Parkinson's Disease and Tremors

Current Strategies

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Disclosures

• I have no conflicts of interest
**Parkinsonism – neurological syndrome:**

• Bradykinesia: (slow and reduced scale)
• Rest tremor: “pill rolling”
• Rigidity: resistance to passive movement
• Postural instability: falls, flexed posture

**Parkinsonism Differential Diagnosis**

• Neurodegenerative
  – Parkinson’s disease
  – Parkinson’s plus degenerative diseases
  – Mild parkinsonism in aging, AD, FTD
  – Other hereditary: e.g., Wilson’s disease, Huntington’s disease

• Acquired
  – Drug-induced parkinsonism
  – Structural lesions, trauma, vascular
  – Toxic: manganese, CO, cyanide, MPTP
  – Infections: (e.g. post encephalitic parkinsonism in early 20th century); HIV
Drug-induced Parkinsonism

• Neuroleptics
  – Less likely with atypicals (particularly quetiapine and clozapine)

• Anti-emetics
  – Prochlorperazine, metaclopramide

• Calcium-channel blockers - flunarizine

• Methyldopa

• Possibly – amiodarone, lithium

Drug-induced Parkinsonism

Epidemiology
  – More common with aging
  – More common among women
  – May have a genetic predisposition

• Onset usually quick (50% within 1 month)

• Not progressive

Resolution after stopping the drug
  – 60% resolve within 2 months (some almost immediately)
  – Some take up to 2 years to resolve
  – Some ‘unmasked’ idiopathic PD
Idiopathic Parkinson’s Disease

- Second most common neurodegenerative disease after Alzheimer's Disease
- Approx 1.5 million in the US with Parkinson's disease
- About 50,000 new cases diagnosed each year in the US
- Mean age of onset 60 years
  - Prevalence 1% in >65 age; 2.5% in >80 age group
  - < 40 years is young onset (low prevalence)
- Cause is unknown, and there is presently no cure
  - 10-15% of cases may be familial
  - Possible gene-environment interaction in other cases
Pathophysiology

- Substantia nigra degenerates, results in dopamine deficiency in striatum and motor symptoms

Diagnosis

Clinical diagnosis, but *not* a diagnosis of exclusion

- Bradykinesia and at least one of the following:
  - Rest tremor
  - Rigidity
  - Postural Instability (later feature)
Diagnosis

• Exclude use of dopamine blocking meds
• Exclude common metabolic problems: TSH, CA, CBC, lytes, hepatic dysfunction
• Observation of casual gait is highly informative
• Rest tremor is a great clue but is absent in 25% of cases

Supportive criteria for PD diagnosis:
- Unilateral onset with asymmetry persisting
- Progressive symptoms
- Excellent response to levodopa
- Preclinical clues (constipation, anosmia, REM Behavior Disorder)
Ddx: Parkinson’s Plus Syndromes

- Early falls, apathy, or diplopia suggest
  - Progressive Supranuclear Palsy

- Postural hypotension, autonomic dysfunction, or cerebellar findings suggest
  - Multiple System Atrophy

- Significant cognitive impairment suggests
  - dementia with Lewy bodies

Initial Work-up

- MRI to exclude other disease processes (e.g., vascular, hydrocephalus)

- Screen for Vitamin B12 and supplement if <300pg/ml

- Screen for depression & anxiety
  - Often co-occur with early PD and should be treated
    - SSRI or SNRI first line therapy
Early Symptoms

Bradykinesia

- Paucity of movement
- Decreased amplitude of movement
- Micrographia
- Hypophonia
- Masked facies
- Reduced gesturing
- Reduced arm swing
PD Tremor

- Tremor at rest
- Often involves the thumb
- Typically slow 3-5 hertz tremor
- Improves with movement but can reemerge with sustained posture

Gait Abnormalities

Earlier signs/milder disease
- Small stride length
- Step changes/ dragging feet
- Stooped posture
- Reduced arm swing
Gait Abnormalities

Later signs

- Trouble initiating gait, changing directions, crossing thresholds
- Festinating gate - difficulty stopping (later sign)
- Postural instability (pull test)
Mild Cognitive Impairment

• 25-30% prevalence estimates; definitions have varied

• May be present even at early diagnosis
  – May not impact functioning

• Testing may demonstrate impairment in
  – Executive functioning (planning and executing tasks)
  – Attention difficulties (particularly in groups with multiple conversations)
  – Slowed thinking (time to complete tasks)
  – Word finding (due to slowed thinking, not loss of words)
  – Learning, organizing, and remembering new information
  – Imagery and spatial processing (making a mental picture)

Mild Cognitive Impairment

• Evaluation for other treatable causes
  – Vitamin B-12 deficiency
  – depression
  – fatigue
  – sleep disturbances

• PD does not cause acute fluctuation in cognition
  • Look for other cause, med effect, infection, etc.
PD Dementia

- Rate of progression to dementia remains unclear
  - Patients with PD have twice the rate of dementia compared to general pop

- Treatment in mild-moderate PD dementia (MMSE 10-24)
  - Rivastigmine 3-12mg
  - Improvements in language, memory, and praxis

Schmitt, Am J of AD & Other Dementias 2010

Initiating Treatment for Motor Symptoms

- No disease slowing therapy is available

- Delay pharmacologic treatment until symptoms interfere with function (work or social)

- Start with physical therapy, followed by development of exercise routine

- Pharmacologic therapy is aimed at dopamine replacement or preservation
Exercise

- Engagement in regular cardiovascular exercise improves fitness and walking performance
- Engagement in balance exercise decreases falls

Clinical Implication:
- Goal: 150 min/week of cardiovascular exercise
  - Exercise walking, swimming, stationary bike, elliptical, etc.
- Regular balance exercise
  - Yoga, Tai chi, dance

Li, NEJM 2012; Uhrbran, J of the Neurological Sciences 2015;
National Parkinson’s Foundation: Fitness Counts
http://www.parkinson.org/Improving-Care/Education/Education--For-Patients/NPF-Literature

How PD Medications Work

Courtesy of Dr. Jill Osterm, UCSF
Treatment: PD Medication trial

- Pragmatic RCT of newly diagnosed PD patients
- Levodopa-sparing therapy (dopamine agonist or MAO-BI) vs. levodopa
- 1620 patients followed for median 3-years
- Outcomes:
  - Mobility and QOL

PD MED Collaborative Group; The Lancet 2014

- Improvements in both groups in mobility score; average difference favors levodopa
- No difference in summary score (mobility, ADLs, emotional well-being, stigma, social support, cognition, communication, bodily discomfort)

PD MED Collaborative Group; The Lancet 2014
• Levodopa with higher risk of dyskinesia earlier;
• Risk similar over time

![Graph showing risk of dyskinesia over time]

Figure 5: Risk of developing dyskinesia in levodopa and levodopa-sparing groups

Treatment

• Carbidopa-levodopa (Sinemet) – high potency, reliable, quick onset
  – most efficacious treatment for motor symptoms of PD
  – ‘on-off’ phenomenon and dyskinesias develop at rate of 10% annually for older patients, but more rapidly for younger patients
  – First line therapy for ≥ 65 years old
  – Carbidopa prevents peripheral conversion of levodopa to dopamine allowing for lower effective doses that may last longer
### Treatment

**Carbidopa-levodopa cont.**
- 3x daily dosing at least 1 hour before meals
- Can add COMT inhibitor (entacapone, tolcapone) for improvement of bioavailability of levodopa & duration of effect
- Protein: competes with amino acids to cross the blood-brain barrier, will decrease clinical efficacy if taken with protein load

<table>
<thead>
<tr>
<th>Common side effects</th>
<th>Less common</th>
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<tbody>
<tr>
<td>Nausea</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>Psychosis</td>
</tr>
<tr>
<td>Headache</td>
<td>Depression</td>
</tr>
<tr>
<td>Insomnia</td>
<td>GI bleeding</td>
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<tr>
<td>Dyskinesias</td>
<td>Sudden sleep episodes</td>
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</tbody>
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### Treatment: levodopa sparing

**MAO-B inhibitors: mild potency**
- Selegiline, rasagiline
  - Delay need for levodopa for a few months on average
  - Risk of serotonin syndrome; monitor when taking SSRI
  - At high doses inhibit MAO-A; avoid tyramine

**Dopamine agonists, non-ergot: moderate potency**
- Pramipexole, Ropinirole, Rotigotine
  - Decreased motor fluctuations compared with levodopa
  - Impulse control disorders (e.g., compulsive gambling, snacking, sexual interests, video games), daytime sleepiness, insomnia all common (10-20%)
On-Off Phenomenon

Motor Fluctuations in PD

https://youtu.be/koL0PWCJ4lo
Dyskinesias

- Involuntary choreiform and dystonic movements
- 30-40% of patients develop dyskinesia
- Rates appear similar for MAO-BIs and dopamine agonists
- Patients on levodopa may develop them earlier
- Risk factors for dyskinesia development:
  - Younger age of onset
  - Increasing disease severity
  - Higher levodopa dosage
  - Longer disease duration

Dyskinesia Treatment

- If dyskinesia mild and not bothersome to patient – no treatment
- Bothersome / interfering with function
  - treat with amantadine
**Treatment Escalation**

- Approach to patient with wearing off phenomenon
  - Increase levodopa dose or frequency of dosing
  - If dyskinesias then develop, or duration of effect too short:
    - Add dopamine agonist or COMT
    - Lower the levodopa dose
  - Consider deep brain stimulation

**Deep Brain Stimulation**

- Best for patients with on-off phenomenon despite maximal oral therapy
- Patients must still have some benefit from levodopa, good cognition, good general health
- Expected benefits
  - Increased ‘on’ time
  - Reduced dyskinesias
  - Lower/fewer medications
- Risks
  - 2% peri-operative hemorrhagic stroke risk
  - 4% infection risk
When to Refer to a Neurologist

- Around time of diagnosis
- Poor response to medications
- Cognitive complaints
- Dysphagia
- Falls

What type of movement disorder is this?

https://youtu.be/nNQAFm2OYXQ
What type of Movement Disorder is this?

1. Parkinson’s tremor
2. Chorea
3. Essential tremor
4. Dyskinesia

Essential Tremor

- Prevalence: 1-6% of population
- Onset peaks in 3rd and 6th decades
- Women and men equally affected
- 50-70% have a family history of essential tremor
- Can be disabling
Essential Tremor

- Clinical diagnosis
- Features:
  - Upper extremity high frequency tremor
  - Present with limb movement and sustained posture
  - Head tremor (50%)
  - Voice tremor (30%)
  - Legs or chin (15%)
  - Patients often report tremor improves with alcohol

Essential Tremor

- Differential diagnosis:
  - Parkinsonism (no rigidity, bradykinesia, postural instability, or resting tremor)
  - Medication-induced tremor
    - Corticosteroids
    - Valproate
    - Lithium
    - SSRI
    - B-agonist
  - Enhanced physiologic tremor
    - Hyperthyroidism
    - Hyperglycemia
Essential Tremor

- Treatment if tremor interferes with ADLs or causes psychological stress
  - 1st line: propranolol or primidone
  - Alternatives: gabapentin, topiramate, alprazolam, sotalol
  - Botulinum toxin injection for head tremor when orals ineffective

- 15% have severe disabling tremor
  - Consider deep brain stimulation
    - 60-90% improvement in sx

Summary

- Parkinsonism: think about medication induced before diagnosing PD
- PD is a clinical diagnosis
- Treat with exercise & balance training first (and ongoing)
- Levodopa remains best pharmacologic treatment for motor symptoms
- Can start with DA in younger patients – watch for compulsive behaviors
• Deep brain stimulation reserved for severe motor symptoms on maximal oral medications
• Essential tremor – action & sustained posture
• Rule-out medication induced and enhanced physiologic
• Treat if interfering with function: propranolol or primidone