Idiopathic restless legs syndrome: clinical definition, pathophysiology and treatment

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I have no conflicts of interest to disclose

Definition of restless leg syndrome/Willis-Ekbom disease

Allen RP et al; Sleep Med 2014 15:860-873

RLS/WED: a neurological sensorimotor disease disturbing sleep and quality of life with variable expression due to genetic, environmental and medical factors.

The symptoms vary considerably in frequency from <1/month or year to daily, and severity from mildly annoying to disabling.

Symptoms may also remit for various periods of time.

RLS/WED is diagnosed by ascertaining symptom patterns that meet the essential criteria

Five essential criteria (all must be met)

Allen RP et al; Sleep Med 2014 15:860-873

1. Urge to move the legs usually–but not always–accompanied or felt to be caused by uncomfortable sensations in the legs

2. Begin or worsens with rest or inactivity

3. Worse in the evening or at night than during the day

4. Improves partially or completely with movement

5. The clinical picture is not accounted for as symptoms primary to another medical or a behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping)
Specifiers for clinical course

**Chronic-persistent**: symptoms occur on average at least twice weekly over the past year (when untreated)

**Intermittent**: symptoms occur on average < twice weekly over the past year, with at least five lifetime events

**RLS in children**
The description of these symptoms should be in the child’s own words.

Supportive clinical features

- Positive response to dopaminergic treatment
- Periodic limb movements (during sleep or resting wakefulness)
- Positive family history of RLS
- Lack of profound daytime sleepiness

Differential diagnosis of RLS

- **Restlessness**
  - Akathisia (inner body restlessness without a desire to move, no worsening at night)
  - Anxiety
  - Rhythmic foot tapping

- **Unpleasant sensations in the legs**
  - Polineuropathy, radiculopathy
  - Leg cramps
  - Venous stasis
  - Skin problems
  - Painful legs and moving toes
  - Leg edema
  - Positional discomfort
Two main phenotypes of RLS

Early onset primary or idiopathic RLS
- Peak onset 20-40 years
- Frequent family history
- Slow evolution
- Normal (>50ng/ml) ferritin, normal clinical examination

Late onset
- Peak onset after 40 years
- Less frequent family history
- More rapid disease evolution
- Frequent association with other diseases ("secondary RLS")

Inherited and acquired factors in RLS

RLS in the cognitively impaired: Special criteria

Dopaminergic responsiveness
Patient's past history as reported by a family member, caregiver or friend is suggestive of RLS.
A first-degree biological relative (sibling, child, or parent) has RLS.
Observed periodic limb movements while awake or during sleep.
Periodic limb movements of sleep recorded by polysomnography or actigraphy.
Significant sleep-onset problems.
Better quality sleep in the day than at night.
The use of restraints at night (for institutionalized patients).
Low serum ferritin levels.
End-stage renal disease.
Diabetes.
Clinical, electromyographic, or nerve-conduction evidence of peripheral neuropathy or radiculopathy.

From Ahls et al. 2002
Conditions associated with RLS

Neurological
- Parkinson’s disease
- SCA 3, MSA
- Charcot-Marie-Tooth II
- Friedreich ataxia
- Multiple sclerosis
- Myelitis, siringomyelia
- Post-polio syndrome
- Radiculopathies
- Polyneuropathies
- ADHD (Attention deficit Hyperactivity Disorder in children)
- Poliomyelitis
- Stroke

Medical
- Uremia
- Pregnancy
- Iron deficiency
- B12, Folate, Mg deficiencies
- Diabetes
- Fibromyalgia
- Rheumatoid arthritis
- Gastrectomy
- Hypothyroidism
- Sjögren’s syndrome
- Amyloidosis
- COPD, Hepatitis C

Pathophysiology of RLS

Strong genetic background
- Several susceptibility loci, with single nucleotide polymorphisms (SNPs) on chromosomes: 2p14 (MEIS1), 6p21.2 (BTBD9), 15q23 (MAP2K5/SCOR1), 9p24.1–p23 (PTPRD), and 16q12.1
- No causal sequence variants identified in familial primary RLS

Central iron dysfunction
- Tyrosin-hydroxylase - an essential enzyme for the conversion of Levodopa in dopamine needs Fe as cofactor
- Iron deprivation in young rats induces changes in dopaminergic function
- Low CSF ferritin in RLS: deficit in brain iron acquisition

Pathophysiology of RLS - 2

CSF/serum ferritin

CSF ferritin / CSF transferrin

RLS Controls

Low CSF ferritin in RLS: deficit in brain iron acquisition
Iron-deficient anemia (IDA) → more RLS

Increased RLS frequency in blood donors (with multiple blood donations)  (Silber et al 2003; Allen et al 2004)

31% of 251 patients in a community population first diagnosed of IDA (Hb<14 in m o 12 in f + serum ferritin <20 mcg/mL) have clinically significant RLS  (Allen et al, Am J Hematol 2013)

4-5 times higher than in the general population (7%)

For RLS, serum ferritin levels <50 mcg/mL are relevant

Pathophysiology of RLS - 3

Altered dopaminergic activity

Dopaminergic agents improve RLS

Dopamine antagonists (neuroleptics) trigger or aggravate RLS

- Diencephalic-spinal A11 dopamine neurons
- Major source of dopamine to the spinal cord
- Dopamine modulates sensory, motor and autonomic function in the spinal cord
- Experimental lesions in A11 resemble RLS
- Normal A11 pathology in RLS. PD?

Treatment of RLS

Guided by the severity and frequency of the symptoms

Measure ferritin levels. Treat with oral iron if <50 ng/mL

Occasional, non-severe: no treatment or clonazepam, L-dopa

Several types of drugs. If dopaminergic: the lowest dose possible

<table>
<thead>
<tr>
<th>3 options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopaminergic</strong></td>
</tr>
<tr>
<td>Pramipexole &lt; 0.36 mg</td>
</tr>
<tr>
<td>Ropinirole &lt; 4 mg</td>
</tr>
<tr>
<td>Rotigotine &lt; 1.4</td>
</tr>
<tr>
<td>Ropinirole Prof Rel &lt; 4 mg</td>
</tr>
<tr>
<td>Pramipexol Prof Rel</td>
</tr>
<tr>
<td><strong>Antiepileptics</strong></td>
</tr>
<tr>
<td>Gabapentin 800-2400mg</td>
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<tr>
<td>Pregabalin 75-300mg</td>
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<tr>
<td><strong>Opioids</strong></td>
</tr>
<tr>
<td>Oxicodone/naloxone Slow Release 10-40mg</td>
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<tr>
<td>Tramadol 50-150 mg</td>
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<tr>
<td>Others</td>
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</tbody>
</table>
Problems: Augmentation

A complication of long-term dopaminergic treatment in RLS

Definition: An increase of RLS symptoms under dopaminergic therapy

- Earlier onset of symptoms .................................................. 100%
- Symptom severity increased beyond that seen at baseline
- Shorter latency to onset of symptoms when at rest .............. 33%
- Expansion of symptoms to the upper limbs and trunk .......... 7-10%
- Overall increase in the intensity of symptoms ..................... 96%
- Shorter effect of the medication

Tolerance and augmentation share the last two criteria.

Key factors in augmentation

Four crucial points:

- Half-life of the drug
- Dosages used: the lower the better
- Duration of treatment
- Presence of low serum ferritin levels

Not reported with non-dopaminergic drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose range</th>
<th>Augmentation</th>
<th>Period of time studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Dopa</td>
<td>100-200</td>
<td>60-100%</td>
<td>30 weeks</td>
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<tr>
<td>Pramipexole</td>
<td>0.25-0.75</td>
<td>5-9%</td>
<td>1 y</td>
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<tr>
<td>Ropinirole</td>
<td>0.5-4</td>
<td>4%</td>
<td>1 y</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>0.5-4</td>
<td>1.5% 6 m</td>
<td>5 y</td>
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<td></td>
<td></td>
<td>3% 12 m</td>
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<td>5% (1-3 mg 5 y)</td>
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<td></td>
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<td>8% (4 mg 5 y)</td>
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Restless Abdomen

A phenotypic variant of restless legs syndrome

<table>
<thead>
<tr>
<th>Age at presentation, y</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
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<tbody>
<tr>
<td>30</td>
<td>N</td>
<td>U</td>
<td>F</td>
</tr>
<tr>
<td>Drug</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom duration, m</td>
<td>5A</td>
<td>5B</td>
<td>F</td>
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<tr>
<td>Severe effects</td>
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<tr>
<td>Dysphagia</td>
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<td>Abnormal sleep duration</td>
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<tr>
<td>Sleep efficiency</td>
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<td>Sleep apnea</td>
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<td>Sleepiness</td>
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<td>Epidemiology</td>
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<td>Diagnosis</td>
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<tr>
<td>Response to dopaminergic therapy</td>
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<tr>
<td>Pharmacologic treatments of sleep</td>
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</tbody>
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Tentative diagnosis of restless legs syndrome

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Height</td>
<td>180cm</td>
<td>175cm</td>
</tr>
<tr>
<td>Weight</td>
<td>85kg</td>
<td>70kg</td>
</tr>
<tr>
<td>BMI</td>
<td>27</td>
<td>25</td>
</tr>
</tbody>
</table>

*Please consider all patients as having restless legs syndrome.*

PERIODIC LIMB MOVEMENTS DURING SLEEP (PLMS)

PLMS are very frequent in RLS
They can also occur independently of RLS
PD, MSA, narcolepsy, RBD,
Drugs such as antidepressants can induce or worsen PLMS

May be very prominent, fragment sleep and disturb the bed partner
Patient may not complain
Clinical relevance out of RLS is uncertain