Restless Legs Syndrome

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University Hospitals
Outline of Talk

- Diagnosis/classification
- Symptomatology
- Evaluation
- PLMS
- Epidemiology
  - Prevalence
  - Risk factor
- Effect of Quality of Life

- Pathophysiology
- Genetics
- Treatment
Diagnosis of RLS

• Diagnosis is entirely clinical and based upon

  **Four essential criteria**

  • 1) Urge to move often associated with uncomfortable sensation
  • 2) Symptoms worsen in evening
  • 3) Symptoms worsen with inactivity
  • 4) Temporary relief of symptoms with movement

• Rule out RLS mimics
  • Nocturnal leg cramps
  • Peripheral neuropathy
  • Pain from myelopathy
  • Akathisia
  • Peripheral vascular disease
Determine Severity

- Frequency
  - How many times out of the week?
- Duration
  - What time does it start?
  - How long does it bother you?
- Intensity
  - How much does it bother you?
  - Does it prevent you from falling asleep?
  - How much relief do you get from movement?
- Does it effect your personal life?
  - Cannot get in car at night.
  - Avoid going to parties.
Approach to Assessing the RLS patient

"Well, your reflexes are fine."
Sleep History

- Take a Sleep history
  - Insomnia: initiation / maintenance
  - Sleep hygiene
  - Proper sleep schedule
    - 7-8 hours sleep
    - Regular bed and wake time
  - Obstructive sleep apnea
  - Excessive daytime sleepiness
    - Drowsy driving
Social History

- Occupational History
  - Especially if excessively sleepy
  - Occupational hazard
- Exercise History
  - Exercise can help RLS symptoms
- Alcohol
- Caffeine
Neurological Examination

- Peripheral neuropathy (diabetic)
  - Lower extremity sensory exam: LT, PP, JPS, vibratory
  - Reflexes especially ankle jerks
- Spinal cord
  - Motor exam / ask about bowel/bladder
  - Spastic reflexes
- Parkinson’s Disease
  - Facial hypomimia
  - Cogwheel rigidity
  - Resting tremor
  - Bradykinesia
  - Shuffling gait
Laboratory Testing

**Primary RLS**
- Serum ferritin
  - Normal 20-400 $\mu$g/L
  - Less than 50 $\mu$g/L warrants treatment
  - If low then also check iron and CBC

**Secondary RLS**
- If neuropathy
  - Check blood glucose
  - Neurological consult
  - If ↑ reflexes/weakness
    - B12 level
    - Neurological consult
  - Serum ferritin
Primary Restless Legs Syndrome

- RLS in the absence of precipitating comorbidity
- Occurs early in life
  - From first to fourth decade of life
  - Pediatric RLS: ‘growing pains’
- Family history
- More common in women
Secondary RLS

- Peripheral Neuropathy
  - Esp. diabetic
- Pregnancy
  - 25%-30%
- Parkinson’s Disease
  - 20%-25%
- End Stage Renal
  - 40%-60%

- Iron deficiency
- Spinal cord disease
- Multiple sclerosis
  - 25%-30%
RLS Symptomatology
REST Study

Category, Symptom Reported as Most Troublesome

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Primary Care Population</th>
<th>Community Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inability to get comfortable</td>
<td>58.2%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Pain</td>
<td>21.4%</td>
<td>19%</td>
</tr>
<tr>
<td>Uncomfortable feelings</td>
<td>27.0%</td>
<td>8.9%</td>
</tr>
<tr>
<td>urge to move</td>
<td>11.1%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Inability to fall asleep</td>
<td>11.8%</td>
<td>13.5%</td>
</tr>
<tr>
<td>Inability to stay asleep</td>
<td>10.2%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Interrupted sleep</td>
<td>9.3%</td>
<td>14.7%</td>
</tr>
<tr>
<td>Insufficient sleep</td>
<td>6.0%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td>15.8%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Difficulty concentrating day</td>
<td>6.0%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Twitching/jerky movements</td>
<td>3.4%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Depression</td>
<td>26.2%</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

Hening 2004
Ancillary Features of RLS

- Family History
- Response to dopaminergic agent
- Insomnia

REST Trial

Sleep Latency

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15 mins</td>
<td>8.5%</td>
</tr>
<tr>
<td>15–30 mins</td>
<td>22.3%</td>
</tr>
<tr>
<td>30–60 mins</td>
<td>35.9%</td>
</tr>
<tr>
<td>1–2 hours</td>
<td>17.4%</td>
</tr>
<tr>
<td>2–3 hours</td>
<td>7.3%</td>
</tr>
<tr>
<td>&gt;3 hours</td>
<td>8.0%</td>
</tr>
<tr>
<td>No answer given</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Ancillary Features of RLS

- **Periodic Limb movements during sleep (PLMS)**
  - Occurs in up to 80%-90% of patients with RLS
  - Contraction of the anterior tibialis muscle, less often hamstring, iliopsoas and arms
  - Movements in sleep most often legs occur every 30-40 sec over 4-6 hours
Periodic Limb Movements

- PLMs seen during wakefulness (PLMW): specific for RLS
  - Build-up of energy and legs just move (jump)
  - Opposed to volitional movement to alleviate RLS symptoms
- Usually occurs in first 2/3 of night
- PLMI correlates modestly with RLS severity

Garcia-Borreguero 2004
PLMS in RLS & Age

- Periodic limb movements
- Frequency PLMS ↑ with age
  In a linear fashion

![Graph showing the relationship between PLMS index and age groups. The graph indicates a positive correlation with age, and the trend is linear.](image)

**LM parameters found in the different patient age subgroups**

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Kruskal–Wallis ANOVA p &lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total sleep</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total, index</td>
<td>18.9 (10.44)</td>
<td>0.016</td>
</tr>
<tr>
<td>PLMS, index</td>
<td>9.0 (9.38)</td>
<td>0.016</td>
</tr>
<tr>
<td>Isolated, index</td>
<td>9.9 (2.72)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>NREM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total, index</td>
<td>19.9 (10.73)</td>
<td>0.015</td>
</tr>
<tr>
<td>PLMS, index</td>
<td>10.8 (11.10)</td>
<td>0.015</td>
</tr>
<tr>
<td>Isolated, index</td>
<td>9.1 (3.09)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>REM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total, index</td>
<td>15.5 (10.32)</td>
<td>0.04</td>
</tr>
<tr>
<td>PLMS, index</td>
<td>2.9 (5.09)</td>
<td>0.057</td>
</tr>
<tr>
<td>Isolated, index</td>
<td>12.5 (5.27)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Ferri 2008
**RLS Epidemiology**

- **REST study:** RLS Epidemiology, Symptoms, Treatment
  - Multicenter trial Europe and U.S.
  - Face to face or phone interview asking all four criteria
  - N = 15,391

### Table 2. Prevalence of RLS Symptoms by Country and Degree of Severity

<table>
<thead>
<tr>
<th>Country</th>
<th>Questionnaires Distributed, No.</th>
<th>Fully Completed Questionnaires, No. (%)</th>
<th>Any Frequency</th>
<th>≥Once/wk</th>
<th>≥Twice/wk</th>
<th>≥Twice/wk and of Moderate or Extreme Distress</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>2010</td>
<td>1884 (93.7)</td>
<td>203/1884 (10.8)</td>
<td>125/1884 (6.6)</td>
<td>103/1884 (5.5)</td>
<td>79/1884 (4.2)</td>
</tr>
<tr>
<td>Germany</td>
<td>2040</td>
<td>1929 (94.6)</td>
<td>79/1929 (4.1)</td>
<td>53/1929 (2.7)</td>
<td>38/1929 (2.0)</td>
<td>25/1929 (1.3)</td>
</tr>
<tr>
<td>Italy</td>
<td>2036</td>
<td>1768 (86.8)</td>
<td>119/1768 (6.7)</td>
<td>74/1768 (4.2)</td>
<td>55/1768 (3.1)</td>
<td>43/1768 (2.4)</td>
</tr>
<tr>
<td>Spain</td>
<td>2020</td>
<td>1896 (93.9)</td>
<td>92/1896 (4.9)</td>
<td>66/1896 (3.5)</td>
<td>58/1896 (3.1)</td>
<td>37/1896 (2.0)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>2082</td>
<td>1950 (93.7)</td>
<td>167/1950 (8.6)</td>
<td>109/1950 (5.6)</td>
<td>95/1950 (4.9)</td>
<td>45/1950 (2.3)</td>
</tr>
<tr>
<td>United States</td>
<td>6014</td>
<td>5964 (99.2)</td>
<td>454/5964 (7.6)</td>
<td>346/5964 (5.8)</td>
<td>289/5964 (4.8)</td>
<td>187/5964 (3.1)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>16,202</strong></td>
<td><strong>15,391</strong></td>
<td><strong>1114/15,391</strong> (7.2)</td>
<td><strong>773/15,391</strong> (5.0)</td>
<td><strong>638/15,391</strong> (4.1)</td>
<td><strong>416/15,391</strong> (2.7)</td>
</tr>
</tbody>
</table>

Allen 2005
RLS Epidemiology

- European and North American populations
  - Prevalence range
    - United States 7.6%
    - Italy 6.7%
  - France 10.8%
  - United Kingdom 8.6%

- Asian
  - India 2.1%
  - Singapore 0.6%
  - Korea 1.0-7.5%
  - Native 2.0%

- South America

Allen 2005
RLS and cardiovascular disease in SHHS

RLS
- Possible relation to hypertension
- Coronary artery
- Cardiovascular disease

Unadjusted Frequencies

<table>
<thead>
<tr>
<th></th>
<th>RLS (n=179)</th>
<th>No RLS (n=3254)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>63.7%</td>
<td>55.9%</td>
<td>0.04</td>
</tr>
<tr>
<td>Coronary Artery</td>
<td>16.3%</td>
<td>24.6%</td>
<td>0.003</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>19.5%</td>
<td>29.6%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Adjusted Model: Age, Sex, BMI, race, DM, SBP, smoking, cholesterol

<table>
<thead>
<tr>
<th></th>
<th>Odds ratios</th>
<th>RLS</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1.60</td>
<td>1.60</td>
<td>(0.92-1.82)</td>
</tr>
<tr>
<td>Coronary Artery</td>
<td>2.05</td>
<td>2.05</td>
<td>(1.38-3.04)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>2.07</td>
<td>2.07</td>
<td>(1.43-3.00)</td>
</tr>
</tbody>
</table>

Winkelman 2008
Hypertension & RLS

- **PLMS**
  - Sympathetic activation
  - Immediate ↑ SBP>DBP
  - ↑ in HR

<table>
<thead>
<tr>
<th></th>
<th>PLMS-noMA</th>
<th>PLMS-MA</th>
<th>Paired t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta SBP</td>
<td>18.0 ± 8.6 (6–34)</td>
<td>25.0 ± 7.1 (17–39)</td>
<td>*p &lt; 0.05</td>
</tr>
<tr>
<td>Delta DBP</td>
<td>9.0 ± 3.5 (4–15)</td>
<td>12.6 ± 3.6 (8–20)</td>
<td>*p &lt; 0.05</td>
</tr>
<tr>
<td>Delta HR</td>
<td>7.9 ± 2.4 (4–11)</td>
<td>11.5 ± 3.4 (5–15)</td>
<td>*p &lt; 0.01</td>
</tr>
</tbody>
</table>

Pennestri 2007
REST & Quality of Life

SF-36

- Well validated tool measuring quality of life.
- 8 areas equally weighted to give score out of 100.

![Graph showing SF-36 scores for different conditions.](Allen 2005)
RLS Pathophysiology

Dopaminergic dysfunction ↔ Iron deficiency

Hormonal dysfunction
Dopaminergic Dysfunction

- **Strongest evidence**
  - Dopaminergic agonists effective in treating RLS
  - Dopamine-receptor blocking drugs cause RLS

- **Conflicting evidence**
  - Normal CSF DA metabolites in RLS
  - SPECT looking at DA binding of D2R
    - Basal ganglia: studies show normal or mildly reduced binding
    - Striatum: normal binding; ↑ D2R binding capacity
  - Normal histopathology of basal ganglia

Michaud 2002
Eisensehr 2001
Iron Deficiency

- RLS associated with iron deficiency (ESRD, pregnancy)
- RLS treated with iron

**Ferritin:** major iron storing protein
- Decreased serum ferritin in 20% RLS
- Decreased CSF ferritin
- Decreased ferritin staining in neuromelanin cells SNigra

**Transferrin:** iron transport protein
- Increased in 23% men (3.8%) and 13.5% women (8.3%)
- Increased staining in neuromelanin cells in Substantia Nigra

Connor 2003
Hormonal Dysfunction

- Suggested by RLS assoc with pregnancy
  - Recently pregnant women with RLS shown to have increased plasma estradiol
- Suggested by diurnal variation
  - Melatonin secretion increases with darkness
  - Melatonin inhibits dopamine release

Dzaja 2009
Linkage studies: familial aggregates
- Detects rare variants as phenotype is first identified
- 40%-90% of primary RLS have relatives with RLS
- German families: Chromosome 12q: RLS1
- Italian families: Chromosome 14q: RLS2
- American families: Chromosome 9p

Genome-wide association studies
- Chromosome 6p: BTBD9, gene for PLMS also assoc with low ferritin
- Chromosome 2p: MEIS1
- Chromosome 15q: MAP2K5
RLS Behavioral Treatment

- Sleep hygiene
  - Regular bed/wake times
  - Avoid EtOH
  - Avoid caffeine
- Review medications
  - Antidepressants can worsen
- Physical treatment
  - Exercise
  - Stretching
  - Cooling legs/rubbing
RLS Iron Therapy

- Serum ferritin
  - Normal 20-400 μg/L
  - Treat if below 50 μg/L
  - Can treat if below 60-70 μg/L if severe symptoms

- Ferrous sulfate: oral
  - 325 mg TID before meals but if GI sx with meals
  - Vitamin C 500 mg with iron increases absorption

- Recheck ferritin 3-6 months: aim for midrange ferritin
  - Can increase to 325 mg 4x daily

- Trials of IV iron
  - 1 mg iron dextrane
  - Safety issues
Dopaminergic Therapy

- Carbidopa/Levodopa
  - Start 100/25 mg 1 hour before onset of symptoms
  - Can dose BID to QID
  - Response strongly suggestive of RLS
  - Good for mild, intermittent RLS
  - Can add COMT inhibitors
  - Do not exceed 400 mg of levodopa

- High doses of levodopa and low ferritin
  - Risk for augmentation
Augmentation

- Acute worsening of RLS symptoms in setting of initiation or dose increase *dopaminergic therapy*
  - 2 hour earlier onset (time) of symptoms
  - ↑ intensity of urge to move or discomfort
  - Latency to symptoms at rest shortens
  - Duration of medication symptom relief shortens
  - Spread of symptoms to previously uninvolved limbs

- What to do.
  - Stop the offending agent
  - Start dopaminergic agonist or opioid
Dopamine Agonists

- **Ropinorole (Requip)**
  - Placebo controlled trials: ↓ IRLS from 11.0 to 13.5
  - Decreases PLMI: $76.4 \pm 34.5$ vs. $19.8 \pm 18.0$
  - Mean/median dose: 1.8/1.5 mg
  - Start 0.25 mg x 3 days, 0.5 mg x 5 days, then 1 mg
  - Max dose: 4mg / day

- **Pramipexole (Mirapex)**
  - ↓ IRLS from 12.0 to 17.0 in dose-dependent fashion
  - Decreases PLMI: 0.25 mg $\rightarrow$ ↓ $45.8 \pm 33.56$ to $9.4 \pm 11.40$
  - Start 0.125 mg x 3 days, 0.25 x 5 days, then 0.5 mg
  - Max dose: 2.5-3.0 mg / day

References:
- Manconi 2007
- Bliwise 2005
Gabapentin

- Good choice for
  - RLS assoc with peripheral neuropathy
  - Liver failure with intact kidney function
  - Chronic pain
- ↓ IRLS by 8.4 ± 1.3
- Decreases PLMS by almost 50%
- Increases total sleep time
- Titration
  - Start 100-300 mg at night
  - Increase by 300 mg/weak
  - Can use BID or TID for severe RLS
  - Max 3600 mg/day
Opioid Medications

- Use in augmentation or severe / advanced RLS
- Drugs of choice in pregnancy (Class B)
- Oxycodone
  - Mean dose of 11.4 mg → 52% improve IRLS scale
  - PLMS 38.8 to 18.4
- Methadone
  - 15 mg/day
- Tramadol