IN SEARCH OF THE PATHOGENESIS OF PARKINSON'S DISEASE:

Clues From Environmental and Genetic Factors

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PARKINSON'S DISEASE

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

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Incidence Data

- 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

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New US Incidence Data

- *Incidence of PD: variation by age, gender and race/ethnicity,* Van Den Eeden et al., Am J Epidemiol 2003
- 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

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Cigarette Smoking

- 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

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Caffeine Consumption

- 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_{2A} receptors in the striatum
- Blockage or inactivation of A_{2A} receptors are known to protect against excitotoxic and ischemic neuronal injury
- Adenosine A_{2A} antagonists significantly reduce the MPTP-induced nigrostriatal lesions
- Therefore, caffeine may protect against dopaminergic toxicity via its antagonistic action at the A_{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 mananese 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

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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

Locus	Chromosomal location	Gene	Mode of inheritance
PARK1	4q21.3	*α-Synuclein*	Autosomal dominant
PARK2	6q25.2-27	*Parkin*	Autosomal recessive
PARK3	2p13	Unknown	Autosomal dominant
PARK4	4p15	Unknown	Autosomal dominant
PARK5	4p14	*UCH-L1*	Autosomal dominant
PARK6	1p35-p36	Unknown	Autosomal recessive
PARK7	1p36	*DJ-1*	Autosomal recessive
PARK8	12p11.2-q13.1	Unknown	Autosomal dominant
PARK9	1p36	Unknown	Autosomal recessive (Kufor-Rakeb syndrome)
PARK10	1p32	Unknown	Late-onset susceptibility gene

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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 α-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.)

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