What Causes Parkinson’s Disease? An Epidemiologic Perspective

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DISCLOSURES

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Outline

• Historical perspective
• Genetic Causes
• Environmental Causes
• Gene-environment interaction
• Implications for treatment & prevention
Early Theories of Parkinson’s Disease Etiology

• 1817 (Parkinson): Rheumatic, physical hardship
• 1858 (Charcot): Fright, terror
• 1888 (Gowers): Inherited in no more than 15%
• 1920’s - 1960’s (Poskanzer): Post-infection
• 1960’s - 1970’s (Mjones, Kondo, Martin): Inherited as dominant or multifactorial
Genetic Causes of PD

Does Parkinson’s Disease Pass From Parent To Child Due To Changes In The DNA?
Mutation in the α-synuclein gene identified in families with Parkinson's disease (Golbe et al., 1996; Polymeropoulos et al., 1997).

Few cases worldwide **BUT**

- α-synuclein a key component in Lewy bodies (Spillantini, 1998)
- Abundant expression in nerve terminals (Lewy neurites) (Goedert 2001)
Twins: Mother Nature's Controlled Study

• MZ (identical) twins ~100% shared genes
• DZ (fraternal) twins ~50% shared genes

Hypothesis: If PD is a genetic disorder, 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 PD

Tanner, et al, JAMA, 1999; Goldman et al, Ann Neurol 2019
Genetic Causes of PD

Mendelian Associations
LRRK2, GBA, SNCA, VPS 35 & recessive forms
~ 15% - 20%

Combined effects of multiple genetic variants
Nalls et al, Lancet Neurol, 2015
– Risk score for PD using 6 PD study populations:
  • 13% explained by Genetic Risk Score
  • 11% Family history; 6% sex; 5.9% age
  • 63% by hyposmia – a symptom of PD
Taken Together, Single Genes & Combined Genetic Risks Explain Only Part of PD Causes
Environment & PD
MPTP-Induced Parkinsonism
Langston, Ballard, Tetrud 1983

Cluster in young narcotics addicts
Similar to PD: Same signs; Improve w/ l-dopa;
Same side effects

BUT
MPTP use is rare; Not a likely cause of PD

⇒ In the laboratory, the toxicologic effects of MPTP suggested that similar chemicals, present in the environment, could cause PD
Some Factors Associated with a Higher Risk of Parkinson’s Disease

- Pesticides
- PCBs
- Head Injury
- Solvents

- Age
- Metals?
- Welding?
- Physical Inactivity
- Air Pollution?
- Male Sex
Environmental Risk Factors Are Common – But Only A Few of the People Exposed Develop PD

Why?
Combined Effects of Genes and Environment Likely

This Is Called Gene – Environment Interaction
Parkinson’s Disease: A Complex Disorder

Genetics loads the gun

Environment pulls the trigger
Gene – Environment Interaction & PD

Some Examples
Head Injury & PD

Mild-moderate head injury associated with PD in >70% of studies.

- 2-3 fold increased risk

**BUT** only some people with head injuries develop PD

Why?
Gene-Environment Interaction in PD

Gene: $\alpha$-synuclein

Environment: Head injury

Lewy Bodies are mostly aggregated $\alpha$-synuclein protein
Gene- Environment Interaction: Head Injury & Synuclein Gene Variant

Example 2: Paraquat & PD

- Commonly used herbicide
- > 100 crops
- Agricultural, landscaping uses
- Banned in EU
- Use in the US, worldwide has been increasing
Paraquat & PD

• Study 1: ~ 80,000 Farmers in the AHS mixing or applying pesticides: PD risk increased x 2.5

• Study 2: ~ 500 PD cases & 500 controls in 8 PD centers; Lifelong, occupational histories: PD risk increased x 2.8
Example 2: Gene-Environment Interaction in PD

**Gene**: GSTT1 (glutathione transferase T1)
- Protects against oxidative stress

**Environment**: Paraquat
- Causes oxidative stress
Example 3: Gene-Environment Interaction in PD

Gene: *ABCB1* (p-glycoprotein, MDR1)

Environment: Hexachlorobenzene
P-glycoprotein (MDR1; ABCB1)

- Membrane efflux pump on BBB endothelium
- many xenobiotic substrates
Alaska Native Subsistence

• 33% of caloric needs of rural Alaskans

• Dietary exposure to POPs

Hexachlorobenzene – An Organochlorine Pesticide & Persistent Organic Pollutant (POP) Bioconcentrated in the Arctic
Serum Hexachlorobenzene (HCB) & ABCB1 in PD

Study in Alaska Native People

Goldman, Tanner et al, In Preparation
Causes of Parkinson's Disease - Theoretical

- 1 Gene
- 1 Environment
- >1 Genes
- >1 Environment
- Complex Combinations
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!
Preventing Parkinson’s Disease: Public Health Perspective

1. **Primary Prevention**
   - Prevent Pathogenesis; Preserve Health

2. **Secondary Prevention**
   - Prevent Prodromal Symptom Onset
   - Prevent parkinsonism/dementia onset

3. **Tertiary Prevention**
   - Prevent progression of disease: parkinsonism, dyskinesias, dementia, etc.

**HEALTH**
- PRE-CLINICAL
- PRODROMAL PD
- PARKINSON’S DISEASE

**Striatal dopamine**
- 0%
- 20%
- 40%
- 60%
- 80%
- 100%
PRIMARY PREVENTION OF PARKINSON’S DISEASE

PROOF OF PRINCIPLE
Is Preventing PD Possible?

**Preliminary Results**

Primary Prevention:

- Remove causative factors
- Disease process never initiated

Increased Risk of PD Was **Not** Observed in Farmers Using Gloves During Pesticide Application

Furlong, Tanner, Goldman, et al, 2015

*PARAQUAT* *PERMETHRIN*

**GLOVES**  **NO GLOVES**
POTENTIAL PROBLEMS

• Environment may not be cleaned up
• People may not follow health recommendations

Solution:
Prodromal disease is an equally valid target population for prevention
Some Factors Associated with a Lower Risk of Parkinson’s Disease – Interventions to Prevent PD?

- Physical activity
- Higher serum urate
- Vitamin D
- Female sex
- Certain drugs?
- Medi Diet?
- Coffee & Tea
Conclusion

A combination of public health and targeted medical interventions has the potential to significantly reduce Parkinson’s disease.
How can I get involved?

Visit Fox Trial Finder
https://foxtrialfinder.michaeljfox.org

Visit ClinicalTrials.gov webpage
https://clinicaltrials.gov/ct2/show/NCT03100149

UCSF Clinical Trials
Contact: 415-514-6257 or 415-353-8328
Selected Studies at UCSF

- Micro-PD – Microbiome in PD & wearing off
- TOPAZ – Home based fracture prevention in PD
- Fox Insight – Online for people with or without PD, at risk, care partners
- PPMI 2.0 – Online & in clinic at risk & early PD
- WATCH PD – Wearables to measure PD function
- SPARX – Physical activity to slow PD progression
- Numerous clinical trials of drugs or surgery
THANK YOU!!

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The Valley Foundation

Neurotoxin Exposure Treatment Research Program

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