Clinical cases in Parkinson’s Disease

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• In 1817 James Parkinson provided the first clinical description in the “An Essay on the Shaking Palsey” from observations of six patients (three only casually examined). He described tremor, fixed posture and paralysis and coined the term bearing his name Parkinson’s disease.
Disrupted signaling between basal ganglia, cortex, and thalamus

Degeneration of neurons in substantia nigra pars compacta

Loss of dopaminergic input to striatum

Corpus striatum

Caudate nucleus

Putamen

Globus pallidus

Cortex

Thalamus

Midbrain

Pathophysiology of Parkinson’s Disease
Braak Model

- Begins in dorsal motor nucleus of glossopharyngeal and vagus nerves, anterior olfactory nucleus, and enteric nerve cell plexus
- Proceeds in rostral direction toward neocortex

Braak stage

1-2
- Premotor

3-4
- Motor

5-6
- Cognitive decline

Motor Symptoms

• Tremor at rest
• Bradykinesia
• Rigidity
• Postural instability
• Decreased arm swing when walking
• Micrographia
• Hypophonia
• Masked face
• Slow, shuffling gait
• Stooped posture

Waters CH. Diagnosis and Management of Parkinson's Disease. 3rd ed. 2002.
# Non-motor Symptoms

<table>
<thead>
<tr>
<th>Cognitive/Psychiatric</th>
<th>Autonomic</th>
<th>Sensory/Pain</th>
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<tbody>
<tr>
<td>• Anxiety</td>
<td>• Drenching sweats</td>
<td>• Tingling sensation</td>
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<tr>
<td>• Depression</td>
<td>• Dyspnea</td>
<td>• Akathisia</td>
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<tr>
<td>• Fatigue</td>
<td>• Orthostatic hypotension</td>
<td>• Olfactory deficit</td>
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<tr>
<td>• Slow thinking</td>
<td>• Sexual dysfunction</td>
<td>• Diffuse pain</td>
</tr>
<tr>
<td>• REM</td>
<td>• Seborrhea</td>
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<tr>
<td>• Sleep fragmentation</td>
<td>• Constipation</td>
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<tr>
<td>• Hallucinations</td>
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<tr>
<td>• Dementia</td>
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</tbody>
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Waters CH. *Diagnosis and Management of Parkinson’s Disease*; 2002.
Tremor

- **Parkinsonian**
  - AGE > 50 years
  - Hands resting pill rolling, legs, jaw
  - Head tremor uncommon
  - 4-7 HZ
  - Cogwheel rigidity
  - Incidence increases with every decade
  - Anticholinergic, dopaminergic

- **Essential**
  - AGE > 10 years
  - Family hx common
  - Hands, head vocal
  - 8-12 Hz
  - Improves with alcohol
  - B-blockers, primidone
  - Methazolamide, Topomax, Keppra
Case #1 Mr. W

58 y/o RH man with 10 year history of PD. He has been experiencing tremor with pouring and using utensils for 15 years. He is tired, constipated, slow and the tremor is progressing. He has tried Artane which resulted in dry mouth and teeth loss. Azilect was tried and discontinued after 2 months. He is not sure how much benefit he gets from CD/LD 25/100 two tablets 3XD.
Case Mr. W

- Medical History:
- HTN
- DM
- PD
- ED
Case Mr. W

Current medications:

• Enalapril
• Metformin
• Viagra
• Sinemet 25/100 two tablets 3XD
• Omeprazole
Case Mr. W

Neurological examination:
- Resting tremor right more than left
- Bilateral action tremor
- Two hours since last dose
- Symmetrical slowing with RAM
- Posture mildly stooped
- Gait slow cautious
- Brisk reflexes, right hip flexor 4/5
Case Mr. W

- Why is he not responding to medication?
- Is weakness part of Parkinson’s Disease?
- How would you work him up?
Work up

- TSH, T4, PTH, ANA, B-12
- 24 hour urine: copper, heavy metal
- Celiac panel
- Antiphospholipid antibody
- MRI
Case Mr. W

- Test results:
- Vitamin B12 was 113
Case Mr. W

- He was tapered off of CD/LD
- He was diagnosed with ET
- Treated with B12 injections first
- Tremor improved with normal B12 levels
- Topiramate was added with excellent results
Case #2 JD

- 42 y/o left-handed man with one year history of tremor and clumsiness with coordination. He is a salesman and has frequent presentations. His colleagues wonder if he has a drinking problem or confidence issues. His wife is embarrassed and it bothers her when he “shakes”. He is becoming more self conscious and keeps his hand in his pocket. He is worried about his job and the stress makes the tremor worse. He decided not to apply for the management position. He is tired and believes it is from the “trashing and kicking all night” reported by his wife. She has moved to another room 3 years ago. He is becoming withdrawn and not interested in meeting friends for golf. He has been in good health and is presently not taking any medication.

- His father had tremor and he was much older when the tremor started. No tremor in siblings.
Case JD

- Neurological Exam: MMSE 30
- Mild facial masking, decreased blink rate, hypophonia, right hand resting tremor 4-6HZ, rigidity, decreased RAM r>l. He can arise from chair without difficulty, posture normal, decreased arm swing on the right. Hand writing normal amplitude.
Case JD

- What is best for JD now vs. long term?
- If he was your brother what would you give him?
Modern Developments in Symptomatic Parkinson’s Disease Medications

- 1860: Belladona
- 1940: Benzhexol and Benztropine
- 1967: Levodopa
- 1969: Amantadine
- 1970: Decarboxylase inhibitors
- 1974: Dopaminergic agonists
- 1976: Apomorphine
- 1982: Monoamine oxidase-B inhibitors
- 1988: Sustained-release levodopa preparations
- 1995: Catechol-O-methyltransferase inhibitors
- 2000: Adenosine A2A antagonists
- 2004: AMPA antagonists
### Currently Approved Therapies

<table>
<thead>
<tr>
<th>CLASS</th>
<th>AGENT</th>
<th>MONO-Rx</th>
<th>ADJ to LD</th>
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<tbody>
<tr>
<td>Dopamine</td>
<td>Sinemet®</td>
<td>√</td>
<td>NA</td>
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<tr>
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<td>Parcopa®</td>
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<tr>
<td>Dopamine Agonists</td>
<td>Parlodel®</td>
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<td></td>
<td>Permax®</td>
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<td>Mirapex®</td>
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<td>Requip®</td>
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<td>Symmetrel®</td>
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<td>Apokyn®</td>
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<tr>
<td>Anticholinergics</td>
<td>Cogentin®</td>
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<tr>
<td>COMT Inhibitors</td>
<td>Comtan®, Stalevo®</td>
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<td>Tasmar®</td>
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<tr>
<td>MAO-B Inhibitors</td>
<td>Eldepryl®, Zelapar®</td>
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<tr>
<td></td>
<td>AZILECT® (rasagiline tablets)</td>
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# Motor Fluctuations in Patients on Chronic Levodopa

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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| Hyperkinetic  | - Peak-dose chorea  
               - Diphasic dyskinesia                                                      |
| Dystonic      | - Early-morning dystonia  
               - End-of-dose dystonia  
               - Peak-dose dystonia                                                      |
| Hypokinetice | - Early-morning akinesia  
               - End-of-dose deterioration, 'wearing-off effect'  
               - Sudden 'switching off’                                                  |

Comparison of the Agonist Pramipexole vs Levodopa on Motor complications in Parkinson's Disease

- 31% of patients at 2 years or less had dyskinesias, and 38% of patients who were on levodopa therapy had wearing off.
Case JD

• He has significant functional impairment and needs to keep his employment.
• Consider all treatment outcomes; short and long term.
• Discuss options with the patient and provide opportunity for the patient to participate in the treatment decision.
Case #3 MA

• 54 y/o man on levodopa/carbidopa (total dose of 1,000 mg of levodopa per day) for about 3 years with some improvement of his motor difficulties initially. Subsequently Pramipexole, was added and gradually increased to achieve a target dose of 4.5 mg per day within 2 months.
Case MA

- He developed persistent involuntary forward flexion movement of his neck, which caused local discomfort and further impairment of speech, eye contact, and swallowing.
Case MA

- What is your next step?
Case MA

- Dopaminergic medication-induced facial dystonia is a well-recognized complication in MSA.
- Anterocollis-amelioration by Levodopa and deterioration by dopamine agonists
- Parmipexole was discontinued.
- Two months later after PT and Speech therapy the anterocollis resolved.
Case #4 Mr. P

- 62 y/o RH man with 7 year history of PD. He comes in with progressive worsening of gate, more shuffling, fatigue. He has difficulty with his wife. She feels he does not care for her or the family. His face shows no desire or interest in her. He responds with “I don’t care” when she asks what he wants for dinner. He needs to reassure her there is no other woman. He is on medical disability and stays home most days. He would like to contribute more with household chores and to feel like a valuable member of society. His grand-daughter does not want to be near him because he looks mad. The medicine is wearing off 30 minutes before the next dose.
Case Mr. P

Medical history

- PD for 7 years
- Depression 25 years
- Generalized anxiety 10 years
Case Mr. P

- Medications:
  - Carbidopa/levodopa 25/250 4 times a day and is lasting about 3.5 hours
  - Ropinarole 4 mg three times a day
  - Zoloft 50 mg once a day
Case Mr. P

- Exam:
- Marked facial masking, seborrheic dermatitis, hypophonia, resting tremor mild, rigidity moderate left>right. He can rise from chair without pushing off. Posture is stooped, shuffles, turns enblock, pull test is positive without recovery. Mild dyskineasia. Handwriting is small and becomes smaller as he continues to write.
End-dose failure, "wearing off," motor fluctuations?

- dystonia in extremity
- Pain
- Freezing
- Anxiety
- sweating
Treatment for wearing-off

- increase the Levodopa dose.
- increase the frequency of Levodopa
- controlled-release Levodopa,
- MAO-B inhibitors: Azilect, Selegiline
- Dopamine agonists
- add Comtan a catechol-O-methyltransferase inhibitor
Apomorphine

- very severe "off" states
- subcutaneous administration
- very rapid 5 to 15 minutes rescue from the "off." It induces a good "on." $t_{1/2}$ 0.5h
- Tigan pre-treatment 250mg tid x7 days
- Domperidone 20mg tid x14 days
- 45 minutes to 2 hours after administration it produces a powerful emetic effect.
Comtan/Entacapone

- extends the levodopa half-life by about 85% from 1 to 1.5 h to about 2.25 h
- increase on time by 1-1.7 hours.
- Off time reduced by about 1.1-1.5 hours.
- Use with levodopa only
- Sudden withdrawal may cause akinetic crisis
- Urine discoloration – reddish orange
- Maximum 8 tablets per day 1600 mg of comtan/entacapone
Amantadine

- 100mg (400/d maximum)
- Increased DA synthesis
- An amphetamine-like action releasing catecholamine from presynaptic stores
- Blocking DA & NE re-uptake
- Mild anticholinergic
- Antiglutamate via antagonism at NMDA receptor
AAN Practice Parameter 2006 to reduce off time

- Entacapone and rasagiline should be offered (Level A recommendation)
- Paraglide, pramipexole, ropinirole, and tolcapone should be considered (Level B). Tolcapone and paraglide should be used with caution and require monitoring for toxicities
- Apomorphine, cabergoline*, Amantadine and selegiline may be considered (Level C)
- Sustained-release CD/LD and bromocriptine may be disregarded (Level C)
- Relative efficacy
  - Ropinirole may be chosen over bromocriptine (Level C)
  - Insufficient evidence for other relative efficacies (Level U)

*Not available in the United States

Case Mr. P

• Selegiline 5 mg in am was added.
• Follow up appointment in 2 months revealed marked improvement in motor ability. More ON time
• Improved family relationship
• He is looking for a part time job
Case #5 TP

- 36 y/o rh man with 3 year history of right sided tremor, shuffling gait, intermittent dysarthria, micrographia, right shoulder pain which he attributed to MVA. PMH celiac disease. Over the last month he is having early dystonia, ED. Has tried Requip, Stalevo, Sinemet, Amantadine, Wellbutrin, Keppra.
Case TP

- He has been on gluten free diet and has obtained some benefits in regards to having more clear thought process.
- He has also tried Glutathione infusions in Florida with some benefits for few days.
- He is presently on supplements only.
Case TP

Medical history
- Celiac disease
- Parkinson’s disease
- Depression
- ED
Case TP

- On exam he has marked facial masking, tachyphemia, decreased voice volume, moderate resting tremor r>I, rigidity, shuffling gate, micrographia, light headed upon rising from the chair with no orthostatic hypotension.
Case TP

• He was started on Rasagiline .5 mg half a tablet once a day because of his sensitivity to all previous medications. He was gradually increased to 1 mg over several months. In 4 months he was re-evaluated. His mood was better, marked improvement in facial expression with no benefit for the tremor.
Case TP

- He had marked rigidity. He had tried DA and did not tolerate them. Sinemet 25/100 ½ tablet was introduced in the morning and tapered up at his tolerance. In two months he was taking Sinement one tablet 4 time a day with improvement in rigidity and gait. Tremor was not better. He underwent DBS-STN with good improvement of the tremor and motor function and was able to go back to work.
Case #6 Mrs. RW

- 54 y/o woman with 1 year history of stiffness, left hand tremor, bradykinesia. Her symptoms are mild and do not interfere with any activity. She has been in good health and thought this is mainly stress or menopause. She is not sleeping well.
Case #6 Mrs. RW

Medical history

• Menopause
• Generalized anxiety

Medications

Tylenol for joint pain
Case #6 Mrs. RW

- Neurologic exam showed facial masking, mild hypophonia, resting tremor mild in the left hand and rigidity with activation. She was started on Rasagiline 1 mg. Two years there was progression of her symptoms and Ropinarole was added. At increased dosed of Ropinarole she was getting more sleepy. This improved once switched to XR. 4 months later she called with sudden deterioration and could not get out of bed.
Case #6 Mrs. RW

• She was given Risperdal instead of Ropinarole by her pharmacy. This had a profound affect on her and she could hardly move and stayed in bed. In a month she fortunately discovered the mistake. She could not get back to her baseline for several months. Sinemet 25/100 was added 5 years from the treatment onset and she has remained on one tablet 4 times a day. She has no dyskinesia, no wearing off. She is holding on to her corvette.
Thank you.