The Concept of Parkinson‘s Disease: Time for a Redefinition ?

TC 24 Movement Disorders
XXII WCN, Santiago - Chile 2015

Werner Poewe
Dept. of Neurology
Medical University of Innsbruck

MEDIZINISCHE UNIVERSITÄT
INNSBRUCK

Disclosures

Werner Poewe reports personal fees from AbbVie, Allergan, AstraZeneca, BIAL; Boehringer-Ingelheim, Boston Scientific, GlaxoSmithKline, Ipsen, Lundbeck, Medtronic, MSD, Merck-Serono, Merz Pharmaceuticals, Novartis, Orion Pharma, Teva, UCB and Zambon (*consultancy and lecture fees in relation to clinical drug development programmes for PD).*
Royalties: Thieme, Wiley Blackwell, Oxford University Press and Cambridge University Press

Learning Objectives

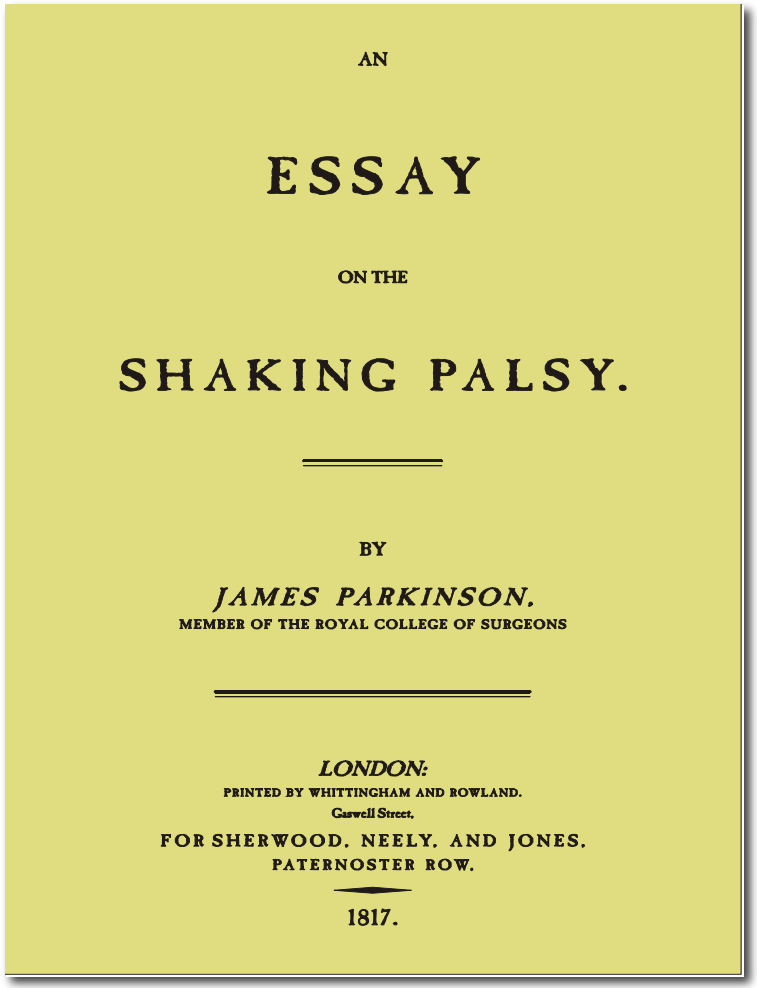
- Understand issues around the current definition and diagnostic criteria of PD
- Appreciate the importance of non-motor presentations of PD
- Understand challenges and opportunities for PD biomarkers
- Understand the concepts of ‚preclinical‘ and ‚prodromal‘ PD
- Become familiar with new MDS criteria for PD

Key Messages

- Current PD definition faced with several issues
- Need to incorporate non-motor symptoms
- Need to define criteria for ‚prodromal' PD

- Revised criteria for PD (‚MDS criteria') &
- Research criteria for prodromal PD published

The “Shaking Palsy” - A Motor Disease



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON.
MEMBER OF THE ROYAL COLLEGE OF SURGEONS

LONDON:
PRINTED BY WHITTINGHAM AND ROWLAND.
Gaswell Street.
FOR SHERWOOD. NEELY. AND JONES.
PATERNOSTER ROW.
1817.

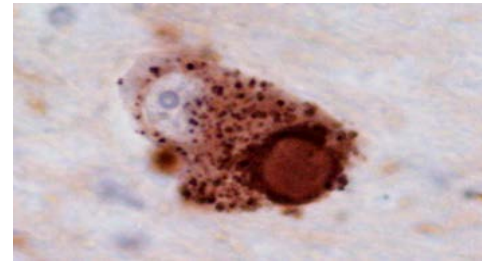
In his *Essay on the Shaking Palsy* (1817), James Parkinson focused on the motor aspects of the disorder:

“Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.”

What is Parkinson’s disease ?

- **a clinical syndrome**
  * defined by the presence of cardinal motor features

- **a neuropathological entity**
  * defined by α-synuclein positive neuronal and axonal inclusions and cell loss in the SNc



PDS BRC Criteria for Idiopathic Parkinson's Disease *Definition of a Parkinsonian Syndrome*

Bradykinesia,

<u>plus one of</u>

- **Rigidity**
- **4 - 6 Hz rest tremor**
- **Postural instability, not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction**

PDS BRC = Parkinson's Disease Society Brain Research Center.
Gibb WR, et al. *J Neurol Neurosurg Psychiatry.* 1988;51:745-752.

PDS BRC Criteria for Idiopathic Parkinson's Disease *Supportive Prospective Criteria*

- **Unilateral onset**
- **Persistent asymmetry affecting side of onset most**
- **Rest tremor present**
- **Progressive disorder**
- **Excellent response (70% – 100%) to levodopa**
- **Severe levodopa-induced chorea**
- **Levodopa response for five years or more**
- **Clinical course of ten years or more**

PDS BRC = Parkinson's Disease Society Brain Research Center.
Gibb WR, et al. *J Neurol Neurosurg Psychiatry.* 1988;51:745-752.

UK PDS BB Criteria for PD
- Exclusion criteria -

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- *More than one affected relative*
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- *Early severe dementia with disturbances of memory, language, and praxis*
- Babinski sign
- Presence of cerebral tumour or communicating hydrocephalus on CT scan
- Negative response to large doses of levodopa (if malabsorption excluded)

Conceptual Issues in the Definiton of PD

- Nigrostriatal DA deficiency&SNc neuronal loss occur prior to onset of motor features
- Specific NMS may occur before onset of motor features
- aSNC pathology may involve extranigral sites before affecting the SNc
- Genetic PD (eg LRRK2) may show classical clinical presentation without Lewy pathology
- PD may not be a single disease entity

FEATURED ARTICLE

Time to Redefine PD? Introductory Statement of the MDS Task Force on the Definition of Parkinson's Disease

Daniela Berg, MD,[1*¶] Ronald B. Postuma, MD, MSc,[2¶] Bastiaan Bloem, MD, PhD,[3] Piu Chan, MD, PhD,[4] Bruno Dubois, MD, PhD,[5] Thomas Gasser, MD,[1] Christopher G. Goetz, MD,[6] Glenda M. Halliday, PhD,[7] John Hardy, PhD,[8] Anthony E. Lang, MD, FRCPC,[9] Irene Litvan, MD,[10] Kenneth Marek, MD,[11] José Obeso, MD, PhD,[12] Wolfgang Oertel, MD,[13] C. Warren Olanow, MD, FRCPC,[14] Werner Poewe, MD,[15] Matthew Stern, MD,[16] and Günther Deuschl, MD[17]

Mov Disord 2014;29:454-462

- Key Issues
  - What is the Gold Standard for defining PD?
  - Does early dementia exclude PD?
  - Are there subtypes of PD?
  - When does PD begin?

What is the Gold Standard for the Definition of PD ?

A patient with classic clinical PD died without autopsy; can one never say they are „sure“ she had PD ? Why is autopsy the gold standard if it is almost never available (and might become outdated, once we have good biomarkers). Furthermore, don‘t genetic studies suggest that pathology can be inconclusive ? A patient from a family of pathologically confirmed LRRK2 PD who meets clinical criteria for PD, but has no Lewy bodies (LB) on autopsy, or patients with parkin mutations without LB; do they not have PD ?

Genetics of Parkinson's disease

Causative genes			
Gene	**Chr.**	**Inheritance**	**Phenotype**
LRRK2	12	AD	Late onset parkinsonism
SNCA	4	AD	Parkinsonism, dementia, autonomic failure
VPS35	8	AD	Late onset parkinsonism
PRKN	6	AR	Young-onset parkinsonism, slow progression
PINK1	1	AR	Young-onset parkinsonism, slow progression
DJ1	1	AR	Mild young-onset parkinsonism

Risk Genes		
Gene	**Chr.**	**Phenotype**
ATP13A2	1	Juvenile-onset parkinsonism, supranucl. gaze palsy
PLA2G6	14	Late-onset parkinsonism, dystonia
MAPT	17	Late-onset parkinsonism
SNCA (var.)	4	Late-onset parkinsonism
GBA	1	Late-onset parkinsonism, depression

FEATURED ARTICLE

Time to Redefine PD? Introductory Statement of the MDS Task Force on the Definition of Parkinson's Disease

Daniela Berg, MD,[1*¶] Ronald B. Postuma, MD, MSc,[2¶] Bastiaan Bloem, MD, PhD,[3] Piu Chan, MD, PhD,[4] Bruno Dubois, MD, PhD,[5] Thomas Gasser, MD,[1] Christopher G. Goetz, MD,[6] Glenda M. Halliday, PhD,[7] John Hardy, PhD,[8] Anthony E. Lang, MD, FRCPC,[9] Irene Litvan, MD,[10] Kenneth Marek, MD,[11] José Obeso, MD, PhD,[12] Wolfgang Oertel, MD,[13] C. Warren Olanow, MD, FRCPC,[14] Werner Poewe, MD,[15] Matthew Stern, MD,[16] and Günther Deuschl, MD[17]

Mov Disord 2014;29:454-462

- Key Issues
  - What is the Gold Standard for defining PD?
  - Does early dementia exclude PD?
  - Are there subtypes of PD?
  - When does PD begin?

The PDD vs DLB Dilemma

A patient developed cognitive impairment 18 months after PD diagnosis; he has PD dementia (PDD). Another developed cognitive impairment
10 months after PD diagnosis; according to current definitions, the initial diagnosis was „wrong“, and she has DLB. Does this make sense ?

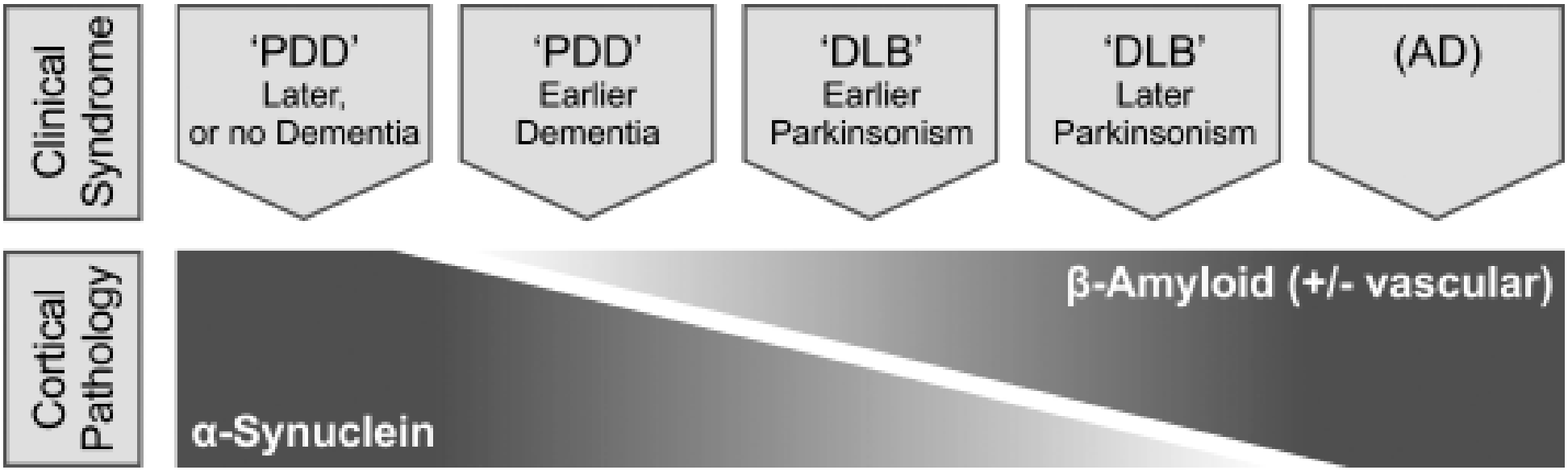
Berg & al., MDJ 2014

FEATURED ARTICLE

Time to Redefine PD? Introductory Statement of the MDS Task Force on the Definition of Parkinson's Disease

Daniela Berg, MD,[1*¶] Ronald B. Postuma, MD, MSc,[2¶] Bastiaan Bloem, MD, PhD,[3] Piu Chan, MD, PhD,[4] Bruno Dubois, MD, PhD,[5] Thomas Gasser, MD,[1] Christopher G. Goetz, MD,[6] Glenda M. Halliday, PhD,[7] John Hardy, PhD,[8] Anthony E. Lang, MD, FRCPC,[9] Irene Litvan, MD,[10] Kenneth Marek, MD,[11] José Obeso, MD, PhD,[12] Wolfgang Oertel, MD,[13] C. Warren Olanow, MD, FRCPC,[14] Werner Poewe, MD,[15] Matthew Stern, MD,[16] and Günther Deuschl, MD[17]

Mov Disord 2014;29:454-462



FEATURED ARTICLE

Time to Redefine PD? Introductory Statement of the MDS Task Force on the Definition of Parkinson's Disease

Daniela Berg, MD,[1*¶] Ronald B. Postuma, MD, MSc,[2¶] Bastiaan Bloem, MD, PhD,[3] Piu Chan, MD, PhD,[4] Bruno Dubois, MD, PhD,[5] Thomas Gasser, MD,[1] Christopher G. Goetz, MD,[6] Glenda M. Halliday, PhD,[7] John Hardy, PhD,[8] Anthony E. Lang, MD, FRCPC,[9] Irene Litvan, MD,[10] Kenneth Marek, MD,[11] José Obeso, MD, PhD,[12] Wolfgang Oertel, MD,[13] C. Warren Olanow, MD, FRCPC,[14] Werner Poewe, MD,[15] Matthew Stern, MD,[16] and Günther Deuschl, MD[17]

Mov Disord 2014;29:454-462

- Key Issues
  - What is the Gold Standard for defining PD?
  - Does early dementia exclude PD?
  - Are there subtypes of PD?
  - When does PD begin?

Clinical Subtyping of PD

- Criteria used in Cluster Analysis Studies -

- Age at onset
- Motor phenotype
    - Tremor-dominant
    - Non-tremor dominant
- Speed of progression
- Motor complications
- Cognitive dysfunction
- Depression

Graham&Sagar, 1999; Gasparoli&al. 2002; Dujardin&al.,2004; Lewis&al., 2005; Schrag&al.,2006; van Rooden&al.,2011;Liu&al.,2011; Marras⟪2013

Structure of Future PD Criteria

- Parkinsonism to remain core clinical criterion
- Expert clinical examination as Benchmark
- Criteria to include positive and negative features
- Criteria to be weighted (‚red flags‘)
- Criteria to include time componenent
- Different levels of certainty (‚clinical PD‘ vs ‚possible PD‘)
- Include ancillary diagnostic tests

Berg et al., MDJ 2014

Towards a new definition of PD

- **Clinically Established PD**
  - Anchored on Bradykinesia plus at least 1out of RT, Rigidity
  - At leat 2 supportive criteria
  - Absence of absolute exclusion criteria
  - No ‚red flags‘
- **Clinically Probable PD**
  - Absence of absolute exclusion criteria
  - Presence of ‚red flags‘ counterbalanced by supportive criteria

Berg&Postuma&MDS Task Force, in progress

FEATURED ARTICLE

Time to Redefine PD? Introductory Statement of the MDS Task Force on the Definition of Parkinson's Disease

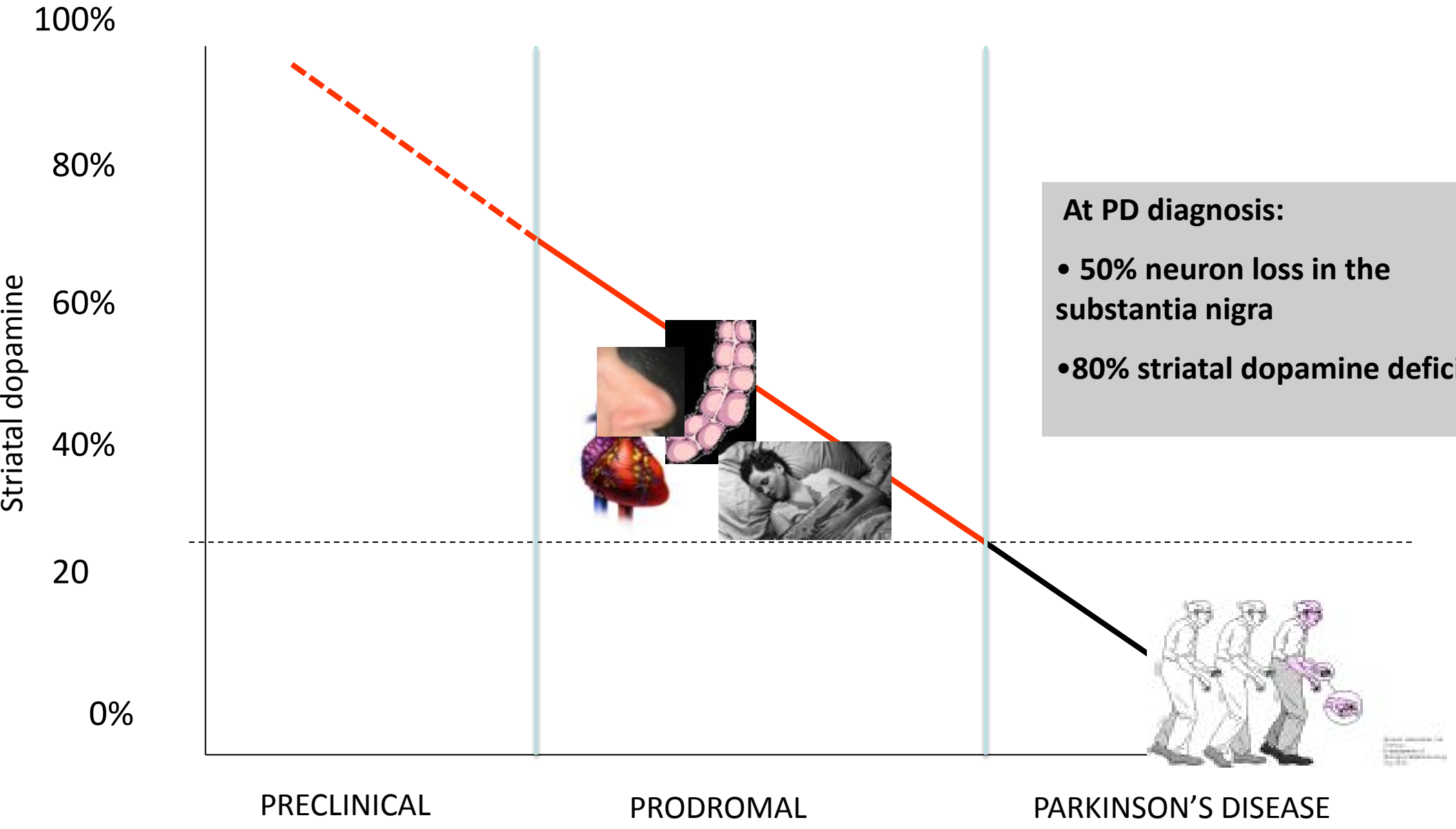
Daniela Berg, MD,[1*¶] Ronald B. Postuma, MD, MSc,[2¶] Bastiaan Bloem, MD, PhD,[3] Piu Chan, MD, PhD,[4] Bruno Dubois, MD, PhD,[5] Thomas Gasser, MD,[1] Christopher G. Goetz, MD,[6] Glenda M. Halliday, PhD,[7] John Hardy, PhD,[8] Anthony E. Lang, MD, FRCPC,[9] Irene Litvan, MD,[10] Kenneth Marek, MD,[11] José Obeso, MD, PhD,[12] Wolfgang Oertel, MD,[13] C. Warren Olanow, MD, FRCPC,[14] Werner Poewe, MD,[15] Matthew Stern, MD,[16] and Günther Deuschl, MD[17]

Mov Disord 2014;29:454-462

- Key Issues
  - What is the Gold Standard for defining PD?
  - Does early dementia exclude PD?
  - Are there subtypes of PD?
  - When does PD begin?

Conceptual Issues in the Definiton of PD

- Nigrostriatal DA deficiency&SNc neuronal loss occur prior to onset of motor features
- *Specific NMS may occur before onset of motor features*
- *aSNC pathology may involve extranigral sites before affecting the SNc*
- Genetic PD (eg LRRK2) may show classical clinical presentation without Lewy pathology
- PD may not be a single disease entity


100%
80%
60%
40%
20
0%
Striatal dopamine
PRECLINICAL
PRODROMAL
PARKINSON'S DISEASE
At PD diagnosis:
• 50% neuron loss in the substantia nigra
•80% striatal dopamine deficit

The Onset of Nonmotor Symptoms in Parkinson's Disease (The ONSET PD Study)

Claustre Pont-Sunyer, MD,[1] Anna Hotter, MD,[2,3] Carles Gaig, MD, PhD,[1] Klaus Seppi, MD, PhD,[2,3] Yaroslau Compta, MD, PhD,[1] Regina Katzenschlager, MD, PhD,[3,4] Natalia Mas, MD,[1] Dominik Hofeneder, MD, PhD,[3,5] Thomas Brücke, MD, PhD,[3,5] Angels Bayés, MD, PhD,[6] Karoline Wenzel, MD,[3,7] Jon Infante, MD, PhD,[8] Heidemarie Zach, MD,[3,9] Walter Pirker, MD, PhD,[3,9] Ignacio J. Posada, MD, PhD,[10] Ramiro Álvarez, MD,[11] Lourdes Ispierto, MD,[11] Oriol De Fàbregues, MD, PhD,[12] Antoni Callén, MD,[12] Antoni Palasí, MD,[12] Miquel Aguilar, MD, PhD,[13] Maria José Martí, MD, PhD,[1] Francesc Valldeoriola, MD, PhD,[1] Manel Salamero, PhD,[1] Werner Poewe, MD, PhD,[2,3] and Eduardo Tolosa, MD, PhD[1]*

Mov Disord 2014 (Epub ahead of print)

- 109 PD patients vs 107 controls from 12 centres in Spain and Austria

- PD patients fulfilling UK Brain Bank criteria

- onset of motor symptoms > 40 years
- < 12 months from diagnosis of PD
- untreated for motor PD symptoms
- H&Y stage < 2.5

- age and sex matched healthy Controls

- no known neurological disorders
- without family history of PD
- must not be caregivers of a PD patient

ONSET-PD-Study: NMS in PD vs controls

NMS	PD	Controls	*p*
NMS number, mean	8.5 (SD 4.55)	4.4 (SD 3.76)	**<0.001**
MDS-UPDRS-I score	8.33 (SD 5.22)	4.33 (SD 4.64)	**<0.001**

- 17/31 NMS were significantly more frequent in PD than controls.
- In more than 50% of PD pts. NMS preceded the onset of MS.

C. Pont-Sunyer et al, Movement Disorders , 2014

ONSET-PD Study: ‚Preclinical' NMS - when do they begin?

- Significantly more common > 2 yrs pre PD
  - *Smell loss*
  - *Constipation*
  - *Nightmares/dream enacting behaviours*
  - *(mood disturbances*)

- Significantly more common < 2 yrs pre PD
  - *Memory Complaints*
  - *Fatigue*
  - *Anhedonia*
  - *Apathy*

C. Pont-Sunyer et al, Movement Disorders 2014

A number of populations “At Risk” for PD have been proposed

- Persons with clinical features highly predictive of the onset of PD in the future: “prodromal” PD: e.g., RBD, hyposmia
- Persons with genetic susceptibility: primary & “risk” genotypes
- Persons exposed to certain toxicants, traumatic brain injury, other exposures

A number of populations "At Risk" for PD have been proposed

THE DILEMMA:

Predictive value very low for most "at risk" features

brain injury, other exposures

Olfactory function as a single screening test for PD risk

- **Impaired olfaction present in > 90% PD patients**
- **For HAAS assuming 7or less on bsit as impaired:**
  - **Sensitivity = 0.79**
  - **Specificity = 0.53**
  - **PPV = 0.014**
  - **NPV = 0.996**
- **Limitations:**
  - **Low specificity and PPV**

Courtesy Dr. Web Ross

ONSET-PD Study: ‚Preclinical' NMS - when do they begin?

- Significantly more common > 2 yrs pre PD
  - *Smell loss*
  - *Constipation*
  - *Nightmares/dream enacting behaviours*
  - *(mood disturbances)*

- Significantly more common < 2 yrs pre PD
  - *Memory Complaints*
  - *Fatigue*
  - *Anhedonia*
  - *Apathy*

C. Pont-Sunyer et al, Movement Disorders (in press)

Risk Factors for Neurodegeneration in Idiopathic Rapid Eye Movement Sleep Behavior Disorder: A Multicenter Study

Postuma et al, Ann Neurol 2015

- Multicentric follow-up study in 305 Patients with iRBD (279 w. follow-up Data)
- Questionnnaire-based assessment of Baseline-Data: *demographics, lifestyle, pesticide exposure, occupation, co-morbidities, medication use, family history, autonomic & motor symptoms*
- Outcome: development of dementia or parkinsonism

Risk Factors for Neurodegeneration in Idiopathic Rapid Eye Movement Sleep Behavior Disorder: A Multicenter Study

Postuma&al., Ann Neurol, 2015

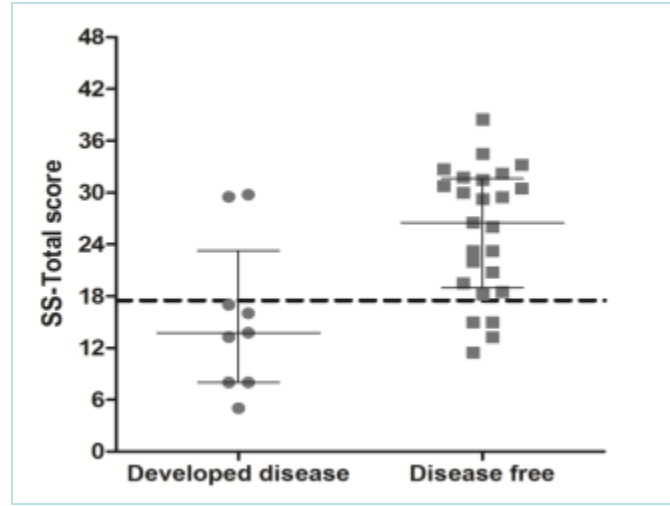
- after 2.5 a 93 (33 %) converters:
  - *39 (42 %) PD*
  - *47 (50.5 %) Dementia*
  - *7 (7.5 %) MSA*

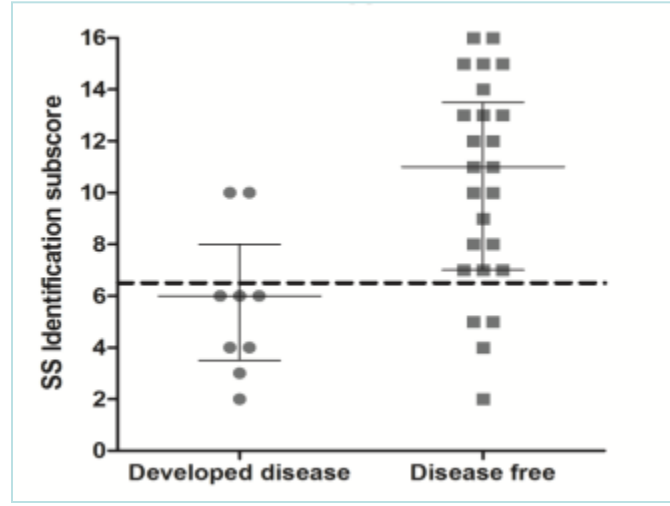
- conversion rates:
  - *15 % at 2 yrs*
  - *25 % at 3 yrs*
  - *36 % at 4 yrs*
  - *41 % at 5 yrs*

Philipp Mahlknecht, MD, PhD
Alex Iranzo, MD
Birgit Högl, MD
Birgit Frauscher, MD
Christoph Müller, MD
Joan Santamaría, MD
Eduardo Tolosa, MD
Monica Serradell, BSc
Thomas Mitterling, MD
Viola Gschliesser, MD
Georg Goebel, PhD
Florian Brugger, MD
Christoph Scherfler, MD
Werner Poewe, MD
Klaus Seppi, MD
For the SINBAR (Sleep Innsbruck Barcelona) Group

Olfactory dysfunction predicts early transition to a Lewy body disease in idiopathic RBD

Neurology® 2015;84:654-658





Subjects and Methods :

- **34 iRBD patients (29male)**
- **Mean iRBD duration: 10.7 (±7.5)**
- **Follow-up: 5 years**
- **9 developed disease (4 PD, 2 PDD, and 3 DLB) after a mean of 2.4 (±1.7) years**

Baseline Sniffin' Sticks total score and identification subscore

Sensitivity:	**77.8%**	**[44.3-94.7]**
Specificity:	**84.0%**	**[64.7-94.2]**
PPV:	**63.6%**	**[35.2-85.0]**
NPV:	**91.3%**	**[72.0-98.8]**

69 yr old male retired Pediatrician

- presents to sleep lab for suspected sleep apnea
- has noted progressively reduced sense of smell for past 10 years
- over the past year frequent nightmares , wife concerned about violent movements in sleep
- daytime sleepiness, single car accident bedause of SOS
- over the past year troublesome constipation
- never noted trembling or reduced movement speed or dexterity
- neurological exam is normal,no signs of parkinsonism

69 yr old male retired Pediatrician

Polysomnography:
Obstructive Sleep apnoea (CPAP required)
Classical RBD

Smell test (Sniffin-Sticks)
Hyposmia (Score 16.5, Normosmia > 30)

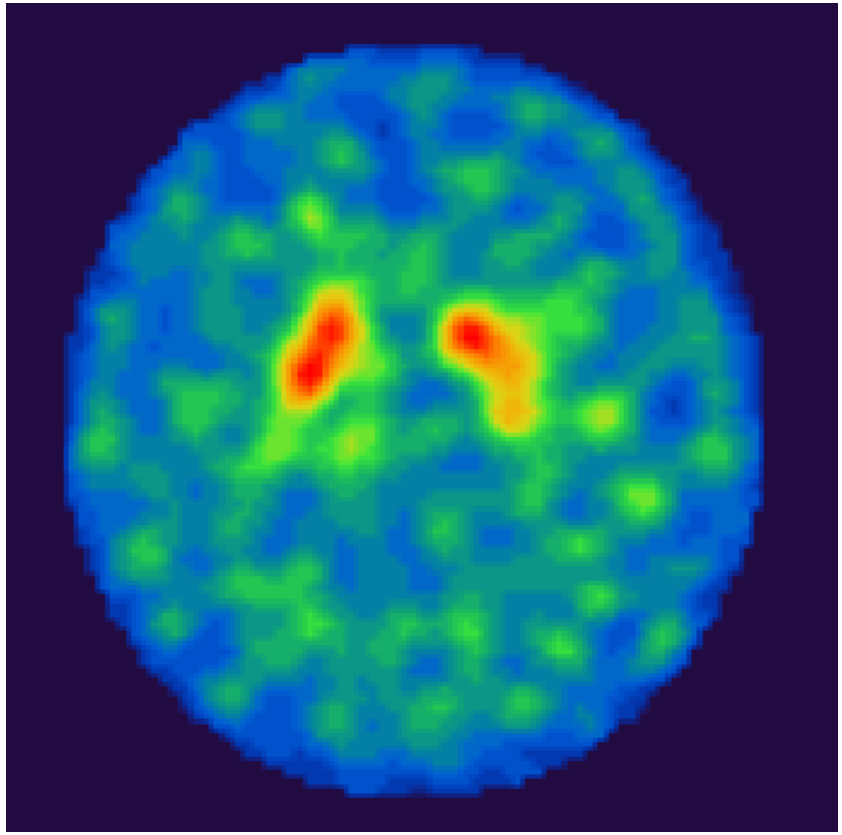
Midbrain Ultrasound (TCS)
Hyperechogenicity left SN

DAT-SPECT:
Slight reduction of DAT binding left putamen

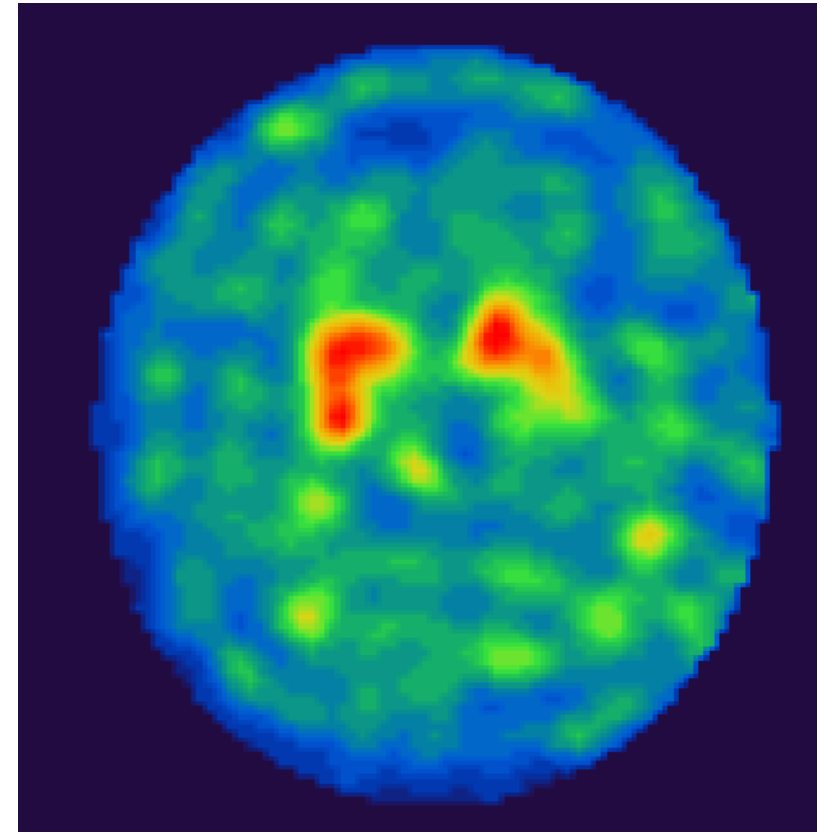
Does this patient have PD ?

DAT-SPECT (iRBD in 2011)

2011



2014



Towards a definition of prodromal PD

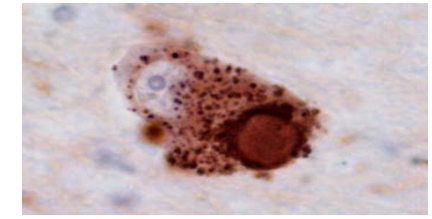
(Berg, Postuma&MDS Task Force)

- Data driven approach based on PD risk markers
- Likelihood of future PD based on prospective studies demonstrating predictive value
- Currently impossible to anchor definite prodromal PD
- Two levels of diagnostic certainty
  - ‚***Possible Prodromal PD‘*** (likelihood 30-80%)
  - ***‚Probable Prodromal PD‘*** (likelihood ≥ 80%)

What is Parkinson's disease ?

- **a clinical syndrome**
  * defined by the presence of cardinal motor features (BUT with many non-motor features !)

- **a neuropathological entity?**
  * defined by α-synuclein positive neuronal inclusions and SNc cell loss (BUT tau pathology without LB's in LRRK2 cases!)



- **a biomarker supported clinical syndrome ?**
  * imaging
  * molecular (genomic, proteomic)
  * tissue biopsy