Parkinson Disease: Diagnosis and Evolution

MDS-ES Africa online course 2021

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NS-PARK/FCRIN Network
University of Toulouse III
Outline

• Clinical Features
  Classical motor signs
  Non-motor symptoms

• Diagnosis
  Accuracy and clinical criteria

• Progression
What is Parkinson disease?

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

• A neuropathological syndrome
  – *defined by α-synuclein positive neuronal cytoplasmic (Lewy bodies) and axonal (Lewy neurites) inclusions and cell loss in the SNc)*

• A DA-deficiency syndrome

• A biomarker-defined syndrome?
PD PATHOLOGICAL FINDINGS

• Lewy body inclusions seen in individuals without clinical evidence of PD (pre-clinical cases?)

• Lewy bodies (mainly consist of α-synuclein) not found in typical individuals with PD with Parkin and some LRRK2 non-G2019S mutation carriers

• Marked variability in pathological findings even among carriers of identical mutations
**PD CARDINAL MOTOR SIGNS**

**Bradykinesia**  (core sign)
- Micrography
- Hypomimia
- Decreased blink rate
- Small step/Shuffling gait
- Diminished arm swing

**Plus one of:**
- **Resting tremor** (4 - 6 Hz) : “pill rolling“
- **Rigidity**: "lead pipe" or like a "cogwheel"
Non-motor symptoms (NMS) of PD

- Disorders of sleep-wake cycle regulation
- Neuropsychiatric features
  - Cognitive dysfunction
  - Disorders of mood and affect
- Autonomic dysfunction
- Sensory symptoms and pain
- Olfactory dysfunction
The burden of non-motor symptoms

- 20% of PD patients present with non-motor symptoms (NMS) and this is associated with a delayed diagnosis of PD (O'Sullivan et al 2008)
- Non-motor symptoms have, as a whole, a greater impact on HRQoL than motor symptoms
- Non-motor symptoms progression contributes importantly to HRQoL decline in patients with PD
- After 20 years of disease, the predominant problems in PD are non-motor symptoms
The PRIAMO study: a multicenter assessment of non-motor symptoms and their impact on QoL in PD

QoL=Quality of Life
Early non-motor symptoms

<table>
<thead>
<tr>
<th>Non-motor symptoms proposed as early signs of idiopathic PD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Probable early signs</strong></td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Olfactory deficit</td>
</tr>
<tr>
<td>REM sleep behaviour disorder</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td><strong>Possible early signs</strong></td>
</tr>
<tr>
<td>Restless-legs syndrome</td>
</tr>
<tr>
<td>Apathy</td>
</tr>
<tr>
<td>Fatigue</td>
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<tr>
<td>Anxiety</td>
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</tbody>
</table>

- Hyposmia, or olfactory dysfunction – occurs in up to 90% of PD patients and may predate clinical PD by at least 4 years
- Constipation – occurs in up to 60–80% of PD patients and may precede parkinsonian symptoms by 10 years
- RBD – may precede motor symptoms by years, with 15–38% of RBD patients subsequently diagnosed with PD
- Depression – may occur in ~28% of patients with early-stage PD

RBD = rapid eye movement sleep behavioural disorder

Tolosa et al. Neurology 2009; 72 (7 Suppl): S12
Viewpoint

What Are the Most Important Nonmotor Symptoms in Patients with Parkinson’s Disease and Are We Missing Them?

David A. Gallagher, MRCP,1 Andrew J. Lees, MD, FRCP,2 and Anette Schrag, MD, PhD, FRCP1*

1Department of Clinical Neuroscience, Institute of Neurology, Royal Free Campus, London, United Kingdom
2Reta Lila Weston Institute of Neurological Studies, University College London, United Kingdom

89 PD patients
- NMSQ: mean of 11 NMS per patient
  * Nycturia 62 %
  * Urgency 58 %
  * Memory impairment 57 %
  * Constipation 48 %
  * Depressed mood 48 %

- Chart review: mean of 4.8 NMS per patient
PD symptoms – the patient’s perspective

- 265 consecutive PD patients asked to rank their 3 most troublesome symptoms in the last 6 months
- Patients divided into early (<6 years) and late PD groups (≥6 years) from symptom onset (based on mean time from symptom onset to the development of motor complications)

<table>
<thead>
<tr>
<th>Top 5 most prevalent complaints</th>
<th>Early PD</th>
<th>Advanced PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slowness</td>
<td></td>
<td>Fluctuating response to medication</td>
</tr>
<tr>
<td>Tremor</td>
<td></td>
<td>Mood changes</td>
</tr>
<tr>
<td>Stiffness</td>
<td></td>
<td>Drooling</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td>Sleep problems</td>
</tr>
<tr>
<td>Loss of smell and/or taste</td>
<td></td>
<td>Tremor</td>
</tr>
</tbody>
</table>
Outline

• Clinical Features
  – classical motor signs
  – non-motor symptoms

• Diagnosis
  – accuracy and clinical criteria

• Progression
Based on History + Clinical features (+ some tests)

- **Progressive** neurological disease characterised by *akinesia*, *rigidity*, *rest tremor* and *postural & gait* disturbance

- 2 presentations
  - main symptom: *asymmetric tremor*
  - main symptom: *asymmetric akinesia and rigidity*

- Called “idiopathic” Parkinson disease to differentiate it from other causes of parkinsonism

Tolosa *et al* 2006; Edwards, Quinn & Bhatia 2008
Classification of Parkinsonism

- Neurodegenerative parkinsonism
  - Idiopathic Parkinson’s disease (IPD)
    - Sporadic
    - Genetic
  - Atypical parkinsonian disorders

- Symptomatic parkinsonism
  - Drug-induced
  - Vascular parkinsonism
  - Basal ganglia lesions
  - Toxic (MPTP, CO, CN, MN)
  - Encephalitis
  - Frontal meningioma
Clinical criteria for the diagnosis of Parkinson disease

CLINICAL CRITERIA – most used criteria in clinical practice and in clinical research

• Old criteria
  – UKPDSBB (1988)

• New criteria
  – MDS-PD criteria (2015)

PDS BRC Criteria for Idiopathic Parkinson Disease

- Asymmetrical onset
- Persistent asymmetry affecting side of onset most
- Rest tremor present (5-Hz)
- Progressive disorder
- Excellent response (70% – 100%) to levodopa
- Levodopa response for five years or more
- Levodopa-induced limb chorea
- Clinical course of ten years or more
- Absence of atypical features

Clinical diagnosis associated with an unavoidable misdiagnosis error

- Hughes et al, 1992 (London brain bank)
  • about 25 % of patients diagnosed with PD did not have neuropathologic criteria

- Rajput et al, 1991 (Canada)
  • in patients diagnosed at onset with PD only 64 % received a post-mortem diagnosis of PD

- Mis-diagnosis higher at symptoms onset and lower in movement disorders centres (vs general neurologists and primary care physicians) (lowest 10%)
Patients (n=131) with an initial diagnosis of PD (by general practitioner or neurologist)

<table>
<thead>
<tr>
<th>Parkinson’s disease</th>
<th>109</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Parkinson’s disease</td>
<td>22 (15%)</td>
</tr>
<tr>
<td>Possible PD</td>
<td>2</td>
</tr>
<tr>
<td>PSP</td>
<td>4</td>
</tr>
<tr>
<td>MSA</td>
<td>3</td>
</tr>
<tr>
<td>Vascular</td>
<td>6</td>
</tr>
<tr>
<td>Tremor (mainly essential)</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
</tbody>
</table>

Patients (n=124) with a final diagnosis of probable PD

<table>
<thead>
<tr>
<th>Parkinson’s disease</th>
<th>109</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Parkinson’s disease</td>
<td>15 (19%)</td>
</tr>
<tr>
<td>APD</td>
<td>1</td>
</tr>
<tr>
<td>Vascular</td>
<td>1</td>
</tr>
<tr>
<td>Tremor (mainly essential)</td>
<td>9</td>
</tr>
<tr>
<td>Drugs</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
</tr>
</tbody>
</table>

**GOLD STANDARD: clinical diagnostic criteria – movement disorders experts**

- 15% of patients with a diagnosis of PD did not fulfil criteria for PD. Most of them would not have had any benefit from dopaminergic treatment.
- 19% of patients with MDE-confirmed PD, had not been diagnosed as such.

Schrag et al. J Neurol Neurosurg Psychiatry 2002
MDS Clinical Diagnostic Criteria for Parkinson’s Disease

Ronald B. Postuma, MD, MSc, Daniela Berg, MD, Matthew Stern, MD, Werner Poewe, MD, C. Warren Olanow, MD, FRCPC, Wolfgang Oertel, MD, José Obeso, MD, PhD, Kenneth Marek, MD, Irene Litvan, MD, Anthony E. Lang, OC, MD, FRCPC, Glenda Halliday, PhD, Christopher G. Goetz, MD, Thomas Gasser, MD, Bruno Dubois, MD, PhD, Piu Chan, MD, PhD, Bastiaan R. Bloem, MD, PhD, Charles H. Adler, MD, PhD, and Günther Deuschl, MD
MDS Clinical Diagnostic Criteria for PD

**Benchmark: Expert Clinical Examination**

- **Bradykinesia**, plus one of
  - Rigidity
  - 4 - 6 Hz rest tremor

**Supportive Criteria**

- Excellent response to levodopa
- Presence of levodopa-induced dyskinesia
- Rest tremor of a limb
- Presence of either olfactory loss or sympathetic cardiac denervation (MIBG scintigraphy)

MDS Diagnostic Criteria for PD
‘Red Flags’

- Rapid progression of gait impairment (wheelchair in 5 yrs)
- No progression over 5 yrs
- Severe dysphonia, dysarthria or dysphagia within 5 yrs.
- Inspiratory stridor
- Severe autonomic failure within 5 yrs (symptomatic OH, urinary incontinence or retention)
- Recurrent falls within 3 yrs
- Disproportionate anterocollis or limb contractures within 10 yrs
- Absence of typical PD NMS over 5 yrs
- Persistent motor symmetry

Postuma et al, Mov Disord. 2015
MDS Diagnostic Criteria for PD

Absolute Exclusion Criteria

- Unequivocal cerebellar signs
- Downward vertical gaze palsy
- Dx of FTD (behavioural variant or PPA) within 5 yrs
- Parkinsonism restricted to legs for > 3 yrs.
- Exposure to anti-DA drugs consistent with (dose, timing) drug-induced parkinsonism
- Absence of L-Dopa response
- Cortical sensory loss, limb apraxia, progressive aphasia
- Normal functional imaging of presynaptic DA system

MDS Diagnostic Criteria for PD

Certainty levels

• **Clinically established PD**
  – Maximising specificity
  – ≥90% will have true PD
  – Many true cases will not meet these criteria initially

• **Clinically Probable PD**
  – Balancing sensitivity and specificity
  – ≥80% will have true PD
  – ≥80% of true PD will be captured

MDS Clinical Diagnostic Criteria for PD

• “Clinically Established PD”
  – Anchored on bradykinesia plus at least one out of rest tremor and rigidity
  – At least 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

MDS PD Criteria Validation Study

• 8 Movement Disorder centres
• Expert neurologist as gold-standard for PD or non-PD
• Second neurologist (unaware of gold-standard dx) evaluated presence/absence of each item from MDS diagnostic criteria

• Primary outcome:
  – overall accuracy, sensitivity and specificity

Postuma et al, MDJ, 2018
MDS PD Criteria Validation Study

626 subjects with Parkinsonism (434 PD vs 192 non-PD)

• Main results ref criteria for "Probable PD"
  – sensitivity: 95% (vs 89% UKBBC)
  – specificity: 89% (vs 79% UKBBC)
  – accuracy: 93% (vs 86% UKBBC)

• Sensitivity/specificity of criteria for "Clinically Established PD": 59% / 99%

Postuma et al, MDJ, 2018
# DIAGNOSING PD: Contribution of ancillary tests

No definite diagnostic test (except genetic testing)

<table>
<thead>
<tr>
<th>TEST</th>
<th>OUTCOME</th>
<th>INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Dopa response</td>
<td>positive</td>
<td>argues for PD</td>
</tr>
<tr>
<td></td>
<td>negative</td>
<td>may question PD</td>
</tr>
<tr>
<td>Olfactory testing</td>
<td>hyposmia</td>
<td>consistent with PD</td>
</tr>
<tr>
<td></td>
<td>normosmia</td>
<td>may question PD</td>
</tr>
<tr>
<td>Structural MRI</td>
<td>normal</td>
<td>consistent with PD</td>
</tr>
<tr>
<td></td>
<td>abnormal</td>
<td>points to secondary or atypical parkinsonism</td>
</tr>
<tr>
<td></td>
<td>(structural BG lesions, frontal meningeoma, atrophy midbrain / putamen / cerebellum, diffusivity changes)</td>
<td></td>
</tr>
<tr>
<td>DAT-Spect</td>
<td>abnormal</td>
<td>consistent with PD</td>
</tr>
<tr>
<td></td>
<td>normal</td>
<td>excludes PD</td>
</tr>
<tr>
<td>TCS</td>
<td>hypoechogenic midbrain</td>
<td>consistent with PD</td>
</tr>
<tr>
<td></td>
<td>normoechogenic midbrain</td>
<td>questions PD</td>
</tr>
<tr>
<td>Genetic testing</td>
<td>positive for mutation</td>
<td>confirms genetic PD</td>
</tr>
<tr>
<td>(eg LRRK2, VPS35, PARKIN, PINK-1, DJ-1, GBA)</td>
<td></td>
<td></td>
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</table>
MRI at 1.5T in MSA (vs PD)

"RED FLAGS": MSA signs (Sensitivity >50%; Specificity >90%)

- putaminal atrophy
- putaminal hypointensity
- putaminal rim sign
- pontocerebellar atrophy
- MCP atrophy a./o. hyperintensity
- hot cross bun sign
- ↑ putaminal diffusivity
- hypointensity on GRE T2* or SWI at higher field strengths

Several combinations of 2 different markers were sufficient to obtain >95% discrimination between MSA and PD patients.
The role of DAT-SPECT in movement disorders

G Kagi, K P Bhatia and E Tolosa

*J Neurol Neurosurg Psychiatry* 2010 81: 5-12

- Does a normal DAT-SPECT exclude PD?
- Sensitivity of DAT-SPECT < 100%
- DAT-SPECT or [18F]dopa PET: 5.7–14.7% SWEDD
Genetically defined Parkinsonism

'Classical' PD

Early Onset PD

Complex Phenotypes

PARK 1
PARK 4
PARK 8
PARK 17

PARK 2
PARK 6
PARK 7
PARK 19B

PARK 9
PARK 15
PARK 19
PARK 20
FREQUENCY OF MUTATIONS IN EARLY ONSET PD

• N = 953 cases of PD with onset before age 51

• Genetic testing for SNCA, PRKN, PINK1, DJ1, LRRK2, GBA

• 16.6% positive (6.7% PRKN, 3.6% LRRK2, 6.7% GBA, 0.2% DJ1)

• 40.6% with disease onset < 30 yrs positive

Alcalay et al, Arch Neurol 2010
Outline

• Clinical Features
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  – non-motor symptoms

• Diagnosis
  – accuracy and clinical criteria

• Progression
PD PROGRESSION

Disability

Age

Death

Nursing home
Dementia
Hallucinations
Hypotension
Falls

Motor complications & dyskinesias

bilateral

unilateral

5 yrs to death

Preclinical
Prodromal
Pre-motor

Signs and symptoms

RBD
Constipation
Depression
Hyposmia...

-4–6 yrs

Ferreira JJ
Annualised change in UPDRS-Total scores in placebo groups in PD RCTs

**DATATOP study** (Parkinson Study Group, 1993)  14 points
Lazabemide study (Parkinson Study Group, 1996)  9 points
Coenzyme Q$_{10}$ study (Shults et al, 2002)  9 points
ELLDOPA study (Fahn et al, 2004)  11 points
TEMPO study (Parkinson Study Group, 2002)  8 points
TCH346 (Olanow et al, 2006)  8 points
CEP-1347 (Parkinson Study Group, 2007)  8 points
ADAGIO (Rascol et al, 2011)  6 points
Progression of MDS-UPDRS Scores Over Five Years in De Novo Parkinson Disease from the Parkinson’s Progression Markers Initiative Cohort

Annualised progression:
MDS-UPDRS total = 4.70 pts.
MDS-UPDRS I = 0.92 pts.
MDS-UPDRS II = 0.99 pts.
MDS-UPDRS III = 2.70 pts.

Part 3 unmedicated:
4.02 per yr

Part 3 medicated:
1.77 per yr
### Motor complication rates* with initial levodopa therapy

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Complication Rate</th>
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<tbody>
<tr>
<td>Retrospective uncontrolled studies</td>
<td>50–80% after 5–6 years</td>
</tr>
<tr>
<td>(Poewe et al., 1986)</td>
<td></td>
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<tr>
<td>Community-based studies</td>
<td>30–40% after 5 years</td>
</tr>
<tr>
<td>(Schrag et al., 2000)</td>
<td></td>
</tr>
<tr>
<td>Young-onset PD</td>
<td>90% after 5 years</td>
</tr>
<tr>
<td>(Quinn et al., 1987; Schrag et al., 1998)</td>
<td></td>
</tr>
<tr>
<td>Randomised controlled trials (RCTs)</td>
<td>16% after 9 months</td>
</tr>
<tr>
<td>(PSG 2000; Whone et al., 2003; ELLDOPA)</td>
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<tr>
<td></td>
<td>30–40% after 2 years</td>
</tr>
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**Currently established risk factors:** age, LD-dose, disease duration

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*Refers to motor fluctuations and dyskinesias – most of the studies listed assessed both; young-onset PD refers to dyskinesias only

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L-dopa resistant motor symptoms in PD

- Axial and limb deformities
  - camptocormia
  - antecollis
  - lateral trunk flexion
  - „striatal“ limb deformities
  
(Doherty et al, Lancet Neurol 2011)

- Postural instability
- Falls
- Freezing of gait

- Dysarthria
- Dysphagia
Long-term prognosis of PD - Sydney multicentre study -

149 patients recruited into low-dose L-dopa versus bromocriptine trial

<table>
<thead>
<tr>
<th></th>
<th>15 years(^1)</th>
<th>20 years(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors</td>
<td>52</td>
<td>30</td>
</tr>
<tr>
<td>Prevalence of “L-dopa resistant” symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Falls</td>
<td>81%</td>
<td>87%</td>
</tr>
<tr>
<td>Choking</td>
<td>50%</td>
<td>48%</td>
</tr>
<tr>
<td>Symptomatic OH</td>
<td>35%</td>
<td>48%</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>41%</td>
<td>71%</td>
</tr>
<tr>
<td>Depression</td>
<td>50%</td>
<td>-</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>50%</td>
<td>74%</td>
</tr>
<tr>
<td>Dementia</td>
<td>48%</td>
<td>83%</td>
</tr>
<tr>
<td>Nursing home care</td>
<td>40%</td>
<td>48%</td>
</tr>
</tbody>
</table>

Dementia in Parkinson disease

- **Sydney study**: 83% after 20 years from disease onset (Hely et al, MDJ 2008)

  - 224 patients with PD (116 women).
  - **Baseline**: 26% patients (51) had dementia (cross-sectional prevalence)
  - **8-year cumulative prevalence**: 78% (95% confidence interval [CI], 71.1-84.0).
  - **Risk factors**: hallucinations before baseline (OR= 3.1; 95% CI, 1.6-6.2) and akinetic-dominant or mixed tremor/akinet  ic PD (OR = 3.3; 95% CI, 1.2-8.5).

Incidence x 3 to 6: 70 years old PD patients have a life expectancy of about 8 years, 5 without dementia and 3 with dementia...
Dynamics of PD Progression

- Lack of independence in activities of daily living
- Levodopa-induced motor complications
- Disability from PD
- Motor symptoms
- NMS
- Disability milestones

Schwab and England scale score = 50%

PD, Parkinson’s disease.
Adapted from Coelho M and Ferreira JJ. (Nat Rev Neurol, 2012)
Summary

• PD diagnosis is a clinical exercise
• Diagnostic accuracy is suboptimal in early disease
• New diagnostic criteria may help
• Ancillary tests (imaging, genetics) significantly enhance diagnostic certainty
• Progression of disability driven by motor and non-motor features