RESTLESS LEGS SYNDROME AND PERIPHERAL MOVEMENT DISORDERS

Cynthia L. Comella, MD
Rush University Medical Center
Chicago, IL
RESTLESS LEGS

A Clinical Study of a Hitherto Overlooked Disease in the Legs Characterized by Peculiar Paresthesia („Anxietas Tibiarum“), Pain and Weakness and Occurring in two Main Forms, Asthenia Crurum Paraesthetica and Asthenia Crurum Dolorosa. A Short Review of Paresthesias in General

by

KARL-AXEL EKBOM

STOCKHOLM 1945
Willis-Ekborn Disease (WED)

Thomas Willis
1621-1675

Karl Axel Ekbom
1907-1977
RLS/WED: 5 Essential Diagnostic Criteria

Essential criteria for restless legs syndrome

- An urge to move the legs usually/not always accompanied by or caused by uncomfortable and unpleasant sensations in the legs
- The urge to move or the unpleasant sensations:
  - begin or worsen during periods of rest or inactivity
  - are partially or totally relieved by movement,
  - are worse in the evening or night than during the day
- Not solely accounted for as symptoms due to another condition

Allen et al on behalf of RLS Study Group. Sleep Med 2014
Supportive of an RLS/WED Diagnosis

- Periodic limb movements (during wakefulness or sleep)
- Response to dopaminergic therapy
- A positive family history of restless legs syndrome in first degree relatives
- Lack of expected daytime sleepiness

Allen et al on behalf of RLS Study Group. Sleep Med 2014
RLS mimics: meeting 4 diagnostic criteria

- Leg cramps
- Leg edema
- Positional discomfort
- Peripheral neuropathy

- RLS diagnostic index: includes supportive criteria
  - Sens 93%, Spec 99%, PPV 99%

- Cambridge-Hopkins Diagnostic Questionnaire: includes probes for mimics of RLS
  - Sens 88%, Spec 94%, PPV 87%

RLS/WED: Specifiers

- **Intermittent RLS**
  - Occur < 2 times per week for past year

- **Chronic persistent RLS**
  - Occur on average at least twice weekly for the past 1 year

- **Refractory RLS**
  - No benefit monotherapy (adverse effects, augmentation, loss of benefit)

Allen et al on behalf of RLS Study Group. Sleep Med 2014
Restless Legs Syndrome

- “Can’t get comfortable”
- “Can’t fall asleep”
- Wake up and feel “antsy”
- “Crampy, itchy calves”
- “Tingling in legs”
- “Dread going to bed at night”
- Avoid long car rides or airplanes

Periodic Limb Movements in Sleep

Patient #4
Periodic Movements In Sleep - Typically Are Leg Flexions

Patient #3
Resting Myoclonus While Awake That Is Clustered

© 1991 Movement Disorder Society, Inc.
Prevalence of RLS in Primary Care Centers

- Primary care centers in US and Europe
- Validated RLS questionnaire
- 16,202 people > 18 years
- 7.2% endorse RLS symptoms
  - 5.0% with symptoms once per week
  - 2.7% with moderate to severe RLS
- Higher in women than men

REST general population study
Risk of RLS associated with other disorders

- Increased risk of RLS:
  - Cardiovascular disease
  - Hypertension
  - Diabetes
  - Depression

- Whether RLS increases risk of cardiovascular disease is controversial
  - Women with RLS: HR 1.43 (95% CI 1.02-2.00)
    - Longer duration associated with increased risk

Trenkwalder et al. Lancet Neurol 2018
Li et al Neurology 2018
RLS: A Heterogeneous Disorder

- Phenotype similar but varying underlying pathophysiology
  - Genetics
  - Reduced central iron
  - Abnormal brain dopaminergic activity
    - Receptor mediated?
RLS: Complex genetic disorder

- **Genome-wide Association studies**
  - 6 single nucleotide polymorphisms account for a small percent (<10%) of genetic susceptibility
    - MEIS1 (2p) (strongest most consistent)
    - BTBD9 (6p)
    - MAP2K5/LBXCOR1 (15q)
    - PTPRD
    - TOX3
  - Meta-analysis of studies: 22-23 variants, 3 new variants found within the past year

- **Whole exome sequencing and whole genome sequencing**

Winkelmann et al. Sleep Med 2017
Scharmair et al. Lancet 2017
Didriksen et al, Comm Biol 2020
Iron and RLS

- Systemic iron deficiency associated with RLS
  - Anemia
  - Pregnancy
  - Blood donors

- Prevalence of RLS is 32% in anemia (6X greater than normal)

- Severity of RLS correlates with degree of ferritin reduction

- Replacement of iron improves symptoms of RLS

Earley et al. Sleep Med 2014
Allen et al Am J Hematol 2013
CSF Iron and Ferritin

RLS (▲) compared to controls (■)

RLS also with increased CSF transferrin c/w central iron deficiency

Iron studies in RLS with and without anemia

- 196 RLS patients without anemia (IDNA), 26 anemia (IDA), and 63 controls were included.
  - serum ferritin, iron, transferrin, and total iron-binding capacity
- 42.3% of RLS patients **without anemia** had iron deficiency.
  - Women more susceptible for IDNA
    - relative risk of 5.51 ($p < 0.0001$)
    - younger age at RLS onset compared to women with RLS without iron deficiency anemia ($P < 0.01$).
- Non anemic RLS with tendency to higher risk of severe/very severe daytime sleepiness during the day
- Non-anemic RLS patients had longer duration of RLS younger age at onset

Xiao-Yung Zhu et al. Front Neurol 2020
Dopamine and RLS

- Dramatic response to dopaminergic agents
  - Levodopa and dopamine agonists
  - Low doses
- Exacerbated by centrally active dopamine receptor antagonists

Allen R. Sleep Med 2004;5:385-391
Earley et al. Sleep Med 2014
RLS and PD: DAT scan and MRI R2* imaging

Meta-analysis:
Decreased serum ferritin likely underlies increase seen in PD

Linke et al. Mov Disord 2004;19:1158-62
Functional MR studies: Brain networks in RLS

- **RLS vs Control:**
  - Networks with *higher* intra-network connectivity:
    - salience, executive, cerebellar and lower cerebello-frontal cortex
  - Networks with *lower* connectivity:
    - cerebello-parietal connectivity in untreated patients, in regions associated with attention, response inhibitory control, and processing of sensory information

- **Dopaminergic treated RLS:**
  - Intact cerebello-parietal communication and increased thalamic connectivity to the prefrontal regions thalamus.

  Tuovinen et al. Eur J Neurol 2021
Summary

Pathophysiology of RLS: ?

- MRI studies showed no structural brain lesions and confirmed a central iron deficiency.
- Neurotransmission abnormalities: dopaminergic and opiate systems.
- Structural and functional studies showed an involvement of the thalamus, sensorimotor cortical areas, and cerebellum in RLS.
- Abnormal network of connectivity.

Provini and Chiari. Sleep Med Clin 2015
Tuovinen et al. Eur J Neurol 2021
Gap: lack of animal models

"If it only happens when you rub your tummy, it's not Restless Leg Syndrome."
The IRLSSG task force generated consensus guide-lines for assessing RLS-like behavior in rodent models.

Surrogate behavioral measures were recommended.

- Activity-based techniques
- Sold standard vPSG approaches to assess sleep disturbances and PLMS
- Specific pharmacological interventions or induction of iron deficiency to rescue or worsen the RLS-like behavior in rodents.

Salminen et al. Move Disord 2020
Therapeutic approach to RLS
## Placebo Effects in RLS

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response rate</strong></td>
<td>40% (CI 32-48)</td>
<td>68% (CI 63-73)</td>
</tr>
<tr>
<td><strong>IRLS</strong></td>
<td>-1.48 (CI -1.8 to -1.1)</td>
<td>-2.62 (CI -3.0 to -2.3)</td>
</tr>
<tr>
<td>(Pooled random-effects estimator)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PSG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Pooled random-effects estimator)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PLMS</strong></td>
<td>-0.11 (CI -0.2 to -0.03)</td>
<td>-0.88 (CI -1.1 to -0.71)</td>
</tr>
</tbody>
</table>

Fulda S, Wetter TC. Brain 2008;131:902-917
Placebo response: change from baseline in restless legs in RCT studies

The placebo response greater:
- trials with longer duration
- evaluating pharmacologic interventions
- idiopathic RLS
- industry-funded

Maria A. Silva et al. Neurology 2017;88:2216-2224
Nocebo effects in RLS

Maria A. Silva et al. Neurology 2017;88:2216-2224
Treatment of RLS: non pharmacologic

- Correction of iron deficiency
  - Serum ferritin < 75 µg/l; transferin saturation < 20-75%
  - Assess for cause of iron deficiency

- Iron replacement
  - Strongest evidence ferric carboxymaltose infusion 500 mg X2
    - Low incidence of anaphylaxis
  - Oral ferrous gluconate, ferrous sucrose
  - Follow ferritin level to avoid iron overload

- Assess medications that trigger or enhance symptoms
  - Serotonergic antidepressants, DRBA, antihistamines

Hogl and Comella, Mov Disordr 2015
Avini et al, Eur J Intern Med, 2019
Allen et al. Sleep Med 2018
Garcia-Malo et al. Sleep Med 2020
Treatment of RLS
Non-pharmacologic

- Exercise
- Cognitive behavioral therapies
- Massage, compression stockings
- Acupuncture
- Counter-stimulation
- Vibratory devices (Relaxis®)
  - FDA approved (2014) device for RLS

Comella C. Neurotherapeutics 2014
When do you use drugs to treat RLS

Symptoms impair quality of life, daytime functioning or sleep

Winkelman et al. Neurology 2016
Practice guideline summary: Treatment of restless legs syndrome in adults


ABSTRACT

Objective: To make evidence-based recommendations regarding restless legs syndrome (RLS) management in adults.

Methods: Articles were classified per the 2004 American Academy of Neurology evidence rating scheme. Recommendations were tied to evidence strength.

Results and recommendations: In moderate to severe primary RLS, clinicians should consider prescribing medication to reduce RLS symptoms. Strong evidence supports pramipexole, rotigotine, cabergoline, and gabapentin enacarbil use (Level A); moderate evidence supports ropinirole, pregabalin, and IV ferric carboxymaltose use (Level B). Clinicians may consider prescribing levodopa (Level C). Few head-to-head comparisons exist to suggest agents preferentially. Cabergoline is rarely used (cardiac valvulopathy risks). Augmentation risks with dopaminergic agents should be considered. When treating periodic limb movements of sleep, clinicians should consider prescribing ropinirole (Level A) or pramipexole, rotigotine, cabergoline, or pregabalin (Level B). For subjective sleep measures, clinicians should consider prescribing cabergoline or gabapentin enacarbil (Level A), or ropinirole, pramipexole, rotigotine, or pregabalin (Level B). For patients failing other treatments for RLS symptoms, clinicians may consider prescribing prolonged-release oxycodone/naloxone where available (Level C). In patients with RLS with ferritin ≤75 μg/L, clinicians should consider prescribing ferrous sulfate with vitamin C (Level B). When nonpharmacologic approaches are desired, clinicians should consider prescribing pneumatic compression (Level B) and may consider prescribing near-infrared spectroscopy or transcranial magnetic stimulation (Level C). Clinicians may consider prescribing vibrotherapy with secondary RLS, clinicians should consider prescribing vitamin C and E supplementation (Level B) and may consider prescribing ropinirole, levodopa, or exercise (Level C). Neurology® 2016;87:2585–2593
Evidence based practice guidelines

- **Strong evidence**
  - pramipexole, rotigotine, cabergoline (augmentation)
  - gabapentin encarbil
  - Ropinirole
  - Oxycodone/nalaxone

- **Moderate evidence**
  - Pregabalin, IV ferric carboxymaltose (regardless of ferritin level), oral ferrous sulfate with vitamin C bid with low ferritin, pneumatic compression, oxycodone

- **Insufficient evidence**
  - Gabapentin, clonazepam, bupropion, clinidine, botulinum toxin, valproic acid

- **Comparative studies of treatments not conclusive**

  Winkelman et al. Move Disord 2018
  Winkelman et al. Neurology 2016
Carbidopa/Levodopa

- Carbidopa/levodopa
  - Very effective
  - 50-600 mg levodopa given at bedtime
  - Short term side effects minimal
    - nausea, vivid dreams

- Chronic use associated with augmentation in 50-84% patients

Dopamine agonists for RLS

- Improved RLS severity
- Improved PLMS
- FDA approved
  - Ropinirole
  - Pramipexole
  - Rotigotine patch

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo</th>
<th>Ropinirole 0.125</th>
<th>Ropinirole 0.25</th>
<th>Ropinirole 0.50</th>
<th>Ropinirole 0.75</th>
<th>Ropinirole 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted Mean Change From Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total IRLS rating week 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=186</td>
<td>n=190</td>
<td>n=144</td>
<td>n=135</td>
<td>n=135</td>
<td>n=131</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rotigotine patch

- Severity at baseline
- Severity during night
- Severity during day at rest

- placebo
- 1mg
- 2mg
- 3mg

Direct Dopaminergic Agonists

Adverse Effects

- Nausea, dizziness, somnolence, headache
- Orthostatic hypotension
- Rebound (occurs during the night)
- Augmentation (10-80%)
- Impulse control disorders (5-17%)

Augmentation: Limiting Side Effect of Levodopa Therapy

- RLS symptoms occur 2h earlier
- Two of the following
  - Increased overall intensity
  - Latency at rest shorter
  - Symptoms in previously unaffected body area
  - Duration of treatment benefit reduced
  - PLM first occur or worsen

Garcia-Borreguero et al. Sleep Med 2013
Garcia-Borreguero et al. Sleep Med 2015
Therapeutic response during treatment with dopamine agonists.

Diego Garcia-Borreguero, and Irene Cano-Pumarega BMJ 2017
Shifting treatment paradigm for RLS

Alpha-2 Delta Calcium Channel Ligands

Dopamine agonists

Romero-Peralta et al, Chest 2020
De Biase et al. Expert Opin Pharmacother 2019
Wanner et al. Adv Pharmacol 2019
Alpha-2 Delta Calcium Channel Ligands

- Gabapentin
- Gabapentin encarbil (Horizant®)
- Pregabalin (Lyrica®)
Gabapentin Enacarbil

- Prodrug of gabapentin
- Better, more consistent absorption
- 3 double blind, placebo controlled studies
- GBE 600-2400mg

- Reduced IRLS
  - GBE: -13.6
  - Placebo: -9.3

- Responders
  - GBE: 70.2%
  - Placebo: 42.2%

- No difference in effect among doses
- AE’s somnolence, dizziness increased with increasing doses

VanMeter. CNS Drugs 2012
Pregabalin vs Pramipexole in RLS

- 719 RLS patients
- 52 week study
  - Placebo vs Pregab vs Prami (12 weeks)
  - Pregab vs Prami (40 weeks)
- Pregab with greater improvement
- Discontinuation for AE
  - Pregabalin 27.5%
  - Prami 0.5 mg 24%
  - Prami 0.25 mg 18.5%
- Augmentation at 52 weeks
  - 2.1% pregabalin
  - 5.3% prami 0.25mg
  - 7.7% prami 0.5mg

Garcia-Borreguero et al. Sleep 2014
Other Treatments for RLS

- Opioids and opiates (most with renal clearance)
  - Codeine
  - Tramadol
  - Oxycodone
  - Methadone (5-15 mg) in refractory RLS or augmentation

- Benzodiazepine agonists
  - Temazepam
  - Eszopiclone
  - Clonazepam

Winkelmann et al. Mov Disord 2018
Prolonged Release Oxycodone-Naloxone For Severe RLS

- 306 severe RLS failing prior treatment
  - Placebo vs oxy (22 mg)-nal (11 mg) for 12 weeks (Fig A)
  - OLE 40 weeks (Fig B)
- DB Drug AE’s causing withdrawal
  - PL 7%; Oxy-nal 15%
- OLE dose oxy 18 mg (10.5)
  - 20% dropout: most AE
- Efficacy similar to that seen with DA
- No reports of augmentation

Trenkwalder et al. Lancet Neurol 2013
The Appropriate Use of Opioids in the Treatment of Refractory Restless Legs Syndrome

Michael H. Silber, MBChB; Philip M. Becker, MD; Mark J. Buchfuhler, MD; Christopher J. Earley, MBChB, PhD; William G. Ondo, MD; Arthur S. Walters, MD; and John W. Winkelmann, MD, PhD; for the Scientific and Medical Advisory Board, Restless Legs Syndrome Foundation

Abstract

Restless legs syndrome (RLS) is a distinct disorder, differing from chronic pain in many ways. Refractory RLS is characterized by unresponsiveness to dopamine agonists or alpha-2-delta ligands due to inadequate efficacy, augmentation, or adverse effects. This may result in severely impaired quality of life, profound insomnia, and suicidal depression. Opioid therapy is a mainsay in the management of these patients. This article summarizes the basic science and clinical evidence in support of their use, including the positive result of a large controlled multicenter study of 306 subjects, and outlines an approach to their use in clinical practice. Treatable explanations for RLS refractoriness, such as low iron stores, and other therapeutic options, such as combination therapy, should be considered before prescribing opioids. The agents most commonly used are oxycodone and methadone, but tramadol, codeine, morphine, and hydrocodone can also be considered. Controlled-release medication should be used for evening dosing and short-acting drugs, if needed, during the day. Effective doses are considerably lower than used for chronic pain (oxycodone 10-30 mg daily; methadone 5-20 mg daily) and the risk of opioid use disorder is relatively low. However, sensible precautions should be undertaken, including assessing opioid risk with standard questionnaires, using an opioid contract, using urine drug screens, consulting state prescription drug monitoring programs, and frequent reevaluation of effectiveness and side effects. Opioid use in selected patients with refractory RLS may be life-transforming with favorable risk-benefit ratio.
Use of opioids in RLS

- Consider alternative therapies first
  - Iron if iron deficient
  - Change meds that can worsen RLS
  - Combination of non-opioid medications

- Indications
  - RLS not adequately controlled with first line agents
  - Treatment resistant augmentation

- Discuss risk of addiction with patient
- Monitor use
- Low doses
- QT interval prolongation especially methadone

Worsening RLS and augmentation

Mackie and Winkelman. CNS Drugs 2015
Garcia- Borreguero et al. Sleep Med 2016
RLS: Take home points

- Subjective diagnosis
- Check ferritin level, transferrin
- Treat when symptoms interfere with QOL
- Use non-dopaminergic drugs first
- If DA, use at lowest dose and with longest half life
- If augmentation, reduce and d/c DA, use other agents including opioids if necessary
Peripheral movement disorders

- Hemifacial spasm
- Painful Legs, Moving Toes
- Belly Dancer’s dyskinesia
- Jumpy stump
- Focal myoclonus due to peripheral nerve injury
- Complex regional pain syndrome
- ? Dystonia due to peripheral injury
Hemifacial spasm: effect botulinum toxin
Hemifacial spasm

- Unilateral
- Upper face first
  - Spreads to lower face, platysma
- Brief repetitive contractions
  - Tonic and clonic contractions
- Sudden eye closure with elevation eyebrow
- Persists in sleep
- Clicking in ear (stapedius)
- Chronic (remissions < 10%)
- 2:1 female
- Asians > Caucasians

- Aberrant blood vessel with local demyelination of facial nerve (PICA, AICA, VA)
- Ephaptic trasmission
Assessing severity

- Validation of the new hemifacial spasm (HFS) questionnaire "HFS score"
  - clinical (HFS clinical)
  - health-related quality of life (HRQOL)
- Good internal consistency
- Intra-rater reliability
- Inter-rater reliability
- Face validity

Wabbels b, Yaqubi A. J Neural Transm 2021
Vascular decompression for HFS (Janetta procedure)

- Posterior fossa microvascular decompression
  - PICA (most frequent)
  - AICA
  - Vertebral basilar

- Minimal evidence based reports
  - Up to 90% of patient with improvement,

- Adverse effects
  - Hearing loss in approximately 14%
  - Permanent facial nerve palsy

Kaufmann and Price J Neurosurg 2019
Bartindale et al. Otolaryngol Head Neck Surg 2018
Lee et al World Neurosurg 2019