

Sleep Neurology: Restless Legs Syndrome

Importance, Identification and General Management

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Disclosures

- Compensated to give current lecture
- Some therapy options “off label”
- Nothing else

- Awareness
- Recognition
 - Signs and Symptoms
 - Diagnosis
- Review of treatment

Overview

Overview of Restless Legs Syndrome

Definition and Basic Description

Per ICSD – 3 – TR:

“Restless legs syndrome (RLS) is a sensorimotor disorder characterized by a complaint of strong, nearly irresistible urge to move the limbs”

Also known As

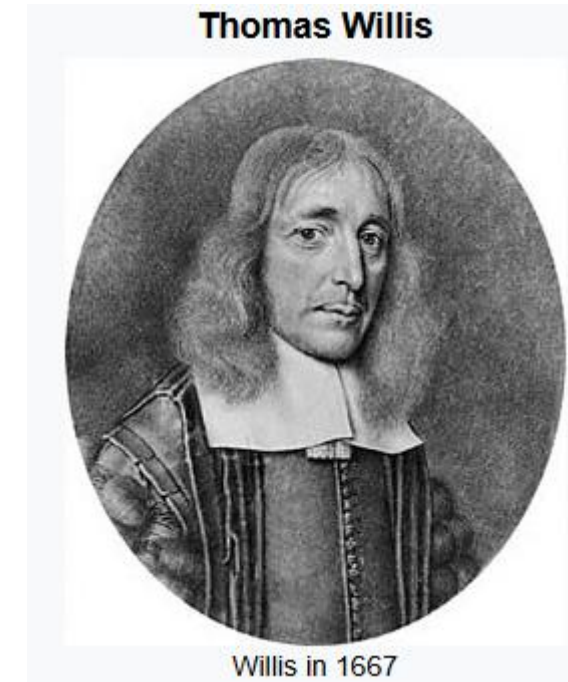
Willis-Ekbom disease

Pathophysiology

Brain iron deficiency, central nervous system dopamine regulation and genetics appear primary factors

Impact on Quality of Life

Left untreated, RLS can reduce quality life due to both discomfort and sleep loss



Prevalence and Demographics

Global Prevalence of RLS

RLS affects about 5-10% in European and North American population based studies

Although “clinically significant” closer to 2-3%

Asian countries studies suggest lower prevalence

Age Group Susceptibility

Increases with age up to 60-70 years

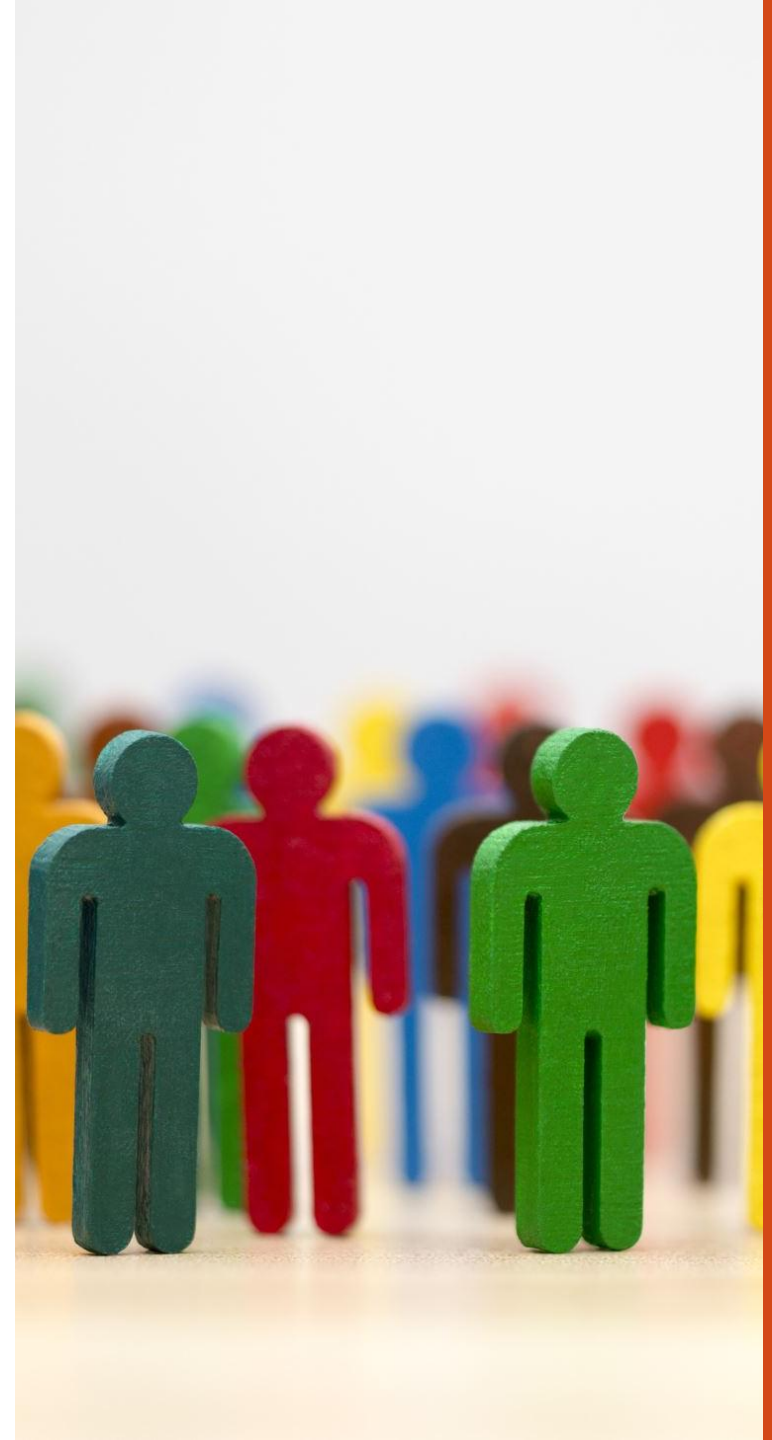
Pediatric prevalence 2-4% in UK/US and Turkish studies

Moderate to severe 0.5-1% (teens more than younger children)

Gender Differences

RLS tends to be more prevalent in women compared to men, indicating gender-related susceptibility.

Except in pediatrics



Risk Factors

- Family history
 - 2-6x greater for 1st degree relatives
 - Early-onset
 - Suggestion of autosomal dominant but likely more complex gene-environment pattern
 - Multiple gene loci associated with but no causative
- Iron deficiency/ferritin
- Pregnancy
 - Peak in 3rd trimester
 - Predictors: family history RLS, RLS in prior pregnancy and possibly low hemoglobin, low folate, high estradiol
- Chronic Renal Failure
 - 2-5x higher than general population
 - Often improve within 1 month of kidney transplant
- Other medical co-morbidities
 - Multiple Sclerosis (chronic progressive sub-type with spinal cord involvement)
 - Parkinson's Disease (often after onset of motor symptoms)
 - Prolonged immobility
- Medications
 - Sedating antihistamines, antidepressants

Signs and Symptoms of Restless Legs

Common Sensations

Urge to move often but not always with other uncomfortable sensations

Often difficult to describe but commonly described are “restless”, “uncomfortable”, “twitchy”, “need to stretch”, “urge to move”

Can be painful but uncommonly described as “numb” or “cold”

Can be superficial but often deep

Common Characteristics

Symmetric or asymmetric but rarely purely unilateral and not limited to joints

While legs (calves) most frequently/severely effected, can also be described in arms

****Urge to Move****

Typical Sensations and Discomfort

Diagnostic Criteria per ICSD-3-TR

1) Urge to move the legs

MUST: begin/worsen with rest/inactivity, be partially/totally relieved with movement and occur exclusively or predominately in evening or night

2) Not accounted for by mimic condition

Leg cramps, positional discomfort, myalgia, venous stasis, leg edema, arthritis, habitual foot tapping

3) Cause concern, distress, sleep disturbance, or impairment in other important areas of function

Mental, physical, social, occupational, educational, behavioral

40% individuals without RLS may report need to move at rest while those meeting all criteria improves specificity to only about 70%, but differentiating from cramps and positional discomfort improves to 94%



Impact on Sleep and Daily Activities

Sleep Disruption

Most troubling symptom and often primary reason to seek medical care

Sleep interruptions/disturbances resulting in poor sleep quality

Daytime Fatigue

Reports of fatigue and sleepiness, although typically unremarkable Epworth Sleepiness Scale scores

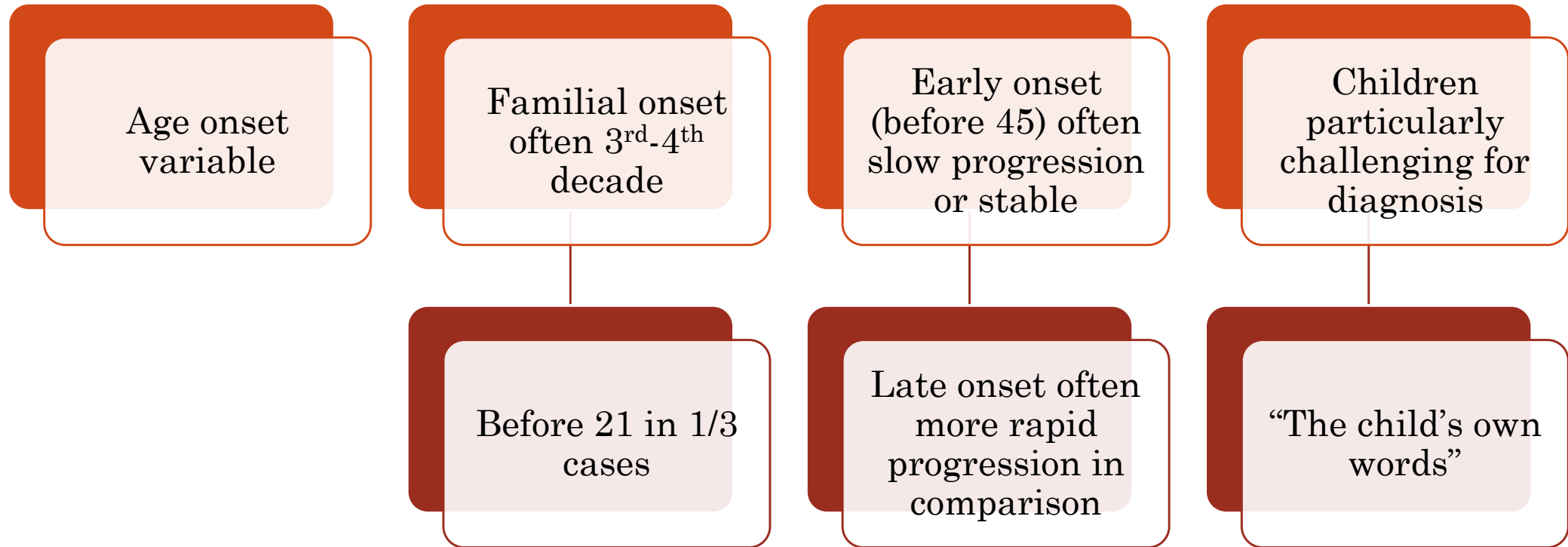
PLMS

Supportive of diagnosis, can occur in sleep or quiet rest (transition between waking/sleep)

Increased prevalence of mood and Anxiety disorders as well as ADHD

About $\frac{1}{4}$ with RLS have ADHD, and 12-35% of those with ADHD meet criteria for RLS

Clinical Course



Management and Treatment Options

Workup and Investigations



Clinical diagnosis



Blood work

Ferritin

CBC, B12, folate

Creatinine,
glucose/HgbA1c



Sleep Study

Optional

International RLS Study Group Rating Scale

- 10 item questionnaire
- Rates severity and impact of RLS on respondent's life
- Each question rating 0 to 4 (“not affected” to “very severe”)
- 1 to 10 – mild
- 11 to 20 – moderate
- 21 to 30 – severe
- 31 to 40 – very severe

Medications and Therapies



Medication Options

Treatment involves dopamine agonists, iron supplements, anticonvulsants, and opioids

Non-Pharmacological Therapy

Pneumatic compression therapy offers a beneficial non-drug treatment alternative for patients.

Self-Care and Lifestyle Modifications



Avoid aggravators

Limiting intake of caffeine and alcohol as well as nicotine and certain medications when able

Regular Exercise

Moderate regular exercise, stretching

Improved Sleep Hygiene

Practicing good sleep habits enhances rest quality and helps manage Restless Leg Syndrome symptoms effectively.

American Academy of Sleep Medicine clinical practice guideline

- AASM recommends use (over no use) of:
 - Gabapentin enacarbil, gabapentin, pregabalin
 - IV ferric carboxymaltose (with appropriate iron status)
 - IV low molecular weight iron dextran, IV ferumoxytol, ferrous sulfate
 - Dipyridamole, extended-release oxycodone “and other opioids”
 - Use of bilateral high-frequency peroneal nerve stimulation
- AGAINST standard use of pramipexole, transdermal rotigotine, ropinirole
 - *may be used in those who place higher value on reduction in symptoms with short-term use and lower value on adverse effects with long-term use (augmentation)
- Against bupropion, carbamazepine, clonazepam, valerian, valproic acid and cabergoline

Iron

- Serum ferritin $\leq 75\text{ng/mL}$ or transferrin less than 20% iron therapy should be started
 - Caution ferritin may be falsely high in liver disease or inflammatory disease, transferrin saturation helpful for verification
- Typically recommended 65mg elemental iron BID 1 hour before meal (ferrous sulfate 325mg BID most common form)
 - Can be combined with 100-200mg vitamin C for improved absorptions
- AE = nausea and constipation
- May not be effective for severe RLS
 - IV iron can be considered if oral not tolerated or not effective
- Low molecular-weight iron dextran recommended due to low risk of anaphylaxis
 - IV iron can see improvement in symptoms 2-4 weeks after but may take 6 weeks
 - Ferric caroxymaltose 1g over 1 hour shown to improve with ferritin $<100\text{ng/mL}$ and transferrin $<45\%$
- Recheck 12 weeks with oral and 8-16 weeks with IV

Medications- Dopaminergic

- Dopaminergic
 - FDA approved: oral pramipexole (max 0.5mg daily), oral ropinirole (max 3 to 4mg daily) and rotigotine patch (max 3mg)
 - Very effective short term but watch for augmentation
 - Worsening of symptoms response to medication
 - Earlier symptoms, spread of symptoms, shorter treatment effect window
 - Possibly more likely in short acting
 - Increases can further augmentation – lower dose instead
- Patch may have risk of skin reaction (change daily and alternate location ideally not using same site for 14 days)
- Impulse control
- Sleep attacks

Medications- Alpha-2-Delta Ligand

- Gabapentin enacarbil FDA approved at 600mg a day
 - Better GI absorption
 - Insurance rarely covers
- Not formally FDA approved but effective:
 - Pregabalin (150 to 450mg per day) and gabapentin (300mg up to 1200 or 2400mg a day- better absorption with multiple doses max at 600mg/dose ≥ 2 hours apart)
- AE: dizziness, sedation, weight gain
- Renally cleared, unchanged- adjust with renal function

Medications- Opioids

- Typically reserved in significant cases where other management strategies have failed
- Consider risk for abuse
- Clinical monitoring recommended with contract, urine toxicology , regular appointment and prescription monitoring programs
 - Tramadol 50 to 100mg/day
 - Codeine 30 to 180mg/day
 - Oxycodone 10 to 30mg/day
 - Methadone 2.5mg to 20mg
 - Buprenorphine hydrochloride/naloxone (sublingual film or tablet) 0.5 to 6 mg/day
- Long acting may be more beneficial than short acting

Noninvasive Peripheral Nerve Simulation (NPNS)

- Bilateral peroneal nerve stimulation
- FDA granted De Novo status for Noctrix Health's NTX100 Tonic Motor Activation (TOMAC) System [Nidra] in 2023 (had “breakthrough device” status since 2020)



Photo credit: Noctrix Health

Quality Measures for Care of Adult Patients with RLS

- Accepted diagnostic criteria and Assessment of iron stores in efforts to help improve accuracy of RLS
 - Ferritin regarded as most sensitive
 - Iron within year may not need repeat testing unless potentially indicated (blood loss, worsening symptoms)
- Assessment of symptom severity including within 12 months of starting evidence-based treatment to decrease severity
 - Exception if refractory to at least 2 other medications or unable to tolerate at least 2 other medications → Improvement on 2nd or 3rd line medications may be limited
 - Excluded if mild severity, recommended an IRLSSG Rating Scale (IRLS) severity < 15
 - Symptoms affect multiple domains including sleep disturbance, mood disturbance, daytime sleepiness and daytime dysfunction

Quality Measures for Care of Adult Patients with RLS

- Counsel side effects and assessing for impulse control as well as augmentation to minimize complications
 - Side effects for
 - DA = impulse control, augmentation, n/v, HA, dizziness, fatigue, somnolence, insomnia, hallucinations, site reactions (rotigotine)
 - Alpha-2-ligand = swelling, imbalance, change in cognition, dizziness, weight gain, suicidality, dry mouth and somnolence
 - Opioid = sleep disordered breathing, change in mood, sedation, constipation and potential for abuse (among others)
 - Iron = n/v/d, constipation, dark colored stools
 - Ask about augmentation at every visit
 - Max Planck diagnostic criteria
 - At least 4 hours earlier
 - Additional body parts
 - Faster symptoms, shorter duration response or paradoxical response (better at lower dose, worse at higher)

➤ [J Clin Neurosci](#). 2025 Mar;133:111075. doi: 10.1016/j.jocn.2025.111075. Epub 2025 Jan 28.

Impact of continuous positive airway pressure therapy on restless legs syndrome in patients with coexistent obstructive sleep apnea: A qualitative systematic review

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Affiliations + expand

PMID: 39879879 DOI: [10.1016/j.jocn.2025.111075](#)

Conclusion

Nature of Disorder

Restless Legs Syndrome is a common neurological condition affecting many individuals worldwide.

Diagnosis- Urge. To. Move.

Proper diagnosis and treatment can effectively manage symptoms and improve quality of life.

Awareness of Augmentation

Workup

Sleep study optional, iron workup, medication review

Resources

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End

Questions?

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