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
Idopathic 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
Clinical diagnosis, but not a diagnosis of exclusion

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

Exclude use of dopamine blocking meds

Exclude common metabolic problems: TSH, CA, CBC, lyes, hepatic dysfunction

Observation of casual gait is highly informative

Rest tremor is a great clue but is absent in 25% of cases
Diagnosis

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

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

- 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
- 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)

- Levodopa with higher risk of dyskinesia earlier;
- Risk similar over time
### 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

**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>
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<tr>
<td>Headache</td>
<td>-- Depression</td>
</tr>
<tr>
<td>Insomnia</td>
<td>-- GI bleeding</td>
</tr>
<tr>
<td>Dyskinesias</td>
<td>-- Sudden sleep episodes</td>
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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

Courtesy of Dr. Jill Osterm
Adapted from Hauser RA. Geriatrics. 2006;61:14-20.
**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 mild and not bothersome to patient – no treatment
- Bothersome / interfering with function
  - treat with amantadine
- 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
  - Consider deep brain stimulation
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

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

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
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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

• 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