Learning Objectives

- To increase awareness of a common but overlooked medical condition
- To increase diagnostic accuracy
- To present potential treatments—both pharmacologic and non-pharmacologic
Restless What???

Diagnosis is Clinical

History of Willis-Ekbom Disease - RLS

- Initially described by Thomas Willis in 1685 – unable to sleep “[bed] place of greatest torture”
- T. Whittmaack – 1861 “Anxietas Tibiarum”
- George M. Beard – 1880 “fidgetiness, etc.” – “Neurasthenia”
- J.C. Mussio-Fournier and F. Rawak – 1940 “Hyperkinesis of the lower extremities caused by paresthesias occurring during rest” – in mother and sister of their patients
- F.G. Allison – 1943 – “leg jitters”
- K.A. Ekbom – 1944 – “restless leggs”
Definition of WED/RLS

- A neurologic sensory-motor disorder characterized by:
  1. An urge to move the legs (akathisia) usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs, i.e. "creepy crawlies, etc." (1995 criteria)
  2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting

3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching at least as long as the activity continues

4. The urge to move legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day
Definition of WED/RLS

5. The occurrences of the above features are not solely accounted for as symptoms primary to another medical or a behavioral condition such as myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, or habitual foot tapping (2012 criterion added to increase specificity)

WED/RLS May Affect Multiple Medical Disciplines

- Primary Care including OMM
- Internal Medicine
- Pulmonology/Sleep Medicine
- Hematology
- Nephrology
- Pediatrics
- Obstetrics and Gynecology
- Neurology/Movement Disorders
- Psychiatry
- Endocrinology/Diabetology
- Pain Management
- Cardiovascular Medicine
- Orthopedics
- Rheumatology
Epidemiology of WED/RLS

- Common but frequently underdiagnosed disorder
  - Prevalence is between 2.4%-10.8% in USA and Europe, 1.1%-2% in Asians and South Americans
- Incidence is higher in women and increases with age
- Estrogen use increases risk of developing RLS
- RLS in pregnancy doubles risk later in life
- WED/RLS is associated with depression and vice versa
- Also associated with cardiovascular disease but findings have not been consistently replicated

Pathophysiology of RLS/WED

- Very complex with findings often contradictory with emphasis on"
  A. Disturbed iron metabolism
  B. Dopaminergic dysfunction, other neurotransmitters
  C. Genetics
  D. Central opiateergic system
  E. Neuropathy link
Pathophysiology of RLS/WED

- In summary:
  - Insufficient iron leads to relative hypoxia and death of dopaminergic cells
  - Dopaminergic feedback loops and neural networks are disturbed causing spinal hyperexcitability
  - Peripheral neuropathy may impede spinal inhibition of excitation pathways
  - Multiple genes and single nucleotide polymorphisms may predispose to RLS esp. Autosomal Dominant Form
  - Central opiateergic system may be protective, i.e. severe symptoms of RLS can be reversed by IV opiates
  - Parasympathetic/sympathetic imbalance may result in relative peripheral arterial or venous insufficiency

Neuroimaging in WED/RLS

- MRI – no structural lesions in RLS patients
- MRI – decreased brain iron in red nucleus and substantia nigra in RLS patients
- MRI Spectroscopy – decreased N-Acetyl-aspartase/creatine ratio in medial thalamus in RLS patients
- PET Scan – decreased striatal (basal ganglia) binding potential in WED/RLS patients
Neuroimaging in WED/RLS

- Diffusion Tensor Imaging MRI – suggests loss of axonal density and myelin in motor and somatosensory areas in RLS patients
- Transcranial Ultrasonography – four studies revealed hypoechogenicity in the substantia nigra of RLS patients correlating with disease severity

*All of the above are research related, normal clinical use is not recommended

**Figure 1** MRI R2* Images in a 70-Year-Old RLS Patient and a 71-Year-Old Control Subject. Much lower R2* relaxation rates indicating less iron density are apparent in the restless legs syndrome (RLS) case in both red nucleus and substantia nigra. Allen, R. P., Barker, P. B., Wehrl, F., Song, H. K., and Earley, C. J. (2001). MRI measurement of brain iron in patients with restless legs syndrome. *Neurology* 56(2), 263–265.
Fig. 2. Typical medial thalamic 1H-MRS spectra obtained from a control individual (A) and a patient with RLS (B). Note the lower NAA peak in the patient with RLS compared with the control individual. Cho, choline-containing compounds; Cr, creatine-phosphocreatine; ml, myoinositol. (From Rizzo G, Tonon C, Testa C, et al. Abnormal medial thalamic metabolism in patients with idiopathic restless legs syndrome. Brain 2012;135:3716; with permission.)

FIG. 3 Representative example of (11C)methylphenidate BP in the striatum of a patient with RLS and a control individual. (From Earley CJ, Kawabata H, Wong DP, et al. The dopamine transporter is decreased in the striatum of subjects with restless legs syndrome. Sleep 2011;34:344; with permission.)
Overall Approach to RLS Treatment

- Quit nicotine, alcohol, caffeine
- Regular exercise and stretching
- Lose weight
- Sleep hygiene (delay bedtime and waketime)
- “Active relaxation” in the evening (reading, card games, crosswords, active discussion, sexual activity)
- Avoid frequent blood donations
- Avoid: benadryl, anti-psychotics, SSRI’s, SNRI’s, mirtazepine, metachlopramide, etc. if possible
- Assess for and correct iron deficiency

Medical Treatment of WED/RLS

- Start low – go slow
- Dopaminergic agents
  - Ropinirole (Requip) – faster onset and shorter duration of action
  - Pramipexole (Mirapex) – slower onset/longer duration
  - L-Dopa (mostly in Europe) – rapid onset; use only for airplane travel, automobile trips, boring lectures, etc.; beware tardive dyskinesia, skin lesions or melanoma history
  - Rotigotine patch – for patients with symptoms throughout the day and for those hospitalized and NPO, etc.
Medical Treatment of WED/RLS

- Side effects include sedation, orthostatic hypotension, and impulse control disorders (warn patients and do not use in those prone to gambling, binge eating, etc.)
- Augmentation = iatrogenic worsening

Medical Treatment of WED/RLS

- Alpha-2-Delta agonists – Gabapentin (Neurontin), Gabapentin Enacarbil
- Pregabalin (Lyrica)
- Major side effects – dizziness, gait instability, and weight gain
- Can be used in place of dopamine agonists or as supplement to keep DA dose lower
- DA’s and Alpha-2-Deltas are first line therapies
Medical Treatment of WED/RLS

- Opiates – Oxycodone – Naloxone E.R.
  - Recent trial showed benefit in patients who failed first line agents
- Methadone – can be beneficial for long term treatment
- IV opiates have shown benefit for inpatient hospital use only
- Side effects – OIC, drowsiness, tolerance
  - do not prescribe in patients with history of substance abuse
- Augmentation has been reported with Tramadol
- Peripheral vasodilators – early treatment – questionable benefit

Medical Treatment of WED/RLS

- Benzodiazepines – clonazepam has been used with variable success in RLS patients with variable degree of anxiety as well as periodic limb movements of sleep. Oversedation, tolerance, and addiction can occur. Paradoxical effect in children with ADHD.
- Iron supplementation – IV and PO in iron deficient or anemic patients (Ferratin, Serum Iron, and IBC)
- Vitamins C & E – reduce symptoms of RLS in ESRD patients with RLS
- Folate and Vitamin D – Mild benefit in appropriate patients
- Other supplements including homeopathic remedies – questionable benefit except for Valerian!
Non-Pharmacologic Management of WED

- Limited peer reviewed literature
- Soap bar in bed – essential oils and esters?
- Deep massage – 100% effective in India study; return of symptoms 2 weeks after D.C. in another study
- Pyriformis release, trigger point therapy, myofascial release, deep tissue and sports massage, ointments
- Reiki massage, reflexology, Botox, yoga, Biofeedback
- External electrical stimulation
- Enhanced external counter pulsation (EECP)
- Endovenous laser ablation (Sup. Venous Insufficiency)
- Relaxis – timed vibratory stimulation (FDA approved)
- Near-Infrared Light (generates venous nitric oxide)
- Acupuncture + TDP Radiation, DBS (China)

Other Medical Conditions Associated with WED/RLS

- End Stage Renal Disease (ESRD)
  - 7-68% have RLS, increases with age
  - Undertreated may lead to cardiovascular disease
  - Often present with sleep disorders, i.e. OSA, etc.
  - Other medications may trigger RLS symptoms
Other Medical Conditions Associated with WED/RLS

- Treatment of RLS in ESRD
  - Address iron deficiency, add Vitamins C & E
  - Gabapentin or Dopamine Agonists
  - Treat OSA, PLMS, Depression (Wellbutrin), other conditions
  - Non-Pharmalogical treatments, i.e. bedside ergometer, etc.

Pregnancy and WED/RLS

- RLS in pregnancy – 3 x incidence of non-pregnant females
- Worse in third trimester – usually disappears with delivery
- Can reappear with subsequent pregnancies
- A pre-existing form of RLS worsens in pregnancy
- Hormonal influence
- Iron and folate effects
Pregnancy and WED/RLS

- Treatment – avoid triggers, immobility
- Moderate exercise, massage, yoga
- Iron, folate supplementation
- Gabapentin, Pregabalin – first line
- D.A.’s – questionable
- Clonazepam, Opiates – for rare selected cases only

Pediatric Growing Pains and RLS

- RLS initially described in children in 1995
- Prevalence 2-4%. Many have PLMD.
- Younger children have difficulty describing symptoms
- Positive family history helps support diagnosis
- Overlap between RLS and Growing Pains (1823)
- Similar diagnostic criteria as in adults
Epidemiology

- RLS found in 17% of children in general pediatric clinics and 5.9% referred to sleep clinics
- PLMD – in 8.4% of those referred to sleep clinic and 7.7-11.9% of children from community

Pediatric Growing Pains and RLS

- Pathophysiology – genetics, DA dysfunction, iron
- Clinical Manifestations – 78-85% of children and adolescents with growing pains have RLS
- Diagnosis – similar criteria but more challenging than adults (IRLSSG)
  - PLMD may precede diagnosis of RLS in some cases
Pediatric Growing Pains and RLS

- Differential Diagnosis – arthritis, tendon or ligament strain/sprain, growing pains, sore leg muscles, Osgood-Schlatter Disease, chondromalacia patella, etc.
- Combined growing pains criteria – from Walters, AS et al

Pediatric Growing Pains and RLS

- Treatment of RLS
  a) Iron replacement
  b) DA's, Clonidine, Gabapentin, Clonazepam (care with ADHD)
Summary

- WED/RLS is relatively common
- There is high morbidity in RLS
- Mortality rate is increased in RLS/ESRD
- Index of suspicion is key to diagnosis
- Pharmacologic and non-pharmacologic treatments are available
  - [www.wemove.org](http://www.wemove.org) (education and support group)

Questions??
11. Askenasy, Nadir, M.D. , Ph.D.; Aserinsky, Jean-Jacques, M.D., Ph.D. Rest Leg Syndrome in Neurologic and Medical Disorders. Sleep Med Clin 2015