Causes for Parkinson’s Disease

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Why shall we talk about PD?

Prevalence will double by 2040 (surpassing Alzheimer’s) due to ↑ Ageing, ↑ Diagnosis, ↓ Smoking

↑ Disability -> ↑ Personal, Societal, Economic Burden

Need to understand the complex pathogenesis of PD

*PD development is likely to require the simultaneous failure of multiple cellular homeostatic/protective mechanisms.*

Find targeted and effective ‘Neuroprotective’ therapies to be started at early prodromal PD stages

Dorsey and Bloem, JAMA Neurol 2018 (referring to D. France’s book *How to survive a Plague*)
PD as model of *Multifactorial Disease*

- Heritable (Mendelian) 5-10% vs. Idiopathic PD ≈ 90%
- Idiopathic PD is caused by the interaction between 3 factors:
  1. Ageing
  2. Genetic Predisposition
  3. Environmental Factors

**Known genetic variants**
- Parkin
- Pink-1
- DJ-1
- SNCA
- LRRK2
- VPS35
- GBA mutations
- SNCA variants
- ATP13A2
- GTP-CH1
- Het Parkin

**Risk Factors**
- Pesticides
- Solvents
- Heavy Metals
- Infections?
- Altered Microbiota?
- Head injury

**Chronic exposure to toxins needs predisposition for brain accumulation**

**‘Pure’ environmental factors**

- Hom mutations in Recessive PD genes: Full penetrance
- Het mutations in Dominant PD genes: Low penetrance
From the discovery of the α-syn gene (SNCA) and the presence of α-syn in Lewy Bodies (1997), research found strong evidence for a cell-to-cell propagation of pathology in PD (also AD, ALS).

**WHAT IS THE TRIGGER of α-SYN PATHOLOGY?**

Desplats et al., PNAS 2009; Luk et al., Science 2012; Goedert, Science 2015; Brettschneider, Nat Rev Neurosci 2015
What is the Trigger of initial α-syn aggregation?

(1) Genetics

GBA1 mutations (10-11% of PD) reduce neuronal ability to degrade α-syn. Risk for Dementia 3-fold higher than for PD -> diffuse α-syn pathology.

↓ GCase activity also in sporadic PD without GBA1 mutations associated with ↑ α-syn accumulation

GCase as potential target of ‘disease-modifying’ therapies in the whole PD population.

Mao et al., Science 2016; Murphy et al., Brain 2014; Cilia et al., Ann Neurol 2016
What is the Trigger of initial $\alpha$-syn aggregation?

(2) Environmental Causes

In a meta-analysis, high-quality case-control studies evidence that exposure to any-type pesticides, herbicides, and solvents, increase the risk for PD.

*Exposure to Paraquat and Maneb/Mancozeb* $\rightarrow$ 2-fold increased risk.

Pesticides (Paraquat) are able to trigger $\alpha$-syn aggregation in the gut and to accelerate the formation of toxic oligomers.

*Uversky et al., FEBS Letters 2008; Cereda and Pezzoli, Neurology 2013; Naudet et al., J Neuropathol Exp Neurol 2017*
Solvents exposure (hydrocarbon) increase the risk for PD. Earlier age at onset and more aggressive disease (clinical and SN terminals loss at imaging).

Association between PD and reduced n-hexane metabolism (Genetically-inherited? Secondary to PD pathology?)
Gene-Environment Interactions (1)

Genetic and Epigenetic Predisposition

CYP2D6 Polymorphism, Pesticide Exposure, and Parkinson’s Disease

Alexis Elbaz, MD, PhD, Clotilde Leveque, MSc, Jacqueline Clavel, MD, PhD, Jean-Sébastien Vidal, MD, Florence Richard, MD, PhD, Philippe Amouyel, MD, PhD, Annick Alpérovitch, MD, MSc, Marie-Christine Chartier-Harlin, PhD, and Christophe Tzourio, MD, PhD


Glutathione S-transferase M1 (GSTM1) null subjects heavily exposed to solvents are at increased risk of PD

Elbaz et al., Ann Neurol 2004; Dick et al., Occup Environ Med 2007; Goldman et al., Mov Disord 2012; Ferrante and Conti, Microrna 2017

Glutathione S-transferase (GSTT1*0) genotype, which is common and identifies a large subpopulation at high risk of PD from oxidative stressors.

miRNAs may contribute to neurodegeneration process in response to environmental risks (influencing gene expression).

Environmental chemicals (eg pesticides) cause miRNA alterations via increasing oxidative stress and/or triggering inflammatory responses.
a) Occupation-related Risk

Reduced uptake of $[^{18}F]$FDOPA PET in asymptomatic welders with occupational manganese exposure

b) Inherited defect of Manganese excretion (SLC30A10 gene)

- Parkinsonism
- Distonia
- Hypermanganesaemia
- Polycythaemia
- Chronic Liver Disease

Criswell et al., Neurology 2011;
Other Environmental Risk vs. Protective Factors

- **RISK FACTORS**
  - Dairy products (Urate-lowering effects. Contamination by heptachlor epoxide?)
  - Melanoma
  - Traumatic Brain Injury
  - Methamphetamine use

- **PROTECTIVE FACTORS**
  - Physical Activity (↑DA, ↑BDNF)
  - Smoking
  - Coffee and Tea
  - Urate (↑ Nrf2/antioxidant response)
  - Alcohol (urate-elevating effects)
  - Female gender
  - NSAIDs
  - Calcium Channels Blockers

*Figure 4: The balance of genetic and environmental factors that underlie Parkinson's disease occurrence*

What is the Trigger of initial α-syn aggregation?

(3) Microbiota and the gut-to-brain propagation

1) A pathogen passes the GI mucosal lining (increased epithelial permeability?)

2) Triggers α-Syn misfolding in post-ganglionic ENS terminals

3) α-Syn retrogradely propagates along the vagus nerve

4) α-Syn reaches the DMV

5) α-Syn spreads and aggregates in LB throughout the CNS

6) LB induce neuronal death and PD symptoms/signs

How does Gut Microbiota influence PD?

In α-syn overexpressing mouse model of PD:
• **Typical Microbiota** promote α-synuclein pathology
• Depletion of gut bacteria (**Germ-Free**) reduces microglia activation and α-syn pathology
• **Human gut microbiota from PD cases** (but not from HC) enhances motor dysfunction

May Microbiota-induced changes provide a potential explanation of
- **Initial α-syn misfolding** and aggregation triggering PD pathology?
- **Protective effects** associated with smoking and coffee?

**HOWEVER:**
Change in Microbiota alone is not sufficient to trigger α-syn pathology in the ENS: **SCFAs signaling** → **Microglia activation** is needed
→ **Oral feeding by SCFAs induces α-syn pathology without microbiota colonization.**

**OPEN QUESTIONS:**
- What is the role of **SCFAs**? (..protective and anti-inflammatory..)
- Is the **systemic route** associated to Microbiota-induced changes (rather than the vagus nerve)?

_Sampson et al, Cell 2016; Visanji, Mov Disord 2014_
Does Truncal Vagotomy reduce the risk of PD?
(What if the ‘spreading’ involves systemic routes?)

Vagotomy and Subsequent Risk of Parkinson’s Disease

Does Vagotomy Reduce the Risk of Parkinson's Disease?
Ole-Bjørn Tysnes, MD, PhD,1,6 Line Kenborg, MSc, PhD,2
Karen Herlofson, MD, PhD,3
Marianne Steding-Jessen, MSc,2 Arild Horn, MD, PhD,4
Jørgen H. Olsen, DMSc,5 Heinz Reichmann, MD, PhD5

Same Danish population with extended Follow-up 1977–2011
Truncal vagotomy -> nonsignificantly lower PD risk (HR 0.88, 95% CI 0.55–1.21)
Nonsignificantly elevated PD risk >20 years after the surgery (HR 1.14, 95% CI 0.23–2.05)

Danish registry. Follow-up 1977–1995
Nonsignificant lower PD risk at 5 years F-up
(adjusted HR 0.85; 95% CI: 0.56–1.27)
Marginal significance only >20-y F-up (HR 0.53, 95% CI 0.53–0.99)
«limited statistical precision, wide associated CIs»

Vagotomy and Parkinson disease
A Swedish register–based matched-cohort study
9,430 vagotomized patients (3,445 truncal and 5,978 selective) Follow-up 1970–2010
N = 4,930 incident PD during 7.3 million person-years of follow-up.
Truncal vagotomy -> nonsignificantly lower PD risk (HR 0.78, 95% CI 0.55–1.09)

CONCLUSIONS:
- Nonsignificant Risk Reduction (CIs > 1.0)
- Conflicting Data at 20-y F-up

Svensson et al., Ann Neurol 2015; Tysnes et al., Ann Neurol 2015; Liu et al., Neurology 2017
**Limitations of the Braak’s Hypothesis and Open Questions**

1) « Conjecture that LB would be followed by cell death »

-> **No correlation between LB and Neuronal loss in CNS and ENS**
- ≈50% clinical PD with brains not consistent with Braak’s pattern of LB spread
- Cell death may occur in the absence of α-syn: cases with clinical PD with little/no LB
- No Neuronal Loss in the ENS (Myenteric system) despite LB pathology

**What is the role of LBs?** LB have not yet be proven to be harmful: LB may even be protective by sequestering misfolded proteins.

2) « Involvement of the DMN of the Vagus is mandatory »

-> **Rarely involved in prodromal PD stages**
- Healthy elderly with Incidental Lewy Bodies
  -> Only 9% involved DMV (95% with the olfactory bulb as the only site involved)
- α-SYN can transported anterogradely and retrogradely with similar efficiency

**Where does PD start?** The initial site of α-syn accumulation may occur in different areas and explain different subtypes.
Understanding the CAUSES to find the CURE

GBA, LRRK2, VPS35

Preventing α-syn aggregation (SynuClean-D)

Unfolded α-synuclein

Perturbed α-synuclein proteostasis

Macroautophagy

Chaperone-mediated autophagy

Autophagosome

Lysosomal autophagy system

Lysosome-dependent degradation

Ubiquitin–proteasome system

GBA, LRRK2, VPS35

Neuroinflammation

Activated microglia

SCFA?

LRRK2 miRNA

Paraquat Urate DJ-1 miRNA

Impaired mitochondrial biogenesis

Mitochondrial dysfunction

Oxidative stress

Calcium influx

Impaired calcium homeostasis

Caspase activation

Cell death

Preventing α-syn aggregation (SynuClean-D)

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Oxidative stress

Calcium influx

Impaired calcium homeostasis

Caspase activation

Cell death

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Anti-LAG3 Ab?
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