Parkinson’s Disease Update
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What is a movement disorder?

- Neurological disorders that affect ability to move by causing too much or too little movement or by affecting rhythm of movement.

- Examples:
  - Parkinson’s disease
  - Essential tremor
  - Dystonia
  - Ataxia
Parkinson’s disease

- Lifetime risk: 1.5%
- Prevalence:
  - Younger than 45 years old ~ 10% of PD pts
  - 93/100,000 in patient’s 70-79 yo
- Mean age of onset: 60 years old
- Mean duration of disease from dx to death: 15 years
- Men: female ratio: 1.5:1
Unclear

Increased risk with age

Never smokers have 2x risk

Lower risk in caffeine drinkers

Weaker associations:

- Head injury, rural living, lack of exercise, middle age obesity, pesticide exposure, Agent Orange exposure, middle age obesity

Some genetic associations ~2x risk with first degree relative
Cardinal Features of Parkinson’s

- Need 2/3 features to make diagnosis
Cardinal Features of Parkinson’s

- Need 2/3 features to make diagnosis
- Rest tremor
  - Coarse tremor (3-5 Hz) that occurs while relaxing or walking
  - Improves with voluntary movement
Rest tremor
Cardinal Features of Parkinson’s

- Need 2/3 features to make diagnosis
- Rest tremor
- Rigidity – inability to relax muscles, can be noted in arms, legs, neck in Parkinson’s
Rigidity
Cardinal Features of Parkinson’s

- Need 2/3 features to make diagnosis
- Rest tremor
- Rigidity
- Bradykinesia – slowed, effortful movement
Bradykinesia
Postural Instability

- Poor balance
- Becomes a prominent feature as disease course progresses
- Other gait features:
  - Shuffling
  - Freezing
  - Narrowed base
Freezing gait
Other Features Highly Suggestive of Parkinson’s

- Unilateral onset
- Levodopa response
- Dyskinesia with levodopa
- Decreased sense of smell
- REM sleep behavior disorder
Neuropsych symptoms

- Cognitive decline
- Dementia
- Psychosis
- Depression
- Anxiety
- Anhedonia
Sleep abnormalities

- REM sleep behavior disorder
- Restless leg syndrome
- Insomnia
- Daytime somnolence
- Sleep apnea
REM sleep behavior disorder
Autonomic dysfunction

- Urinary incontinence
- Orthostatic hypotension – lightheaded with standing
- Excessive sweating
- Sexual dysfunction
Other symptoms

- GI symptoms:
  - Dysphagia
  - Constipation
  - Drooling

- Reduced facial expression

- Reduced voice volume
How to diagnose Parkinson’s

- History
- Clinical exam
  - Slowness, stiffness, rest tremor
- Sometimes imaging:
  - MRI brain - normal
  - DAT scan
    - Asymmetry of dopamine transporter in basal ganglia
    - Helps distinguish between parkinsonian and other tremor disorder
DAT scan image
<table>
<thead>
<tr>
<th>Other parkinsonian disorders or mimics</th>
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<tbody>
<tr>
<td>Lewy Body dementia</td>
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<tr>
<td>Progressive supranuclear palsy</td>
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<tr>
<td>Multiple systems atrophy</td>
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<tr>
<td>Corticobasal degeneration</td>
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<td>Medication side effects (from some anti-psychotics and anti-emetics)</td>
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<td>Frontal gait disorder</td>
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<td>Pugilistic parkinsonism</td>
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<td>Vascular parkinsonism</td>
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<td>Normal pressure hydrocephalus</td>
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<tr>
<td>Essential tremor</td>
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<td>Psychogenic disorder</td>
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Parkinson’s plus features

- Rapid progression of symptoms
- Lack of tremor or myoclonic tremor
- Symmetric onset
- Minimal response to levodopa
Parkinson’s plus features

- Early onset:
  - Falls (PSP, MSA)
  - Eye abnormalities (PSP)
  - Psychosis or dementia (LBD)
  - Autonomic dysfunction (MSA)
  - Dysarthria or dysphonia (MSA)

- Cerebellar features (MSA)

- Apraxia, alien limb, myoclonus (CBD)
Progressive Supranuclear Palsy
Corticobasal Degeneration
Vascular parkinsonism
Non-medical Treatment of Parkinson’s

- Exercise
  - “beneficial with regards to physical functioning, health-related quality of life, strength, balance and gait speed”

- Physical therapy
  - Balance and strength

- Speech therapy
  - Lee Silverman Voice therapy
  - Swallow therapy

Goodwin, et al
Medications for Parkinson’s

- Anticholinergics
- MAO-B inhibitors
- Dopamine Agonists
- Carbidopa-levodopa
- COMT inhibitors
Lesser Used Meds

- **Anticholinergics**
  - Trihexyphenidyl, benztropine
  - Confusion, hallucinations, fatigue, urinary retention

- **MAO-B Inhibitor**
  - Rasagiline, selegiline
  - Possible disease modification
    - ADAGIO study – supported use of 1mg daily, but no improvement at 2mg daily

Olanow et al.
Dopamine Agonists

- Ropinirole, pramipexole, rotigotine patch
- Use in younger patient’s
- Less risk dyskinesia
- Increased fatigue, edema, compulsions, sleep attacks
Levodopa

- Sinemet (carbidopa-levodopa – IR/CR), Rytary and Duopa
- Most effective treatment for Parkinson’s
- Risk of dyskinesia
- Worsens fatigue, hallucinations, orthostatic hypotension
- Higher and more doses needed
- Motor fluctuations
Common Side effects to Levodopa

- Dyskinesia
- Motor fluctuations
- Psychosis
- Orthostatic hypotension
Rytary

- Time release CD/LD microbeads
- Plasma concentration sustained longer at greater amount
  - IR: <10% at 5-7.5 hrs
  - Rytary: <10% at 10 hours
- Less frequent dosing (e.g. TID vs 5 + times daily)
- Less OFF time ~ 2 hours difference/day
- More ON time without troublesome dyskinesia (~1h)
- Converting from IR to Rytary can be rocky
  - 2 Rytary : 1 IR
Duopa

- intestinal gel formulation of carbidopa/levodopa
- continuously delivered via J-PEG
- 16 hour infusion
  - Rest time for gut
- wear cartridge of med like an insulin pump
- Decreased OFF time (2h) and increased ON time without troublesome dyskinesia (2h)
- Risks: malfunction, infection, intestinal complications
- Requires A LOT OF TIME to determine infusion rate
Dyskinesia

- Involuntary dance-like movement
- Occurs when Sinemet is peak dose
- 64% develop dyskinesia in 4-5 years after onset of treatment with levodopa

Treatment:
- Amantadine
- Reduce levodopa and give more frequently
- Deep brain stimulation

Grandas, F. et al.
Dyskinesia
Motor Fluctuations

- Fluctuating between being ON and OFF levodopa
  - ON symptoms – tremor, slowness controlled, sometimes with dyskinesia
  - OFF symptoms – tremor, slowness, stiffness occur as medication wears off

- Treatment:
  - Decreased dose and increase frequency levodopa
  - Entecapone (COMT inhibitor)
  - Rytary
  - DBS
Psychosis

- Increases with disease progression
- Increases with medications to treat Parkinson’s

Treatment:
- Reduce amantadine, benzodiazepines, dopamine agonists, entacapone first
- Then reduce levodopa
- Anti-psychotics – only seroquel or clozapine
- Cholinesterase inhibitor – e.g. donepezil
- Newer medication, Nuplazid (pimavanserin)
  - Serotonin inverse agonist
Pimavanserin

- **Pimavanserin:**
  - Selective serotonin receptor (5-HT2A) inverse agonist, no blockade of dopamine neurons

- **Nature 2009:**
  - Double blind randomized study versus placebo
  - Primary endpoint (SAPS-PD) positive trend, no significance.
  - Significant - hallucination and psychosis subscores.
  - No change UPDRS, hypotension and sedation vs placebo
Cholinesterase inhibitors

- **Dual purpose:**
  - Cognitive decline
  - Balance
    - 2016 study of Rivastigmine vs placebo
    - Step time variability improved
      - normal walk
      - Simple dual task improved
    - No improvement with complex dual task
    - 45% reduction in falls/month
    - Small increase in gait speed
Neurogenic orthostatic hypotension

- Blood pressure lowers when patient changes position to sitting or standing.
- Due to inability of sympathetic nerves to release norepinephrine upon standing.
- Fludrocortisone, midodrine, droxidopa.
- All worsen supine BP.
Surgical Interventions

- **Deep Brain Stimulation**
  - Subthalamic Nucleus – reduction in levodopa
  - Globus Pallidus interna – fewer issues with cognition and postural instability, better treatment for dyskinesia
  - Thalamus – more for essential tremor

- **Pallidomtomy**
  - Rarely performed now – only unilateral, not reversible
  - Focused ultrasound?

- **Stem Cell treatment** – studies don’t support yet
Deep Brain Stimulation
Deep brain stimulation surgery
Post-DBS
Summary

Send us your Parkinson’s patients and we will help make some of these complicated decisions easier!!


Olanow, CW. Et al (2009), A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease. NEJM 361:1268-78


