Restless Legs Syndrome: *What is Ferritin & Why Do We Want To Be Iron Man or Iron Woman*

Focus Fall 2017 Conference
Poughkeepsie, NY
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40 yo WF with a h/o GM seizure disorder since age 14 and migraine HA, on Depakote for seizure and amitryptiline for migraine, as well as MVI, Ca++, and Vit E was referred to the Ct Center for Sleep Disorders for c/o EDS and a sleep study to r/o OSA. She is single and does not know if she snores. Her ESS=16 (Standard for quantifying sleepiness based on 8 scenarios such as: sitting and reading, watching TV, sitting inactive in a public place, passenger in a car, lying down in the PM, sitting after lunch without alcohol, In a car while stopped in traffic for a few minutes, or sitting and talking to someone, on a scale of 0-never sleep to 3-high chance of sleep)
She sleeps an average of 9 hours on a weeknight and 10 hours weekend. She did report leg twitches for the past 6-9 months, although she has been tired “for years and no one seems to know why.” She is a 3rd grade special ed teacher.

On exam 110/70 HR 72 R14 Wt-118 Ht-5’

HEENT, neck-WNL, Lungs-clear, Heart-RRR, Abd –benign, Ext-tr-1+pre-tibial edema

Labs (done prior to consultation by PMD) Chol-216, LDL-152, WBC-7.0, Hg-13, MCV-86.8, RDW-15.2. CMP-nl x for AST=36.

The patient went for her PSG in 8/01
PSG revealed a sleep efficiency of 87%, sleep stages (as a % of sleep) Stage 1=9%, Stage 2=64%, Stage 3=10%, Stage 4=4%, and REM=12%. REM latency=200 minutes

RDI= 1.3 (7 hypopneas), lowest desat-94%.

Periodic Limb Movements= 333, or 61 PLMS/hr, with a PLM arousal index =29.

Total arousals=201, 161 associated with PLM’s, 36 spontaneous.

I met with her for the first time to discuss the results of her PSG, during which she described leg movements prior to falling asleep. Although she is unaware of her moving in her sleep, her sheets are “messy”.

She was given the diagnoses of RLS.
The Restless Legs Syndrome

- Definition
- Epidemiology
- Risk Factors
- Clinical Features
- Laboratory Findings
- Treatment options
- Vignette
- Resources
The Restless Legs Syndrome

Definition

- Awake Phenomenon
- An intense irresistible urge to move the legs (akathesia) usually associated with sensory complaints (paresthesia or dysesthesia) or a “deep seated sensation in the legs”, “creepy-crawly”, “soda water in the veins”, “ants marching in legs”
- Motor restlessness.
- Worsening of symptoms at rest (sitting or lying down)
- Relieved with moving or walking
- Increased severity in the evening or night.
The Restless Legs Syndrome/WED

- RLS= Willis/Ekbom Disease, first described by Dr Thomas Willis (Britain 1672) noted response to opiates and in the early 1940’s by Dr Karl Ekbom (Sweden). Napoleon may have had it as he had been known to have to get out of bed and pace the halls.

- "The syndrome is so common and causes such suffering, that it should be known to every physician." (Dr K. Ekbom). Almost 100 years later and RLS is still far from having universal awareness amongst medical professionals.
RLS vs PLMD

- Periodic Limb Movement Disorder (PLMD) not synonymous with RLS, but can coexist.
- PLMs are a sleep phenomenon, characterized by periodic episodes of repetitive and highly stereotyped limb movements.
- Patients with PLMD have PLMs as a complaint of insomnia or excessive daytime sleepiness with no other disorder to explain the symptoms.
- PLMs can be asymptomatic, noticed by an observer, usually lower extremity but can be upper as well.
RLS vs PLMD

- RLS/WED is a neurologic disorder.
- Approximately 80% of individuals with RLS have evidence of PLMs on PSG.
- The diagnosis of RLS is based on history, while PLMD requires PSG confirmation.
- Not all patients with RLS have PLMs and not all patients who have PLMs have RLS.
The Restless Legs Syndrome

Epidemiology

- Prevalence in the population between 2.5-15%.
- Prevalence increases with age, women 2x greater than men.
- 25% of pt’s with RLS had sx’s from age 11-20.
- Family history of RLS is common in patients whose symptoms appear before age 40, less familial occurrence and more likely to have neuropathy in patients after age 50.
- Autosomal dominant inheritance - a major susceptibility locus on chromosome 2q, 9p, 12q, 14q, 20p
The Restless Legs Syndrome

Epidemiology

- Has been reported in 20% of women during pregnancy. (higher estrogens c/w controls)
- In 20-62% of patients requiring HD
- African-Americans, Asians and Hispanics are rarely diagnosed with RLS (even in US).
- Can occur in childhood. (2% of children 8-17 yrs in UK and US and 6% of children at sleep center)
- Although common in patients with neuropathy, there does not seem to be a prominent causal relationship between neuropathy and RLS.
RLS/WED: Pathophysiology

- Combined CNS and peripheral PNS.
- No evidence that it is from neurodegeneration (a major concern of young patients).
- The most common cause of CNS abnormality is reduced iron stores.
- Low CNS iron even when blood tests show normal iron studies.
- CSF ferritin is low compared with normal controls.
RLS/WED: Pathophysiology

- CNS US reduced iron echogenicity in the substantia nigra
- MRI of the brain shows reduced iron (striatum, thalamus and red nucleus)
- Autopsy showed reduced ferritin and iron staining and reduced transferrin receptors.
- Reduced iron should cause up regulation of the transferrin receptors so must be more than lack of availability.
- Reduced intracellular iron causes adverse effects on the homeostatic mechanisms that regulate iron into and out of neurons in the brain
- There are other disturbances such as decrease in the dopaminergic system, circadian rhythm, thalamus, decreased glutamate and GABA
RLS/WED: Risk Factors

- Many patients with RLS did not have an identifiable risk factor
- Primary RLS no risk factor secondary with a risk factor
- Reduced iron specifically CNS iron is the most common abnormality
- Reduced total body iron could lead to low CNS iron and cause ROS
- Low serum ferritin levels less than 50 mcg/L correlate with RLS
- This association is more common in patients without a family history
Anemia is not associated with RLS,
Blood donors often develop ROS likely due to low iron rather than low hemoglobin
A low serum ferritin is the best indicator of low iron stores and the only blood test that consistently correlates with our LS
Ferritin is also an acute phase reactant and the normal level increases with age
Therefore a normal ferritin level does not rule out iron deficiency
RLS/WED: Why Fe?
The Restless Legs Syndrome

Clinical Features

- RLS patients have sleep disturbance because of their symptoms and PLMs.
- Sleep onset insomnia due to difficulty relaxing, lying down activates their symptoms, forcing them to be more active.
- Sleep can be delayed for hours in severe cases (prolonged sleep latency).
- Sleep maintenance insomnia due to PLMs which can awaken them.
- Total sleep time can be severely shortened, and can cause significant EDS.
The Restless Legs Syndrome
Clinical Features

- RLS: idiopathic and secondary to iron deficiency with and without anemia, uremia, rheumatoid arthritis and diabetes.
- Treating iron deficiency can alleviate symptoms and improve response to other medications. Even in patients with ferritin levels of 45 may benefit from iron supplementation. Brain iron deficiency may be the critical factor.
- In uremia, need to distinguish from myoclonus, asterixis, tremor or akathisia.
- In one study patients with uremia and RLS were more likely to be anemic (conflicting study). RX anemia led to decrease in symptoms.
Prevalence of RLS was higher in pt with MS than in controls. 19 vs 4% (Manconi, Sleep 2008)

RLS and Parkinson’s- Not clear, range 0-21% of pts with PD have RLS, but not all studies show an increased prevalence.

Venous Insufficiency- 23% seeking therapy had RLS. Sclerotherapy 98% initial relief and 72% at 2 yr f/u.

1/3 of pts with fibromyalgia
The Restless Legs Syndrome
Clinical Features

“RLS may coexist with conditions that cause leg pain, such as neuropathy or arthritis, and these conditions may aggravate each other. Thus, patients with pain from another known cause who report having insomnia should be asked specifically about characteristic symptoms of RLS…” Earley, C.J. NEJM 2003
The Restless Legs Syndrome
Clinical Features

- **Severity:**
  - **Mild:** occurs episodically with mild disruption at sleep onset, causing little distress.
  - **Moderate:** less than 2x/week, but a significant delay in sleep onset, moderate sleep disruption and mild impairment of daytime function.
  - **Severe:** >2x/week, severe sleep disruption and marked daytime symptoms.
  - **Acute:** <2 weeks, **Subacute:** >2 weeks less than 3 months, **Chronic:** >3 months
Laboratory Testing

- PSG not required, a clinical diagnosis.
- Need to exclude secondary causes, such as iron deficiency or renal failure.
- Exact testing debatable. There is consensus re: iron studies (ferritin and Fe sat). CBC.
- If renal function has not been assessed, would consider BUN/Cr.
Treatment Options

- Non-pharmacologic
- Vitamins/minerals
- Alpha-2-delta Ca-channel ligands (e.g. gabapentin/Horizant)
- Dopaminergic
- Sedative/hypnotic agents
- Anticonvulsant
- Opiates
- Devices/Miscellaneous
Treatment Options

- Intermittent- Not frequent enough to warrant daily medication- Non-pharmacologic, a2dCaCh ligands, DA agonist, benzos, low dose opiates.
- Daily: Non-pharm, a2dCaCh ligands, DA agonist, benzo, low potency opioids.
- Refractory- Daily RLS despite Tx with non-pharm a2dCaCh ligands or DA agonist. Change gabapentin to gaba enacarbil, change to a different DA agonist, add gaba/benzo/opioid, add high dose opioid or tramadol.
Non-pharmacologic

- Avoid caffeine, alcohol, cigarettes
- Hot baths
- Massages
- Exercise
- Sclerotherapy for varicose veins.
- Good sleep hygiene.
- Stop offending agents (SSRI’s, antihistamines)
Non-pharmacologic

- PCD’s! Chest Jan 2009 Vol 135
- Relaxis Pad - Vibratory stimulation (retail $599-$699+ tax or $50/mo)
- Restiflic - a foot wrap that applies targeted pressure. Cost $199 but only a 1 time cost
Vitamins/Minerals: Fe

- Iron supplementation is effective in treatment of RLS in patients with Fe-deficiency.
- Although associated with ferritin < 50, replacement is recommended if ferritin < 75.
- Cannot be done empirically because of risk of iron overload.
Vitamins/Minerals: Fe

- Oral iron is not well absorbed in the most common form such as iron sulfate.
- Iron needs to be ingested in the correct form and in the correct way.
- Needs to be taken on an empty stomach with vitamin C 250-500 mg.
- Cannot be taken with calcium supplements or dairy.
- For those that are unable to tolerate p.o. iron IV iron may be an option.
- IV iron for malabsorption.
- IV iron does carry a risk of anaphylaxis.
Vitamins/Minerals: Others

- ? link of Folate deficiency, with decrease in symptoms after being treated with Folate.
- Mg++ for Mg deficiency
- Vitamin C, E, B12 - reports are suggestive but no controlled trials.
Alpha-2-delta calcium channel ligands

- Gabapentin 100-300-600-1800mg in 2 divided doses in late PM and 1-2 hrs before bedtime (renal adjustments) cheap.
- Gabapentin enacarbil (Horizant) 300-600mg at 5PM with food (renal adjustment)
- Pregabalin (Lyrica) 50-75mg à 150-450mg 1-3 hours before bedtime (renal adjustment)
Dopaminergic

- Although the most studied agents for treating idiopathic RLS not sole 1\textsuperscript{st} line.
- Levadopa/carbidopa, bromocriptine (Parlodel), pergolide (Permax), Pramipexole (Mirapex), ropinirole (Requip). Pergolide only Category B, taken off market b/o valve disease.
- Rebound- tendency of symptoms to recur late at night leading to poor sleep in the early morning.
- Augmentation- symptoms develop earlier in the day and more severe than pre-treatment. Increase in meds leads to increase augmentation.
- Most common in L-Dopa. Less in SR, Parlodel, Permax, Mirapex.
- Side fx’s-GI, N/V, lightheaded, or HA
Dopamine agonist

- Pramipexole and Ropinirole - Less likely to cause side effects.
- Were sole DOC for daily RLS until $\alpha_2$-dopamine ligands.
- FDA approved.
- Side effects - Nausea, lightheadedness, fatigue, rare nasal congestion, constipation, insomnia, leg edema - all reversible.
- Sleep attacks rarely occur (described in PD doses).
- Compulsive eating, shopping, gambling, hypersexuality
- Amantadine, Selegiline
Dopa vs a2dcc ligand

- For patient's with severe RLS comorbid depression obesity or metabolic syndrome a dopamine agonist may be preferred.
- For patient's with comorbid pain anxiety insomnia or impulse control disorder as or addiction alpha-2 delta calcium channel ligand.
- For other patients the risk of augmentation and rebound or other side effects need to be considered.
Sedatives/Hypnotics

- Clonazepam- according to AASM practice parameters- “effective in the treatment of PLMD and possibly RLS (option).
- Improves quality of sleep by reducing fragmentation.
- May cause hangover effect in elderly (confusion or daytime sleepiness)
- May also treat other sleep disorders (RBD)
- Clonazepam (0.5-4mg), Temazepam (15-30mg), Triazolam (.125-.5mg), Zolpidem (5-20mg), Zaleplon (5-20mg)
Anti-convulsants

- Alpha 2 delta calcium channel ligands: gabapentin (Neurontin), gabapentin enacarbil (Horizant). Effective in the treatment of RLS but often used first due to excellent safety profile.

- Valproic acid and lamotrigine have been reported to be effective in some cases.

- Carbamazepine is effective in the treatment of RLS (Guideline). Black box warning for aplastic anemia and agranulocytosis.
Opiates

- Codiene (30-60mg), oxycodone (5-30mg), methadone (2.5-20mg), Tramadol (50-100mg)

- Stronger opiates reserved for most severe or refractory patients.

- Constipation and addictive behavior in some, though many have been on constant doses for years.
Miscellaneous

- Clonidine
- gamma hydroxybutyrate/sodium oxybate
- Baclofen
- Hemodialysis/kidney transplant
- Surgical decompression of spinal cord compression.
- “No specific recommendations can be made regarding treatment of pregnant women...or children regarding RLS or PLMD.”
Vignette

- A ferritin level = 5.
- The patient was started on Fe++ and Mirapex, with complete resolution of symptoms.
- “Thank you for diagnosing my RLS. For years I’ve felt tired and frustrated. Now I am happy and energetic! Thanks again.”
- The patient was also found to have sprue.
- On a gluten free diet and iron, 1 ½ years later, her ferritin = 58 and she is asymptomatic off Mirapex.
- “Celiac Disease Screening Recommended for Restless Leg Syndrome (RLS) with Iron Deficiency” Sleep Med 2009 Jan 10
Who do you want to be when you grow up?
Resources

- Restless Legs Syndrome Foundation (www.RLS.org)
- Earley, CJ NEJM May 22, 2003 (348;21)
- Sleep Disorders Medicine - 2nd edition by Dr. Sudhansu Chokroverty
  - Practice Parameters for the Treatment of RLS and PLMD, AASM report. 2013
  - Uptodate.com- Sept 2017