Parkinson’s Disease

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Disclosures:
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Parkinson’s Disease: outline

• PD – the clinical syndrome
• Descriptive epidemiology
• Pathology of PD
• Treatments for PD
• Etiology

1817 – James Parkinson

6 people: 3 seen only on the street
First complete description of motor syndrome

- Insidious onset
- Late life
Parkinson’s Disease: The Motor Syndrome

- Resting Tremor
- Bradykinesia
- Rigidity
- Loss of Postural Reflexes

PD Descriptive Epidemiology

- PD occurs everywhere in the world
- 95% of cases begin after age 50
- Incidence increases with age at least through the 9th decade
- Men > women
- Risk may be related to ethnicity or geography
- Unclear if incidence (proportion of new cases) is increasing over time
- Absolute number of cases is expected to double worldwide as population ages

Parkinson’s disease: pathology – classical

- Lewy bodies, Lewy neurites; Protein aggregates; alpha-synuclein
- Substantia nigra depigmentation; Loss of dopaminergic neurons
- Healthy, Parkinson’s disease
Parkinson’s disease: clinical course

- Stage 1: Unilateral involvement
- Stage 2: Mild bilateral involvement
- Stage 3: Mild to moderate bilateral involvement, some postural instability, independent
- Stage 4: Severe disability, able to walk/stand unassisted
- Stage 5: Wheelchair bound or bedridden

PD non-motor symptoms: categories

- Autonomic
  - Orthostasis
  - Constipation
  - Urinary urgency
  - ED
- Sleep
  - RBD
  - Poor sleep maintenance
- Sensory
  - Loss of smell
  - Loss of taste
  - Pain
- Psychiatric
  - Fatigue
  - Depression
  - Anxiety
  - Apathy
  - Psychosis
- Cognitive
  - Executive dysfunction
  - Impaired attention
  - Impaired visuospatial function
  - Relative preservation of anterograde memory
  - PD-MCI
  - PDD

Langston 2006
Some Clues from the Honolulu Asian Aging Study

Midlife olfactory deficits predict Lewy bodies
Midlife constipation predicts PD
Midlife obesity predicts PD

Correctly identified odors

Per cent with Lewy Bodies

Correctly identified odors

Midlife olfactory deficits predict Lewy bodies

Ross et al, 2000

Midlife constipation predicts PD

Abbott et al, 2001

Midlife obesity predicts PD

Ross et al, 2000

Are the first signs non-motor features?

Prodromal features may identify an “at risk” population

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Substantia nigra not first site of injury in PD

Lewy neurites found in olfactory bulb & autonomic nervous system

REM Sleep BD
↓ Heart Rate Variability

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PD Treatment Overview

**Goals of therapy: Parkinson’s disease**

- Slow or halt progression
- Relieve signs and symptoms of disease
- Avoid side effects

PD Treatment: *medications*
Drug Therapies for Parkinson’s Disease

Levodopa (Sinemet)
Immediate Release (IR)
Duopa
Levodopa Continuous Infusion

Long-acting Levodopa
Controlled Release (CR)
Rytary

COMT Inhibitors
Entacapone (Comtan), Tolcapone (Tasmar)

MAO-B inhibitor
Selegiline or Rasagiline

Dopamine agonists
Amantadine
Trihexyphenidyl (Artane)

PD Treatment: medication adverse effects

- **Levodopa (Sinemet/Rytary):** nausea, orthostasis, psychiatric, dyskinesias
- **Dopamine Agonists:** impulse control disorders, edema, psychosis, confusion, orthostasis, dyskinesias, sleep attacks
- **MAO-B inhibitors:** hypertension, insomnia, drug interactions
- **Anticholinergics:** dry mouth, sedation, delirium, confusion, hallucinations, constipation, urinary retention
- **Entacapone:** diarrhea, orange urine
- **Tolcapone:** liver failure
- **Amantadine:** confusion/hallucinations, nightmares, anticholinergic effects, livedo reticularis

PD Treatment: motor fluctuations
Video

PD Treatments: Deep Brain Stimulation (DBS)

Permanently implanted brain pacemaker
1. Lead
2. Extension Wire
3. IPG
• Increases the best “on-medication” state by 4-5 hours daily
• Improves motor function by 25-50%
• Raises the ceiling for off-medication times
• Reduction in medication dosing (30-50%)

Deep Brain Stimulation: GPI vs. STN
PD Treatments: role of exercise

Delay the Disease
Exercise to Fight Parkinson's Symptoms

Videos

Parkinson's Disease Etiology
MPTP-Induced Parkinsonism
The First Big Clue  Langston, Ballard, Tetrud 1983

Cluster of subacute parkinsonism in young narcotics addicts

Similar to PD:
- Same signs as PD
- Progressive worsening in some
- Improves with l-dopa
- Same side effects from l-dopa

BUT
- MPTP injection is rare
- Not a likely cause of PD

The toxicologic effects of MPTP suggested that similar chemicals, present in the environment, could cause PD

Video

Some Factors Associated with a Higher Risk of Parkinson's Disease

- Pesticides
- Polychlorinated Biphenyls
- Head Injury
- Solvents
- Age
- Metals
- Air Pollution
- Male Gender
Inherited parkinsonism is rare, but yields clues to the cause of typical Parkinson’s Disease

- Current evidence suggests only ~10% of all PD is caused by a single genetic defect
- In many, inherited parkinsonism begins at an earlier than expected age
- In many, inherited parkinsonism has different clinical features than “typical” PD

Normal protein products of these genes are all likely involved in protein degradation or cellular response to toxicant injury or oxidative stress

Head Injury & PD

- Mild-moderate head injury associated with PD in >70% of studies.
- 2-3 fold increased risk
- Biologic Plausibility:
  - Triggers chronic inflammatory process
  - Oxidative stress
  - Protein aggregation
  - Mitochondrial damage
  - Disrupts Blood Brain Barrier

BUT only some people with head injuries develop PD Why?
Gene-Environment Interaction in PD

**Gene:**
α-synuclein

**Environment:**
Head injury

Lewy Bodies are mostly aggregated α-synuclein protein

Gene-Environment Interaction: Head Injury & Synuclein Gene Variant

<table>
<thead>
<tr>
<th>PD Risk</th>
<th>Risk from gene</th>
<th>Risk from head injury</th>
<th>Risk if BOTH</th>
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<tbody>
<tr>
<td></td>
<td>50%</td>
<td>70%</td>
<td>1000%</td>
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Parkinson’s Disease: A Complex Disorder

Genetics loads the gun  
Environment pulls the trigger
Purely Genetic PD is Rare
Purely Environmental PD is Rare

Most PD is likely due to the combined effects of genetic predisposition and environmental exposures

This is a hopeful finding, because environment can be changed!

Is Preventing PD Possible?

Furlong, Tanner, Goldman, et al, 2015

Primary Prevention: Remove causative factors: disease process never initiated

Increased Risk of PD Was Not Observed in Farmers Using Gloves During Pesticide Application
Thank you!