Restless Leg Syndrome and Parkinson’s Disease: Dopamine Deficient States

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Restless Leg Syndrome

- Urge to move legs
  - With or without unpleasant sensations
- Worsened with rest
- Improved with activity
- Worsening in the evening or night

- Supportive factors
  - Family Hx
  - Presence of PLMS

Sensory Phenomenon

- Need to move
- Crawling
- Tingling
- Restless
- Cramping
- Creeping
- Pulling

- Painful
- Tension
- Discomfort
Periodic Limb Movements

- Repetitive, stereotyped
- Movements occur during sleep

Overlap of clinical syndromes

Pathophysiology

- Reduced concentrations of brain iron stores
- Alterations in brain dopamine systems
- Multiple links between Fe and Dopamine
  - Tyrosine Hydroxylase
  - Thy-1 Adhesion molecule
  - Dopamine-2 receptor

- NO LOSS OF DOPAMINE PRODUCING NEURONS
Secondary RLS

- Renal Failure
  - (20-57% in HD patients)
- Iron Deficiency
- Neuropathy
- Pregnancy (26%)
- Other CNS conditions
  - Parkinson Disease
  - Reflects *wearing off* of dopamine replacemeds
- Is Akinesia related to RLS?
  - Fits with dopamine hypothesis

Treatment of RLS

- Dopamine Agonists
  - Ropinerole (*Requip*)
  - Pramipexole (*Mirapex*)
  - Rotigotine (*Neupro*)
    - transdermal
- Anti-epileptics
  - (α₂-blockers of calcium channels)
    - Gabapentin
    - Pregabalin (*Lyrica*)
- Opioids
- Benzodiazepines
- Iron
  - Oral
  - IV iron dextran

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Medications and doses used for RLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Dose (mg)</td>
</tr>
<tr>
<td>L-Dopa</td>
<td>10-200</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>0.125-0.375</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>0.5-3</td>
</tr>
</tbody>
</table>

William G. Ondo
Treatment Complications

- Augmentation (48%)
  - Phase shift
  - Dose escalation

- Drug Side Effects
  - Dopamine agonists
    - Nausea
    - Rare but must monitor
      - Compulsive behaviors
      - "Sleep attacks"

Diagnosis of RLS

- Differential Diagnosis
  - Peripheral Neuropathy
  - Akathisia
  - Nocturnal Leg Cramps
  - Secondary RLS
  - "painful legs and moving toes" syndrome

- Ferritin and iron studies
- Electrolytes
- Optional Studies
  - (particularly when there is NO family hx)
    - NCV/EMG to r/o neuropathy
    - Polysomnography

PD: Clinical Features/Cardinal Signs

- 1817: James Parkinson “An Essay on the Shaking Palsy”
- Onset
  - mean PS 61.6 years; PD 62.4 years
  - rare before age 30; 4-10% cases before age 40
- Affect 1% of the population over 60 years of age
**Cardinal Characteristics**
- Resting tremor
- Bradykinesia
- Rigidity
- Postural instability

**Other**
- Micrographia
- Masked face
- Stooped, shuffling gait
- Decreased arm swing when walking

**Early Signs and Symptoms**
- Difficulty arising from a chair
- Difficulty turning in bed
- Hypophonic speech
- Sialorrhea
- Loss of the sense of smell
- Foot dystonia

**Additional Signs and Symptoms**
- At least two of three: rest tremor, bradykinesia, rigidity
- Absence of a secondary cause—drugs, metabolic, etc.
- Definitive diagnosis can only be made by autopsy
- Pragmatic approach: response to dopamine replacement therapy
  - May want to avoid early use of levodopa in younger patients

**Criteria for Diagnosis**
- Response to levodopa replacement therapy
- Early use of levodopa in younger patients
Pathology of Parkinson’s Disease

18F-DOPA PET scans

Etiology of Parkinson's disease

- Environmental or endogenous toxins
- Single or multiple genes

Pathogenesis
- Free radicals
- Mitochondrial dysfunction
- Iron
- Oxidative stress
- Protein aggregation

Parkinson’s disease(s)
Drug Classes in PD

- Dopaminergic agents
  - Dopamine agonists
  - Levodopa
  - COMT inhibitors
- MAO-B inhibitors
- Anticholinergics
- Amantadine

Reducing the Peripheral Metabolism of Levodopa

*Addition of a COMT Inhibitor Decreases Conversion of Levodopa to 3-OMD in the Periphery*

DDC = dopa decarboxylase; 3-OMD = 3-O-methyldopa; BBB = blood-brain barrier; COMT = catechol-O-methyltransferase.

Levodopa/Carbidopa Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Onset</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Release</td>
<td>20-40 min</td>
<td>2-4 hr</td>
</tr>
<tr>
<td>10/100, 25/100, 25/250</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled Release</td>
<td>30-60 min</td>
<td>3-6 hr</td>
</tr>
<tr>
<td>25/100, 50/200</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stalevo</strong></td>
<td>20-40 min</td>
<td>3-5 hr</td>
</tr>
<tr>
<td>50, 75, 100, 125, 150 Triple combination Carbidopa/levodopa/entacapone</td>
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Benefits of Dopamine Agonists

- Direct receptor stimulation
  - does not require conversion to dopamine
  - does not add additional oxidative stress to remaining nigral neurons
- Delay onset of dyskinesia
- Decrease pulsatile stimulation
- May have a neuroprotective effect

Dopamine agonists reduce dyskinesia:
either as monotherapy or in combination with levodopa
Dopaminergic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing interval</th>
<th>PD dose</th>
<th>RLS dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ropinirole</td>
<td>TID (for PD)</td>
<td>6-24 mg/day</td>
<td>0.5-3 mg/night</td>
</tr>
<tr>
<td>Requip XL</td>
<td>qd</td>
<td>same</td>
<td>same (?)</td>
</tr>
<tr>
<td>Pramipexol</td>
<td>TID (for PD)</td>
<td>0.75-4.5 mg/day</td>
<td>0.125-1 mg/night</td>
</tr>
<tr>
<td>Mirapex ER</td>
<td>QD</td>
<td>same</td>
<td>Same (?)</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>QD, transdermal</td>
<td>2.4 mg/day</td>
<td>Not approved (?)</td>
</tr>
<tr>
<td>Levodopa</td>
<td>TID, q2hr (PO)</td>
<td>300-1200 mg/day</td>
<td>100-250mg/night</td>
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</tbody>
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DAs: Common Adverse Effects

- Nausea, vomiting
- Dizziness, postural hypotension, peripheral edema
- Drowsiness & somnolence, SLEEP ATTACKS
- Confusion, hallucinations
- COPULSIVE BEHAVIOR
  - Gambling, sexual addiction, compulsive eating

TREATMENT ALGORITHM FOR PARKINSON’S DISEASE

- Dx
- COMT inhibitor
- ↑ DOSE
- Combined Therapy
- Dopamine Agonist
- ↑ DOSE
- Surgery
- Experimental RX
- Monitor Exercise
Comparison of RLS vs PD

<table>
<thead>
<tr>
<th></th>
<th>Parkinson Disease</th>
<th>Restless Leg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine dysregulation</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Iron Dysregulation</td>
<td>? +</td>
<td>++</td>
</tr>
<tr>
<td>Dopaminergic cell loss</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Dopamine agonist response</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Levodopa response</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Family history/genetic component</td>
<td>+/-</td>
<td>+++</td>
</tr>
<tr>
<td>Primarily Clinical Dx</td>
<td>+++</td>
<td>+++</td>
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