Parkinson’s Disease

- Progressive, chronic, neurodegenerative disease
- Slow, selective loss of substantia nigra dopaminergic neurons
- Clinical features due to severe loss of striatal dopamine
Epidemiology of Parkinson’s Disease

• About one million affected each year
• Second most common neurodegenerative disease in elderly (after Alzheimers)
• Average age of onset is 60 years
• 5% to 10% of PD patients have symptoms before age 40 (“young-onset PD”)
• Prevalence in population >80 years old is 10%

• Age is single most consistent risk factor
• Onset is insidious
• Male predominance 3/2
• Affects all ethnic and socioeconomic groups
• James Parkinson first described “shaking palsy” in 1817
Typical Progression and Clinical Course

Preclinical Phase

-2 to -6

Honeymoon Period

0

Motor Complication Period

3

Resistant Symptoms

8

Cognitive Decline

15

Years

20

Onset

Diagnosis

Therapy

Pathophysiology

- PD occurs when neurons in the substantia nigra die or become impaired.

- Substantia nigra is located in the midbrain. Dopamine pathways are also connected to the frontal and limbic (emotional) regions of the brain.
• Dopamine is the chemical messenger responsible for transmitting signals between the substantia nigra and the “relay station” of the brain, the corpus striatum, to produce smooth, purposeful muscle activity

• Loss of dopamine in the striatum leaves the patient unable to direct or control their movements in a normal matter
Classification of PD

- Primary, Degenerative form
  - Idiopathic Parkinsonism

- Secondary
  - Toxins
  - Drugs
  - Trauma, Vascular, and Post-Encephalitic
Classification (cont.)

- Parkinson-Plus Syndromes
  - Multi-system atrophy (MSA)
  - Progressive Supranuclear Palsy (PSP)
  - Cortical-basal Ganglionic Degeneration (CBGD)
- Dementia Syndromes
  - Alzheimer’s with PD symptoms
  - Lewy Body Disease
Potential Causes of PD

Genes
- α-synuclein
- Parkin
- UCH-L1
- Susceptibility genes

Environment
- Pesticides
- Rural living
- Other (?)

Pathogenic Mechanisms
- Protein aggregation
- Mitochondrial dysfunction
  - Oxidative stress
  - Inflammation
  - Excitotoxicity

Apoptosis (cell death)

UCH-L1 = ubiquitin hydrolase L1.

Characteristic Motor Symptoms

- Tremor
- Bradykinesia/akinesia
- Rigidity
- Postural instability
PD Symptoms

- Micrographia
- Masked Facies/Hypomimia
- Hypophonia
- Decreased Arm Swing
- Shuffling Gait
- Truncal Flexion
- Fatigue
PD Symptoms (cont.)

• Dysphagia
• Sialorrhea
• Decreased Gastric Emptying
• Dry Eyes
• Seborrhea
Non-Motor Symptoms in PD

- Mental Changes
  - Dementia
  - Depression
- Sleep Disturbance
  - Fragmented Sleep
  - REM behavioral sleep disorder
Non-Motor Symptoms in PD

- Dysautonomia
  - Constipation
  - Sexual dysfunction
  - Bladder dysfunction
  - Sweating
  - Orthostasis
- Pain
  - Untreated patients
    - Shoulder and back pain
  - Treated patients
    - Off dystonia (foot pain)
Diagnosing PD

• At least 2 of 4 cardinal features:
  • Rest tremor (4-6 Hz)
  • Rigidity
  • Bradykinesia
  • Postural instability+
• Diagnosis more difficult when tremor absent
• Asymmetric onset
Diagnosing PD (cont.)

- Almost all patients with idiopathic PD will improve with L-dopa therapy
- Parkinson-Plus syndromes will not improve as dramatically
Diagnosing PD (cont.)

- No abnormalities of routine x-rays, labs, EEG, or EKG
- CT/MRI
- PET scan
- SPECT scan
Factors to consider when initiating therapy

• 1. Age of patient
• 2. Severity of symptoms
• 3. Cognitive status
• 4. Comorbidities/concomitant meds

Olanow CW et al. Neurology 2001:56 (suppl 5):S1-S88
Treating PD

• Also it is important to ask the patient.....

  • What symptoms bother you most?

  • How much do these symptoms interfere with daily function and lifestyle?
Management of PD

Diagnostic assessment

Motor symptoms
- Tremor
- Bradykinesia
- Rigidity
- Gait impairment

Non-motor
- Autonomic dysfunction
- Sleep disorders
- Skin disorders
- Deconditioning

Affective
- Anxiety
- Depression
- Apathy
- Psychosis

Cognitive
- Neuropsychological deficits
- Intention deficits
- Dementia
- Delirium, agitation

Disease Progression
Medication Management

• Mainstay of therapy is dopaminergic medication
  
  • Dopamine replacement
  • Activate dopamine receptors
  • Stimulation of dopamine release
  • Inhibit dopamine uptake
Levodopa (L-dopa)  
(→ Dopamine)  
Give with carbidopa (reduces nausea)  
Carbidopa/LEVodopa (Sinemet®)  

Dopamine Agonists  
(Mimic dopamine)  
Pramipexole (Mirapex®)  
Ropinerole (Requip®)  
Apomorphine (Apokyn®)  
Rotigotine (Neupro patch®)  

COMT-Inhibitors  
(→ Slow dopamine breakdown)  
Entacapone (Comtan®)  
Tolcapone (Tasmar®)  
Stalevo  

Anticholinergic Medications  
(Reduce relative excess acetylcholine)  
Trihexiphenidyl (Artane®)  
Benztropine (Cogentin®)  

MAO Inhibitor, Other  
Selegiline (Eldepryl®)  
Amantadine (Symmetrel®)  
Zydis Selegiline (Zelapar®)  
Rasagiline (Azilect®)
PD Treatment – Mild Disease

• With treatment, pt has good control throughout the day without any clear ups or downs
• Grade 1-2 tremor, bradykinesia, rigidity
• No retropulsion
• No significant dementia
What is your first choice?

1. No treatment
2. Amantadine
3. Anticholinergics
4. Rasagiline/Selegiline
5. DA: Ropinirole/Pramipexole
6. Carbidopa/Levodopa IR/CR
7. Carbidopa/Levodopa/Entacapone
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Amantadine

- Antiviral agent for the Asian flu
- Anticholinergic, dopaminergic, and NMDA blocking effects
- Mild-to-moderate benefit
- **Adverse effects:** anticholinergic + livedo reticularis, pedal edema
- **Dose:** 100 bid to qid
Amantadine

- Provides mild-to-moderate benefit
- Neuropsychiatric adverse effects limit use in older patients or those with dementia
- Antidyskinetic effect: can reduce dyskinesia by about 45%, but benefit lasts less than 8 months

Thomas, A et al. JNNP. 2004;75:141-143.
Livedo Reticularis
Anticholinergics

• Option for young patients (<60 years) whose predominant symptom is resting tremor

• Available agents:
  – trihexyphenidyl (Artane)
  – benztropine (Cogentin)

• Adverse effects often limit use due to:
  – Memory impairment  
  – Dysphoria
  – Confusion  
  – Antimuscarinic effects
  – Hallucinations  
  – Dry mouth
  – Sedation  
  – Blurred vision

MAO Inhibitors

Selegiline 1989

Oral Disintegrating Selegiline
Rasagiline 2006
Rasagiline

• An irreversible selective MAO-B inhibitor

• Administered orally once per day

• No amphetamine or amphetamine-like metabolites

• FDA approved for the treatment of PD as both initial therapy and adjunctive therapy
MAO-B Inhibitors

- Inhibit monoamine oxidase B enzyme, which breaks down dopamine following its action in synaptic cleft
- Selegiline is an irreversible MAO-B inhibitor
  - DATATOP study
    - Provided slight symptomatic benefit
    - delayed the need to begin levodopa therapy by 9 months
  - Inconclusive evidence in humans that selegiline slows progression in PD

PD Treatment – Moderate Disease

- Pt feels more kick in with meds, sometimes wears off between doses
- Grade 1-2 tremor, bradykinesia, rigidity
- ± Mild dyskinesias
- May have retropulsion, but usually recovers unaided
- No significant dementia
What is your first choice?

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2. Amantadine
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5. DA: Ropinirole/Pramipexole
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Dopamine Agonists

- Ergot-derived dopamine agonists - First generation:
  - pergolide (Permax®)
  - bromocriptine (Parlodel®)

- Non–ergot-derived dopamine agonists - Second generation:
  - ropinirole HCl (Requip®)
  - pramipexole (Mirapex®)
  - apokyn injection
  - rotigotine (Neupro patch®)

Dopamine Agonists

- Pramipexole (0.5-1.5 mg po tid)
- Pramipexole ER (up to 4.5 mg/day)
- Ropinirole (3-6 mg po tid)
- Ropinirole 24 ER (6-24 mg po qd)
- Apomorphine (0.2-0.6 mL sc prn; Max: 0.6 mL/dose, 5 doses/day, 2 mL/day)

**Adverse effects**: hallucinations, nausea, ICD, sleepiness, edema
Levodopa

- Most effective drug for parkinsonian symptoms

- 1970: Carbidopa/Levodopa (Sinemet) Approved by the FDA. Rapidly became the drug of choice for PD

- Large neutral amino acid; requires active transport across the gut-blood and blood-brain barriers

- Side effects: nausea, postural hypotension, dyskinesias, motor fluctuations
Levodopa (cont.)

- Motor fluctuations
  - Up to 50% of patients after 5 years of treatment
  - 70% of patients after 15 years of treatment
  - End-of-dose “wearing off” phenomenon
  - Unpredictable “on-off” fluctuations
- Dyskinesias
  - Peak dose or diphasic
- Neuropsychiatric disturbances
  - Hallucinations
  - Confusion

Parcopa
(Carbidopa/levodopa Orally Disintegrating Tablets)

- RapiTab technology dissolves rapidly on the tongue without need for water
- Same strength and dosage schedule as conventional carbidopa/levodopa
- Equivalent benefit and side effects
- Rapid access to medication, convenient
Response to Levodopa and Progression of Parkinson’s Disease

Early PD
- Long duration motor response
- Low incidence of dyskinesias

Moderate PD
- Shorter duration motor response
- Increased incidence of dyskinesias

Advanced PD
- Short duration motor response
- “On” time consistently associated with dyskinesias

PD Treatment – Severe Disease

- Motor fluctuations
- Dyskinesias
- Sometimes no “on” response
- Retropulsion
- ± Cognitive dysfunction, hallucinations
What is your first choice?

1. No treatment
2. Amantadine
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8. DEEP BRAIN STIMULATION
Apomorphine (Apokyn®)

• The only injectable DA available

• Apomorphine sc has been shown in controlled clinical trials to effectively abort OFF episodes in patients already on maximal oral therapies

• Apomorphine is a highly potent DA

Rescue Therapy
Apomorphine

- Subcutaneous injection
- Fast acting: 7.5-10 min
- Short duration of action: 40-120 min
- Consistent response: rare dose failures
- Similar response to levodopa
- Pretreatment with antiemetic (trimethobenzamide)
- Long term, consistent effect
COMT Inhibitors

- Only used in combination with levodopa
- Inhibit levodopa catabolism/extend duration of levodopa effect
- Indicated for treatment of patients with PD experiencing end-of-dose “wearing off” with levodopa
- COMT inhibitors available:
  - entacapone (Comtan)
  - tolcapone (Tasmar) – may cause hepatic toxicity
  - Stalevo

Tasmar® (tolcapone) Prescribing Information. Roche Laboratories, Inc. 1998.
Surgical Options

• Surgical Treatments
  • Pallidotomy/Thalamotomy
  • Deep brain stimulation
Deep Brain Stimulation

Figure 2.1 Parts of the brain stimulation system
Other Areas

- Constipation
- Urinary Symptoms
- Orthostatic Hypotension
- Male Impotence
- Depression
Treatment

- Other
  - Diet
  - Hydration
  - Exercise
  - Stress Management
  - Counseling
  - Education
Research

• Neuroprotective Studies
• Symptomatic Relief
• Alternative Therapy
  • Exercise
  • Dietary Supplement
  • Spiritual/Prayer
• Surgical Studies
  • Stem cells
  • RPE
Research (cont.)

• New Drugs
  • DUOPA (carbidopa/levodopa) enteral suspension indicated for the treatment of motor fluctuations in advanced PD
  • Droxidopa for orthostatic hypotension
  • Rytary, a combination of short acting and long acting levodopa
Websites

• American Parkinson’s Disease Association
  • www.apdaparkinson.org
• National Parkinson Foundation
  • www.parkinson.org
• Michael J. Fox website
  • MichaelJFox.org
• For community resources
  • www.healingwell.com