Case Studies in Movement Disorders

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Primary Care Internal Medicine Course
October 22, 2019
Disclosures

No financial relationships relevant to the content of this presentation
“Nothing is more revealing than movement.”

“Movement never lies. It is a barometer telling the state of the soul’s weather to all who can read it.”

- Martha Graham
Movement Disorders

- Neurological syndromes characterized by either an excess or paucity of voluntary or automatic movements.
- Often associated with pathology/dysfunction of the basal ganglia or their connections.
Basal Ganglia Anatomy

- **Basal ganglia** = group of gray matter structures located deep in the cerebral hemispheres and in the diencephalon and mesencephalon

- Comprised of:
  - Striatum (caudate/putamen)
  - Globus pallidus
  - Substantia nigra
  - Subthalamic nucleus

- Functional circuits with cortex and thalamus
Characterizing Movement Disorders

- Topography
- Symmetry
- Nature (? stereotyped)
- Overflow to other body parts
- Velocity
- Rhythm
- Relation to voluntary movement
- Relation to specific tasks
- Relation to posture
- Relation to sleep
- Associated sensory symptoms
- Suppressibility
- Aggravating factors
- Precipitating factors
- Ameliorating factors
- Distractability
Movement Disorders: Phenomenology

**HYPOKINETIC**
- Parkinsonism

**HYPERKINETIC**
- Tremor
- Chorea
- Ballism
- Athetosis
- Dystonia
- Myoclonus
- Tics/stereotypies
Case 1: 63 yo contractor with tremor

- HPI: 63 yo RH male with 2 year history of left-sided stiffness and intermittent left hand tremor.
  - Present at rest and when holding objects
  - Pain/stiffness in shoulder diagnosed as “frozen shoulder”
  - Decreased dexterity in left hand

- PMHx: hyperlipidemia, hypothyroidism, gastroesophageal reflux disease, psoriasis

- Medications: ASA, rosuvastatin, esomeprazole, levothyroxine

- FHx: negative for tremor
Clinical Signs of Parkinsonism

- Tremor
- Stiffness (rigidity)
- Slowness of movement (bradykinesia)
- Postural instability
Pathology of Parkinson’s Disease

- Loss of dopamine-producing neurons in “substantia nigra”
- Decreased dopamine levels in striatum
- “Lewy bodies” – abnormal protein aggregates containing $\alpha$-synuclein
Differential Diagnosis of Parkinsonism

- Primary (Neurodegenerative)
  - Parkinson’s Disease
  - “Parkinson’s Plus” Syndromes
  - Heredodegenerative
- Other
  - Vascular (stroke)
  - Repeated head trauma
  - Brain infection
  - Drugs/toxins
Drug-Induced Parkinsonism

- Dose-related side effect of dopamine receptor-blocking agents and dopamine-depleting drugs
- Difficult to distinguish clinically from other forms of Parkinsonism
- Older patients more susceptible
- Extrapyramidal side effects can last for weeks to months after discontinuation of offending agent
Causes of Drug-Induced Parkinsonism

- **Antipsychotics**
  - Haloperidol
  - Chlorpromazine
  - Perphenazine
  - Olanzapine
  - Risperidone
  - Aripiprazole
  - Ziprasidone

- **Anti-nausea medications**
  - Metoclopramide
  - Prochlorperazine
  - Promethazine
  - Droperidol

- **Dopamine depleting agents**
  - Tetrabenazine
  - Valbenazine/deutetrabenazine
  - Reserpine
Structural Causes of Parkinsonism

- Vascular Parkinsonism
- Hydrocephalus (e.g. NPH)
- Post-traumatic

*Not everyone with Parkinsonism needs an imaging study, but should be considered if any atypical features*
DaT Scan: Role in Diagnosis?

• Dopamine transporter imaging
  – $[^{123}I]$ ioflupane binds to dopamine transporters on healthy dopamine-producing cells
  – Approved by FDA in 2011
  – Not covered by all insurance

• Differentiates neurodegenerative Parkinsonism from:
  – Essential tremor
  – Drug-induced Parkinsonism
  – Vascular Parkinsonism

• Likely useful in certain clinical settings, but not a “gold standard”
Clinical Features to Suggest Atypical Parkinsonism

- Falls at presentation
- Symmetry at onset
- Rapid progression
- Lack of tremor
- Early signs of autonomic nervous system dysfunction
- Poor response to levodopa
Atypical Parkinsonian Syndromes

- Eye movement abnormalities, axial rigidity, early falls
- Early autonomic dysfunction, cerebellar ataxia, pyramidal signs
- Early cognitive impairment (executive, visuospatial), hallucinations
- Highly asymmetric akinetic-rigid syndrome, cortical signs
- Progressive supranuclear palsy
- Multiple system atrophy
- Dementia with Lewy bodies
- Corticobasal syndrome
“Parkinsonism”

Heredodegenerative

Autosomal dominant?

Drug-induced Parkinsonism?

Dopamine antagonist?

Lower body predominant?

MRI

Vascular

NPH

Alternative diagnosis

DaT

? Parkinsonism

Neurodegenerative Parkinsonism

Idiopathic PD

Treat as PD

PD + AD

Consider neuropsych, FDG-PET

DLB

“Red flags” (consider MRI)

Symmetric?

Asymmetric?

Corticobasal syndrome

MSA-P

Early falls, axial rigidity?

PSP

Early cognitive impairment?

“Parkinsonism”

No “red flags”

Autonomic dysfunction?
Treatment of Parkinson’s Disease

- **Dopaminergic agents**
  - **Levodopa** (given with carbidopa)
  - Dopamine agonists
    - Pramipexole
    - Ropinirole
    - Rotigotine (patch)
    - Apomorphine

- **COMT inhibitors**
  - Entacapone
  - Tolcapone

- **Amantadine**

- **MAO-B inhibitors**
  - Selegiline
  - Rasagiline
  - Safinamide

- **Adenosine A$_{2A}$ receptor antagonist**
  - Istradefylline

- **Anticholinergics** (primarily for tremor)
  - Trihexyphenidyl
  - Benztropine
# PD Medications: Why the Details Matter

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<th><strong>CARBIDOPA/LEVODOPA</strong></th>
<th><strong>PRAMIPEXOLE (Mirapex®)</strong></th>
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<td>6 mg/24 hr</td>
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Levodopa vs. Dopamine Agonist

**LEVODOPA**
- Pros: More effective
- Cons: Increased risk of dyskinesias

**AGONIST**
- Pros: Longer-acting
- Cons: More short-term side effects (nausea, sleepiness, confusion, impulse control)

**OLDER**
- High comorbidity
- Cognitively impaired

**YOUNGER**
- Low comorbidity
- Cognitively intact
Treatment of PD: Enzyme Inhibitors
COMT and MAO-B inhibitors

- Block dopamine breakdown

- Currently available COMT inhibitors
  - Entacapone (available separately or in combination with C/L)
  - Tolcapone (rarely associated with serious liver damage)

- Currently available MAO-B inhibitors
  - Selegiline
  - Rasagiline
  - Safinamide
Surgical Management of PD: Deep Brain Stimulation

- High-frequency stimulation of STN or GPi effective in treating PD motor symptoms
- Indicated for idiopathic PD responsive to dopamine replacement, esp. with motor fluctuations or DA-related side effects
- Not indicated for atypical Parkinsonism
- Relatively contraindicated if dementia or significant depression
Case 1: When to Refer

- Diagnostic uncertainty
- Medication complications
- Motor fluctuations
- ? Candidate for surgical treatments
- Dementia/psychosis
- Access to clinical trials
Case 2: 83 yo gentleman with tremor

- HPI: 82 yo RH male with 6-7 year history of tremor.
  - Slight tremor in right hand when he was in service, resolved after one year
  - Now present in both hands (right>left) affecting writing and use of utensils
  - Exacerbated by anxiety, fatigue
  - Equivocal response to EtOH

- PMHx: atrial fibrillation s/p pacemaker, hyperlipidemia, vitamin B12 deficiency, osteoarthritis

- Medications: vitamin B12, rivaroxaban, MVI

- FHx: negative for tremor.
Tremor

• Rhythmic, oscillatory movement produced by alternating or synchronous contraction of antagonist muscles

• Classified based on:
  – Phenomenology
    • Rest (typically associated with Parkinsonian disorders)
    • Action
      – Postural
      – Kinetic
      – Task-specific or position-specific
  – Anatomic distribution
    • Upper/lower limbs
    • Head/neck
    • Voice
    • Trunk
  – Etiology
Essential Tremor

- Most common movement disorder (estimated prevalence up to 5% of population)
- Incidence increases with age (but can affect young individuals)
- Familial (autosomal dominant): ~ 50% with positive family history
- Most often bilateral upper extremity postural/kinetic tremor; can also affect legs, head/neck, voice
- May be responsive to alcohol
## Parkinsonian tremor vs. Essential tremor

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>ET</th>
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<tr>
<td>Tremor type</td>
<td>Typically rest</td>
<td>Postural/kinetic</td>
</tr>
<tr>
<td>Tremor onset</td>
<td>Asymmetric</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Head/neck involvement</td>
<td>Typically absent</td>
<td>May be present</td>
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<tr>
<td>Other signs?</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Response to alcohol?</td>
<td>Not beneficial</td>
<td>Beneficial</td>
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</table>
Treatment of Essential Tremor

• First-line agents
  – Propranolol: 40-240 mg/d
  – Primidone: 25-750 mg/d

• Second-line agents
  – Topiramate: 100-300 mg/d
  – Gabapentin: 1200-1800 mg/d
  – Benzodiazepines

• Likely not efficacious: zonisamide, levetiracetam, pregabalin

• Surgical options
  – Deep brain stimulation (Vim nucleus of thalamus)
  – Focused ultrasound therapy
Case 2: When to Refer

- Diagnostic uncertainty
- Failure to respond, intolerance to first-line agents
- Consideration of advanced treatment options (e.g. surgery)
Case 3: Is It ET or PD?

- **HPI:** 73 yo RH teacher with 8-10 yr h/o tremor
  - Initially with action (affecting handwriting, utensils)
  - Increasing left hand tremor over past few years
  - Intolerant of primidone due to side effects
  - Tried on low dose carbidopa/levodopa, pramipexole with unclear benefit

- **PMHx:** hyperlipidemia, asthma, cervical spondylosis

- **Medications:** atorvastatin, budesonide-formoterol inhaler

- **FHx:** strong FHx of tremor, including paternal grandmother (head/hands), father (hand), 5 paternal uncles/aunts (either head or hands), two first cousins
Case 3: ET and PD

- Patients can have both essential tremor and Parkinson’s disease
- Unclear relationship between ET and PD
- Focus on treating the symptomatic component
- May potentially require combination of medications
Enhanced Physiologic Tremor

- Most common type of tremor
- High-frequency, low-amplitude postural tremor
- Causes
  - Stress-induced: emotion, exertion, anxiety, fever
  - Drug-induced
  - Related to systemic disease:
    - Thyrotoxicosis
    - Hypoglycemia
    - Drug/EtOH intoxication/withdrawal
Causes of Drug-induced Tremor

- Bronchodilators (e.g., β-agonists, theophylline)
- Steroids
- Mood stabilizing agents (e.g., lithium, valproic acid)
- Selective serotonin reuptake inhibitors (SSRIs)
- Dopamine antagonists
- Stimulants (e.g., caffeine, methylphenidate, amphetamines, pseudoephedrine)
- Amiodarone
Orthostatic Tremor

- Limited to legs/trunk, exclusively with standing
- Relieved by sitting or walking
- Typically fast, ~13-18 Hz, tremor
- May be relieved by clonazepam or gabapentin
Case 4: 78 yo woman with head and hand tremor

- HPI: 78 yo RH female with ~ 8 yr h/o tremor
  - Side-to-side head tremor when supine
  - When dozing off, often wakes up finding head turned to the left
  - Over past 5 years, incoordination and cramping in the right hand

- PMHx: hypertension, hyperlipidemia, GERD

- Medications: ASA, amlodipine, atorvastatin, losartan, omeprazole

- FHx: negative for tremor or other movement disorder
Dystonia

- Syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures

- Classification
  - Etiology
    - Primary (> 20 genetic causes of DYT)
    - Secondary (i.e. perinatal injury, postinfectious, trauma, drug-induced, toxic)
  - Anatomic distribution
    - Focal (torticollis, blepharospasm, spasmodic dysphonia, writer’s cramp)
    - Segmental (i.e. Meige syndrome)
    - Multifocal
    - Hemidystonia
    - Generalized (typically childhood onset)
  - Age of onset
Treatment of Dystonia

- Often difficult to treat

- Pharmacologic
  - Anticholinergic: trihexyphenidyl, benztropine
  - Benzodiazepines
  - Baclofen (oral or intrathecal)

- Botulinum toxin
  - Treatment of choice for focal dystonias
  - May require repeated injection ~ 3 months
  - May develop immunoaresistance due to development of circulating antibodies

- Deep brain stimulation: globus pallidus interna (GPI)
Chorea

• Involuntary, irregular, purposeless, rapid and unsustained movements that flow from one body part to another

• Associated features
  – Parakinesia: incorporation of movements into semipurposeful actions
  – Motor impersistence: inability to maintain voluntary contraction
Differential Diagnosis of Chorea

- Huntington’s disease
- Tardive dyskinesia
- Drug-induced
- Infectious/immunological: Sydenham’s (post-streptococcal), postencephalitic, SLE, autoimmune/paraneoplastic
- Hyperthyroidism
- Chorea gravidarum (pregnancy)
- Neuroacanthocytosis
- Essential chorea
Myoclonus

• Sudden, brief, shock-like involuntary jerks caused by contraction or inhibition of one muscle or multiple muscles
  – Asterixis = negative myoclonus

• May be spontaneous or in response to stimulus or voluntary action

• Classification
  – Anatomic distribution: focal, segmental, multifocal, generalized
  – Pathophysiology: cortical, cortical-subcortical, subcortical-nonsegmental, segmental, peripheral
  – Etiology
Tics

- Recurrent, nonrhythmic, stereotyped movements (motor) or sounds (vocal)
- Often preceded by premonitory sensation
  - Usually relatively brief and intermittent
  - May be complex movements
- May be suppressible for short periods of time
Case 5: 59 yo woman with recent onset tremor

- HPI: 59 yo F with 8-10 mo h/o lightheadedness, right hand tremor.
  - Lightheadedness/dizziness with standing, diagnosed with orthostatic hypotension
  - Developed new onset right hand tremor, rest>action
  - Concern for possible Parkinson’s disease

- PMHx: breast cancer treated with mastectomy/chemoradiation, chronic low back pain, type II diabetes, orthostatic hypotension, hyperlipidemia

- Medications: pravastatin, metformin, glipizide

- FHx: negative for tremor or Parkinsonism
Functional Movement Disorders: Clinical Clues

- Abrupt onset
- History of precipitating event
- Inconsistent movements
- Incongruous movements that do not fit recognized patterns
- Spontaneous remission
- Decreased movement with distraction
- Increased movement during observation or examination

- Entrainment of the movement to frequency of repetitive movement
- Association with false weakness, sensory loss, or pain
- Responsiveness to placebo or suggestion
- Unresponsive to drugs for organic movement disorders
Key Points

• Movement disorders are characterized as hypokinetic or hyperkinetic disorders.

• Diagnosis is generally made based on careful history and exam.

• Parkinsonian disorders account for the majority of hypokinetic syndromes.

• Hyperkinetic disorders are characterized by the phenomenology of the abnormal movements.
Next Best Steps

• Neurology consultation should be considered when there is question about diagnosis, lack of expected response to treatment, or progression of symptoms.
Questions?

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