IN SEARCH OF THE PATHOGENESIS OF PARKINSON’S DISEASE:
Clues From Environmental and Genetic Factors

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General Considerations

- The second most common progressive neurodegenerative disorder
- The most common neurodegenerative movement disorder
- Symptoms and neuropathology are well characterized
- Pathogenesis of PD is not clear
- May be multifactorial and heterogeneous in etiology
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Classical Clinical Features

- Resting Tremor
- Cogwheel Rigidity
- Bradykinesia
- Postural Instability
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Associated Clinical Features

- Micrographia
- Hypophonia
- Hypomimia
- Shuffling gait / festination
- Drooling
- Dysphagia
- Autonomic dysfunction
- Depression
- Dementia
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Descriptive Epidemiology

Prevalence Rate: 150-200 per 100,000
Rare for individuals < 40 years of age
1% for individuals > 60 years of age
2% for individuals > 85 years of age
Men > Women

NPF estimates up to 1.5 million cases in the US
More difficult to obtain data

Comparison among geographic regions is hampered by differences between studies in diagnostic criteria and case ascertainment methods (door to door surveys, clinical records, population-based cohorts)

Systematic Review of Incidence Studies of PD (Twelves et al, Movement Disorders, 2003)

26 incidences studies; 5 used methods sufficiently similar for comparison

Annual incidence rate 16-19/100,000/year for 4 studies and 8.4/100,000/year for Italy study
New US Incidence Data

- Newly diagnosed PD cases in 1994-1995 among the Kaiser Permanente Medical Care Program of N Calif. (A large HMO)
- 588 cases from 4.78 million population
- The age- and gender-adjusted incidence rate was 13.4/100,000
- Only 4% cases under age 50; rate rapidly increased over age 60
- The rate for men (19.0/100,000) was 91% higher than that for women (9.9/100,000)
- The age- and gender-adjusted rate per 100,000 was highest among Hispanics (16.6), followed by non-Hispanic Whites (13.6), Asians (11.3), and Blacks (10.2)
- The data suggest that the incidence of PD varies by age, gender, and race/ethnicity
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Environmental Factors

- Many epidemiology studies
- Rural living / agricultural work
- Cigarette smoking, coffee drinking
- MPTP (mitochondrial complex I inhibitor)
- Pesticides/herbicides (rotenone, paraquat, dieldrin)
- Heavy metal (iron, manganese)
- Hydrocarbon solvents
- Diet
Apart from age, the most consistently reported epidemiologic finding is an inverse association with cigarette smoking.

- 50% decreased risk among smokers; inverse dose-response relationship
- Nicotine protects rat brain mitochondria against experimental damage
- Nicotine reduces MAO-B activity
Prior coffee, tea, noncoffee caffeine consumption is consistently associated with a reduced risk of PD

There is inverse dose-response relationship

Five fold reduction in risk of PD in those who drank over 4 (6 oz) cups coffee/day

Risk reduction benefits men more than women

Caffeine antagonizes adenosine A\textsubscript{2A} receptors in the striatum

Blockage or inactivation of A\textsubscript{2A} receptors are known to protect against excitotoxic and ischemic neuronal injury

Adenosine A\textsubscript{2A} antagonists significantly reduce the MPTP-induced nigrostriatal lesions

Therefore, caffeine may protect against dopaminergic toxicity via its antagonistic action at the A\textsubscript{2A} receptor
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Diet

• Parkinson’s disease risks associated with dietary iron, manganese, and other nutrient intakes (Powers, et al., Neurology 2003)

• A high intake of iron, especially in combination with high manganese intake, may be related to risk for PD

• No strong associations were found for either antioxidants or fats

• Dietary folate deficiency and elevated homocysteine level
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1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP)

- Synthetic “designer” street drug that is neurotoxic and first recognized in 1983
- Selective destruction of substantia nigra cells in humans, nonhuman primates and rodents, producing irreversible signs of parkinsonism
- Crosses BBB and enters astrocytes where MPTP is converted to MPP+ by MAO-B; MPP+ enters dopaminergic neurons through the dopamine reuptake system; it then depletes ATP levels by blocking mitochondrial respiration, particularly at the Complex I ubiquinone binding site
- Environmental toxin can cause PD-like syndrome
- MPP+ bears chemical structural similarities to the herbicide paraquat and isoquinoline derivatives that are widely distributed in the environment
- Useful animal model to study dopaminergic dysfunction, but may not reflect real PD pathogenesis because of lack of Lewy body pathology
Rotenone

- Rotenone is a common pesticide used widely in household vegetable gardens and is also used to kill or sample fish populations in lakes and reservoirs.
- It is a naturally occurring compound derived from the roots of certain plant species and is biodegradable.
- It is a high-affinity and specific inhibitor of mitochondrial complex I.
- It is very hydrophobic and can cross biological membranes easily.
- Chronic systemic low-dose rotenone exposure induces features of PD in rats, including selective nigrostriatal dopaminergic degeneration and formation of ubiquitin- and α-synuclein-positive inclusions.
- Marked microglial activation with minimal astrocytosis is another pathological feature; progressive oxidative damage and caspase-dependent cell death are also observed.
- Rotenone model links mitochondrial dysfunction/oxidative stress/proteolytic stress & pesticide exposure to the mechanism of sporadic PD.
- Rotenone has not be shown to produce parkinsonism in humans.
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Genetic Factors

• PD may be multifactorial in etiology with genetic contributions
• Familial cases are relatively rare (5-10%)
• The younger the age of symptom onset, the more likely genetic factors play a dominant role
• Twin studies
  – World War II veteran twins study
  – High risk ratio for concordance in monozygotic vs dizygotic twins if PD onset <50 years
• Mitochondrial DNA (complex I) defects
• At least ten single gene mutations identified
• Ubiquitin-proteasome system
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<th>Locus</th>
<th>Chromosomal location</th>
<th>Gene</th>
<th>Mode of inheritance</th>
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Alpha-Synuclein

- Small flexible monomeric protein of 140 a.a.
- Abundantly expressed in CNS
- Presynaptic protein of unknown normal function
- Part of a gene family
- Lewy bodies and Lewy neurites found in PD contain aggregates of $\alpha$-synuclein
- Mutations cause autosomal dominant PD
- Although mutations are extremely rare, it is the first gene identified to cause familial PD
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Parkin

- Expressed primarily in CNS as E3 ubiquitin ligase
- Involved in ubiquitination and protein degradation through the ubiquitin-proteasome system
- Mutations cause autosomal recessive juvenile parkinsonism
- Clinical features include young onset, dystonia, slow clinical course, responsiveness to levodopa, early/severe dopa-induced motor complications
- Pathologic features include loss of nigrostriatal and locus ceruleus neurons, no Lewy bodies or Lewy neurites
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Ubiquitin C-terminal Hydrolase (UCH-L1)

• An enzyme that hydrolyzes the C terminal of ubiquitin-protein complex to generate ubiquitin monomers that need to be recycled to clear other unwanted proteins

• Mutation causes impaired clearance of abnormal proteins through the ubiquitin-proteasome system

• Autosomal dominant inheritance found in 2 siblings in one German family with typical PD
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Ubiquitin-Proteasome System

- Degrades misfolded or mutated proteins
- Mutation in the components of the system is the hallmark of familial PD
- Alpha-synuclein, parkin, UCH-L1
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Pathogenesis

- Ubiquitin-proteasome system
- Mitochondrial system
- Oxidative stress
- Alpha-synuclein
- Environmental factors (rotenone, etc.)