Fundamentals of Restless Legs Syndrome

Wisconsin Sleep Society
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Disclosures

• I am NOT receiving direct or indirect payment from a commercial entity for honorarium, travel or other expenses

• I do NOT have relevant financial interest or affiliations with any commercial / corporate organizations
Educational Objectives

• To name the diagnostic criteria for restless legs syndrome (RLS)
• To identify therapeutic treatment options for RLS
• To describe symptoms of augmentation related to dopaminergic drugs
Outline

• History of RLS
• RLS pathophysiology and risk factors
• Diagnostic criteria and clinical work up
• Treatment options
• DA and augmentation
• Summary
"Wherefore to some, when being a bed they betake themselves to sleep, presently in the arms and legs, leapings and contractions of the tendons, and so great a restlessness and tossing of their members ensue, that the diseased are no more able to sleep, than if they were in a place of greatest torture"
Ekbom Syndrome

Asthenia crurum paraaesthetica

A new syndrome consisting of weakness, sensation of cold and nocturnal paresthesia in legs, responding to certain extent to treatment with priscol and doryl.

Karl Axel Ekbom

Ekbom. Acta Medica Scandinavica. 1944
Ekbom Syndrome

He offered further diagnostic guidance in 1960:

“The following criteria should be borne in mind. The sensations appear only when the patient is at rest, most often in the evening and early part of the night, and produce an irresistible need to keep the legs moving. Furthermore, the sensation are not felt in the skin but deep down inside the legs.”
RLS (Willis-Ekbom disease – WEB) rlshelp.org

REST Primary Care Study

- RLS screening questionnaire
- USA, Germany, UK, France & Spain
- 23,052 patients completed
- 9.6% RLS weekly symptoms

Hening. Sleep Med. 2004
Troublesome RLS Symptoms

- Sleep-related symptoms: 43.4%
- Uncomfortable feelings in legs: 27.0%
- Pain: 21.4%
- Inability to stay still/urge to move: 11.8%
- Inability to get comfortable: 11.1%
- Exhaustion/fatigue: 10.2%
- Twitching/jerks of legs: 9.3%
- Daytime sleepiness: 6.0%
- Not stated: 15.8%
Time to Fall Asleep in RLS: 69% report sleep onset insomnia

Hening. Sleep Med. 2004
Times Woken at Night in RLS:
60% report waking > 3 times per night
RLS Pathophysiology

• RLS may be due to:
  – Low brain iron concentrations
  – Abnormal brain dopamine metabolism
  – Hypoactive opioid system
  – A combination of above factors
RLS Pathophysiology – Cont.

- Both CNS and spinal cord may be involved
- Strong genetic risk
RLS & Genes

• A monogenic cause for RLS has not been identified
• 6 different genes may play a role
• Linkage reported to:
  – RLS – 1: Chromosome 12q
  – RLS – 2: Chromosome 14q
  – RLS – 3: Chromosome 9p24-p22
RLS Epidemiology

• Prevalence is 2.5-10%
• Predominant in women 2:1
• 1/3 seek medical attention
• ↑ incidence in Northern European

Borreguero. Sleep Med Rev. 2006
RLS Risk Factors

- Iron deficiency / frequent blood donations
- Kidney failure
- Diabetes
- Neuropathy / Spinal stenosis
- Parkinson’s
- Affects 2.9-32% of pregnant women

Borreguero. Sleep Med Rev. 2006
Diagnosis

• Always clinical
• 2012 - International Restless Legs Syndrome Study Group (IRLSSG) revised diagnostic criteria
• Added a fifth criterion
• All criteria must be present

Allen RP. Sleep Med. 2014
Essential Dx Criteria

1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs

2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting

Wijemanne S. Sleep Med. 2015
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.

4. Worse in the evening or night than during the day or only occur in the evening or night.
5. The above features are **not solely accounted for by other medical or behavioral conditions**, such as myalgias, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping, and other nocturnal sensory-motor symptoms.

Wijemanne S. Sleep Med. 2015
Differential Diagnosis

- **Common:** Leg cramps, positional discomfort, local leg injury, arthritis, leg edema, venous stasis, peripheral neuropathy, radiculopathy, habitual foot tapping/leg rocking, anxiety, myalgia, drug-induced akathisia
- **Less common:** Myelopathy, myopathy, vascular or neurogenic claudication, hypotensive akathisia, orthostatic tremor, painful legs and moving toes.
Difficult Diagnosis

- Patients may have one or more of the differential diagnosis in addition to RLS (e.g. RLS and neuropathy)
- Must focus on characteristics of each condition for both diagnosis and assessment of impact.
- If diagnosis is unclear may want to do a “trial” drug treatment.
Diagnostic Criteria for RLS

Mnemonic

- Urge to move
- Rest induced
- Gets better with activity
- Evening and night accentuation
- Not caused by other conditions

Wijemanne S. Sleep Med. 2015
## International Restless Legs Syndrome Rating Scale

### Key diagnostic criteria for RLS are:*2
- An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant leg sensations
- Symptoms begin or worsen during periods of rest or inactivity, such as lying or sitting
- Symptoms are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues
- Symptoms are worse or occur only in the evening or at night

It is important to consider if the patient’s RLS is due to underlying conditions, including but not limited to pregnancy, renal failure, iron deficiency.

- Have the patient rate his/her symptoms with the following ten questions.
- The patient and not the examiner should make the ratings, but the examiner should be available to clarify any misunderstandings the patient may have about the questions.
- The examiner should mark the patient’s answers on the form.

### IN THE PAST WEEK...

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall, how would you rate the RLS discomfort in your legs or arms?</td>
<td>(4) Very severe (3) Severe (2) Moderate (1) Mild (0) None</td>
</tr>
<tr>
<td>Overall, how would you rate the need to move around because of your RLS</td>
<td>(4) Very severe (3) Severe (2) Moderate (1) Mild (0) None</td>
</tr>
<tr>
<td>symptoms?</td>
<td></td>
</tr>
<tr>
<td>Overall, how much relief of your RLS arm or leg discomfort did you get</td>
<td>(4) No relief (3) Mild relief (2) Moderate relief (1) Either complete</td>
</tr>
<tr>
<td>from moving around?</td>
<td>or almost complete relief (0) No RLS symptoms to be relieved</td>
</tr>
<tr>
<td>How severe was your sleep disturbance due to your RLS symptoms?</td>
<td>(4) Very severe (3) Severe (2) Moderate (1) Mild (0) None</td>
</tr>
<tr>
<td>How severe was your tiredness or sleepiness during the day due to your RLS</td>
<td>(4) Very severe (3) Severe (2) Moderate (1) Mild (0) None</td>
</tr>
<tr>
<td>symptoms?</td>
<td></td>
</tr>
<tr>
<td>How severe was your RLS as a whole?</td>
<td>(4) Very severe (3) Severe (2) Moderate (1) Mild (0) None</td>
</tr>
<tr>
<td>How often did you get RLS symptoms?</td>
<td>(4) Very often (3) Often (2) Sometimes (1) Occasionally (0) Never</td>
</tr>
<tr>
<td>This means 3 to 5 days a week</td>
<td></td>
</tr>
<tr>
<td>This means 0 to 2 days a week</td>
<td></td>
</tr>
<tr>
<td>When you had RLS symptoms, how severe were they on average?</td>
<td>(4) Very severe (3) Severe (2) Moderate (1) Mild (0) None</td>
</tr>
<tr>
<td>This means 8 hours or more per 24 hour day</td>
<td></td>
</tr>
<tr>
<td>This means 0 to 2 hours per 24 hour day</td>
<td></td>
</tr>
<tr>
<td>Overall, how severe was the impact of your RLS symptoms on your ability</td>
<td>(4) Very severe (3) Severe (2) Moderate (1) Mild (0) None</td>
</tr>
<tr>
<td>to carry out your daily affairs — for example carrying out a satisfying</td>
<td></td>
</tr>
<tr>
<td>family, home, social, school or work life?</td>
<td></td>
</tr>
<tr>
<td>How severe was your mood disturbance due to your RLS symptoms — for</td>
<td>(4) Very severe (3) Severe (2) Moderate (1) Mild (0) None</td>
</tr>
<tr>
<td>example angry, depressed, sad, anxious or irritable?</td>
<td></td>
</tr>
</tbody>
</table>

### Scoring criteria are:
- Mild (score 0-10)
- Moderate (score 11-20)
- Severe (score 21-30)
- Very Severe (score 31-40)

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*Key diagnostic criteria developed by the International Restless Legs Syndrome (IRLS) Study Group in collaboration with the National Institutes of Health.


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Supportive Clinical Features in diagnosing RLS

- Periodic limb movements
  - wakefulness (PLMW) (quiet waking during the sleep period)
  - Sleep (PLMS)
- Response to dopaminergic therapy
- Family history of RLS among first degree relatives.
- Lack of profound daytime sleepiness

Allen et al. Sleep medicine 2003
1. Signs of leg discomfort such as rubbing or kneading the legs and groaning while holding the lower extremities are present.

2. Signs of leg discomfort are exclusively present or worsen during periods of rest or inactivity.

3. Signs of leg discomfort are diminished with activity.

Allen et al. Sleep medicine 2003
RLS Dx Cognitively Impaired

4. **Excessive motor activity in the lower extremities** such as pacing, fidgeting, repetitive kicking, tossing and turning in bed, slapping the legs on the mattress, cycling movements of the lower limbs, repetitive foot tapping, rubbing the feet together, and the inability to remain seated are present.

Allen et al. Sleep medicine 2003
RLS Dx Cognitively Impaired

5. Criteria 1 and 4 occur only in the evening or at night or are worse at those times than during the day

• All five criteria must be present to diagnose

Allen et al. Sleep medicine 2003
RLS in Pediatrics

- Affects 1.9% of school aged children and 2% of adolescents.
- 38% of adults had symptoms prior to age 20.
- 10% report symptoms before age 10.
- 12-35% of children with ADHD meet criteria for RLS.
Pediatric diagnosis of RLS

1. All four adult criteria are present; and
2. Child describes leg discomfort

Or

1. All four adult criteria are present; and
2. Two or three supportive criteria are present

Allen et al. Sleep medicine 2003
RLS Supportive Criteria - Child

- Sleep disturbance for age
- Biologic parent or sibling with definite RLS
- PLMI $\geq 5$/hr in PSG

Allen et al. Sleep medicine 2003
Periodic Limb Movement Disorder

1. PSG Findings:
   a) Repetitive, highly stereotyped limb movements
   b) 0.5–10 s in duration
   c) Minimum amplitude of 8 mV above resting EMG
   d) In a sequence of 4 or more movements
   e) Separated by an interval of more than 5 s (from limb movement onset to limb movement onset) and less than 90 s (typically there is an interval of 15–40 s)

Hornyak. Sleep Med Rev. 2006
Periodic Limb Movement Disorder

2. The PLMS index > 5/h in children and 15/h in adults
3. There is clinical sleep disturbance or complaint of daytime fatigue
4. The PLMS are not better explained by another current sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder

Hornyak. Sleep Med Rev. 2006
Diagnosing RLS

• Primary RLS
  – 50%-60% may include iron deficiency.
  – Not related to any other disorder
  – Idiopathic (Familial > 50%)
  – Occurs earlier in life and more benign
Diagnosing RLS

• **Secondary RLS**
  – Most commonly associated with iron deficiency, pregnancy, or end stage renal disease (all linked to low iron)
  – Occurs later in life with faster progression
  – Worse than primary RLS
Medications Worsening RLS

- Antihistaminergic agents
- SSRI / SNRI
- TCA’s
- Mirtazapine
- Atypical antipsychotics
- Antiemetic agents
- Amphetamines / methylphenidate
- Alcohol
- Caffeine
- PPI’s (interfere with iron absorption)

Hoque. JCSM. 2010
Diagnostic Workup

• **History is diagnostic**
  – Sensitivity & specificity >90%

• Polysomnography is NOT routinely indicated

• EMG for co-existing symptoms of neuropathy, radiculopathy, or myelopathy

• Central nervous system MRI for myelopathy or stroke, if suspected
# Laboratory Tests

## Anemia Workup
- CBC with indices
- Iron
- **Ferritin**
- B12 & Folate
- Magnesium
- Iron binding capacity

## Endocrine Workup
- Thyroid studies
- Fasting glucose
- Glucose tolerance test
- Electrolytes to check renal function
- Serum creatinine and BUN
Non Pharmacological Therapy

- Try before prescribing medications
- Mild to moderate physical activity
- Good sleep hygiene
- Hot baths, massage
- Engrossing mental activity
- Schedule sedentary activities earlier in the day
- Exercise or housework later in the day
- Avoid triggers
- Compression devices
- Acupuncture
Exercise and RLS/PLMS

- Two groups – exercise and non-exercise group. End point was improvement in RLS symptoms.
- Exercise group had a pronounced reduction in IRLS scale compared to the non-exercise group after 12 weeks of exercise.
Exercise and RLS

• One trial showed doing body resistance training and 30 min. of walking on treadmill three times per week was beneficial
Opioid Hypothesis for RLS and exercise

- It is well known that exercise increases the release of endogenous opioids (enkephalins and endorphins).
- The improvement in RLS/PLMS with exercise is compatible with the hypothesis that the endogenous opioid system with its enkephalins and endorphins is hypoactive in RLS.
Vibratory Sensory Neurostimulation

• Relaxis ® - FDA approved for Primary RLS
• Provides vibrational counter stimulation
• Contraindications
  – PE / DVT past 6 months
  – Leg skin disorders such as eczema, psoriasis, cellulitis, non-healing wounds
  – Secondary RLS
"THIS SHOULD SOLVE YOUR PROBLEM!"
Pharmacological Therapy

FDA Approved Options

• Dopaminergic agonists (most widely used)

  • Reduce RLS symptoms and PLM’s
    – Ropinirole (Requip)
    – Pramipexole (Mirapex)
    – Rotigotine transdermal (Neupro)

• Gabapentin Enacarbil (Horizant)
ropinirole - Requip

- First DA to be approved in US and Europe for RLS.
- Starting dose is 0.25mg 1-3 hours before bed.
- Increase to 0.5mg after 2 days & 1mg by end of one week.
- Maximum dose is 4mg.
- Mean effective dose is 2mg.
- MINIMUM dose should always be used to prevent augmentation.
- Slightly better symptom control and less side effect with ropinirole than pramipexole.
pramipexole - Mirapex

- Starting dose is 0.125mg 2-3 hours before bed.
- Maximum recommended dose is 0.75mg
- Effective daily doses range from 0.25 – 1mg.
- Plasma concentration for both pramipexole and ropinirole peak 2 hours after ingestion
Adverse Effects with DA

- Nausea (25-50%)
- Headaches (7-22%)
- Fatigue (1-19%)
- Dizziness (6-18%)
- Vomiting (5-11%)
rotigotine - Neupro

- Transdermal system
- Starting dose is 1mg.
- Increase dose weekly up to 3mg.
- May have lower rates of augmentation.
- Good option if daytime symptoms due to therapeutic plasma levels over 24 hours.
rotigotline – side effects

- Application site skin reaction (22-58%)
- Nausea (17-19%)
- Headache (4-11%)
- Fatigue (0.5-11%)
Other adverse Effects with DA

• Sleep attacks – especially at higher doses
• 6-17% of patients develop impulse control disorders
• Ergot Derivatives (Cabergoline, Pergolide) – No longer used due to risk of cardiac valvular fibrosis and other fibrotic effects.
Other Pharmacological Therapy

- Other dopaminergic drugs (levodopa)
- Calcium channel alpha-2-delta (α2δ) ligands
  - Gabapentin, gabapentin enacarbil, pregabalin
- Opioids
- Clonazepam
- Iron
Levodopa

• May be beneficial when used sparingly in patients with infrequent symptoms.
• Avoid as chronic treatment due to high risk of tolerance, augmentation, and rebound symptoms.
• Up to 80% augmentation rate with levodopa treatment
• Dose is 0.5-1 tab of 25/100mg
Calcium channel alpha-2-delta (α2δ) ligands
Gabapentin, gabapentin enacarbil, pregabalin

- Gabapentin - gamma aminobutyric acid (GABA) analog.
- Now favored as 1st line treatment of RLS
- Doesn’t cause augmentation or impulse control disorder
- Beneficial if painful symptoms of RLS
- Consider in patients with anxiety or impulse control disorder.
- May improve sleep onset and maintenance problems better than ropinirole.
Gabapentin dosing.

- 100-300mg 2-3 hours before bed or before onset of symptoms.
- Increase dose weekly to maximum total dose of 900-2400mg
- Side effects: dose dependent, but generally mild to moderate.
- Dizziness, somnolence, peripheral edema.
Gabapentin enacarbil - Horizant

• Approved by the FDA April 2011 for mod. to severe RLS
• Is a prodrug of gabapentin
• 600mg once daily administration, typically at 5pm with food. (max. dose 1200mg)
• Provides increased gabapentin exposure over longer time periods than gabapentin.
• Side effects: dizziness, somnolence, headache, nausea, and fatigue.
Opioids

- Endogenous opioids are decreased in the sensory pathways in the brains of RLS patients.
- Typically not used 1st line
- Option if failed other drugs
- Useful in combination with alpha-2-delta (α2δ) ligands, DA’s or as monotherapy
Opioids – Cont.

• Methadone has shown good efficacy and no augmentation. Start at 5-10mg, max. dose 40mg
• Codeine start at 15-30mg/day, max 120mg/day
• Hydrocodone start at 5-10mg/day, max 30mg/day
Iron

- RLS experts recommend treatment if ferritin is <75ng/ml.
- Ferrous sulfate 325mg
- Take with vitamin C for absorption
- Iron should be monitored to prevent overload.
- Consider IV iron if unable to tolerate orally
Pediatric treatment of RLS

- No medication have been approved by the FDA for pediatric RLS.
- Replenish iron stores if low (< 50ng/ml)
- Clonidine at HS (dosed at 0.2mg – 0.4mg) can be useful if severe sleep-onset problems in school-aged children with RLS.
- Gabapentin can improve sleep quality and reduce sensory symptoms of RLS.
Augmentation

- First described in 1996 by Allen and Early.
- A severe and potentially disabling exacerbation of RLS, sometimes leading to continuous persistence of symptoms, even for 24 hours a day.
- Worsening of RLS after starting a medication to treat RLS
- Is a medication effect and dose dependent
- Progressively earlier onset of symptoms
Augmentation – cont.

- Begin after a shorter period of rest.
- Spread of symptoms to upper limbs and trunk
- More intense
- Increasing requirement of drug
- Symptoms become refractory to high doses
Augmentation – Cont.

• In one study, only 25% of the sample using DA drugs had good response without augmentation.
• 50% of patients treated with pramipexole (Mirapex) are expected to experience augmentation after 10 years of use.
• Low ferritin (<20ng/ml) increased the risk of augmentation
Managing Augmentation

• No formal guidelines available.
• If mild, no change may be necessary.
• Can try dosing earlier
• Split the total dose
• Switch to extended-release form
• Reducing the current dose
Managing Augmentation – Cont.

• If persistent, then taper, discontinue and change to another class.

• Methadone at 10-40mg in divided doses can be helpful in severe cases and used during weaning of DA.

• Symptoms usually resolve in weeks to months after stopping the DA.

• Always check ferritin
Managing Augmentation – cont.

- Changing from one DA to another is controversial.
- Restarting after a drug free holiday is not recommended as rapid augmentation usually occurs.
Rebound and Tolerance

- **Rebound** typically manifests as increase in symptoms late at night or early in AM
- Related to short half-life in DA’s
- Rebound needs to be distinguished from augmentation.
- **Tolerance**, or loss of efficacy, occurs commonly with all drugs used long-term.
- Need to increase dose for better control.
RLS Therapeutic Strategies

Check serum ferritin
If <75 ng/ml, treat with oral iron

Non-pharmacological measures
Good sleep hygiene, exercise
Eliminate medications that worsen RLS
CBT, vibrational device

Moderate Daily RLS

As monotherapy:
Alpha-2-delta ligand (gabapentin, gabapentin enacarbil, pregabalin)
DA (ropinirole, pramipexole, rotigotine)

Severe RLS

As monotherapy:
Alpha-2-delta ligand (gabapentin, gabapentin enacarbil, pregabalin)
DA (ropinirole, pramipexole, rotigotine)

Use combination therapy
Alpha-2-delta ligand, DA or opioid

Severe RLS

Medications taken as needed
Codeine, oxycodone, levodopa

Intermittent RLS

Augmentation with DA
Check serum ferritin, if low oral iron.
Reduce dose or change to another class of medication:
Alpha-2-delta ligand (gabapentin, gabapentin enacarbil, pregabalin) or an opioid.

ICD with DA
Reduce dose or discontinue DA.
Change to alpha-2-delta ligand (gabapentin, gabapentin enacarbil, pregabalin) or an opioid.

Refractory RLS

Methadone as monotherapy or as add on therapy

IV iron (even with low normal ferritin)
IT morphine

Wijemanne S. Sleep Med. 2015
Summary

• RLS is prevalent and treatable
• Remove precipitating factors
• Check ferritin
• Non pharmacological treatments
• Augmentation is a major therapy-related complication
• Non-DA drugs should be tried first
Summary – Cont.

• Consider calcium channel alpha-2-delta (α2δ) ligands (gabapentin, gabapentin enacarbil, pregabalin) as first line.

• Consider a low dose DA such as ropinirole or pramipexole and monitor.

• Opiods used second line or as combination therapy
Thank you