Parkinson’s disease –
Motor and Non-motor features

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• Disclaimer: there is a lot of info in the slides (like my colleagues too). Digest what you can while you are here in Virtual Aspen and use the slides as future references.
Aspen - movement disorders connection

*Populus tremuloides* - quaking or trembling aspen

PD course and symptoms

Braak et al., 2004; Kalia et al., 2015
UK PD Society Brain Bank diagnostic criteria

• Inclusion criteria
  • Bradykinesia
  • One of the following:
    • Muscular rigidity
    • Rest tremor
    • Postural instability
  • Supportive criteria
  • Begins on one side
  • Asymmetric
  • Rest tremor
  • Progressive disorder
  • Responds to levodopa

• Clinico-pathological studies
  • High positive predictive value
  • Sensitivity ~90+% 
  • Expert clinician diagnosis more sensitive


• Essential criterion: parkinsonism
  • Bradykinesia
  • Plus at least 1 of rest tremor or rigidity

• ABSOLUTE exclusion criteria
  • Cerebellar abnormalities
  • Downward vertical supra nuclear gaze palsy
  • Prob Behav variant FTD or PPA
  • Lower limb park > 3 years
  • DA blockers
  • No levodopa response
  • Unequivocal cortical sensory loss
  • Normal functional neuroimaging presynaptic DA system
  • Other explanation

• Clear and dramatic beneficial response to DA therapy
• Levodopa induced dyskinesia
• Rest tremor
• Olfactory loss or MIBG with cardiac sympathetic denervation


**TABLE 1. LRs of risk and prodromal markers**

<table>
<thead>
<tr>
<th>Marker</th>
<th>LR^+</th>
<th>LR^-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodromal markers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSG-proven RBD</td>
<td>130</td>
<td>0.62</td>
</tr>
<tr>
<td>or Positive RBD screen questionnaire with &gt;80% specificity</td>
<td></td>
<td></td>
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<tr>
<td>or Dopaminergic PET/SPECT clearly abnormal (e.g., &lt;55% normal 2 SDs below mean)</td>
<td>2.3</td>
<td>0.76</td>
</tr>
<tr>
<td>or Possible subthreshold parkinsonism (UPDRS &gt; 3 excluding action tremor)</td>
<td>40</td>
<td>0.65</td>
</tr>
<tr>
<td>or Abnormal quantitative motor testing</td>
<td>10</td>
<td>0.70</td>
</tr>
<tr>
<td>or Olfactory loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Erectile dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Excessive daytime somnolence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Symptomatic hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Severe erectile dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Urinary dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Depression (≥ anxiety)</td>
<td>3.5</td>
<td>0.60</td>
</tr>
<tr>
<td>or Anxiety</td>
<td>4.0</td>
<td>0.43</td>
</tr>
<tr>
<td>or Dyskinesia</td>
<td>2.2</td>
<td>0.88</td>
</tr>
<tr>
<td>or Freezing of gait</td>
<td>1.9</td>
<td>0.87</td>
</tr>
<tr>
<td>or Falls</td>
<td>1.8</td>
<td>0.85</td>
</tr>
</tbody>
</table>


**PD progression – motor features**

- Pre-motor/prodromal period
- Parkinon's disease diagnosis
- Advanced/late
- Psychosis
- Fluctuations
- Dyskinesia
- Bradykinesia
- RBD
- Rigidity
- Depression
- EDS
- Postural instability
- Freezing of gait
- Falls
- Urinary symptoms
- Constipation
- Orthostatic hypotension
- Dementia
- Pain
- Fatigue
- MCI
- Motor complications

Kalai and Lang Lancet 2015
RECAP: PD cardinal motor features

Cardinal features

• Bradykinesia
• Asymmetric rest tremor
• Rigidity
• Gait and postural impairment

T = Tremor
R = Rigidity
A = Akinesia/bradykinesia
P = Postural instability

New images of PD

Armstrong and Okun JAMA Neurol 2020
PD case

Mr. Joe Aspen is a 72 year old male who comes for evaluation. He was diagnosed with PD about 7 years ago with right hand rest tremor, dragging his right leg, and smaller handwriting. He was followed by another neurologist who started dopaminergic medications with improvement and gradual dose increases.

In the past few years, he has experienced dyskinesias, worsened balance, and occasional falls. He occasionally stumbles and freezes up which has been embarrassing and stressful at work or in social situations. He fell once on the golf course but thinks he may have been dehydrated on a hot day. His tremors are reasonably controlled with medications but are worse when he is stressed. He recently retired since he was overwhelmed at work especially when juggling his personnel and clients. He has always been an avid exerciser and golfer. However, since retiring, he does not feel like it as much and has more right sided shoulder and hip pain. His wife thinks he may be grouchy because his sleep is terrible but this is long standing, with yelling in his sleep for many years. He has more urinary problems at night and trouble getting out of bed to go to the bathroom. Last year, he tried a bladder medication but it made him see distorted people in the bedroom at night.

His wife shares with you a list of her concerns including his involuntary movements, falls, constipation, denial about symptoms, and her worry about the future. He is most interested in further management of his walking and balance symptoms.

Early PD motor signs and symptoms

- Unilateral rest tremor
- Reduced spontaneous arm swing
- Decreased facial expression
- Loss of dexterity in one hand
- Micrographia
- Softer speech
- Unilateral foot dystonia (young onset)
- Pain in one shoulder
Advancing PD motor signs and symptoms

- Increased motor severity
- Motor fluctuations
  - Wearing off
  - Dyskinesias
- Unpredictable responses
- Night-time off periods
- Early morning akinesia
- Freezing of gait
- Postural reflex impairment
- Falls
- Dysphagia

HINT
- Ask patients about their “typical” day
- Keep a diary of symptoms through the day and night, along with timing of medication and meals

https://www.epda.eu.com/media/1432/wearingoff.jpg

Advancing PD motor signs and symptoms

- Dyskinesias
  - Three main types
    - Peak dose
    - Diphasic
    - Dystonia

https://www.invigoratept.com/blog/parkinsons-dyskinesia-a-bookmarkable-guide
Freezing of gait (FoG)

- A brief, episodic absence or a marked reduction of forward progression of the feet despite the intention to walk
  - Trembling in place
  - Shuffling forward, or
  - Complete akinesia

- Situational
  - Initiation
  - Turns
  - Environmental obstacles
  - Dual tasking

Okuma Pract Neurol 2014; Nonnekes et al., Lancet Neurol 2015; Gilat et al., Park Rel Dis 2018

Falls

- PD-related
  - Postural instability
  - Inappropriate weight shift
  - Freezing of gait
  - Dyskinesias
  - Orthostatic hypotension
  - Decreased attention
  - Visual impairment
  - Urinary dysfunction
  - Medication timing

- External
  - Environment
  - Uneven surfaces, obstacles
  - Foot wear

Okuma 2014; Vandenbossche et al., 2013; Bohnen et al., 2019
Okuma Pract Neurol 2014; Nonnekes et al., Lancet Neurol 2015; Gilat et al., Park Rel Dis 2018

Fasano et al., Mov Dis 2017
**Dysphagia**

- Occurs in up to 100% of patients in advanced disease stages
- Mild oropharyngeal symptoms as well as esophageal dysfunctions are very common in early stage PD
- Pooled prevalence for oropharyngeal dysphagia
  - 35% subjectively and 82% with objective, instrumental measures
- In subjectively, nondysphagic PD patients, over 50% have oropharyngeal disorders on fiberoptic endoscopic evaluation of swallowing (FEES) or video fluoroscopic swallowing study (VFSS)

**Phases of swallowing**

- Preoral/oral prep
- Oral/propulsion/processing and transport
- Pharyngeal phase
- Esophageal phase

**Table 2 Clinical Predictors for Aspiration-Associated Dysphagia in PD**

<table>
<thead>
<tr>
<th>Clinical Risk Factors</th>
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<tbody>
<tr>
<td>H&amp;Y &gt; 3</td>
<td></td>
</tr>
<tr>
<td>UPDRS III &gt; 26</td>
<td></td>
</tr>
<tr>
<td>BMI &lt; 20/relevant unintended weight loss</td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td>Saliva drooling, salivorrhrea, reduced oral bolus control*</td>
<td></td>
</tr>
<tr>
<td>Dysarthria</td>
<td></td>
</tr>
<tr>
<td>Disease duration &gt; 10 years</td>
<td></td>
</tr>
</tbody>
</table>

*Patients report being unable to hold food in the mouth.
BMI, body mass index kg/m²; H&Y, Hoehn & Yahr staging; UPDRSIII, Unified Parkinson’s Disease Rating Scale, motor part. According to [Zerrill et al., 2014; Coelho et al., 2010; Han et al., 2011; Johnston et al., 1997; Lam et al., 2007; Müller et al., 2001; Perez-Urret et al., 2012; Simons, Eisenmann, Fietzek, & Kastner, 2015; Warnecke et al., 2013].

**PD progression – non-motor features**
Non-motor features in PD

- **Behavior**
  - Mood
  - Cognition and dementia
  - Hallucinations and psychosis
  - Impulse control disorders
  - Fatigue
  - Apathy

- **Sleep**
  - Insomnia
  - REM behavior disorder
  - Excessive daytime somnolence

- **Autonomic function**
  - Gastrointestinal
  - Genitourinary
  - Cardiovascular
  - Thermoregulatory
  - Dysphagia
  - Drooling

- **Sensory/musculoskeletal function**
  - Olfaction
  - Visual system
  - Pain
  - Posture
  - Skin

*Schapira et al., Lancet Neurol 2017; Seppi et al., Mov Dis 2019; Goldman and Guerra Neurol Clinics 2020*

Impact of non-motor symptoms

- Present throughout course of PD
- Substantial impact
- Outcomes and quality of life
- Non-levodopa responsive

- PRIAMO study (n=1072)
  - 98.6% reported at least 1 non-motor symptom
  - Most frequent: fatigue (58.1%), anxiety (55.8%), leg pain (37.9%), insomnia (36.9%), bladder (35%), drooling (31%), concentration (31.4%)
  - Most frequent domains: psychiatric, sleep, GI, pain, fatigue, urinary, attention/memory

*Hely et al., Mov Dis 2005; Barone et al., Mov Dis 2009*
Depression

- Common, prevalence ~40%
- Pre-motor phase of PD
- Intrinsic and/or reactive
- Subsyndromal
- Common symptoms
  - Sadness
  - Decreased interest (anhedonia)
  - Anxiety

Anxiety

- Common in PD and also under recognized...
- Prevalence range: 5-40%
- About 1/3 of PD have 2 or more anxiety disorders
- Contexts:
  - Depression
  - Generalized anxiety disorder**
  - Panic disorder
  - Phobias (social, agoraphobia)**
  - Obsessive-compulsive disorder
  - Non-motor fluctuations, particularly in the “off” state

- Ask about the timing of the anxiety symptoms (both mental and physical)
Apathy in PD

- Primary loss of motivation
- Behavioral, cognitive, affective
- Prevalence 15-70%
- Troublesome to caregiver
- Can be separate from depression

Cognitive impairment

- Broad spectrum and range in severity
  - “Bradyphrenia”
  - Mild cognitive impairment (PD-MCI)
  - Dementia (PDD)

- Cognitive domains affected
  - Heterogeneous
  - Frequently executive function, working memory, attention, visuospatial function

- Differing rates of progression

HINT
- Get input from patient and informant
- Cognition is more than just memory
- Not due to “normal aging”
- Ask if these symptoms are a change
- Assess functional impact
Cognitive changes in early and mild PD

Aarsland et al., 2009

Yarnall, Breen, Duncan et al., 2014

Cognitive impairment in incident, untreated Parkinson disease

Aarsland et al., 2009

Yarnall, Breen, Duncan et al., 2014

Cognitive Performance and Neuropsychiatric Symptoms in Early, Untreated Parkinson’s Disease

Range ~20-40%

Defining PD dementia and PD MCI

Clinical Diagnostic Criteria for Dementia Associated with Parkinson’s Disease

Emre et al., Mov Dis 2007; Litvan et al., Mov Dis 2012

• Core features
  • Dementia syndrome, insidious onset, slow progression in context of PD
  • Impairment in > 1 cognitive domain
  • Decline from pre-morbid level
  • Deficits severe enough to impair daily life (independent of motor symptoms)
• Associated clinical features
  • Cognitive: attention, executive function, visuospatial, memory, language
  • Behavioral: apathy, mood, psychosis, excessive sleepiness

Emre et al., Mov Dis 2007; Litvan et al., Mov Dis 2012
Psychosis in PD

- Affect > 50% of PD patients on chronic dopaminergic therapy
- More recent reports also in de novo PD
- Significant contributor to nursing home placement, morbidity and mortality
- Risk factors: advanced age, advanced disease, cognitive impairment, sleep disturbance, medications
- Broad phenomenology
- Visual hallucinations as most common type but other sensory modalities can occur

HINT

Kelly et al., 2020

Impulse control behaviors/disorders

- Range of symptoms
  - Pathological gambling
  - Compulsive shopping
  - Hypersexuality
  - Binge eating
- Repetitive, reward seeking behaviors
- Prevalence 14-40%
- Risk factors
  - Psychiatric, addiction history
  - Dopamine agonists
  - Impaired decision making

• Counsel about medications
• Ask, ask, ask!

HINT

Kelly et al., 2020
Fatigue

- Symptoms:
  - Overwhelming sense of tiredness
  - Lack of energy
  - Feeling of exhaustion

- Common and disabling in PD

- Peripheral
  - Localized muscular fatigue
  - Inability to perform force during repeated muscle contractions

- Central
  - Difficulty initiating and sustaining physical and mental tasks
  - Independent of cognitive and physical impairments

Sleep disturbances

- Night-time

  - Primary sleep
    - Insomnia
    - Sleep fragmentation
    - RLS/PLMS
    - Sleep apnea
    - REM sleep behavior disorder

  - PD-related
    - Recurrent motor symptoms
    - Akathisia
    - Cramps/rigidity/pain
    - Poor mobility

- Day time

  - Excessive daytime sleepiness
    - Medication effects
    - Sleep attacks
    - Nocturnal sleep disruption
    - Cognitive changes

- Circadian disruption
REM sleep behavior disorder

- Initial description in 4 elderly men (Schneck 1986)
- Intermittent loss of REM sleep EMG atonia
- Appearance of complex motor activity associated with dream mentation
- May precede onset of parkinsonism and dementia
- Strongly associated with synucleinopathies (PD, MSA, DLB)
- Sleep disruption & caregiver injury

Conversion 6.3%/year, with 73.5% converting after 12 years

Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study

Autonomic symptoms

- Include:
  - Cardiovascular
  - Gastrointestinal
  - Genitourinary
  - Thermoregulatory

- Estimated prevalence:
  - 14-80% (variable measures)

- Significant effect on quality of life
  - Constipation > orthostatic BP > urinary (nocturia) (Chaudhuri 2006, Magerkurth 2005)
PD: Brain first or gut (body) first?

Gastrointestinal symptoms

- Gut-origin hypothesis
- Constipation
  - Prodromal marker
  - Due to delayed colonic transfer, low motility, defecatory dysfunction
  - Prevalence: 70-80%
  - Peripheral and central nervous system involvement
- Nausea/vomiting
  - For some, medication related

Abbott et al., 2001; Shannon et al., 2012; Chung et al., 2016; Borghammer and Van Der Berge 2019; Bindas et al., 2021
Genitourinary dysfunction

- **Symptoms**
  - Urinary frequency and/or urgency; nocturia; incomplete bladder emptying; urge incontinence, incontinence

- **Common (up to 60%)**
- May be seen in early and later PD
- **Mechanism**
  - Usually detrusor or sphincter muscle hyperactivity → Urinary urgency, frequency, nocturia
  - Less frequently: hypoactive detrusor → Delayed emptying, difficulty initiating, recurrent UTIs
  - Paradoxical co-contraction of urinary sphincter

- **Sexual dysfunction**
  - Changes in libido
  - Erectile dysfunction

Orthostatic hypotension (OH)

- **Definition**: >20mm Hg drop systolic or >10 diastolic on change to upright position
- **Prevalence**: 30-58%
- **Pathophysiology**: central/peripheral
  - Early cardiac sympathetic denervation

- **May occur early (15% at onset) or precede motor signs**
  - If severe and early, concern for Multiple System Atrophy

- **Medication contributions**
  - PD medications

- **Hidden costs of OH**
  - Falls
  - Fatigue
  - Anxiety
  - Cognitive changes
Thermoregulatory dysfunction

• Symptoms include:
  • Excessive sweating
  • Intolerance of hot environments
  • Flushing

• May relate to timing of PD medication response or cycle
  • “Off” or “on” periods, including peak dose dyskinesia

• Hypothalamic dysfunction

• Limited treatments – adjust PD meds, beta blockers (propranolol), cool packs

Musculoskeletal issues

• Postural deformities
• Camptocormia
• Antecollis
• Pisa syndrome
• Scoliosis

Tinazzi et al., Neurol 2015; Michel et al., Clin Neuropharmacol 2015
Dermatologic features

- Seborrhea - oily, flaking or inflamed skin
- Dry skin
- Excessive sweating
- Too little perspiration
- Livedo (with amantadine)

Summary

- PD involves multiple systems with a wide range of motor and non-motor symptoms
- Not just a movement disorder!
- Not just late stage symptoms
- Requires a comprehensive and interdisciplinary approach for evaluation and management

Thank you for your attention!

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