What’s Shaking? Tremors and Movement Disorders

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Objectives

- Overview of Parkinson’s disease
- Review phenomenology of Parkinson’s disease
- Discuss the differential diagnosis of PD
- Review medications used to treat PD
- Updates on surgical treatment for PD with DBS
- Briefly highlight possible future treatment approaches with gene therapy for PD

Parkinson's Disease

- A movement disorder and the second most common neurodegenerative disease after Alzheimer's disease.
- As many as one million individuals in the US live with Parkinson's disease.
- About 50,000 new cases are diagnosed each year in the US.
- Mean age of onset 60 years.
- Cause of the disease is unknown, and there is presently no cure.
PD is primarily caused by degeneration of dopamine neurons.

**Pathology**

**Normal**

**PD**

Courtesy of Kapil D. Sethi, MD, FRCP (UK)

**Histology of PD Showing Lewy Body**

**Proposed Etiology of Parkinson’s Disease**

- GENES
  - α-synuclein
  - Parkin
  - UCH-L1
  - Other

- PATHOGENIC MECHANISMS
  - Protein aggregation
  - Mitochondrial dysfunction
  - Oxidative stress
  - Inflammation
  - Excitotoxicity

- ENVIRONMENT
  - Pesticides
  - Rural living
  - Other (?)

UCH-L1 = ubiquitin hydrolase L1.

Cardinal Clinical Features of PD

Motor Features:
- Tremor
- Rigidity
- Bradykinesia/akinesia
- Postural instability (later stages)
Non-motor Symptoms in PD

- Neuropsychiatric symptoms  
  - depression, apathy, anxiety, hallucinations, dementia
- Sleep disorders  
  - RLS, PLM, REM behavior disorder, EDS, vivid dreaming, insomnia
- Autonomic symptoms  
  - bladder disturbances, urgency, nocturia, frequency, sweating, orthostatic hypotension,
- Sexual dysfunction  
  - hypersexuality, erectile dysfunction, impotence
- Gastrointestinal symptoms  
  - dysphagia/choking, reflux, nausea, constipation,
- Sensory symptoms  
  - pain, paresthesia, olfactory disturbance
- Other:  
  - fatigue, diplopia, blurred vision, seborrhea, weight loss

Typical Progression and Clinical Course

- Preclinical Phase: -2 to -6
- Honeymoon Period: 0
- Motor Complication Period: 3
- Resistant Symptoms: 8
- Cognitive Decline: 15
- Therapy
- Diagnosis

PD: Motor Complications (Moderate PD)

- "ON" Dyskinesia
- Good "ON," without dyskinesia
- "OFF"
**PD: Differential diagnosis**

- 75% of parkinsonism in specialty clinic is “idiopathic PD”
- 25% atypical (“Parkinson’s Plus”) or secondary

**Atypical Parkinsonism**
1. Rapid progression
2. Early prominence of Red Flags...
   - Autonomic failure (MSA), Cerebellar signs (MSA-C)
   - Falls (MSA, PSP…)
   - Axial/Dysphagia (PSP)
   - EOM/Gaze palsies (PSP)
   - Alien limb, cortical sensory (CBD)
   - Dementia (DLB, AD)
   - Psychosis (DLB)
3. Lack of response to levodopa (!!!)
4. Relative Symmetry
5. Relative Lack of tremor

**Secondary Parkinsonism**
1. Vascular
2. Drug-induced (antipsychotics, antiemetics)
3. Other:
   - dystonia-park (Lubag, DYT3)
   - NPH/hydrocephalus
   - calcification
   - infxs/post-infxs
   - (rarely: trauma, tumor, PKAN, Wilson’s, Juvenile Huntington’s, psychogenic)

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**Parkinsonism Differential Diagnosis**

- Absence of secondary causes:
  - Medication induced parkinsonism (Tardive)

<table>
<thead>
<tr>
<th>Generic</th>
<th>(Trade Name)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Thorazine®</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>Permitil®, Prolixin®</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Haldol®</td>
</tr>
<tr>
<td>Loxapine</td>
<td>Loxitane®, Daxolin®</td>
</tr>
<tr>
<td>Mesoridazine</td>
<td>Serentil®</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Reglan®</td>
</tr>
<tr>
<td>Molindone</td>
<td>Labinex®, Moheut®</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>Trilafon® or Triavil®</td>
</tr>
<tr>
<td>Piperacetazine</td>
<td>Quide®</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>Compazine®, Combid®</td>
</tr>
<tr>
<td>Promazine</td>
<td>Spaspine®</td>
</tr>
<tr>
<td>Promethazine</td>
<td>Phenergan®</td>
</tr>
<tr>
<td>Thiethylperazine</td>
<td>Toremif®</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Mellaril®</td>
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<tr>
<td>Thiothixene</td>
<td>Navane®</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>Stelazine®</td>
</tr>
<tr>
<td>Triflupromazine</td>
<td>Vespar®</td>
</tr>
<tr>
<td>Trimeprazine</td>
<td>Tranipl®</td>
</tr>
</tbody>
</table>

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**Audience Question:**
What is the likely diagnosis?

1. Essential tremor
2. Drug induced tremor
3. Parkinson’s disease
4. I have no idea- refer to a neurologist!

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**ET vs PD Tremor**

<table>
<thead>
<tr>
<th>Essential Tremor (ET)</th>
<th>Parkinson’s disease (PD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action/Postural</td>
<td>Rest</td>
</tr>
<tr>
<td>Symmetric</td>
<td>Asymmetric</td>
</tr>
<tr>
<td>5-10 Hz</td>
<td>4-6 Hz</td>
</tr>
<tr>
<td>Flexion/extension tremor, flapping</td>
<td>Pronation/supination, rolling</td>
</tr>
<tr>
<td>Head/neck/voice involved</td>
<td>Chin, legs involved</td>
</tr>
<tr>
<td>Primidone, propranolol, alcohol</td>
<td>Dopamine-responsive</td>
</tr>
<tr>
<td>No other parkinsonism</td>
<td>Rigiditty, Bradykinesia, Posture/Gait</td>
</tr>
<tr>
<td>Associated features: hearing loss, mild ataxia</td>
<td>Associated features: anosmia, MCI, RBD, constipation, ANS…</td>
</tr>
<tr>
<td>50-70% (+) family history (80% young)</td>
<td>5-10% (+) family history</td>
</tr>
</tbody>
</table>
Parkinson’s Disease Medications

**• LEVODOPA**
  - Sinemet IR / CR
  - Stalevo (Sinemet + Comtan)
  - Parcopa (dissolvable)

**• DOPA DECARBOXYLASE INHIBITOR**
  - Carbidopa (Lodosyn)

**• COMT INHIBITORS**
  - Tolcapone (Tasmar)
  - Entacapone (Comtan)

**• MAO-B INHIBITORS**
  - Selegiline (Eldepryl/Zelapar)
  - Rasagiline (Azilect)

**• DOPAMINE AGONISTS**
  - Pramipexole (Mirepex)
  - Ropinirole (Requip)
  - Bromocriptine (Parlodel)
  - Apomorphine (Apokin)
  - Rotigotine (Neupro) (7/12)

**• ANTICHOLINERGICS**
  - Trihexyphenidyl (Artane)
  - Benztropine

**• NMDA RECEPTOR ANTAGONIST**
  - Amantadine (Symmetrel)

Case: Pt is a 50 yr old who presents with mild unilateral rest tremor, bradykinesia, and rigidity.

What would you use as first line therapy?

1. Carbidopa/Levodopa (Sinemet)
2. Rasagiline (Azilect)
3. Pramipexole (Mirepex)
4. Ropinerole (Requip)
5. Selegiline (Eldepryl)
6. Trihexyphenidyl (Artane)

**Sinemet – (Carbidopa/Levodopa)**

- First developed in the late 1960s, rapidly became the drug of choice for PD
- Most effective Rx for majority of symptoms
- Large neutral amino acid, requires active transport across the gut-blood and blood-brain barriers
- Rapid peripheral decarboxylation to dopamine without a (L-aromatic-amino-acid decarboxylase inhibitor) >75 mg/day (carbidopa)
- Most PD patients will eventually need some levodopa

**Sinemet Formulations**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Onset</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Release</td>
<td>20-40 min</td>
<td>2-4 hours</td>
</tr>
<tr>
<td>10/100, 25/100, 25/250</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled Release</td>
<td>30-60 min</td>
<td>3-6 hours</td>
</tr>
<tr>
<td>25/100, 50/200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parcopa (dissolvable carbidopa/levodopa)</td>
<td>20-40 min</td>
<td></td>
</tr>
</tbody>
</table>

Side effects:
- nausea, postural hypotension, sedation, neuropsychiatric effects
Dopamine Agonists:

- Bromocriptine (Parlodel) - D1, D2, ergot
- Pergolide (Permax) - D1, D2, ergot
- Pramipexole (Mirapex) - D3, D2, non-ergotamine
- Ropinerole (Requip) - D2, D3, non-ergotamine
- Apomorphine (Apokyn)
- Rotigotine (Neupro) – DA Patch (7/12)

Often choice for young onset patients

- Advantages:
  - Longer half-live than levodopa
  - Not metabolized or effected by protein intake
  - Not associated with dyskinesia alone as much as with levodopa
  - Delays need for levodopa
- Disadvantages:
  - More expensive then levodopa
  - Cognitive and behavioral side effects

COMT- Inhibitors

Entacapone (Comtan)
- Dosage: 200 mg w/each Sinemet
- Reduces off time (1-2 hours)
- Side effects: diarrhea (5%), dopaminergic symptoms, discolored urine

Tolcapone (Tasmar)
- First COMT-inhibitor licensed in the U.S.
- Dosage: 100mg TID or 200mg TID
- Reduces off time (2-3 hours)
- Side effects: diarrhea (15%), acute fulminant hepatic necrosis - mandatory monitoring of liver function enzymes, q2-4 wks for 1st 6 months, then less often

Stalevo

Treatment of end-of-dose “wearing off”

<table>
<thead>
<tr>
<th></th>
<th>Carbidep</th>
<th>Levodopa</th>
<th>Entacapone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stalevo 50</td>
<td>12.5mg</td>
<td>50mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>Stalevo 75</td>
<td>18.7mg</td>
<td>75mg</td>
<td>200mg</td>
</tr>
<tr>
<td>Stalevo 100</td>
<td>25mg</td>
<td>100mg</td>
<td>200mg</td>
</tr>
<tr>
<td>Stalevo 125</td>
<td>31.25mg</td>
<td>125mg</td>
<td>200mg</td>
</tr>
<tr>
<td>Stalevo 150</td>
<td>37.5mg</td>
<td>150mg</td>
<td>200mg</td>
</tr>
<tr>
<td>Stalevo 200</td>
<td>50mg</td>
<td>200mg</td>
<td>200mg</td>
</tr>
</tbody>
</table>
MAO-B Inhibitors

Eldepryl (Selegiline) (5mg BID)
- Irreversible MAO-B inhibitor
- Developed as an anti-depressant; metabolized to methamphetamine
- Data unclear that it slows progression in PD
- Should not be used in conjunction with SSRI antidepressants, foods high in tyramine, (risk of serotonin syndrome)

Rasagiline (Azilect)- FDA approval 5/06, (0.5mg, 1 mg QD)
- No amphetamine breakdown products
- Interest in possible neuroprotective properties
- Novel delayed-start study design

Medication for Parkinson’s Disease

Motor Fluctuations in PD

Off Medications On Medications

Case: 68yo female with moderate PD who is experiencing motor fluctuations and peak dose dyskinesia.

Current medications:
Mirepex 0.5mg TID
Sinemet 25/100 2 tabs TID
Azilect 1.0 mg QD

How would you adjust her medications?
A. Increase Mirepex to 1.0mg TID
B. Add Comtan 200mg TID
C. Change Sinemet to 25/100 1 1/2 tabs QID
D. Refer to a neurologist!
PD: Progression

<table>
<thead>
<tr>
<th></th>
<th>Mild PD</th>
<th>Moderate PD</th>
<th>Advanced PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor Symptoms</td>
<td>Predominantly motor, minor non-motor</td>
<td>Advanced motor symptoms, more bothersome non-motor</td>
<td>Continued motor, more axial, non-motor symptoms become most disabling features</td>
</tr>
<tr>
<td>Non-motor Symptoms</td>
<td>Minimal/Mild: anosmia, constipation, RBD</td>
<td>More bothersome: MCI, depression, ANS symptoms</td>
<td>Severe: Dementia, psychosis, ANS failure, frequently the most disabling features</td>
</tr>
<tr>
<td>Treatment Response</td>
<td>Robust, consistent</td>
<td>Motor complications: wearing off (fluctuations) and dyskinesia</td>
<td>Motor no longer focus, may need to lower dopaminergic meds.</td>
</tr>
</tbody>
</table>

Deep Brain Stimulation Therapy

An implantable system that modulates brain activity to improve motor symptoms of PD

Components
- Lead and Extension
- Neurostimulator (IPG)
- Physician Programmer
- Patient Controller

Surgical Treatment Options

Deep Brain Stimulation
- Device-based therapy
- Delivers electrical stimulation

Advantages
- Non-destructive
- Adjustable
- Reversible
- Can be turned on and off, lending itself to rigorous evaluation
- Safer for bilateral use

Disadvantages
- Risks of chronically implanted device
- Infection, migration, device failure
- Pt needs access to programming
- Finite battery life
- Cost
- Cosmesis

What are some of the currently approved indications for DBS?

1. Essential tremor
2. Primary dystonia
3. Parkinson’s disease
4. Obsessive compulsive disorder
5. All of the above
History of DBS and Current FDA Approved Indications

1987  First DBS implanted, ET
1995  DBS approved (Europe, Canada, Australia) for ET and PD tremor
1997  DBS approved (USA) for ET and PD tremor
1998  DBS approved (Europe, Canada, Australia) for advanced PD
2002  DBS approved (USA) for advanced PD
2003  DBS HDE approved (USA) for primary dystonia
2009  DBS HDE approved (USA) for OCD

Traditional Surgical Procedure

- Performed using stereotactic neurosurgical techniques
- Frontal approach used

DBS Lead Placement
Stereotactic Neurosurgical Procedure

The technical goal of surgery:
- Place an electrode within the motor territory of the desired nuclear target
- Not encroaching on neighboring white matter or grey matter structures... this may lead to major adverse effects

Mechanism of DBS

- Exact mechanism not fully understood.
- Produces a functional inactivation by multiple possible mechanisms.
- DBS also activates axons and generates a diversity of effects at a local and at a system level.
- Results in increased and decreased firing rates, change in firing patterns, synchronization and oscillatory properties of the network.

Pathophysiology
basal ganglia interconnected loops
Bilateral Deep Brain Stimulation vs Best Medical Therapy for Patients With Advanced Parkinson Disease
A Randomized Controlled Trial

Bilateral Deep Brain Stimulation vs Best Medical Therapy for Patients With Advanced Parkinson Disease
A Randomized Controlled Trial

Levodopa response - helpful predictor of outcome

Pre-Op: Off Meds
Pre-Op: On Meds

Subthalamic Nucleus (STN) DBS for PD

Pre-Op: Off Meds
Post-Op: Off Meds, Bilateral STN DBS
Globus Pallidus (Gpi) DBS for PD

Pre-Op: Off Meds
Post-Op: Off Meds, Bilateral Gpi DBS

Gene Therapy for Parkinson’s Disease

• Adeno-Associated Viral Vector (AAV2)
  – A tool for gene transfer
  – Is genetically engineered in which all AAV genes have been removed and the DNA coding sequences required to express the desired gene are inserted
Gene Therapy for PD

**AAV GAD**
Glutamic acid decarboxylase- enzyme which controls the production of inhibitory neurotransmitter GABA
- Unilateral infused into the STN
- Positive Phase II study: 6 months 23.1% improvement in off UPDRS vs 12.7% in sham surgical group. (p<0.04).

**AAV AADC**
Aromatic acid decarboxylase- enzyme involved in making DA, converts levodopa to dopamine
- Bilateral infusion into the Putamin
- Mild improvement in off UPDRS motor score
- F-Fluorometatyrosine PET imaging showed a dose related increased uptake in the putamen

**AAV Neuturin- (Cere-120)**
Neurotrophic factor- may help DA cells survive
- 1st Phase II trial negative (putamin), 2nd Phase II trial (putamin + SN) underway

Conclusions
- PD remains a common and complicated disease to treat.
- Fortunately, there are many medications available to treat the many motor and non-motor symptoms.
- When medical options fail to improve motor fluctuations, deep brain stimulation (DBS) may be an option.
- Recently, gene therapy trials in PD have proven safe, and there is hope this new therapeutic approach might have disease modifying effects.