The Causes of Parkinson’s Disease: Current Theories

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Epidemiology and Incidence of Parkinson’s Disease (PD)

Epidemiology

- PD is the second most common neurodegenerative disorder after Alzheimer’s disease
- Affects 0.3% of worldwide population
  - 1%-2% of people aged >60 years
- Approximately 1.5 million people have PD in the United States (US)
- Men 19.0/100K >women 9.9/100K
- Prevalence predicted to almost double in US from 2005-2030 in individuals aged >50 years

Incidence of PD Increases With Aging

- N=588
- No. PD Cases: 0, 50, 100, 150, 200, 250, 300
- Age groups: 30-39, 40-49, 50-59, 60-69, 70-79
The Parkinson's Complex


Adapted with permission from Langston JW. The Parkinson's complex: Parkinsonism is just the tip of the iceberg. Ann Neurol. 2006;59(4):591-596.

Diagram:
- Parkinsonism
- Substantia Nigra
- Pons
- Basal Forebrain
- Medulla
- Amygdala
- Hypothalamus
- Olfactory Bulb
- Spinal Cord (intermediolateral column)
- Peripheral Autonomic Nervous System (heart, intestinal tract, bladder)
- Olfactory Cortex
- Neocortex
- Temporal Cortex
Parkinson’s Disease

Characteristic Motor Deficits

- **Tremor**
  - Involuntary tremulous motion
- **Rigidity**
  - Stiffness caused by involuntary increase in muscle tone
- **Bradykinesia/akinesia**
  - Slowness or absence of movement
- **Postural instability**
  - Poor balance, loss of postural reflexes, gait disorder

Non-Motor PD Features

• Sleep disorders
  – REM Sleep Behavior Disorder (RBD)
  – Periodic Limb Movements of Sleep (PLMS)
  – Restless Leg Syndrome
  – Sleep Apnea

• Autonomic dysfunction
  – Neurogenic orthostatic hypotension
  – Bowel and bladder dysfunction
  – Temperature regulation/Sweating
  – Cardiac sympathetic denervation

• Sensory abnormalities
  – Pain, numbness, aching
  – Visual disturbances

• Dermatological changes
  – Seborrhea
  – Skin cancer
    • Malignant melanoma

• Olfactory dysfunction
  – Very early sign in PD

• Cognitive dysfunction
  – Executive dysfunction
  – Dementia
    • Lewy Body disease

• Psychiatric disorders
  – Affective disorders
    • Depression
    • Euphoria/Mania
  – Psychosis
    • Paranoia
    • Delusions
    • Obsessive Compulsive behaviors
Conceptual Diagram of the Phases of PD

PD is a 3-Stage Disease

| Phase 1 | Preclinical PD | PD-specific pathology assumed to be present | • Asymptomatic, but will need to be supported by:  
|• Molecular markers (α-synuclein, DJ-1, LRRK2, Parkin, PINK1 mutations)  
• Imaging markers (transcranial sonography, PET, SPECT, DaTscan, DTI, MIBG SPECT, α-synuclein imaging) |
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<tbody>
<tr>
<td>Phase 2</td>
<td>Premotor PD</td>
<td>Presence of early nonmotor signs and symptoms due to extranigral PD pathology</td>
<td>• Nonmotor features commonly occur before the emergence of motor symptoms (olfaction abnormalities; constipation; cardiac involvement; REM sleep behavior disorder; neurobehavioral symptoms)</td>
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| Phase 3 | Motor PD | PD pathology involves substantia nigra leading to dopamine deficiency sufficient to cause classic motor manifestations followed by later nonmotor features | • Presence of fully established disease (bradykinesia, tremor, rigidity)  
• May progress to include late PD features (dysautonomia, sensory symptoms, cognitive decline) |

Stern MB, Lang A, Poewe W. *Movement Disorders*. 2012; 27:54-60
Key Concepts in Understanding PD Pathogenesis

• Lewy Body
  – Neuropathological hallmark of PD
  – Central role of α-synuclein

• Genetics of PD
  – Mutations impacting mitochondrial function
    • PINK1,DJ-1
  – Mutations impacting transport of organelles and vesicles
    • SNCA,Tau
  – Mutations impacting degradation pathways
    • Parkin,DJ-1,β-glucocerebrosidase, UCHL1
  – Mutations impacting reduction in oxidative stress
    • DJ-1

• Environmental role in PD
  – Pesticides/herbicides, infectious agents, metals, hydrocarbons
  – Oxidation reactions related to dopamine itself

• Prion hypothesis
  – Prions are infectious proteins that can cause a group of invariably fatal neurodegenerative diseases by a novel mechanism.
Causes of PD

- PD is heterogeneous
  - Unlikely there is a single etiology
  - “Multiple hit” hypotheses
- Contributing factors may include:
  - Environment
  - Genetics
  - Combination of both
- Abnormal aggregation of $\alpha$-synuclein may play a key role in the development of PD
  - Progression may relate to prion-like process
Lewy Body
Cause of PD Still Unknown

PD is likely the result of interaction between intrinsic, genetic and environmental causes

- Some genes and specific mutations associated with PD have been identified
- Approximately 20% of patients have a family history of PD
- Majority of PD cases are sporadic (also known as idiopathic) in nature
- Rural living, and exposure to environmental toxins, such as pesticides, may contribute to the development of PD
- No single environmental cause of PD has been determined
- Personal habits, including smoking cigarettes and drinking coffee, appear to be associated with a lower risk of PD

Dopamine and Oxidative Stress
Dopamine interaction with Alpha synuclein
Dopamine cells and Calcium influx
Risk Factors for PD

Any Relative PD
1st Degree Rel PD
PD Family History-
Tremor
Constipation
Mood Disorder
Pesticide Exposure
Head Injury
Rural Residence
Beta Blockers
Farming/
Agriculture
Well Water
CCBs
Alcohol
NSAIDs
Past Smokers
Hypertension
Coffee
Ever Smoked
Current Smokers

CCB indicates calcium channel blocker; NSAID, nonsteroidal anti-inflammatory drug.

Environmental Relationships
Northern California in 1980's
AND WE JUST REMOVE THIS MOLECULE AND.. VOILA!

LEGAL AS SEA SALT!

POP!
1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP)

- Northern California neurotoxic “designer” drug resulted in an epidemic of “Parkinson’s disease” in early 1980’s
- Clearly documented a role for environmental toxins in Parkinsonism-provided primate model of PD
- MPTP crosses the BBB and is converted to MPP+ by MAO-B which is taken up by dopamine neurons destroying complex I in mitochondria depleting ATP
- MPP+ is very similar to herbicide paraquat and isoquinoline derivatives that are ubiquitous in our environment
MPTP $\rightarrow$ MPP+$^+$
Environmental Factors in the Etiology of Parkinson’s Disease

• Pesticides
  – Most consistent data on environmental cause
  – Exposure increases risk by almost 2 fold
  – Mitochondrial damage
    • Rotenone
      – Animal models
    • Paraquat
    • Maneb
  – Ubiquitin-proteosomal inhibition
    • Ziram
Environmental Factors in the Etiology of Parkinson’s Disease

• Infectious Agents
  – Entry via nasal or GI portal may explain sites of early involvement
    • H5N1 avian influenza virus
      – Phosphorylation and aggregation of alpha synucleinc
    • Epstein Barr virus
      – May trigger intracellular protein aggregation
  – Parkinsonism
    • Coxsackie virus
    • Japanese encephalitis B
    • West Nile virus
    • HIV
  – Prions
Cigarettes
Cigarette Smoking

• Consistent inverse relationship for PD incidence
• 50% decreased risk. Dose response relationship
• Animal models demonstrates nicotine protection of mitochondria
• Nicotine reduces MAO-B activity
• Pyridines may inhibit uptake of toxic molecules such as pesticides and MPTP
Caffeine
Caffeine

- Caffeine consumption before PD is associated with reduced risk of PD (coffee, tea, caffeinated beverages)
- There is an inverse dose response relationship
- 5X risk reduction for >24 oz coffee per day
- Caffeine blocks Adenosine A2A receptors (excitotoxic mediated cell death)
- Adenosine A\textsubscript{2A} antagonists have been shown to reduce MPTP related dopamine neuronal damage in the substantia nigra
- A\textsubscript{2A} antagonism may explain benefits of caffeine
Dietary Considerations

• Increased risk associated with high amounts of dietary iron in combination with high manganese content
• Possible relationship between low folate levels and elevated homocysteine levels
• Vitamin D deficiency (common in PD) may have relationship to cognitive impairment
• B12 deficiency can contribute to numerous neurological deficits
Other Environmental Factors

- Uric acid levels associated with slower rate of progression of PD
- Head trauma increases risk of developing PD
- Milk consumption raises risk of developing PD
- Occupational risk is greatest and most consistent in farming communities
  - Amish in Northeast US-6% prevalence
Internal Environmental Contributions

• Dopamine can induce oxidative stress
  – Auto-oxidation can result in free radical generation
  – Cells defense is to turn oxidized products into insoluble neuromelanin -reflecting cells with most oxidative stress

• Dopamine interaction with abnormal α-synuclein enhances permeability of synaptic vesicle membranes thereby allowing increased leakage of dopamine into cell body resulting in more oxidation and damage

• Interaction between α-synuclein, calcium and dopamine is required to maintain cell integrity
Genetics of PD

- At least 14 genetic abnormalities identified
  - AD
  - AR-susceptibility genes
  - Genetic mutations code for a variety of cellular functions, all of which can lead to cell death
    - Multiple genotypes, similar phenotype
Genetics and PD

• PD is primarily a sporadic or idiopathic disorder
• The Human Genome Project has helped to better define the gene association
  – Up to 20% of patients with PD have the familial variety
  – Causal and susceptibility genes discovered for PD
  – Monogenic forms (autosomal dominant) account for only a very small portion of patients with PD
  – The younger the patient (<50), the more likely there is a genetic component
  – Genetic abnormalities disrupt vital cellular functions (mitochondria, ubiquitin-proteosome system, excessive/abnormal protein production)
<table>
<thead>
<tr>
<th>Name</th>
<th>AD/AR</th>
<th>Prevalence</th>
<th>Lewy Bodies</th>
<th>Protein Function</th>
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<tr>
<td><strong>Causal Genes and Loci</strong></td>
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<tr>
<td>SNCA (PARK1, PARK4)</td>
<td>AD</td>
<td>Very rare</td>
<td>LB</td>
<td>Vesicle trafficking</td>
</tr>
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<td>LRRK2 (PARK8)</td>
<td>AD</td>
<td>5% familial Caucasian; 1%-2% of sporadic cases</td>
<td>LB</td>
<td>Cytoplasmic kinase</td>
</tr>
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<td>PRKN (PARK2)</td>
<td>AR</td>
<td>Most prevalent in early-onset (&lt;45 years) but relatively uncommon</td>
<td>Nigral degeneration; rare LB</td>
<td>Ubiquitin E3 Ligase</td>
</tr>
<tr>
<td>PINK1 (PARK6)</td>
<td>AR</td>
<td>Rare cause of recessively inherited, early-onset Parkinsonism</td>
<td>Unavailable</td>
<td>Mitochondrial kinase</td>
</tr>
<tr>
<td>UCHL1 (PARK5)</td>
<td>AD</td>
<td>Mean onset: 50</td>
<td>LB</td>
<td>Removes polyubiquitin</td>
</tr>
<tr>
<td>DJ-1 (Park 7)</td>
<td>AR</td>
<td>Early onset</td>
<td>LB?</td>
<td>Peroxiredoxin (antioxidant)</td>
</tr>
<tr>
<td>GBA</td>
<td>AD</td>
<td>Slightly younger onset</td>
<td>LB?</td>
<td>B-glucocerebrosidase</td>
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LRRK2

- Associated with familial and idiopathic PD
- Large, multidomain protein
- Autosomal dominant
- Most prevalent gene associated with PD
  - Among Caucasian patients
    - Up to 5% of familial cases
    - 1%-2% of idiopathic cases
- Its physiological function and its role in PD etiology are unclear
  - May have a role in lysosomal pathways


2012; 27: 1364-1369.
PARK2: Parkin

- Autosomal recessive
- Juvenile Parkinsonism
- Significance
  - Gene most commonly found in early onset
  - Up to 50% of recessive familial patients <45 years express mutation
  - Onset age range 16-72
  - Lewy bodies not a characteristic
  - Positive response to L-dopa

SNCA: $\alpha$-Synuclein

- The first gene associated with PD (1997)
- Autosomal dominant
- Causal gene
  - Critical mutations or overproduction of $\alpha$-synuclein causes misfolding of the protein and subsequent accumulation, resulting in cell toxicity
- Linked to both familial and idiopathic PD
  - Altered the course of research to focus on genetics
  - Originally linked to early onset PD
- PD related to SNCA mutations are very rare

Olanow
What Is α-Synuclein?

• A protein primarily expressed in neural tissue
• Main function of α-synuclein may be the control of neurotransmitter release
• Abnormal configuration is associated with the development of PD
  – α-Synuclein is the main component of Lewy bodies
  – Disrupts synaptic messaging
• Level of causality in PD is not clear
• α-Synuclein toxicity is considered a possible therapeutic target

α-Synuclein

- Unfolded alpha-synuclein
- Alpha-synuclein Oligomers
- LBS
- DAergic neurons in SNpc
- Mitochondrial dysfunction
- NMDA-receptor activation
- Oxidative/Nitrosative stress
- Genetic mutations
  - EOPD
  - LOPD
Prion Hypothesis
α-Synuclein and the Prion Hypothesis

- Prion diseases
  - Misfolded proteins induce misfolding of other proteins with which they come in contact (templating), resulting in a chain reaction leading to cell toxicity and progression of PD

- Postmortem evidence
  - Lewy bodies containing α-synuclein in embryonic dopaminergic cell transplants suggesting prion-like transmission

- Other prion-like PD characteristics
  - Accelerated protein production
  - Proteins not cleared properly
  - Transmissible from cell to cell and between animals

What Is The Role of Abnormal α-Synuclein Aggregation in PD?

Braak Hypothesis
Spread of Lewy bodies as PD progresses

- Lewy bodies (abnormal aggregations of α-synuclein) are a prerequisite for postmortem PD diagnosis
- Braak and colleagues hypothesize that Lewy bodies spread throughout the brain in a predictable pattern as PD progresses
- Pathologic studies in PD patients have found Lewy pathology in brain, cardiac, and enteric autonomic nervous systems
- It is not known whether α-synuclein aggregation is a direct causative factor in the pathogenesis of PD or a protective mechanism against protein-induced cell toxicity


\( \alpha \)-Synuclein as a Prion

PrP \rightarrow PrP^\text{sc} \rightarrow \text{Prion rods} \rightarrow \text{PrP amyloid plaques}

\( \alpha \)-Syn \rightarrow \alpha \)-Syn \rightarrow \alpha \)-synuclein fibrils \rightarrow Lewy body
“Never eat at a diner named Joe’s Greasy Spoon”

“Never cheer for the opposing team at Wrigley Field”

“Never obtain Parkinson’s disease advice from a Starbucks barista (or the internet)”

“Never become complacent about Parkinson’s disease”

“Always surround yourself with an outstanding interdisciplinary team”