Parkinson's Disease for the Internist

10 Things I’d Like You To Know

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Parkinson’s Disease for the Internist

10 Things I’d Like You To Know

- Making the diagnosis
- Differential diagnosis
- Red flags to suggest an alternative diagnosis
- PD or ET?
- DaTScan
- Non-motor features of PD
- Treatment overview
- Drugs for PD
- Surgery for PD
- Hospitalization in PD
Lecturer: a person who talks during someone else’s sleep
Making the diagnosis
Differential diagnosis
Red flags to suggest an alternative diagnosis
PD or ET?
DaTScan

Non-motor features of PD
Treatment overview
Drugs for PD
Surgery for PD
Hospitalization in PD
AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,
MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:
PRINTED BY WHITTINGHAM AND ROWLAND,
Goswell Street,
FOR SHERWOOD, NEELY, AND JONES;
PATERNOSTER ROW.
1817.
An Essay on the Shaking Palsy.

Chapter I.
Definition—History—Illustrative Cases.

Shaking Palsy. (Paralysis Agitans.)

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.
Triad of Parkinson’s Disease

- **Bradykinesia**
- Cogwheel rigidity
- Resting tremor (“pill rolling”)
  - (absent in ~20-30% with PD)

- **Postural instability**
  - (not at presentation in PD)
How accurate is the clinical diagnosis of PD?

- 35% incorrect at initial diagnosis
  - Rajput AH. Can J Neurol Sci 1991
- 24% incorrect at final diagnosis

- How well do movement disorders specialists do?
  - 8.1% revision of diagnosis (DATATOP Study)
  - Positive predictive value: 98.6% at final diagnosis
Recognizing typical features of PD
Recognizing atypical features which cast doubt on the diagnosis of PD (parkinsonian syndrome: PSP, MSA, etc.)
No other tenable diagnosis (ie, drug-induced parkinsonism)
Natural history conforms to PD
UK PD Society Brain Bank Clinical Diagnostic Criteria

- **Step 1**
  - *Bradykinesia* (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
- And at least of the following:
  - Muscular rigidity
  - 4-6 Hz rest tremor
  - Postural instability (with no other cause such as impaired proprioception)
Step 2: Exclusion criteria for PD disease

- History of repeated strokes/stepwise progression
- History of repeated head injury
- History of encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one affected relative*
- Sustained remission
- Strictly unilateral features after 3 years*
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia
- Babinski sign
- Presence of cerebral tumor or hydrocephalus*
- No response to large dose of levodopa
- Exposure to MPTP/other toxin
Step 3. Supportive prospective positive criteria for PD (≥3 required)

• Unilateral onset
• Rest tremor present
• Progressive disorder
• Persistent asymmetry
• Excellent and sustained (>5 yrs) response to levodopa
• Presence of DA dyskinesia
• Clinical course ≥ 10 years
Parkinson’s Disease: Secondary Features

- Decreased arm swing while walking
- Micrographia
- Decreased blink rate
- Decreased facial expression (hypomimia)
- Drooling
- Soft, Monotone Voice
- Freezing
  - Start hesitation
  - Cessation of ongoing movement
- En bloc turning
- Impaired postural righting reflexes
- Flexed posture
- Shuffling gait
- Difficulty arising from a chair or turning in bed
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Parkinsonism: Differential Diagnosis

- **Secondary Causes**
  - Medications
    - Antipsychotics
      - “Atypicals”
    - Antiemetics (metoclopramide)
  - Toxins
    - MPTP
    - Carbon Monoxide
    - Manganese
  - Vascular
  - NPH
  - Structural lesion (rare)

- **Parkinsonian Syndromes**
  - Progressive supranuclear palsy
    - Early Falls
    - Vertical Ophthalmoplegia
  - Multiple system atrophy
    - Parkinsonism
    - Ataxia
    - Dysautonomia (Shy-Drager)
    - Spasticity
  - Corticobasal syndrome
    - Unilateral apraxia
  - Dementia with Lewy Bodies
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Red flags suggesting Atypical Parkinsonism

- Poor response to levodopa (up to 1000 mg/day)
- Early onset dementia
- Early hallucinations or delusions
- Rapidly progressive course ("wheelchair sign")
- Early, disproportionate impairment of gait and balance; early falls
- "Lower half" parkinsonism
- Supranuclear gaze palsy including downgaze
- Early/prominent dysphagia or dysarthria
- Upper motor neuron signs
- Cerebellar signs—dysmetria, ataxia
- Early urinary incontinence
- Early orthostatic hypotension
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<table>
<thead>
<tr>
<th>History</th>
<th>PD</th>
<th>ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age At Onset</td>
<td>55-65</td>
<td>Variable</td>
</tr>
<tr>
<td>Duration of Symptoms Prior to Presentation</td>
<td>Months</td>
<td>Months-Years</td>
</tr>
<tr>
<td>Family History</td>
<td>Usually -</td>
<td>Usually + Autosomal Dominant</td>
</tr>
<tr>
<td>Response to EtOH</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Physical Exam</td>
<td>PD</td>
<td>ET</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Position of Maximal Activation</td>
<td>Rest</td>
<td>Posture and Movement</td>
</tr>
<tr>
<td>Frequency</td>
<td>3-6 Hz</td>
<td>6-12 Hz</td>
</tr>
<tr>
<td>Morphology</td>
<td>Pill-Rolling</td>
<td>Flexion-Extension</td>
</tr>
<tr>
<td>Onset</td>
<td>Unilateral</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Physical Exam</td>
<td>PD</td>
<td>ET</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------------</td>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>Most Common Body Part(s) Affected</td>
<td>Hand, Foot, Chin, Lips</td>
<td>Hands, Head, &amp; Voice</td>
</tr>
<tr>
<td>Handwriting</td>
<td>Micrographic, No Tremor</td>
<td>Normal Size, Tremulous</td>
</tr>
<tr>
<td>Associated Signs</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Natural History</td>
<td>Noticeably Progressive</td>
<td>Insidiously Progressive</td>
</tr>
</tbody>
</table>
Handwriting: PD vs. ET

Today is a nice day in Belgium.

Forcing horizontal flow in Belgium.
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DaTscan

- DaTscan images the dopamine transporter
- Deficient radiotracer uptake indicates nigrostriatal degeneration
- DaTscan is approved to distinguish essential tremor from parkinsonian tremor
- This is rarely a clinical conundrum

Ba F, Martin WRW. Dopamine transporter imaging as a diagnostic tool for parkinsonism and related disorders in clinical practice. Parkin Rel Disord 2015
DaTscan

- A DaTscan cannot distinguish PD from other PS with presynaptic DA deficit (MSA, PSP, CBS, etc.)
- There are (off label) circumstances where a DaTscan can be helpful to distinguish PD from a mimicker:
  - NPH
  - Vascular parkinsonism
  - Drug-induced parkinsonism
  - Psychogenic parkinsonism
- Consider DaTscan when the cause of parkinsonism:
  - Is legitimately unclear
  - If the result of a DaTscan will have a meaningful impact on diagnosis and therapy and...
  - If the information cannot be obtained in another way such as:
    - Longitudinal follow up
    - Consultation with a movement disorder specialist
    - Trial of levodopa
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PD: Non-Motor Features

- **Sensory**
  - Anosmia
  - Pain
  - Akathisia
  - Internal tremor
  - **Fatigue**
  - Diplopia

- **Autonomic**
  - Orthostatic hypotension
  - Neurogenic bladder
  - Constipation
  - Sweating
  - Dysphagia
  - Erectile dysfunction

- **Sleep**
  - Insomnia
  - RLS
  - REM behavioral disorder
  - Daytime sleepiness

- **Neuropsychiatric**
  - Depression
  - Anxiety
  - Panic attacks
  - Apathy
  - Executive dysfunction
  - Dementia
  - Hallucinations and delusions
  - Impulse control disorder
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Parkinson’s Disease: Treatment

• Goal: Replace (directly or indirectly) the deficiency of DA in basal ganglia

• Polypharmacy is common due to complementary effects of medications

• Dopamine: does not cross BBB therefore give precursor: levodopa

• Much of oral levodopa converted to dopamine prior to crossing BBB by DA decarboxylase

• Therefore, levodopa combined with peripheral DA decarboxylase inhibitor: carbidopa
Levodopa-phobia

- Levodopa is toxic to nigral neurons
- Levodopa stops working after 5 years
- Levodopa causes motor fluctuations
  - Temporarily delayed by initial therapy with an agonist
  - Fluctuations within 5 years of treatment are generally mild
  - Less benefit from an agonist compared to levodopa
  - More side effects from agonist
  - Long term: choice of initial therapy doesn’t seem to matter

**EDITORIAL**

Agonist or levodopa for Parkinson disease?
Ultimately, it doesn’t matter; neither is good enough

William J. Weiner, MD
Stephen G. Reich, MD

Initial dopaminergic therapy for Parkinson disease (PD) with an agonist, rather than levodopa, is associated with a lower risk of mild dyskinesias and motor plus selegiline arm experienced increased mortality and patients had to be re-randomized. Another problem is that the cohort available for the 16-year analy-
Problems with long-term Management of Parkinson’s Disease

- Continuous disease progression
  - No neuroprotective therapy
- Motor fluctuations: delayed onset of effect and end-of-dose wearing off → peaks and valleys
- Paradoxical “hypersensitivity” to dopamine:
  - Involuntary movements: dyskinesias
  - Hallucinations
- Dopamine-resistant problems
  - Imbalance, falls, dysphagia, akinesia (freezing)
- Dementia
Dyskinesias

On Time

Off Time

LEVODOPA

Time
"Don't take any of these red pills, and if doesn't work, don't take any of the blue ones."
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Carbidopa-levodopa

- Immediate release
  - 10/100; 25/100, 25/250
  - Best taken on empty stomach
  - Generally not needed HS

- Controlled release
  - 25/100; 50/200
  - Has not really fulfilled promise
  - Little benefit over IR
  - Can be useful for nocturnal symptoms

- Parcopa
  - Orally dissolvable
  - Not rapidly acting
  - Advantage: no need for water; dysphagia
New Formulations of Levodopa

- Rytary
  - Sustained/variable release
  - Decreases off time compared to IR
- Levodopa intestinal gel (Duopa)
  - Can be considered for motor fluctuations
Drugs for Parkinson’s Disease

- Anticholinergics (trihexyphenidyl; benztropine)
  - Oldest treatment for PD
  - Not used much today
  - Anticholinergic side effects

- Amantadine
  - Antiviral
  - Useful for early PD and sometimes advanced PD
  - New use: dyskinesias
  - Side effects: livedo reticularis; edema; anticholinergic effects
Drugs for Parkinson’s Disease

• Dopamine agonists: work directly on DA post-synaptic receptors
  – Pramipexole, ropinirole, rotigotine (patch)
  – Apomorphine (acute rescue therapy)
  – Benefit
    • Forestall early fluctuations
    • Once daily preparations available
    • Adjunct to levodopa for off time
  – Less beneficial than levodopa
  – Side effects
    • Edema
    • Weight gain
    • Somnolence
    • Impulse control disorders
    • Hallucinations
    • Orthostatic hypotension
Drugs for Parkinson’s Disease

- Catechol-O-methyl transferase inhibitors
  - Entacapone, tolcapone
  - Impair catabolism of dopamine $\rightarrow$ prolong half-life
  - Adjuncts to levodopa for off time
  - Generally well tolerated
  - Entacapone: may cause diarrhea (delayed; colitis)
  - Tolcapone: small risk of hepatotoxicity; monitoring of LFTs

- MAO-b inhibitors
  - Selegiline, rasagiline
  - Block reuptake and catabolism of dopamine
  - No need for tyramine free diet
  - Useful for initial therapy
  - Adjunct to levodopa for wearing off
  - No proven neuroprotection
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Surgery for PD

• Lesioning procedures
  – Thalamotomy
  – Largely replaced by DBS
  – Emerging therapy: focused ultrasound

Surgery for PD

• Deep brain stimulation
  – Gpi, STN or Vim (tremor)
  – Indications
    • Medically refractory disabling tremor OR
    • Problematic motor fluctuations despite optimal medical therapy
      – Must still demonstrate good response to levodopa
      – Increases quantity of ON time, not quality
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Hospitalization in PD

- Increased risk of delirium
- Falls
- Dysphagia
- Aspiration pneumonia
- Maintain outpatient regimen of meds
- Not all meds are on formulary; have family bring in
- Medications need to be given on time
- Don’t stop PD drugs suddenly
  - Can rarely cause NMS like syndrome
- Avoid dopamine blocking drugs (metoclopramide)
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“My view of students sleeping in my classes is that, what the hell, if they cannot arise from my teaching inspired, let them at least awake refreshed.”

Joseph Epstein

*The Art of the Nap*