Movement Disorders: Principles of Approach in the Primary Care Setting

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“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

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<tr>
<th>HYPOKINETIC</th>
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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
Parkinsonian tremor
Bradykinesia
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
- Heredo-degenerative

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**
  - Reserpine
  - Tetrabenazine
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
  - $[^{123}\text{I}]$ ioflupane binds to dopamine transporters on healthy dopamine-producing cells

- Approved by FDA in 2011
  - 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?

**Neurodegenerative Parkinsonism**

- **Drug-induced Parkinsonism?**
  - Dopamine antagonist?
  - Lower body predominant?

- **MRI**
  - Vascular
  - NPH

- **DaT**
  - ? Parkinsonism
  - Alternative diagnosis

**Neurodegenerative Parkinsonism**

- **Idiopathic PD**
  - Early cognitive impairment?
  - No “red flags”
  - Treat as PD

- **PD + AD**
  - Consider neuropsych, FDG-PET

- **DLB**
  - Early falls, axial rigidity?
  - Symmetric?

- **MSA-P**
  - Autonomic dysfunction?
  - Asymmetric?

- **PSP**

- **Corticobasal syndrome**
  - “Red flags” (consider MRI)

*DLB = Dementia with Lewy bodies, MSA-P = Multiple System Atrophy, PD = Parkinson’s disease, PSP = Progressive Supranuclear Palsy*
Treatment of Parkinson’s Disease

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

- **COMT inhibitors**
  - Entacapone
  - Tolcapone

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

- **Anticholinergics** *(primarily useful for tremor)*
  - Trihexyphenidyl
  - Benztropine

- **Amantadine**
Levodopa vs. Dopamine Agonist

**Pros:**
- Levodopa: More effective
- Dopamine Agonist: Longer-acting

**Cons:**
- Levodopa: Increased risk of dyskinesias
- Dopamine Agonist: More short-term side effects (nausea, sleepiness, confusion, impulse control)

**Younger:** Low comorbidity, cognitively intact

**Older:** High comorbidity, cognitively impaired
Treatment of PD: Enzyme Inhibitors

LeWitt, NEJM 359:2468, 2008
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
  – Rasagilin (controversial role as disease-modifying agent)
  – 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:** 83 yo LH male with 6-7 yr history of tremor.
  - Present in both hands, worse with action
  - Interferes with handwriting, piano playing
  - Exacerbated by anxiety, fatigue
  - Equivocal response to EtOH

- **PMHx:** hypertension, hypothyroidism, peripheral neuropathy, anxiety/depression.

- **Medications:** aspirin, irbesartan, levothyroxine, fluoxetine, alprazolam, gabapentin, 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: ~ 4% > age 40
- 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

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<tr>
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<th><strong>PD</strong></th>
<th><strong>ET</strong></th>
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<tbody>
<tr>
<td>Tremor type</td>
<td>Typically rest</td>
<td>Postural/action</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>
</tr>
<tr>
<td>Other signs?</td>
<td>Present</td>
<td>Absent</td>
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<tr>
<td>Response to alcohol?</td>
<td>Not beneficial</td>
<td>Beneficial</td>
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Treatment of Essential Tremor

- **First-line agents**
  - Propranolol: 40-240 (320) 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
Essential Tremor: Treatment Algorithm

1. Establish diagnosis of ET
2. Education and support
3. Is there a need for medication?
   - Yes: Administer continuous therapy
     - Primidone
     - Propranolol
   - No: Rule out other conditions
4. Administer “as needed” therapy
   - Parkinson, Cerebellar disease, Dystonia, Neuropathy
   - Judicious use of ethanol (60 mL) 10 to 15 min before anticipated event
   - Propranolol 20–80 mg 2 hrs before anticipated event
5. Is tremor not controlled?
   - Yes: Administer combination therapy (primidone + propranolol)
   - No: Benzdiazepines, Gabapentin, Topiramate
6. Is therapy successful?
   - Yes
   - No: BTX injection
   - No: VIM DBS
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, pramipexole.

- **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
- Controversial 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

Sawle, Movement Disorders in Clinical Practice, 1999 (with permission)
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 developing immunoresistance 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
- 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
Tourette syndrome
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
Summary

• 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.

• It is important to exclude reversible causes (e.g., drug-induced) and recognize functional disorders.

• Pharmacologic and/or surgical options may be available for symptomatic treatment.
Thanks!

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