Mimics of Parkinson Disease

February 14, 2016
Overview

• Review of Parkinson Disease (PD) basics
• Other conditions that mimic PD
  – Essential tremor (ET)
  – Normal Pressure Hydrocephalus (NPH)
  – Vascular parkinsonism
  – Drug-induced parkinsonism
  – Atypical parkinsonisms (MSA, PSP, CBD, LBD)
Basics of PD: Signs/symptoms

• Cardinal motor signs:
  – Bradykinesia (slowness)
  – “Cogwheel” rigidity of muscles
  – +/- tremor at rest (frequency of 4-6 Hz)
  – Postural instability

• Common non-motor signs:
  – Sleep problems
  – Depression, anxiety
  – Fatigue
  – Constipation
  – Cognitive changes
  – Urinary urgency, frequency
Basics of PD: How it affects the brain

- Cell loss occurs in substantia nigra
  - Neurons in this region produce dopamine
    - Dopamine helps to regulate movement
  - This loss of dopamine is why so many medications are intended to ↑dopamine in brain
Basics of PD: How it affects the brain

• Alpha synuclein = protein
  – Function in healthy brain unknown

• Lewy bodies = pathological hallmark of PD
  – Made of clumps of alpha synuclein

• In a very small subset of PD patients, hereditary variability in the alpha-synuclein gene contributes to developing PD

http://alzheimersnewstoday.com/
http://www.alzheimerstreatment.link/
www.michaeljfox.org
Basic of PD: Diagnosis

• Usually diagnosed *clinically*

• No definitive test for PD

• To avoid misdiagnosis, consultation with a movement disorder specialist is recommended

• Sometimes it takes several visits to clarify diagnosis

• Brain imaging is usually *not* performed
  – MRI, PET scan, or DaT scan
Basics of PD: Diagnosis

- **DaT scan**
  - FDA approved (2011) to measure dopamine transporter densities in human tissue
  - Injection of radiopharmaceutical agent
  - May assist in distinguishing between **Essential Tremor** and **Parkinsonian Syndromes**
  - Cannot diagnose PD
  - Sensitivity and specificity not 100%

Other conditions that mimic PD

1. Essential tremor (ET)
2. Normal Pressure Hydrocephalus (NPH)
3. Vascular parkinsonism
4. Drug-induced parkinsonism
5. Atypical parkinsonisms
   1. Multiple system atrophy (MSA)
   2. Progressive supranuclear palsy (PSP)
   3. Corticobasal syndrome/degeneration (CBD)
   4. Lewy Body Disease (LBD)
PD mimic: Essential Tremor (ET)

- “Familial tremor”, “benign tremor”, “hereditary tremor”
- Fairly common in older adults, but can occur at any age
  - 8x more common than PD
    - 10 million in U.S.
- Usually affects both hands, often involves head tremor and a shaky quality to voice
- Up to 20% of ET patients may develop Parkinsonian symptoms, PD, or have a family member with PD
PD mimic: Essential Tremor (ET)

- Classically, tremor with action and posture; symmetric (usually)
- Diagnosis is clinical
  - 30-50% cases mis-diagnosed
- Often responds to alcohol
- Long duration
- ~50% improvement in tremor magnitude w/ treatment
- ~30-50% will not respond to medication

For more info: www.essentialtremor.org
PD mimic: Essential Tremor (ET)

- Pathophysiology not clear
- ↑activity in the cerebellothalamocortical circuit
  - GABAergic dysfunction of the cerebellum (dentate nucleus) and brain stem, possibly caused by neurodegeneration in these regions, may lead to tremor within the cerebellothalamocortical circuit

PD mimic: Essential Tremor (ET)

- Common treatment:
  - Medication:
    - Propranolol (Inderal)
    - Primidone (Mysoline)
    - Topiramate (Topamax)
  - Surgery (refractory cases)
    - Deep brain stimulation (DBS)
    - Thalamotomy
    - MRI-guided focused ultrasound (not yet FDA-approved)

PD mimic: Normal Pressure Hydrocephalus (NPH)

- Symptoms:
  - progressive cognitive decline,
  - subcortical dementia,
  - urinary incontinence,
  - gait disorder ("magnetic")

- Imaging: big ventricles

- No known cause, but ↑likelihood:
  - Bleeding from a blood vessel or aneurysm in the brain (subarachnoid hemorrhage)
  - Certain head injuries
  - Meningitis or similar infections
  - Surgery on the brain (craniotomy)

Incidence of 5.5 per 100,000 and prevalence of 21.9 per 100,000 for suspected NPH

PD mimic: Normal Pressure Hydrocephalus (NPH)

- Diagnosis confirmed by cerebrospinal fluid (CSF) removal or by dynamic CSF studies, such as a lumbar drain
  - 70% of those who undergo CSF diversion procedures show some initial gait improvement, but this often subsequently declines
  - Only 1/3 have sustained improvement at 3 years; the cognitive and urinary function generally has a worse long-term outcome than does gait
  - Of 560 cases of dementia seen at the Mayo Clinic from 1990 to 1994, 5 (1%) had suspected NPH, but none of the 3 treated with ventriculoperitoneal shunting (VPS) improved

http://www.med.upenn.edu/cnst/user_documents/grady_113012.pdf
PD mimic: vascular parkinsonism

• Symptoms:
  – Short-stepped gait, without upper body parkinsonism, usually with an erect posture and normal or exaggerated arm swing
  – May have asymmetrical difficulty in positioning the foot or leg when walking
  – May have gait freezing when standing or turning

• Slow onset, gradual progression
• Diffuse changes in the brain: “subcortical white matter ischemia”
• No Lewy bodies or nigral degeneration
• Confirmation: post-mortem studies only
**PD mimic: vascular parkinsonism**

- **Treatment:**
  - Treating vascular risk factors and providing supportive therapy for mobility and falls prevention
  - High-dose levodopa helps some patients with vascular parkinsonism, although this has not been formally evaluated in randomized controlled trials

Diffuse changes in the brain: “subcortical white matter ischemia”

Ali & Morris. Pract Neurol. 2015
PD mimic: drug-induced parkinsonism

- Approximately 7% of people with parkinsonism developed their symptoms after exposure to certain medications
  - Any drug that blocks the action of dopamine
- 2nd most common cause of parkinsonism in older adults (after PD)
- More common in females
- More likely to be symmetrical, less likely associated with tremor (~50%)
- Loss of armswing and bradykinesia – common
- Treatment: stop the offending drug (gradually!)
  - Usually resolves within weeks to months after stopping BUT parkinsonism may persist or progress in 10-50% of patients

## PD mimic: drug-induced parkinsonism

Drugs that can cause symptoms of parkinsonism:

<table>
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<tr>
<th>Drug frequently causing parkinsonism</th>
<th>Drug infrequently causing parkinsonism</th>
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<tr>
<td>Typical antipsychotics</td>
<td>Drug-infrequently causing parkinsonism</td>
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<tr>
<td>Phenothiazine: chlorpromazine, prochlorperazine, perphenazine, fluphenazine, promethazine</td>
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<td>Butyrophenones: haloperidol</td>
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<td>Diphenylbutylpiperidide: pimozide</td>
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<td>Benzamide substitutes: sulpiride</td>
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<td>Atypical antipsychotics</td>
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<tr>
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<td>SSRI: citalopram, fluoxetine, paroxetine, sertraline</td>
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<td>Dopamine depleters</td>
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<td>Reserpine, tetrabenazine</td>
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<tr>
<td>Metoclopramide, levosulpiride, clebopride</td>
<td>Domperidone, itopride</td>
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<tr>
<td>Calcium-channel blocker</td>
<td></td>
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<tr>
<td>Flunarizine, cinnarizine</td>
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</tbody>
</table>

PD mimic: Multiple System Atrophy

**Multiple System Atrophy (MSA)**
- Adult-onset, fatal neurodegenerative disease

**Multiple System Atrophy**
- Olivopontocerebellar Atrophy
  - Cerebellar features
- Shy-Drager Syndrome
  - Degeneration of brainstem and medullary autonomic nuclei
  - Progressive autonomic failure
- Striatonigral Degeneration
  - Parkinsonian features

- Parkinsonian subtype or cerebellar subtype
PD mimic: Multiple System Atrophy (MSA)

- Synucleinopathy
- Can be difficult to distinguish from PD, particularly in the early disease stages
- Diagnosis is clinical
- Often have asymmetrical parkinsonian bradykinesia
- May develop a flexed trunk and neck posture

For more info: https://www.multiplesystematrophy.org/
PD mimic: Multiple System Atrophy (MSA)
PD mimic: Multiple System Atrophy (MSA)

**Presentation**

- **Motor features**
  - Parkinsonism
    - Slowness of movement, rigidity, tendency to fall
  - Cerebellar
    - Cerebellar ataxia

- **Neurology**
  - Parkinsonism
  - Cerebellar features
  - Pyramidal signs
  - Frontal executive dysfunction

- **Ear, Nose, and Throat**
  - Stridor
  - Dysarthria
  - Dysphonia
  - Dysphagia

- **Pneumology**
  - Aspiration pneumonia

- **Cardiology**
  - Syncope
  - Orthostatic hypotension
  - Postprandial hypotension
  - Nocturnal hypertension
  - Leg edema

- **Gastroenterology**
  - Dysphagia
  - Constipation
  - Diarrhea

- **Dermatology**
  - Hypohidrosis or anhidrosis
  - Vasomotor abnormalities

- **Psychiatry**
  - Depression
  - Anxiety

- **Sleep Medicine**
  - REM sleep behavior disorder
  - Sleep apnea
  - Excessive daytime sleepiness
  - Restless legs syndrome

- **Urology**
  - Sexual dysfunction
  - Urinary urgency and frequency
  - Nocturia
  - Urinary urge incontinence
  - Urinary retention
  - Recurrent urinary tract infections

PD mimic: Multiple System Atrophy (MSA)

Presentation

• Non-motor features
  – Cardiovascular
    • Blood pressure dysregulation
    • Syncope, dizziness, weakness
  – Urogenital

Neurology
Parkinsonism
Cerebellar features
Pyramidal signs
Frontal executive dysfunction

Psychiatry
Depression
Anxiety

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Dysphagia
Constipation
Diarrhea

Dermatology
Hyperhidrosis or anhidrosis
Vasomotor abnormalities

Urology
Sexual dysfunction
Urinary urgency and frequency
Nocturia
Urinary urge incontinence
Urinary retention
Recurrent urinary tract infections

PD mimic: Multiple System Atrophy (MSA)

- Cell loss in the striatonigral and olivopontocerebellar structures of the brain and spinal cord accompanied by profuse, distinctive glia cytoplasmic inclusions formed by fibrillized alpha-synuclein proteins
- 3.4-4.9 cases per 100,000 population
- Estimated mean incidence is 0.6-0.7 cases per 100,000 person-years
- Median survival of 6.2-9.5 years from onset
- Bronchopneumonia (48%) and sudden death (21%) are common terminal conditions in MSA

http://emedicine.medscape.com/article/1154583-overview
PD mimic: Multiple System Atrophy (MSA)

- Treatment:
  - May have initial good response to levodopa and may develop levodopa-induced dyskinesia
  - Address autonomic symptoms (such as orthostatic hypotension), sleep disturbance (stridor), etc

Hot cross bun sign refers to the MRI appearance of the pons in MSA
PD mimic: Progressive Supranuclear Palsy (PSP)

- Tauopathy
- Primary disorder of gait and balance, as well as an atypical parkinsonian disorder
- Early falls, difficulty in standing and an uncontrolled descent when sitting
- Typical PSP: symmetric akinetic-rigid syndrome, axial rigidity, supranuclear gaze palsy, continuous frontalis overactivity, reduced blink rate, retrocollis and pseudobulbar palsy

Fig 1. An illustrative image of a patient with progressive supranuclear palsy with 5 years of disease duration and retrocollis. Note that the patient is already in wheelchairs.
PD mimic: Progressive Supranuclear Palsy (PSP)

- Diagnosis is *clinical*
- 3-6 in every 100,000 people worldwide, or approximately 20,000 in U.S.
- More rapidly progressive than PD
- Accumulation of abnormal deposits of the protein tau in nerve cells in the brain
- Severely disability within 3-5 years of onset
- PD medications may provide initial benefit

“Hummingbird sign” in PSP
PD mimic: Corticobasal syndrome

- Tauopathy
- Asymmetrical akinetic–rigid syndrome (like PD)
- Loss of arm swing and 1-sided stiffness often lead to an erroneous diagnosis of PD
- Does not respond well to levodopa treatment

- Inability to make the affected limb follow commands
- Eventually the affected limb feels like it is not a part of their body, a sensation called alien limb
- ~2000–3000 people affected by CBD in the U.S.
PD mimic: Corticobasal syndrome

Corticobasal degeneration (CBD) is a rare progressive neurological disorder characterized by the loss of nerve cells and brain atrophy of multiple areas of the brain including the cerebral cortex and the basal ganglia. The initial symptoms of corticobasal degeneration tend to manifest between the ages of sixty and seventy. Some of the symptoms of CBD are similar to those of Parkinson's disease and often affect only one side of the body.

**Early Symptoms of CBD**

- **Myoclonus**
  - Involuntary, jerking movements

- **Akinesia**
  - Lack of muscle control and movement

- **Bradykinesia**
  - Slow movements

- **Cognitive Impairment**
  - Reduction in mental capacity and memory loss

- **Disequilibrium**
  - Poor balance

- **Dysarthria**
  - Impaired ability to enunciate speech clearly

- **Dysphagia**
  - Problems swallowing

- **Apraxia**
  - Inability to make familiar purposeful movements

- **Limb Dystonia**
  - Repetitive muscle contractions

- **Alien Limb Syndrome**
  - Feeling that one's arms and legs are not connected to the body
PD mimic: Corticobasal syndrome

- Progresses slowly over the course of 6–8 years

- Nerve cell loss and atrophy (shrinkage) of multiple areas of the brain including the cerebral cortex and the basal ganglia

- There is no specific treatment
  - Dystonia and myoclonus may respond to muscle relaxants or anti-seizure medications;
  - Memory and behavior problems may or may not respond to treatments, such as donepezil (Aricept), for Alzheimer's disease
  - Depression and/or anxiety can be treated with an antidepressant, such as sertraline, citalopram or escitalopram

http://www.nature.com/nrneurol/journal/v7/n5/full/nrneurol.2011.43.html
PD mimic: Lewy Body Disease

- Synucleinopathy
- 2nd most common type of progressive dementia after Alzheimer's disease (AD)
- Mean prevalence (likely underestimates):
  - Community-based: 4.2%
  - Clinic-based: 7.5%
- US: incidence 3.5/100,000 person-yrs and 31.6/100,000 person-yrs >65 y/o

- Biggest challenge in LBD = differentiation from AD
- More common at onset of LBD than AD
  - Parkinsonism
  - Visual hallucinations
  - Olfactory dysfunction
  - Constipation
  - Increased salivation
  - RBD
- H/o anxiety and depression more common in LBD than in controls
PD mimic: Lewy Body Disease

• Treatment:
  – Cognition (AD medications)
  – Parkinsonism (levodopa)
  – Hallucinations (clozapine, quetiapine/Seroquel)
  – Antidepressants
  – Sleep aids (melatonin, clonazepam/Klonopin)
PD mimic: Lewy Body Disease

• Severe hypersensitivity reactions to antipsychotics with motor and cognitive worsening can occur in all Lewy body dementias