Brain-first vs. Body-first Parkinson’s disease

- Bad news spreading through networks

Per Borghammer
Professor or Nuclear Medicine & Neuroscience

Dep. of Nuclear Medicine & PET
Aarhus University Hospital
PARKINSON’S DISEASE

Motor symptoms
• bradykinesia (slow)
• rigidity (stiff)
• tremor

Cause
• Lewy pathology
• Dopamine loss

Lewy body
α-synuclein

neuron loss

WORLDWIDE 6 mill. patients
PARKINSON’S DISEASE

Motor symptoms

Pain
Sleep
Anxiety
Dementia
Depression

Hyposmia

Constipation
Bladder
Sexual
Blood pressure

Autonomic damage
PROGRAM

HISTORY OF PD
- neuropathology history
- Braak’s contribution

DOES PD START IN THE GUT
- evidence (epidemiology, histology, animals, patient studies)

DOES PD START IN THE BRAIN
- evidence (histology, patient studies)

IMPLICATIONS
Friedrich Lewy (1885-1950)

1. Dorsal motor vagus
2. Locus ceruleus
3. Globus pallidus

Konstantin Trétiakoff (1892-1954)

Lewy bodies
substantia nigra

1912

1919
Lewy  Tretiakoff  Wohlwill  Den Hartog-Jager  Wakabayashi  Braak

1912 DMV L. coerule.
1919 Nigra
1928 Sympathetic Nervous system
1960 Gangl. coeliacum
2003 Braak staging
Braak brought the periphery back

1919 DMV L. coerule.
1988 Myenteric plexus
Pattern of Lewy pathology in the brain

**BRAAK STAGES**

110 autopsies

Heiko Braak

Braak et al, Neurobiol aging 2003
Braak suggests peripheral start

**NETWORK THEORY**

1. The pathology starts in one place
2. Then spreads through networks
3. Late-stage it is everywhere

Braak et al, Neurobiol aging 2003
Hawkes & Braak, 2007
STAGE 1 - SYMPTOMS

Loss of olfaction years before diagnosis

Constipation years before diagnosis

Svensson et al, Mov Disord 2016
Postuma et al., Mov Disord 2013 26(5)
STAGE 2 - SYMPTOMS

-10 years

DEPRESSION YEARS BEFORE DIAGNOSIS

Aarhus University Hospital
Parkinson risk in idiopathic REM sleep behavior disorder
Preparing for neuroprotective trials

Figure 1: Development of defined neurodegeneration in idiopathic RBD

- 0% Parkinson
- 80% Parkinson (after 10 y)
PROGRAM

HISTORY OF PD
- neuropathology history
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DOES PD START IN THE GUT
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DOES PD START IN THE BRAIN
- evidence (histology, patient studies)

IMPLICATIONS
Evidence for gut start

**Vagotomy and Subsequent Risk of Parkinson's Disease**

Elisabeth Svensson, PhD, Erzsébet Horváth-Puhó, PhD, Reimar W. Thomsen, PhD, Jens Christian Djurhuus, DMSc, Lars Pedersen, PhD, Per Borghammer, DMSc, and Henrik Toft Sørensen, DMSc

**Effect of vagotomy**

- **COMPLETE VAGOTOMY**
  - 47% decreased risk for Parkinson (20 years)
  - Swedish study: 40% reduced risk (10 years)

**VAGOTOMY**

- Controls (n=66,700)
- Vagotomy (n=5,300)

Svensson et al., Ann Neurol 2015  Liu et al., Neurology 2017
Evidence for gut start

Pathological α-Synuclein in Gastrointestinal Tissues from Prodromal Parkinson Disease Patients

Morten Gersel Stokholm, MD,1 Erik Hvid Danielsen, MD, PhD,2 Stephen Jacques Hamilton-Dutoit, MD, DMSc,3 and Per Borghammer, MD, PhD, DMSc1

39 PD patients archived GI tissue removed 1-20 y before diagnosis

22/39 positive (phos-α-syn) up to 20 y before diagnosis
56% positive

12/62 controls also positive 19% positive

Stokholm et al., Ann Neurol 2016
Hilton et al., Acta Neuropathol 2014
Shannon et al., Mov Disord 2012

Lewy pathology in gut 20 years before diagnosis

Esophagus – 7 y before diagnosis
ANIMAL MODEL EVIDENCE

- Prion-like spreading
- supports **GUT-to-BRAIN** spreading of α-syn

Other supportive studies:
- Ulusoy et al., EMBO Mol 13
- Kim et al., Neuron 2019
- Anselmi et al., NPJ PD 2018
- Breid et al., J Virol 2016
- Ayers et al., J Virol 2017
- Holmqvist, Acta Neuropa 14
- Pan-Motojo PlosONE 2010
Animal evidence

Evidence for bidirectional and *trans*-synaptic parasympathetic and sympathetic propagation of alpha-synuclein in rats

Nathalie Van Den Berge¹,² ID · Nelson Ferreira³ · Hjalte Gram³ · Trine Werenberg Mikkelsen¹ · Aage Kristian Olsen Alstrup¹,² · Nicolas Casadei⁴ · Pai Tsung-Pin⁵ · Olaf Riess⁴ · Jens Randel Nyengaard⁶ · Gültekin Tamgüney⁷,⁸ · Poul Henning Jensen³ · Per Borghammer¹,²

Other supportive studies:

Ulusoy et al., EMBO Mol 13
Kim et al, Neuron 2019
Anselmi et al., NPJ PD 2018
Breid et al., J Virol 2016
Ayers et al., J Virol 2017
Holmqvist, Acta Neropa 14
Pan-Motojo PlosONE 2010
2-4 months later

Van Den Berge et al., Acta Neuropathologica 2019

alpha-syn pathology
• aggregated
• proteinase K resistant
• hyperphosphorylated

Nuber et al., Brain 2013

Bacterial artificial chromosome (BAC) expresses human WT alpha-syn
Is RBD a marker of gut-start?

In-vivo staging of pathology in REM sleep behaviour disorder: a multimodality imaging case-control study

Knudsen et al., Lancet Neurol 2018

22 isolated RBD cases compared to PD patients Healthy controls
IMAGING THE BRAAK STAGES

11C-MeNER PET
Gjerløff et al, Brain 2015
Fedorova et al, Neurology, 2017

18F-DOPA PET
Karoline Knudsen et al, Lancet Neurol 2018

11C-donepezil PET
Gjerløff et al, Brain 2015
Fedorova et al, Neurology, 2017

123I-MIBG PET
Tatyana Fedorova et al, Neurology, 2017
Sommerauer et al, J Nucl Med 2017
Garcia-Lorenzo et al, Brain, 2013

Neuromelanin MRI
Sommerauer et al, Brain 2018

NM MR
Allan Hansen et al, Brain 2018

Parasympathetic Braak stage I

Locus coeruleus terminals Braak stage II

Dopamine terminals Braak stage III

Locus coeruleus cell bodies Braak stage II

Sympathetic Braak stage I
BODY-FIRST PARKINSON

Knudsen et al., Lancet Neurol 2018
SO ALL IS GOOD

BRAAK
EPIDEMIOLOGY
HISTOLOGY
ANIMAL STUDIES
IMAGING STUDIES

INCOMPLETE HYPOTHESIS

GUT-FIRST PARKINSON

Braak et al., 2003
PROGRAM

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DOES PD START IN THE GUT
- evidence (epidemiology, histology, animals, patient studies)

DOES PD START IN THE BRAIN
- evidence (histology, patient studies)

IMPLICATIONS
Staging of brain pathology related to sporadic Parkinson’s disease

Heiko Braak a,*, Kelly Del Tredici a, Udo Rüb a, Rob A.I. de Vos b, Ernst N.H. Jansen Steur b, Eva Braak a,†

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Braak et al., 2003

ALL CASES WERE SELECTED – PATHOLOGY IN DMV MANDATORY
Applicability of current staging/categorization of α-synuclein pathology and their clinical relevance

Laura Parkkinen · Tuula Pirttilä · Irina Alafuzoff

Table 4: Topographic distribution of αS immunoreactive lesions in the 39 atypical cases, i.e. not classifiable following current recommendations

ID  Age  Sex  EPS  Dem  AD stage  dmV  RN  LC  SN  nbM  AC  TrEnt  Cx  CA2  Temp-Occ  Ins  Cx  CG  TCx  FCx  PCx
1  79  F  No  Yes  4  0  0  0  0  0  4  3  0  0  0  0  0  0  0  0  0
2  62  F  No  Yes  6  0  0  0  0  0  4  2  0  1  0  0  0  0  0  0  0
3  74  F  No  Yes  2  0  0  0  +  4  2  0  2  0  1  0  0  0  0  0  0
4  79  F  Yes  Yes  6  0  0  0  0  +  3  0  0  0  0  1  1  0  0  0  0  0
5  86  F  No  No  4  0  0  0  0  0  +  0  0  0  0  0  0  0  0  0  0
6  44  M  No  No  0  0  0  0  0  0  0  0  0  0  0  0  0  0  0  0  0
7  68  M  No  No  1  0  0  0  0  0  0  0  0  0  0  0  0  0  0  0  0
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26 76  M  No  No  1  0  0  0  +  0  0  0  0  0  0  0  0  0  0  0  0
27 87  F  No  No  1  0  0  0  +  0  0  0  0  0  0  0  0  0  0  0  0
28 78  M  No  No  1  0  0  0  +  0  0  0  0  0  0  0  0  0  0  0  0
29 84  F  No  Yes  5  0  0  0  +  0  1  na  +  1  0  0  0  0  0  0  0

No pathology in the DMV
Per Borghammer

BRAIN-FIRST vs BODY-FIRST PARKINSON

Borghammer & Van Den Berge, 2019

BRAIN-FIRST PARKINSON

BODY-FIRST PARKINSON

LATE STAGE PD

Pathology everywhere
Brain-to-stomach transfer of α-synuclein via vagal preganglionic projections

Ayse Ulusoy¹ · Robert J. Phillips² · Michael Helwig¹ · Michael Klinkenberg¹ · Terry L. Powley² · Donato A. Di Monte¹

Ulusoy et al., Acta Neuropathologica 2017
BIDIRECTIONAL SPREAD THROUGH VAGUS

Ulusoy et al, Acta Neuropathol 2017

Van Den Berge et al., Acta Neuropathol, 2019
Holmquist, Acta Neuropathol 2014
Kim et al, Neuron 2019
IMAGING – brain-first vs. body-first

- BRAIN-FIRST PARKINSON: 
  - dopamine: SEVERE DAMAGE
  - sympathetic: "NORMAL"
  - parasympathetic: "NORMAL"

- GUT-FIRST PARKINSON: 
  - dopamine: "NORMAL"
  - sympathetic: SEVERE DAMAGE
  - parasympathetic: SEVERE DAMAGE
THE NEXT IMAGING STUDY

BRAIN-FIRST PARKINSON

Denovo PD without RBD

FDopa

MIBG

Donepezil PET

GUT-FIRST PARKINSON

Isolated RBD patients
Imaging body- vs. brain-first PD

- Late-stage PD
- Denovo PD no RBD
- Denovo PD + RBD
- Healthy controls
- Brain-first
- MIBG
- FDOPA
- iRBD
- iRBD outlier
- PAF
- Body-first
- FDOPA PET dopamine brain

Submitted
Top-down RBD vs bottom-up RBD

Top-down RBD

SPECIAL CASES
RBD STARTED AFTER
PARKINSONISM

Brain-first

RBD positive

ALL THESE CASES HAD PRODROMAL RBD
FOR > 4-25 YEARS

submitted
Longitudinal study

LATE STAGE PD
Pathology everywhere

Brain-first

Body-first

Control data

GUT-FIRST PARKINSON

submitted
Parasympathetic denervation
300 autopsies of age 85+ people

...all 85+ living in Vantaa in 1991 asked to participate

124 Lewy-body positive
300 autopsies of 85+ people

BRAAK STAGING

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Lewy pathol

cluster
11 patients
ARRANGING THE CLUSTERS BY TEMPORAL EVOLUTION (hypothetical)

caudo-rostral gradient

**time point** 1  2  3  4  5

**3 medulla (DMV) - START**

* DMV

BRAAK STAGING

**amygdala predominant**

**time point** 1  2  3

**6 amygdala - START**

amygdala

cluster not assigned

skiing slope

mountain profile

Per Borghammer
ARRANGING THE CLUSTERS BY TEMPORAL EVOLUTION (hypothesical)

caudo-rostral gradient

amygdala predominant

BODY-FIRST

BRAIN-FIRST
PROGRAM

HISTORY OF PD
- neuropathology history
- Braak’s contribution

DOES PD START IN THE GUT
- evidence (epidemiology, histology, animals, patient studies)

DOES PD START IN THE BRAIN
- evidence (histology, patient studies)

IMPLICATIONS & NEW AVENUES
IMPLICATIONS – are there differences between the types?

- BRAIN-FIRST
  - Immunological
  - Genetic factors
  - a-syn strains
  - Microbiome
- BODY-FIRST
  - Gut hyper-permeability
SUMMARY

MULTI-MODALITY IMAGING

- BRAIN-FIRST PD
- BODY-FIRST PD

Propagation through networks is important

POST-MORTEM DATA

- CAUDO-ROSTRAL
- AMYGDALA

QUESTIONs

What causes the different subtypes?
How do we diagnose them early?
Require personalized treatment?
THANK YOU
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