Revisiting Restless Legs Syndrome and Leg Cramps in the Renal Patient

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Agenda

• 2 patient cases

• Restless Legs Syndrome in Chronic Kidney Disease (CKD)

• Leg cramps in CKD
  – Using Quinine and its concerns

• Questions & Discussion
Case #1

• +++ comorbidities
  – Dialysis dependent ESRD
  – Renal cell carcinoma → metastasis to pancreas
  – Depression, anxiety
  – Hashimoto thyroiditis

• Some of her current medications:
  – Ondansetron PRN
  – Atorvastatin SCH
  – Sunitinib SCH (for pancreatic ca)
  – Trazodone PRN
  – Mirtazapine PRN
  – Pramipexole PRN
  – Quinine PRN
Case #2

- Irresistible urge to move his legs
  - “want to step out of my dialysis machine”
- Poor sleep → poor quality of life
- Tried pramipexole (Mirapex®) 0.125 mg with little success
  - Drug probably dismissed as ineffective; discontinued
- Now on triazolam to help with sleep
- Anxious that he will become dependent on triazolam
Restless Legs Syndrome (RLS)
Pathophysiology of RLS

- Iron deficiency
- End-stage renal disease
- Diabetes Mellitus
- Parkinson Disease
- Drugs
- Rheumatic Disease
Pathophysiology of RLS

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RLS in End-Stage Renal Disease

• Sensory and motor dysfunction due to uremia
  – Nerve demyelination, distally
  – Sensory (e.g., RLS) occurs before motor (e.g., atrophy)
• Iron deficiency also plays a role
• Reported incidence in dialysis patients 6-60%
• Other reported associations
  – Dialysis duration
  – Body weight
  – Smoking history
RLS in End-Stage Renal Disease

• **Hallmark symptoms**
  – **U**rge to move the legs
  – **R**est or inactivity makes it worse
  – **G**etting up and going makes it better
  – **E**vening or night time onset (daytime also if severe)

• **Descriptors that patients use**
  – Sensation is deep-seated, bilateral, below knees
Managing RLS

Part 1: Assessment

- Adapted from BC Renal Agency
Managing RLS
Part 1: Assessment

Assessment

- Rule out mimic disorders
- Rule out drug-induced RLS
- Assess risk/contributing factors
  - Iron deficiency
  - Sleep deprivation
  - Positive family history
  - Rheumatoid arthritis or Sjogren’s
  - Pregnancy
Rule out mimic disorders

**Mimic Conditions**

- Movement disorders: akathisia, ADHD
- Restlessness secondary to anxiety, depression, psychotic disorders
- Local leg pathology, e.g. peripheral neuropathy, myelopathy, peripheral venous congestion
- Positional discomfort
Managing RLS
Part 1: Assessment

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Drug-induced causes

Drug-induced RLS

Dopamine antagonists:
- Antipsychotics: pimozide, haloperidol, olanzapine, risperidone
- Metoclopramide, promethazine

Antidepressants:
- Mirtazapine (up to 28%)
- SSRI (<5%), e.g. citalopram, escitalopram, fluoxetine, paroxetine, sertraline
- SNRI’s (<5%), e.g. duloxetine, venlafaxine

Stimulants: alcohol, caffeine, nicotine
- Others: TCA’s, carbamazepine, lithium
Managing RLS
Part 1: Assessment

- Rule out mimic disorders
- Rule out drug-induced RLS
- Assess risk/contributing factors
  - Iron deficiency
  - Sleep deprivation
  - Positive family history
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  - Pregnancy
Management of RLS
Part 2: Management

**Initial Recommendation**
- Discontinue or reduce offending drug, if feasible
- Correct iron deficiency – may prevent initial augmentation with dopaminergic therapy
- Encourage good sleep hygiene (see insomnia flowchart) [Click here for link](#)

**Drug options!**
Intermittent RLS

• **Levodopa/carbidopa (Sinemet®)**

• **Efficacy**
  – No consistent subjective improvement in RLS symptoms
  – Very small trials n=5, n=11 but randomized, double-blinded, placebo-controlled
  – Short acting ($t_{1/2}=1.5$ hrs), onset $\frac{1}{2}$ hr, augmentation effect

• **Safety?**
  – Generally well tolerated as reported in trials
  – Agitation, augmentation, dyspepsia, dizziness
Intermittent RLS

• Levodopa/carbidopa (Sinemet®) 100/25 mg tab
  – Start at ½ tab PO HS and/or dialysis, titrate to effect (max 200/50)
  – Doses > 200/50 increase risk of augmentation
  – If night time awakenings, try CR formulation
Daily RLS

- **Dopamine agonists: Pramipexole (Mirapex®)**
- **Efficacy**
  - Meta-analysis of 7 placebo-controlled RCTs totalling over 1200 patients
  - ↓ symptom severity, average 6.7 point improvement in IRLS score (>6 considered clinically important)
  - Longer-acting ($t_{1/2}$=8.5-12 hrs), less augmentation, onset 90-120 minutes
- **Safety**
  - Mild, transient side effects
  - Nausea, headache, somnolence, sleep attacks (rare)
  - Resolve in 10-14 days of treatment
Daily RLS

• Dopamine agonists: Ropinirole (Requip®)
• Efficacy
  – Meta-analysis of 5 placebo-controlled RCTs totalling over 900 patients
  – Average 4 point improvement on IRLS score (>6 considered clinically significant)
  – Longer acting ($t_{1/2}=6$-8 hrs), less augmentation, onset 90-120 minutes

• Safety
  – Same as pramipexole (Mirapex®)
Daily RLS

- Dopamine agonists
- Pramipexole (Mirapex®)
  - 0.125 mg PO 2 hours before HS or before dialysis
  - ↑ by 0.125 mg q7d to effect, max 0.75 mg/day

- Ropinirole (Requip®)
  - 0.25 mg PO 2 hours before HS or before dialysis
  - ↑ by 0.25 mg q7d to effect, max 4 mg/day
RLS with painful neuropathy

- **Gabapentin (Neurontin®)**
  - 100 mg PO HS
  - ↑ by 100 mg q7d to max 300 mg PO HS

- **Pregabalin (Lyrica®)**
  - 25 mg PO HS
  - ↑ by 25 mg q7d to max 75 mg PO HS
Refractory RLS

• Benzodiazepines
  – Generally avoid if possible; Beer’s Criteria
  – Clonazepam (Rivotril®) 0.5 mg PO HS, ↑ 0.5 mg q7d to max 7 mg PO HS

• Clonidine (Catapres®)
  – 0.05 mg PO HS if patient not hypotensive
Leg cramps
What about “leg cramps”?  

• **Painful, sudden, involuntary** muscle tightness in foot, thigh or calf  
• Relieved by **forceful stretching**  
• Commonly experienced at night
What about “leg cramps”?

- **Etiologies:**
  - Idiopathic
  - Leg positioning; *prolonged sitting*
  - *Extracellular fluid volume depletion*
  - *Electrolyte disturbances*
  - Metabolic conditions *e.g.*, *diabetes, hypoglycemia, hypothyroidism, alcoholism*
  - *Drug related: diuretics (potassium-sparing and thiazide-like), inhaled LABA (e.g., salmeterol)*
  - Generalized muscle cramps: donepezil, *statins*
Managing Leg Cramps

• Non-pharmacological approaches are key

• Prevention
  – Physical activity
  – Stretching exercises
  – Proper foot gear
  – Ultrafiltration goals and target weights, diuretic use
  – Avoiding alcohol and caffeine
Managing Leg Cramps

• **Non-pharmacological approaches are key**

• **Treatment**
  – Walking or leg jiggling
  – Hot shower or warm tub bath
  – Ice massage
  – **Addressing any underlying disease-induced and drug-induced causes**
Drug Options

• Variable success
  – Diphenhydramine 12.5-50 mg PO HS
  – Vitamin E (weak evidence)
  – Gabapentin up to 300 mg daily and supplemental dose 100-300 mg after dialysis
    • Helpful if patient also has diabetic neuropathy
  – *always exhaust non-pharmacological measures first
What about Quinine?

• Approved by Health Canada only as an anti-malarial agent
• Marketed in Canada since 1951
Quinine

• Best studied drug for **nocturnal leg cramps** (no evidence for RLS)
• Found effective in some well-designed randomized trials
• Good response from patients anecdotally
• Seen in practice used for **nocturnal or dialysis-related leg cramps** (and RLS?)
  – 200-300 mg PO HS and/or qdialysis
  – Schedule I drug available only by prescription
The Problems with Quinine

- Potentially serious and/or life-threatening side effects
  - Cardiac arrhythmias
  - Thrombocytopenia
  - HUS-TTP (Hemolytic Uremic Syndrome-Thrombotic Thrombocytopenic Purpura)
  - Severe hypersensitivity reactions
The Issues with Quinine

- From the Canadian Adverse Reaction Reaction Newsletter April 2011, as of September 30, 2010:
  - Health Canada received 71 (voluntary) reports of serious ADRs suspected of being associated with quinine
  - 4 of the reports: quinine used as anti-malarial (648 mg PO q8h x 3-7 days)
  - 43 of the reports: quinine used for leg cramps, muscle cramps, nocturnal leg cramps (200-300 mg qhs)
  - 20 of these 43 reports: thrombocytopenia, SJS, vasculitis, cardiac arrhythmia
Time to Quit Quinine?

• From FDA Articles of Interest September 2012:
  – Quinine is not considered safe and effective for treatment or prevention of leg cramps – an “off-label use”
  – Narrow dosing window between therapeutic doses for malaria and toxicity
  – Unapproved quinine products removed from market in 2006
  – Associations with serious, life threatening ADRs, independent of dose and duration of use:
    • Thrombocytopenia
    • Hypersensitivity reactions
    • QT prolongation
## Implications of Quinine in our dialysis/CKD population

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<td>(SJS, cutaneous vasculitis, TEN)</td>
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Current quinine users

• Weighing risk vs. benefit of continuing therapy

✓ Risks:
  ✓ Assess inherent risks for bone marrow suppression, QT prolongation, hypersensitivity reactions
  ✓ Is patient capable of understanding these risks and making an informed decision about whether or not to continue therapy?

✓ Benefits:
  ✓ What is the patient’s response to quinine?
  ✓ Has it resulted in significant improvements in quality of life that no other intervention can accomplish?
  ✓ Attempted and failed all other measures?
Time to Quit Quinine

✓ Exhaust non-pharmacological interventions
  ✓ Balance between prevention and treatment
✓ Manage underlying disease-induced causes
✓ Eliminate underlying drug-induced causes wherever possible
Time to Quit Quinine

✓ Exhaust non-pharmacological interventions
  ✓ Balance between prevention and treatment
✓ Manage underlying disease-induced causes
✓ Eliminate underlying drug-induced causes wherever possible
✓ If possible:

Discontinue Quinine
Back to the cases
Case #1

• **+++ comorbidities**
  - Renal cell carcinoma
  - Depression
  - Hashimoto thyroiditis

• **Current medications:**
  - Sunitinib SCH (renal cell cancer)
  - Ondansetron prn
  - Quinine prn
  - Trazodone prn
  - Mirtazapine prn
  - Atorvastatin SCH
  - Pramipexole prn

  - Hypothyroidism → Metabolic causes of leg cramps
  - Neutropenia thrombocytopenia
  - QT prolonging effects.
  - Trazodone stopped
  - Drug-induced RLS (up to 28%)
  - Held. Follow up in 2 weeks – “cramps were better”
  - RLS responding to therapy
Case #2

- Irresistible urge to move his legs
  - “want to step out of my dialysis machine”
- Poor sleep → poor quality of life
- Tried pramipexole (Mirapex®) 0.125 mg with little success
  - Max dose of pramipexole → 0.75 mg
- Now on triazolam to help with sleep
- Anxious that he will become dependent on triazolam
  - Sleep quality improved, attempting to taper off triazolam
Summary

• Important differences between Restless Legs Syndrome (RLS) and leg cramps and their implications on treatment approach

• Determine underlying disease- and drug-induced causes of RLS and leg cramps often opens up more treatment options

• Difficult to mitigate risks of quinine as they are independent of dose and duration of use – should never be the first choice

• **Quitting Quinine** is a decision of the health care team as much as it is of the patient
Thank you for attending!

"You think you have problems? I have restless leg syndrome in all 1000 legs."
References


• Palmer, BF and Heinrich, WL. Uremic polyneuropathy. In: UpToDate, Berns, JS (Ed), UpToDate, Waltham, MA, 2013.

• Tarsy, D. Treatment of restless legs syndrome in adults. In: UpToDate, Hurtig, HI and Benca, R (Ed), UpToDate, Waltham, MA, 2013.

• U.S. Food and Drug Administration. Serious risks associated with using quinine to prevent or treat nocturnal leg cramps (September 2012). Last updated Aug 31, 2012. Accessed on Aug 21, 2013 at: [http://www.fda.gov/ForHealthProfessionals/ArticlesofInterest/ucm317811.htm](http://www.fda.gov/ForHealthProfessionals/ArticlesofInterest/ucm317811.htm)