with specific sx (REM intrusion)
- Hypocretin/Orexin plays a significant role
- Significantly under-diagnosed
- Current diagnosis is with the MSLT; other options may be available in the future
- Education is important in treatment
- Stimulants, antidepressants, sodium oxybate are the most effective treatments currently
Questions ?