Many Causes of Parkinson’s Disease: An Epidemiologist’s Perspective

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Disclosures: Consultant to Impax, Adamas & Abbvie Pharmaceuticals

Parkinson’s Disease: Cardinal Signs

- Clinical Diagnosis based on recognition
- Differentiate from other disorders causing tremor, slowness, imbalance

PD expected to more than double by 2030

- Clinical projections for persons aged >50 in the world’s ten most populous nations

2005 100% = 4.1 million individuals

- Others, 12%
- Brazil, 4%
- U.S., 3%
- India, 5%
- Europe, 20%

2030 100% = 8.7 million individuals

- Others, 10%
- Brazil, 4%
- U.S., 7%
- India, 8%
- Europe, 14%

(Dorsey et al., 2007)
PD expected to more than double by 2030

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Individuals</th>
</tr>
</thead>
<tbody>
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<td>2030</td>
<td>8.7 million</td>
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CRITICAL NEEDS:

Understand PD etiology to:
- Identify ways to slow or prevent PD onset
- Identify people at risk for PD to allow early intervention + "prodromal PD"

PD projections for persons aged > 50 in the world’s ten most populous nations and Western Europe’s five most populous nations:

- 2005: 4.1 million individuals
- 2030: 8.7 million individuals

Europe, 14% Others, 12%
Brazil, 4% U.S. 8%
India, 8%
U.S. 8%
Brazil, 4%
Others, 10%

CRITICAL NEEDS:

Understand PD etiology to:
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What Causes Parkinson’s Disease?

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
These findings favor monogenic autosomal dominant inheritance and show reason to argue against a multifactorial etiology or heteroplasmy.

Duvoisin & Johnson Brain Pathology 1992

Is Parkinson’s Disease a monogenic disorder?

Twins: Mother Nature’s Controlled Study

- MZ twins share ~100% of genes
- DZ twins share ~50% of genes

Hypothesis: If Parkinson’s disease is primarily a genetic disorder, then concordance in MZ twins should be > than in DZ twins

Results: MZ & DZ concordance similar; Except young onset MZ > DZ

Conclusion: Environment is an important contributor to the cause of most PD

Tanner, et al, JAMA, 1999

Genes and PD – Monogenic Forms
Well – Validated Parkinson’s Disease Associated Genes
Dominant Inheritance

<table>
<thead>
<tr>
<th>GENE</th>
<th>ONSET</th>
<th>MUTATIONS</th>
<th>RISK VARIANTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNCA</td>
<td>Early</td>
<td>~700 mutations (point, exon rearrangements)</td>
<td>Promotor Rep 1, 5, 7</td>
</tr>
<tr>
<td>LRRK2</td>
<td>Typical/late &gt; 50 years</td>
<td>G2019S, G2019S(AJ), R1441x, R1441x(Arab), A30P, A53T, A46K, Duplications, triplications, Promotor Rep 1, 5, 7</td>
<td>Alpha-synuclein processing product mutation, penetrance ~100%</td>
</tr>
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Well – Validated Parkinson’s Disease Associated Genes
Recessive Inheritance

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<th>MUTATIONS</th>
<th>RISK VARIANTS</th>
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<tr>
<td>parkin</td>
<td>Juvenile (age &lt; 40)</td>
<td>~170 mutations (point, exon rearrangement)</td>
<td>Heterozygotes O late onset PD?</td>
</tr>
<tr>
<td>FBXO41</td>
<td>Early (age 40-50)</td>
<td>~50 point mutations</td>
<td>Heterozygotes O late onset PD?</td>
</tr>
<tr>
<td>DJ-1</td>
<td>Early (age 40-50)</td>
<td>~50 point mutations, large deletions</td>
<td>Heterozygotes O late onset PD?</td>
</tr>
<tr>
<td>ATXN13A2</td>
<td>Juvenile (Kufor-Rakeb, atypical PD)</td>
<td>~50 point mutations, large deletions</td>
<td>Heterozygotes O late onset PD?</td>
</tr>
<tr>
<td>GBA</td>
<td>Gaucher’s disease</td>
<td>&gt;300 mutations (point, insertions, deletions, complex)</td>
<td>GD, Heterozygotes O late onset PD, DLB</td>
</tr>
</tbody>
</table>

Heritability of PD

Heritability estimates
- Twin studies: 25% overall, higher in young onset PD, lower in typical onset
- GWAS studies: 25% overall, higher in young onset PD, lower in typical onset

Therefore
Up to 75% of disease liability in typical PD is non-heritable: environment
What Are the Environmental Determinants of Parkinson’s Disease?

Relative risks from case-control and cohort studies of smoking and PD
Hernan, 2002

§ > 50 studies find inverse association with smoking
§ Risk ~ 0.5 in prospective, retrospective, and twin study designs
§ Dose-response: ~ 20% risk reduction/10 pack-years smoked
Greater Midlife Coffee & Tea Drinking is Associated with a Lower Risk of PD (Ross et al, 2000)

Proposed Explanations:

- Adenosine A2A receptor blockers protect against MPTP-induced injury in animals
- Green tea polyphenols protect in animal models
- Coffee drinking &/or cigarette smoking may reflect "preparkinsonian" personality

Adjusted for age and pack-years of smoking

Test for Trend - p=0.001
p=0.979

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p=0.979

Pesticides - Increased Risk:
Since the 1990s, over 20 case-control studies have shown an association of PD and pesticides. PD risk is usually about twice as high in pesticide exposed persons.

BUT
- Broad chemical categories
- Few specific agents identified

SEARCH Study: Case Control Study of Occupational Risk Factors
Tanner et al, Arch Neurol, 2009;66(9):1106-1113

519 PD cases, 511 controls in 8 MD centers
Lifelong, job-task-based occupational histories; other risk factors

Paraquat: OR* = 2.8
(95% C.I.: 0.8, 9.7)

2,4-Diphenoxacyclic acid
(2,4-D): OR* = 2.6
(95% C.I.: 1.03, 6.48)

Mechanism
- Alpha Synuclein aggregation

*adjusted for age, center, smoking

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*adjusted for age, center, smoking
FAME Study: PD in Agricultural Health Study  
(Tanner, Kamel et al., 2011)

52,000 farmers, 32,000 spouses in Iowa & N Carolina screened for PD
112 PD cases, 368 controls
In-person examination, videotape, blood, dust, soil
Lifelong history: occupation, pesticides, other risks

**Paraquat**  
Upper Risk of PD:  
All OR = 2.3 (95% C.I. 1.45, 4.3)  
Men OR = 2.5 (95% C.I. 1.3, 4.7)

**Rotenone**  
Increased Risk of PD:  
All OR = 2.3 (95% C.I.: 1.2, 4.3)  
Men OR = 2.8 (95% C.I.: 1.4, 5.8)

Models adjusted for age, gender, state, ever smoking, ever pesticide use

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**Solvent Exposures in 99 Twin Pairs**  
Discordant for PD  
Goldman et al., 2010

<table>
<thead>
<tr>
<th>Compound</th>
<th>Odds ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-hexane</td>
<td>1.27</td>
<td>0.40-4.07</td>
<td>0.69</td>
</tr>
<tr>
<td>Toluene</td>
<td>1.26</td>
<td>0.46-3.31</td>
<td>0.61</td>
</tr>
<tr>
<td>Xylene</td>
<td>2.24</td>
<td>0.43-11.6</td>
<td>0.34</td>
</tr>
<tr>
<td>CC14</td>
<td>2.32</td>
<td>0.88-6.11</td>
<td>0.089</td>
</tr>
<tr>
<td>TCE</td>
<td>6.11</td>
<td>1.15-32.5</td>
<td>0.034</td>
</tr>
<tr>
<td>PERC</td>
<td>10.5</td>
<td>0.97-113</td>
<td>0.053</td>
</tr>
<tr>
<td>TCE or PERC</td>
<td>8.94</td>
<td>1.70-47.0</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Consistent with occupational cluster (Gash et al 2008) & TCE rat model (Liu et al, 2010)

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**Is There Biologic Plausibility?**  
Laboratory Studies of Toxicants:

In vitro & in animal models, toxicant exposure can cause:

- Paraquat
- Rotenone
- Diellon
- TCE

- Synuclein fibrillary aggregates
- Mitochondrial dysfunction
- Oxidative stress
- Nigral injury
- Behavioral changes

**BUT**

Not all people exposed to these toxicants get PD. Why?
Exposure of the brain to environmental toxicants is controlled by genetically-determined enzymes and transporters throughout the body.

Gene-Environment Interaction
An exposure may cause disease in persons unable to metabolize a toxicant while others are not affected.

Example 1: Gene-Environment Interaction in PD

Gene: α-synuclein
Environment: Head injury

Alpha-Synuclein Rep 1 Gene Variant is Associated with Small Increase in PD Risk

Gene Variant 2 makes more alpha-synuclein protein than Variant 1.
Head Injury & PD

- Mid-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

BUT only some people with head injuries develop PD Why?

BOTH Head Injury & α-Synuclein Rep 1 Gene Variant

1. Risk from gene
2. Risk if head injury
3. Risk if BOTH

50% 70% 1000%


Parkinson’s Disease: A Complex Disorder

Genetics loads the gun

Environment pulls the trigger
Example 2a: Pesticides, Genes & Parkinson’s Disease
Elbaz et al, 2004

- French Farmers Health Insurance (Mutualité Sociale Agricole): 190 PD cases 419 matched controls
- Pesticide use judged by occupational health physician: Never used, exposed by gardening or professional use
- CYP2D6*4 allele genotyping (‘poor metabolizer’) = 2 alleles

RESULTS:

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>Never Exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 1 CYP2D6*4 alleles:</td>
<td>1.00</td>
</tr>
<tr>
<td>2 CYP2D6*4 alleles:</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Only the poor metabolizers exposed to pesticides had increased risk of PD

Example 2b: Paraquat, GST-T1 and Parkinson’s Disease

Goldman et al, 2012

Risk of PD Associated with Joint Occurrence of Paraquat Exposure and a Variant of the GST-T1 Gene

Monogenic Parkinsonism & Environmental Factors: Does Environment Influence LRRK2 Associated Parkinsonism?

- Most common genetic cause, ~1% - 2% of all parkinsonism
- Dominantly inherited
- Penetrance is incomplete, about 30%

Implication: Environmental factors & other genes determine who is affected
Monogenic Parkinsonism & Environmental Factors: Does Environment Influence LRRK2 Associated Parkinsonism?

Most common genetic cause, ~1%-2% of all parkinsonism.

Next step: Investigate environmental exposures in LRRK2 affected and unaffected carriers.

Nonsmoking Carriers of LRRK2 Gly2385Arg Have Increased Risk of PD

An example of gene-environment interaction

LRRK2 Gly2385Arg polymorphism, cigarette smoking, and risk of sporadic Parkinson's disease: A case-control study in Japan.

Dominantly inherited. Penetrance is incomplete, about 30%.

Even in genetic forms of parkinsonism, multiple determinants are likely.

Next step: Investigate environmental exposures in LRRK2 affected and unaffected carriers.

Nonsmoking Carriers of LRRK2 Gly2385Arg Have Increased Risk of PD

An example of gene-environment interaction
Can Combined Effects of Environmental Factors Influence Risk of Parkinson’s Disease?

Head Injury, Paraquat Use and Risk of PD

- Head injury in 29%
- Paraquat used by 17%, all men

<table>
<thead>
<tr>
<th>Head Injury</th>
<th>Paraquat Use</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>1.2</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>1.8</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>4.2</td>
</tr>
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</table>

Head injury and paraquat use were synergistically associated with increased PD risk. Both cause oxidative stress. Joint effects are synergistic in a recent animal model (Hutson, 2011).

Risk of Parkinson’s disease associated with the herbicide paraquat is attenuated by high dietary intake of polyunsaturated fatty acids (OR 0.4, 95% CI 0.2-0.8).

Association of Parkinson’s disease with paraquat stronger in those with low intake of ω3-linolenic acid:

- High intake, - paraquat: 1.0 (referent)
- Low intake, + paraquat: 1.3 (0.7-2.5)
- High intake, - paraquat: 1.4 (0.5-3.9)
- Low intake, + paraquat: 4.5 (1.7-12)

83 PD and 328 controls with complete data in FAME
- Head injury in 19%
- Paraquat used by 17%, all men

89 confirmed cases and 336 matched controls in FAME
- Diet before diagnosis from a food frequency questionnaire

Kamel et al, submitted
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!

NEXT STEP: Secondary Prevention of PD?

† Identify persons “at risk” for PD before symptoms manifest: efficient screening critical
† Intervene to prevent the development of PD: a safe treatment critical

Some Factors Associated with a Higher Risk of Parkinson’s Disease:
Clues to Identify Persons at Risk?

Pesticides
Polychlorinated Biphenyls
Head Injury
Solvents
Air Pollution
Male Gender
Age
Metals?
Genes

Clues to Identify Persons at Risk?
Can an “at risk” profile for PD be identified?

- Hyposmia
- REM Sleep BD
- Constipation
- Substantia nigra not first site of injury in PD
- Lewy neurites found in olfactory bulb & autonomic nervous system

Should neuroprotective trials target persons with these signs?

Some Factors Associated with a Lower Risk of Parkinson’s Disease: Clues for Preventative Therapies?

- Physical activity
- Cigarette smoking
- Coffee & Tea Drinking
- Anti-inflammatory drugs (ibuprofen)
- Statins
- Higher serum urate
- Higher Vitamin D
- Female gender; Estrogens
- Anti-inflammatory drugs (ibuprofen)
- Ca channel blockers
- Higher Vitamin D
- Statins?
- PUFAs?
- Flavonoids?

Are you sure about this? It seems odd that a pointy head and long beak is what makes birds fly.

Association Does Not Prove Causation

Laboratory Studies Needed:
1. Determine pathophysiologic mechanisms
2. Develop candidate treatments
Environmental & Genetic Determinants Cause Similar Pathophysiologic Changes:
Clues to Disease Modifying Treatments?

- Complex dysfunction
- Synuclein aggregation
- Lysosomal/Proteasomal dysfunction
- Rotenone
- Endotoxin LPS
- Paraquat
- Head Injury
- MPP+
- Parkinson
- Complex I
- Ub DJ1 LRRK2
- Urate, NSAIDS, CCBs
- Inverse
- ROS
- Parkinson I&IV
- Some Metals
- Smoking, Caffeine
- Inverse
- Paraquat
- Maneb
- Dieldrin
- Permethrin
- Impaired Golgi Apparatus
- 2,4D PPE, Hygiene, Physical Activity
- Inverse Associations in Populations
- Putative Protective Agents
- Candidates for Disease Modifying Interventions

THANK YOU!!

Colleagues:

Volunteers & Research Partners:
- Patients, Controls, Family & Friends
- Parkinson's Institute Physicians, Scientists & Staff
- CA PD Registry

Sponsors:
- Parkinson's Institute
- The Valley Foundation
- Former & Current Welding Products Manufacturers
- James & Sharron Clark

Donors