International Parkinson and Movement Disorder Society European Section

ean the home of neurology

5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 6

EAN/MDS-ES: Movement disorders for general neurolgists (Level 2)

Diagnosis and early management of Parkinson's disease

Daniela Berg
Tübingen, Germany

Email: Daniela.Berg@uksh.de

UNIVERSITÄTSKLINIKUM
Schleswig-Holstein
Campus Kiel
Klinik für Neurologie

Diagnosis and early management of Parkinson's disease

Daniela Berg

Movement Disorder sessions at the
5th Congress of the European Academy of Neurology
are done in collaboration between MDS-ES and the EAN.

International Parkinson and Movement Disorder Society European Section

ean european academy of neurology

#MDSatEAN

Disclosures

Stock ownership in medically-related fields	**none**
Consultancies / Advisory Boards	**Biogen, BIAL, Lundbeck, UCB Pharma GmbH**
Partnerships	**none**
Honoraria /Participation in a company sponsored speaker's bureau	**AbbVie, Biogen, BIAL, Lundbeck, UCB Pharma GmbH, Zambon, Desitin**
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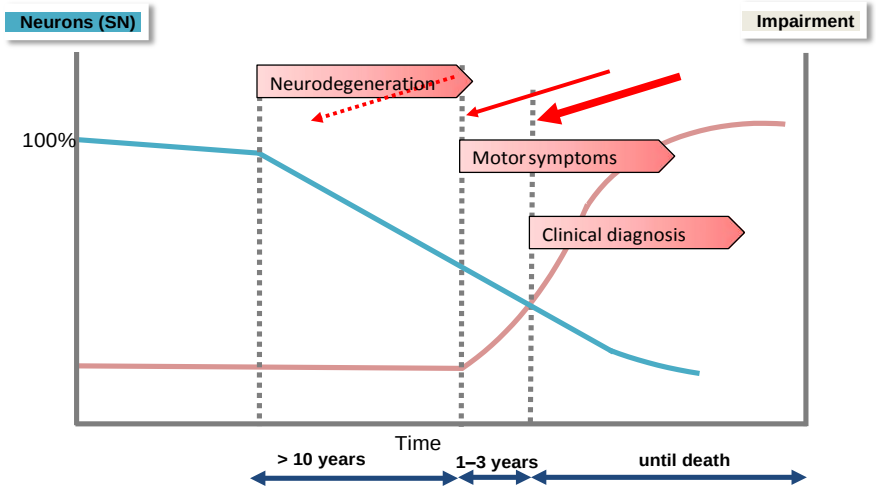
Intellectual Property Rights	**none**
Employment	**Department of Neurology, University of Kiel, Germany, and Hertie-Institute for Clinical Brain Research, Tuebingen, Germany**
Contracts	**none**

Learning objectives and outline

1. Early diagnosis of PD in general practice
2. Current therapeutic recommendations for initiation and early PD management
3. New knowledge about PD pathogenesis being transferred into practice

What is early diagnosis?



Early PD means already advanced neurodegeneration!

Diagnosing PD according to the current MDS Criteria

REVIEW

CME

MDS Clinical Diagnostic Criteria for Parkinson's Disease

Ronald B. Postuma, MD, MSc,[1†*] Daniela Berg, MD,[2†*] Matthew Stern, MD,[3] Werner Poewe, MD,[4] C. Warren Olanow, MD, FRCPC,[5] Wolfgang Oertel, MD,[6] José Obeso, MD, PhD,[7] Kenneth Marek, MD,[8] Irene Litvan, MD,[9] Anthony E. Lang, OC, MD, FRCPC,[10] Glenda Halliday, PhD,[12] Christopher G. Goetz, MD,[13] Thomas Gasser, MD,[2] Bruno Dubois, MD, PhD,[14] Piu Chan, MD, PhD,[15] Bastiaan R. Bloem, MD, PhD,[16] Charles H. Adler, MD, PhD,[17] and Günther Deuschl, MD[18]

Mov Disord 2015

Basis: Studies have suggested that experienced clinicians can diagnose PD with greater accuracy than formal diagnostic criteria (Hughes et al. Neurology 2001)

Clinical expert as benchmark

to codify the diagnostic process to

make it reproducible and

make it applicable by (relative) non-experts

For diagnosis

1. document parkinsonism

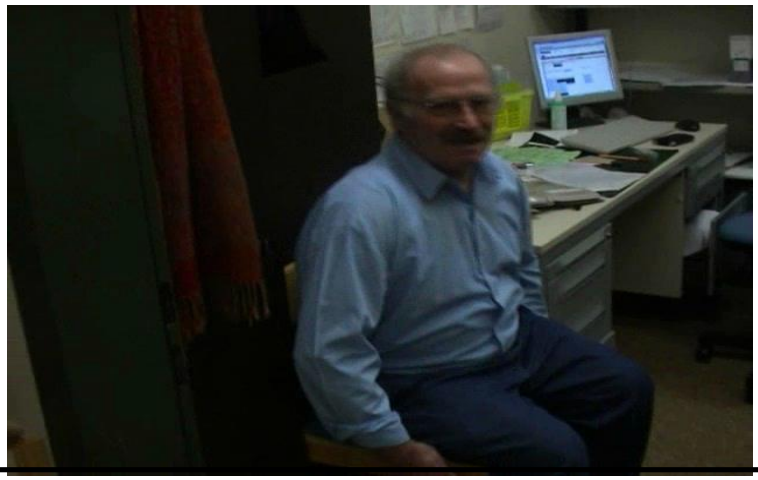
- **bradykinesia** defined as slowness of movement AND decrement in amplitude or speed (or progressive hesitations/halts) as movements are continued.

+ **rigidity/tremor**

For diagnosis

1. document parkinsonism

- bradykinesia + rigidity/tremor
- postural instability is **NOT** core feature for diagnosis anymore



For differential diagnosis

1. incorporate positives and negatives

- positives – '**supportive features**' (dopamine response, dyskinesia, rest temor, MIBG abnormality/olfactory loss (4))
- negatives (supranuclear gaze palsy, drug-induced, *etc*. (19))

2. weigh features

- features simply incompatible with probable PD (EXCLUSION (9))
- other features argue against, but compatible ('RED FLAGS' (10))

Absolute exclusion criteria

1. Unequivocal cerebellar abnormalities
2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades
3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia
4. Parkinsonian features restricted to the lower limbs for more than 3 y
5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism
6. Absence of observable response to high-dose levodopa despite at least moderate symptom severity
7. Unequivocal cortical sensory loss (ie, graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia
8. Normal functional neuroimaging of the presynaptic dopaminergic system
9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is more likely than PD

Red flags

1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset
2. A complete absence of progression of motor symptoms or signs over 5 or more y unless related to treatment
3. Early bulbar dysfunction: severe dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5
4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
5. Severe autonomic failure in the first 5 y of disease. E.g. a) severe orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic or b) severe urinary retention or urinary incontinence in the first 5 y of disease
6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset
7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y
8. Absence of any of the common nonmotor features of disease despite 5 y disease duration
9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia
10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, and no side predominance is observed on objective examination

Red flags

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3. interpret information

sometimes 'exclusion' is not really exclusionary

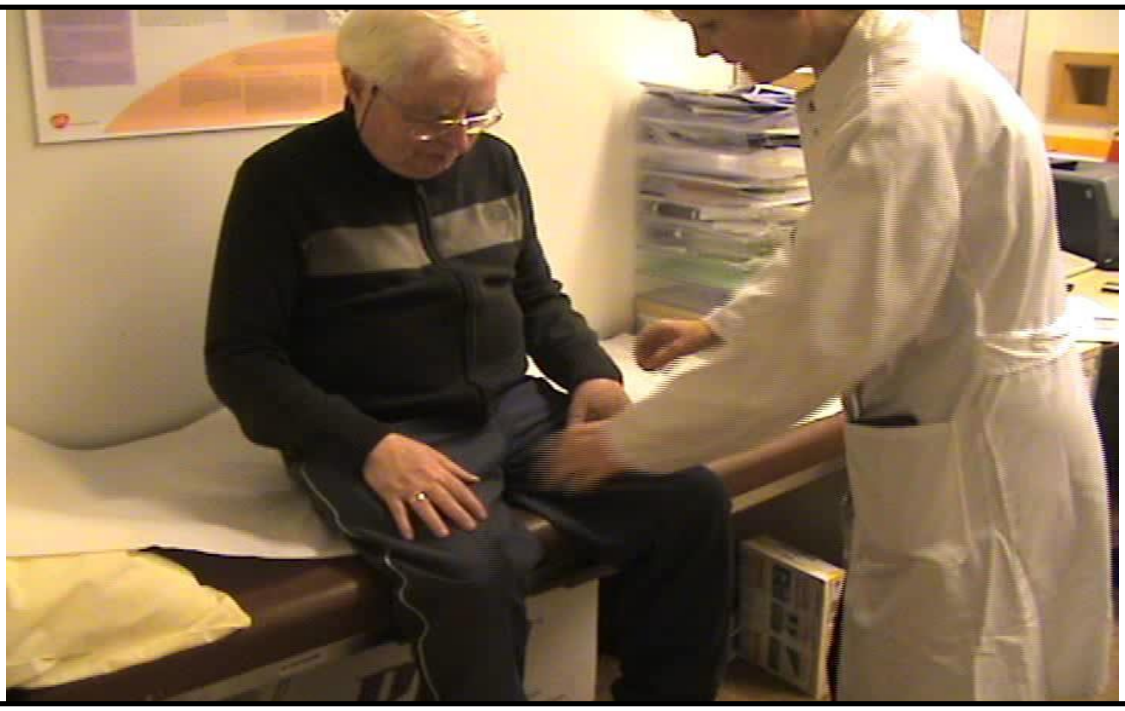
– *e.g.* early falls, what if playing tennis?

So, for criteria interpretation is written into some criteria

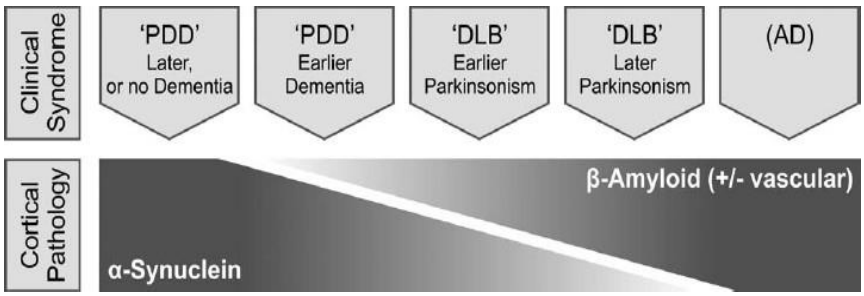
4. incorporate time

Time improves diagnosis, as it gives us:

- chance for atypical features to emerge
- chance to observe treatment response *etc.*

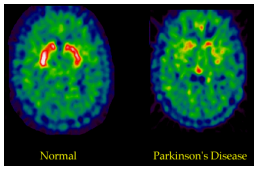


5. Dementia is NOT an exclusion criterion for PD (even if it starts first).



For those patients with dementia who already carry a diagnosis of dementia with Lewy bodies (according to consensus criteria), the diagnosis can optionally be qualified as "PD (dementia with Lewy bodies type)."

6. Ancillary diagnostic tests (possible!)



Depiction of the dopaminergic system
normal scan = exclusion

Testing of olfaction
high sensitivity (80%) and specificity (>80%)

one of the supporting criteria

REVIEW

CME

MDS Clinical Diagnostic Criteria for Parkinson's Disease

Ronald B. Postuma, MD, MSc,[1†*] Daniela Berg, MD,[2†*] Matthew Stern, MD,[3] Werner Poewe, MD,[4] C. Warren Olanow, MD, FRCPC,[5] Wolfgang Oertel, MD,[6] José Obeso, MD, PhD,[7] Kenneth Marek, MD,[8] Irene Litvan, MD,[9] Anthony E. Lang, OC, MD, FRCPC,[10] Glenda Halliday, PhD,[12] Christopher G. Goetz, MD,[13] Thomas Gasser, MD,[2] Bruno Dubois, MD, PhD,[14] Piu Chan, MD, PhD,[15] Bastiaan R. Bloem, MD, PhD,[16] Charles H. Adler, MD, PhD,[17] and Günther Deuschl, MD[18]

Movement Disorders, Vol. 30, No. 12, 2015

Step 1 - Parkinsonism

bradykinesia + ≥1 of rest tremor, rigidity

Step 2 – Differential Diagnosis

3 major classes of criteria

- supportive criteria (4)
- absolute exclusions (9)
- red flags (10)

all interpreted, weighted and applied considering the importance of time!

Certainty levels

Clinically established PD:

maximizing specificity,
goal that at least 90% will truly have PD, presumed that many true PD cases will not meet this level

1) at least two supportive criteria
2) absence of absolute exclusion criteria
3) no red flags

Clinically probable PD:

balancing sensitivity and specificity
goal that at least 80% of patients truly have PD, also that 80% of true PD cases are identified

1) absence of absolute exclusion criteria
2) red flags counterbalanced by supportive criteria
   - if 1 red flag must have ≥1 supportive criterion
   - if 2 red flags, at least ≥2 supportive criteria
   - no more than two red flags allowed

Results of a multicenter, international validation study

- 626 patients with PS in 8 centers – 434 iPD, 192 other PS

diagnostic MDScriteria
plus
UK brain bank criteria

expert gold standard

MDS criteria

overall accuracy= 92.6%, error rate = 7.4%

UK brain bank

overall accuracy = 86.4%, error rate = 13.6%

Mov Disord 2018

MDS Criteria for Clinically Established *Early* PD

Step 1 - Parkinsonism

Bradykinesia + ≥1 of rest tremor, rigidity

Step 2 – Differential Diagnosis

3 major classes of criteria

- supportive criteria (4)
- absolute exclusions (9)
- red flags (10),

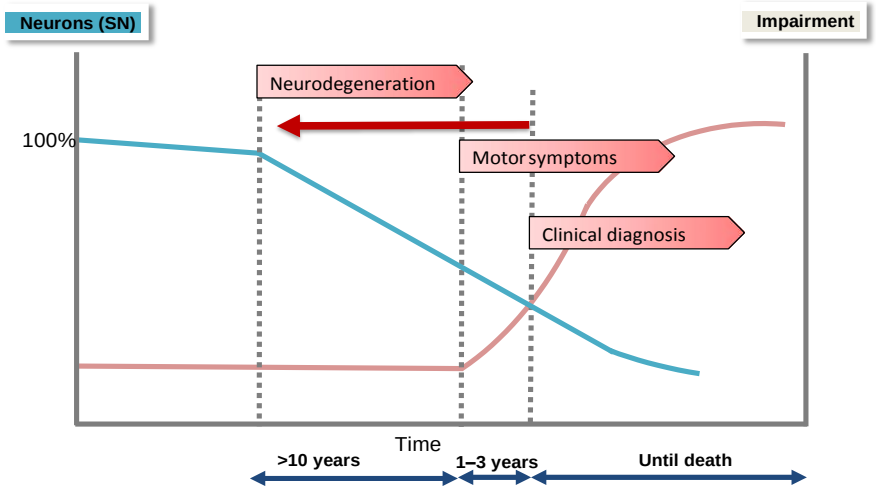
- ***remove all disease duration components***
  (e.g. falls within 3 y, absence of progression within 5 y)
- ***change red flags to absolute exclusions***
- ***supportive criteria no longer required***

Among 212 PD and 152 non-PD patients: **specificity 95.4%, sensitivity 69.8%**

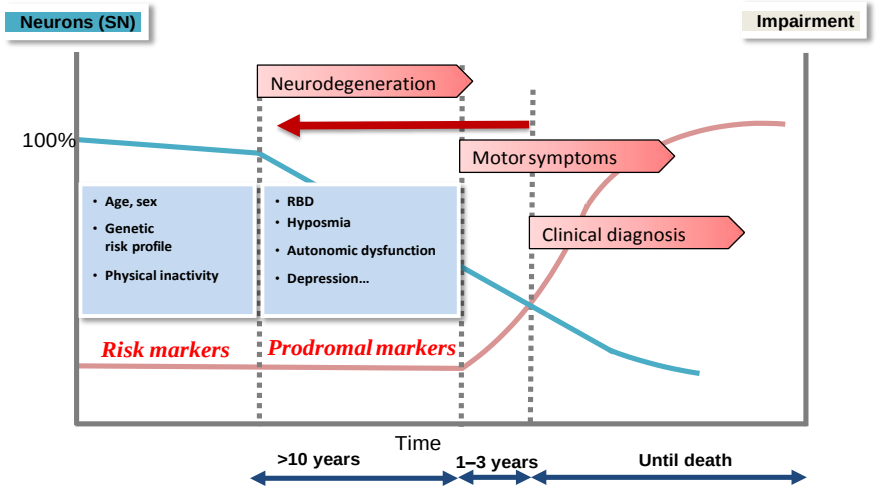
Designed specifically **for studies** of early PD (duration <5 years)

Mov Disord accepted

How to diagnose PD even earlier?



There are risk and prodromal markers we may apply



RBD=REM sleep behaviour disorder

We have scientific criteria to calcuate the probability of an individual to be in the prodromal phase

REVIEW

CME

MDS Research Criteria for Prodromal Parkinson's Disease

Daniela Berg, MD,[1*] Ronald B. Postuma, MD, MSc,[2*] Charles H. Adler, MD, PhD,[3] Bastiaan R. Bloem, MD, PhD,[4] Piu Chan, MD, PhD,[5] Bruno Dubois, MD, PhD,[6] Thomas Gasser, MD,[1] Christopher G. Goetz, MD,[7] Glenda Halliday, PhD,[8] Lawrence Joseph, PhD,[9] Anthony E. Lang, OC, MD, FRCPC,[10] Inga Liepelt-Scarfone, PhD,[1] Irene Litvan, MD,[11] Kenneth Marek, MD,[12] José Obeso, MD, PhD,[13] Wolfgang Oertel, MD,[14] C. Warren Olanow, MD, FRCPC,[15] Werner Poewe, MD,[16] Matthew Stern, MD,[17] and Günther Deuschl, MD[18]

Berg et al. Mov Disord 2015;30(12):1600–1611

Calculation of individual risk according to likelihood ratios of markers

What about therapy?

As early as possible!

Course of motor Parkinson's disease

MAO-inhibitors
Rasagiline
Selegiline

Major side effects:
daytime sleepiness
compulsive behaviors
motor fluctuations (start low!)
edema, hallucinations
livedo reticularis
QTc-prolongation

Dopamine-agonists
Ropinirole, Pramipexole, Rotigotine

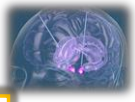
Levodopa

Amantadine

MAO-inhibitors
Rasagiline, Selegiline
Safinamide

COMT-inhibitors
Tolcapone,
Entacapone, Opicapone

Deep brain stimulation



Pump-therapies
Apomorphine
Duodopa

Individual schemes

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 24, 2019 VOL. 380 NO. 4

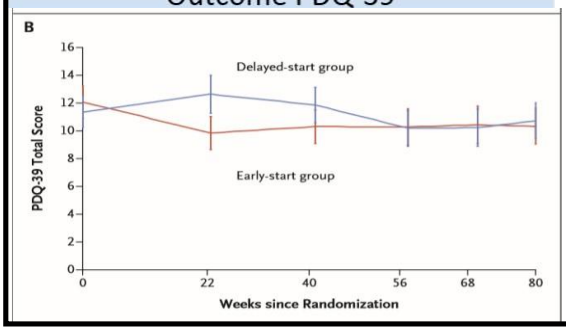
Randomized Delayed-Start Trial of Levodopa in Parkinson's Disease

C.V.M. Verschuur, S.R. Suwijn, J.A. Boel, B. Post, B.R. Bloem, J.J. van Hilten, T. van Laar, G. Tissingh, A.G. Munts, G. Deuschl, A.E. Lang, M.G.W. Dijkgraaf, R.J. de Haan, and R.M.A. de Bie, for the LEAP

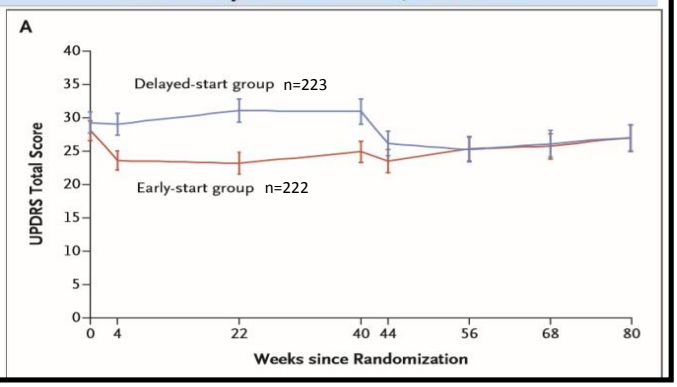
A multicenter study in the Netherlands.
Randomization to:

- Levodopa/carbidopa 100/25 mg TID for 80 weeks
- Placebo TID for 40 weeks followed by levodopa/carbidopa for 40 weeks

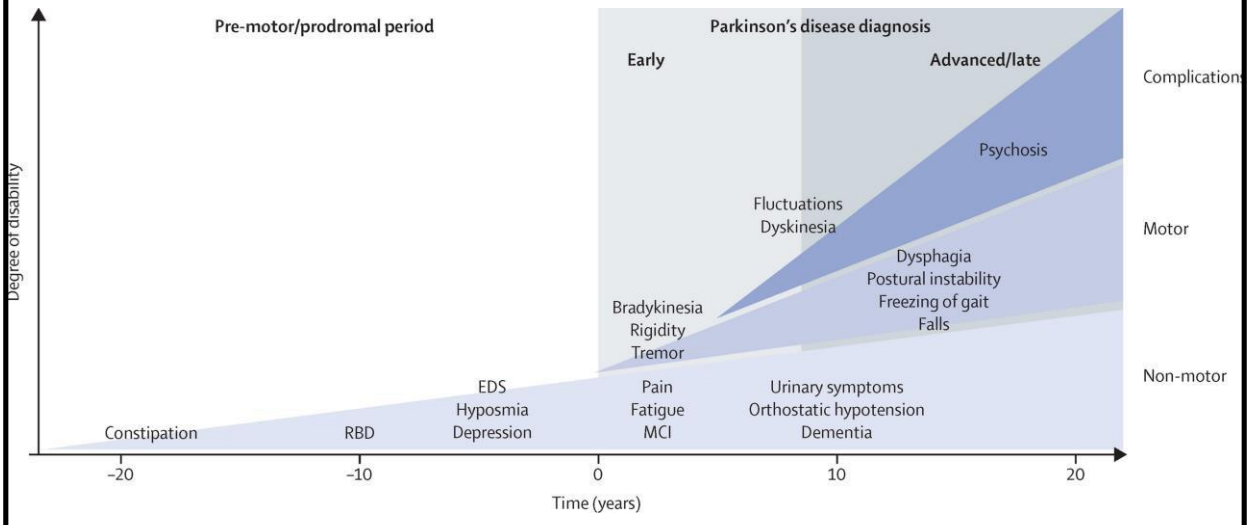
Outcome PDQ-39



Primary Outcome, UPDRS

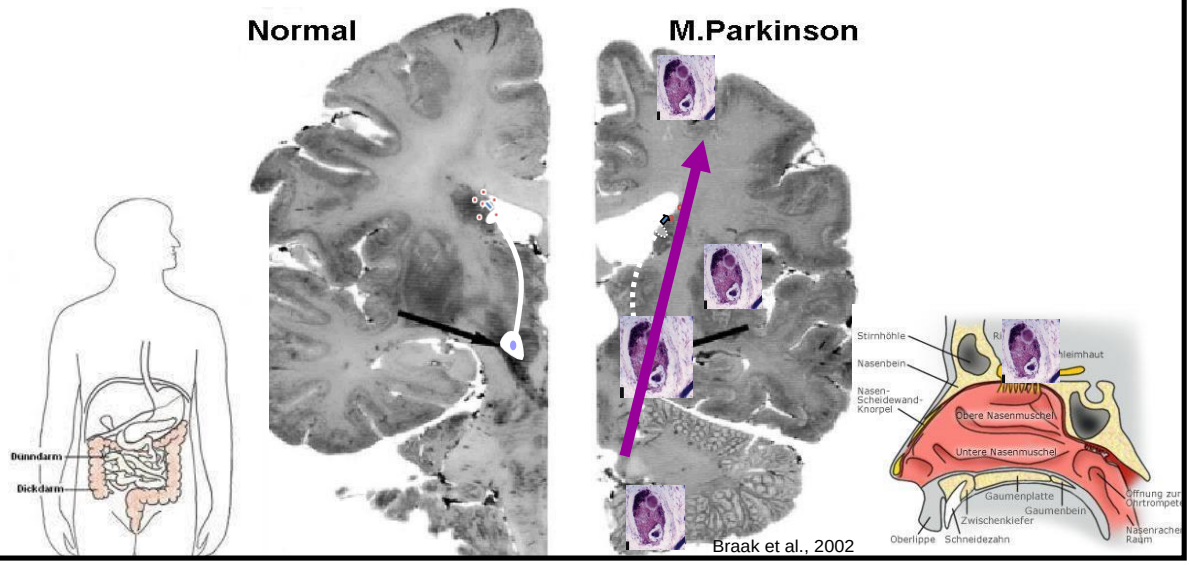


Evolution of symptoms in PD



Kalia et al. 2015, Lancet Neurol

Ascending, spreading neurodegeneration
Starting point most likely outside the brain…



Braak et al., 2002

The major therapeutic challenge

Autonomic dysfunction | **Neuropsyciatric symptomes** | **Sleep & Fatigue** | **Sensoric symptomes**

The major therapeutic challenge

Autonomic dysfunction

- urinary dysfunction
- constipation
- gastroparesis
- sexual dysfunction
- changes in body weight
- orthostatic dysfunction
- hyperhidrosis
- seborrhea
- sialorrhea

Neuropsyciatric symptomes

- depression
- anxiety
- apathy
- dementia
- hallucinations
- psychosis
- compulsive disorders
- dopamine-dysregulation-syndrome
- punding

Sleep & Fatigue

- RBD
- sleep-disturbancies
- sleep attacks
- fatigue
- RLS

Sensoric symptomes

- pain
- visual dysfunction
- hyposmia

MDS COMMISSIONED REVIEW

Update on Treatments for Nonmotor Symptoms of Parkinson's Disease—An Evidence-Based Medicine Review

Klaus Seppi, MD,[1*] K. Ray Chaudhuri, MD,[2] Miguel Coelho, MD,[3] Susan H. Fox, MRCP (UK), PhD,[4] Regina Katzenschlager, MD,[5] Santiago Perez Lloret, MD,[6] Daniel Weintraub, MD,[7,8] Cristina Sampaio, MD, PhD,[9,10] and the collaborators of the Parkinson's Disease Update on Non-Motor Symptoms Study Group on behalf of the Movement Disorders Society Evidence-Based Medicine Committee

Mov Disord. 2019 Feb;34(2):180-198 Review.

Is there anything I can do besides medication?

RESEARCH ARTICLE

The Association Between Lifestyle Factors and Parkinson's Disease Progression and Mortality

Kimberly C. Paul, PhD,[1] Yu-Hsuan Chuang, PhD,[1] I-Fan Shih, PhD,[1] Adrienne Keener, MD,[2] Yvette Bordelon, MD, PhD,[2] Jeff M. Bronstein, MD, PhD,[2] and Beate Ritz, MD, PhD[1,2*]

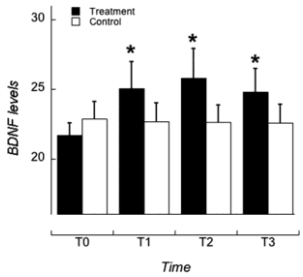
Mov Disord. 2019 Jan;34(1):58-66.

Physical activity, coffee, tea protective

Intensive Rehabilitation Increases BDNF Serum Levels in Parkinsonian Patients: A Randomized Study

Giuseppe Frazzitta, MD[1,2], Roberto Maestri, MS[3], Maria Felice

Neurorehabil Neural Repair 2014



What kind of activity?

It matters that!

Physio-, occupational-, speach therapy

Crowly et al., 2019; Hou et al., 2017; Mak et al., 2017; Lauze et al., 2016; Marusika et al., 2015; Frazzitta et al,. 2014; ….

Nutrition and PD

Mediterranean Diet

High amount of **polyphenols**

Mediterranean Diet Adherence Is Related to Reduced Probability of Prodromal Parkinson's Disease

Movement Disorders 2019

The Association between Mediterranean Diet Adherence and Parkinson's Disease

RN Alcalay, MD, MSc[1,2], Y Gu, PhD[2], H Mejia-Santana, MSc[1], L Cote, MD[1,3], KS Marder, MD, MPH[1,2,3,4], and N Scarmeas, MD, MS[1,2,3]

Movement Disorders 2012

Mediterranean Diet in Preventing Neurodegenerative Diseases.
Gardener H, Caunca MR.

Curr Nutr Rep. 2018

Olive oil

Green tea

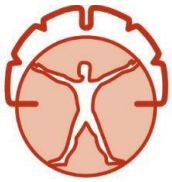
Berries

- ✓ **Modulation of antioxidant enzymes**
- ✓ **Modulation of neuroinflammation and cell survival**
- ✓ **Upregulation of BDNF and GDNF**

Learning objectives and outline

1. Early diagnosis of PD in general practice - MDS criteria
2. Current therapeutic recommendations for initiation and early PD management – early medication, all symptoms, physical/mental activity, "mediterranen" diet
3. New knowledge about PD pathogenesis being transferred into practice - early diagnosis is late in neurodegenerative process, spreading pathology encompassing the whole nervous system leading to many burdensome non-motor symptoms

Thank you for your attention!



International Parkinson and Movement Disorder Society

MDS Task Force on the Definition of Parkinson's disease

Task Force Members

Charles Adler
Bastian R. Bloem
Piu Bill Chan
Günther Deuschl
Bruno Dubois
Thomas Gasser
Christopher Goetz
Glenda Halliday
John Hardy
Anthony Lang
Irene Litvan
Kenneth Marek
Jose Obeso
Wolfgang Oertel
Warren Olanow
Werner Poewe
Matthew Stern

Chairs: Daniela Berg and Ron Postuma