Parkinson’s Disease

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No Conflict of Interest
Parkinson’s disease

- Neurodegenerative process
- Usually sporadic
- Etiology is unclear
- 1-2% risk of acquiring PD for the general population and 2-4% risk in immediate family members
  - Genetic causes in few cases
Parkinson’s disease epidemiology

- US population with PD: 1 million
- US incidence per year 50-60 K per year
- Average age at onset: 62 years
- PD affects ~1% of the population > age 65
- Risk for PD begins to ↑ after age 50
Parkinson’s disease risk factors

- Most important risk factor is **age**
- Male > female (2:1)
- Genetic
  - 2-3 fold increase in risk if **family members** affected
  - Familial Parkinson’s disease is rare

- Environmental
  - **Pesticides**
  - Well water
  - Manganese (miners, welders)
  - Repeated head injury
  - Agent Orange (Vietnam Veterans)
Clinical Features
Clinical Features

- Premotor
- Motor
- Non-motor
Premotor symptoms

- Anosmia
- REM behavioral sleep disorder (RBD)
- Constipation
- Anxiety/depression

- Can occur 10-20 years prior to motor symptoms
Motor Features

- Tremor (rest)
- Bradykinesia
- Rigidity
- Gait impairment
- & Postural instability
Parkinsonism: Cardinal Signs

- **Tremor**
  - *Rest*
  - Re-emergent with posture and ambulation

- **Bradykinesia**
  - *Decrementing* in amplitude and speed (fatiguing)
  - Tested by rapid alternative movements (finger taps, hand opening, foot taps)
  - Distinguish from upper & lower motor neuron weakness, ataxia
  - Hypokinesia: Decrease in the amount of spontaneous body movements

- **Rigidity**
  - Resistance to passive movement
  - *Cogwheel* (ratchety), Leadpipe (smooth)
  - Distinguish from spasticity (direction and velocity dependent) and paratonia

- **Gait impairment / postural instability**
  - Gait: narrow based, shuffling, shortened strides, slow pace, en bloc turns
  - Hesitation at onset & doorways, freezing, festination
  - Decreased arm swing, stooped posture
  - Postural instability often develops later, truncal sway, impaired pull test
Diagnosis of Parkinson’s disease

- United Kingdom PD Society Brain Bank Criteria:
  - **Bradykinesia**
  - Plus one other cardinal feature:
    - Rest tremor
    - Rigidity
    - Postural instability
    - Not visual, vestibular, cerebellar or sensory

- Supportive features:
  - Rest tremor
  - Unilateral onset and persistent asymmetry
  - Progressive, disease course > 10 years
  - L-dopa responsiveness, response > 5 years, severe dyskinesia
  - Response to L-dopa, L-dopa induced dyskinesia, >5 year L-dopa response
  - Absence of atypical features
Diagnosis of Parkinson’s disease: New MDS criteria

TABLE 1. MDS Clinical Diagnostic Criteria for PD—Executive Summary/Completion Form

The first essential criterion is parkinsonism, which is defined as bradykinesia, in combination with at least 1 of rest tremor or rigidity. Examination of all cardinal manifestations should be carried out as described in the MDS–Unified Parkinson Disease Rating Scale.\textsuperscript{39} Once parkinsonism has been diagnosed:

Diagnosis of Clinically Established PD requires:
1. Absence of absolute exclusion criteria
2. At least two supportive criteria, and
3. No red flags

Diagnosis of Clinically Probable PD requires:
1. Absence of absolute exclusion criteria
2. Presence of red flags counterbalanced by supportive criteria
   - If 1 red flag is present, there must also be at least 1 supportive criterion
   - If 2 red flags, at least 2 supportive criteria are needed
   - No more than 2 red flags are allowed for this category

Supportive criteria
(Check box if criteria met)

- 1. Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response a dramatic response can be classified as:
  - a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment), or subjectively (clearly-documented history of marked changes from a reliable patient or caregiver).
  - b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.

- 2. Presence of levodopa-induced dyskinesia

- 3. Rest tremor of a limb, documented on clinical examination (in past, or on current examination)

- 4. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy
Diagnosis of Parkinson’s disease: New MDS criteria

Absolute exclusion criteria: The presence of any of these features rules out PD:

☐ 1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (e.g., sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades)

☐ 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, defined according to consensus criteria\textsuperscript{31} within the first 5 y of disease

☐ 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 severity of disease

☐ 7. Unequivocal cortical sensory loss (i.e., 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 stability is 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 y

☐ 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. This can include:
   a) Orthostatic hypotension\textsuperscript{32}—orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or
   b) Severe urinary retention or urinary incontinence in the first 5 y of disease (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction

☐ 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. These include sleep dysfunction (sleep-maintenance insomni, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations)

☐ 9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor planter response)

☐ 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
Non-motor symptoms of Parkinson’s disease

- **Cognitive impairment**
  - 30% progress to dementia in advanced stages of disease
  - Mild deficits with executive function, processing speed and naming is common
  - Dementia can be related to cortical Lewy body deposition
  - Co-existing vascular dementia and AD are also common

- **Anxiety and depression**
  - Seen in more than 50% of patients
  - Responds well to typical treatments (SSRIs, wellbutrin, SNRIs, buspirone)
  - May also be dopamine dependent

- **Apathy**
  - Lack of incentive and initiation

- **Fatigue**
  - Multi-factorial (central process, sleep, pain, motor, mood, medications)

- **Sleep disorders**
  - REM sleep Behavior disorder (may start years before disease onset)
  - Restless leg disorder, periodic limb movement disorder
  - Sleep fragmentation, wake-sleep cycle disruption, insomnia, OSA
Differential diagnosis of Parkinson’s disease

- Secondary causes
  - **Drug-induced**
    - Neuroleptics
    - Dopamine blocker antiemetics
    - Others: valproic acid, lithium, amiodarone
  - **Vascular** (especially lower extremity parkinsonism)
  - Hydrocephalus (including normal pressure hydrocephalus)
    - Triad of dementia, gait impairment, urinary incontinence (but not always)
    - Over-diagnosed by radiology
    - Rapid clinical course
  - **Post-traumatic**
    - Traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE)
  - **Post-encephalitic**
  - **Toxic**
    - Carbon monoxide
    - Cyanide
    - Manganese
    - MPTP (synthetic drug of abuse, now used to model the disease)
Differential diagnosis of Parkinson’s disease

- Degenerative causes
  - Parkinson Plus syndromes: Progression is faster, response to therapy limited, & additional early features are present
  - Multiple system atrophy (MSA)
    (early falls, autonomic dysfunction, cerebellar ataxia)
  - Progressive supranuclear palsy (PSP)
    (vertical gaze palsy, early falls, cognitive deficits, symmetric)
  - Corticobasal degeneration (CBD)
    (very asymmetric, fixed dystonia, apraxia, cognitive deficit, alien limb phenomenon, cortical sensory deficits)
  - Lewy body dementia (LBD)
    (Early dementia, unprovoked hallucinations)
    - 2nd most common degenerative dementia after Alzheimer
- Other: Heredodegenerative dis, etc.
Brain Regions Affected by Parkinson’s Disease

- Motor Cortex
- Globus Pallidus
- Thalamus
- Striatum
  - Caudate Nucleus
  - Putamen
- Substantia Nigra
  - Pars Reticulata
  - Pars Compacta
- Locus Ceruleus
- Raphe Nuclei
- Brainstem
Parkinson’s disease Pathology

- Key to motor symptoms:
  - Loss of dopaminergic neurons in substantia nigra (pars compacta)
  - These cells project to basal ganglia & regulate their activity
  - This is neither the starting point nor the only affected site
Parkinson’s disease Pathology

- PD is a synucleinopathy
  - Alpha synuclein is accumulated in:
    - Cytoplasmic inclusions known as **Lewy bodies**
    - Neuronal processes in form of **Lewy neurites** in glial cells

- Causing cell dysfunction and death

- What triggers the abnormal accumulation?
  - Mitochondrial dysfunction
    - Caused by oxidative stress, toxins, etc.
  - Breakdown of protein degradation system
    - Ubiquitin-dependent proteasome system (responsible for degradation of alpha synuclein)
    - Precipitated by genetic and / or environmental factors
Parkinson’s disease Pathology

- Complex pathways leading to alpha-synuclein accumulation, Lewy body formation and cell death
Parkinson’s disease Pathology

- Progression of LB pathology from lower brainstem, olfactory bulb and enteric nervous system to substantia nigra to cortex

Parkinson’s disease Pathology

- Progression of Lewy body accumulation in cortical regions is associated with advent of dementia

Parkinson’s disease motor deficits

- Loss of SN pc neurons projecting to **input** parts of basal ganglia
- Terminals are lost first in posterior putamen, then progress to anterior putamen and caudate

- Impacting the function of basal ganglia output nuclei (GPI & SNpr)
- Dysregulation of basal ganglia-thalamo-cortical circuits
- Leading to deficits in movement initiation, sequencing and scaling

**Image:** DaT Scan imaging of presynaptic dopamine transporter (DaT): A) normal, B) PD
Sources of input
- Somatosensory Cx
- Primary motor Cx
- Premotor Cx

BG input nuclei
- Putamen

BG output nuclei
- GPi / SNpr

Thalamic relay nuclei
- Ventral lateral
- Ventral anterior

Cortical targets
- Premotor
- Supplementary motor

Basal ganglia motor channel

Blumenfeld, “Neuroanatomy through Clinical Cases” 2002
SNpc

Striatum (Putamen)

“Direct” Pathway

DA (D1) +

“Indirect” Pathway

DA (D2) -

GABA

GABA

GABA

GABA

Glu

Glu

“Normal”

GPe

STN

GABA

GABA

Inhibitory

Stimulatory

DA = Dopamine
Glu = Glutamic acid
GABA = Gamma amino butyric acid
SNpc → Striatum (Putamen) → GPe
   "Direct" Pathway: DA (D1) + → GABA → GABA → Glu
   "Indirect" Pathway: DA (D2) - → GABA → Inhibitory

Ventral Thalamus → GPe: GABA

Cortical Motor Areas: Glu

Parkinson’s disease

DA = Dopamine
Glu = Glutamic acid
GABA = Gamma amino butyric acid
Parkinson’s disease motor neurophysiology

- Abnormal over-activation of indirect pathway leads to increased inhibitory output of basal ganglia and disruption of normal movements.
Parkinson’s disease motor neurophysiology

- Abnormal over-activation of indirect pathway leads to increased inhibitory output of basal ganglia and disruption of normal movements.
Dopamine therapy normalizes PD motor neurophysiology
Deep brain stimulation (DBS) also normalizes PD motor neurophysiology

- **SNpc**
- **Striatum (Putamen)**
- **GPi/SNpr**
- **STN**
- **Ventral Thalamus**
- **Cortical Motor Areas**

### Parkinson's Disease

- DA (D1)
- DA (D2)
- GABA
- Glu

### Parkinson's Disease: DBS

- DA (D1)
- DA (D2)
- GABA
- Glu

#### Direct Pathway

- DA = Dopamine
- Glu = Glutamic acid
- GABA = Gamma amino butyric acid

#### Indirect Pathway

- Inhibitory
- Stimulatory
Parkinson’s disease Treatment

- No disease modifying treatment is currently available
- Ongoing research indicates potential benefit of a rigorous progressive exercise program
- The potential role of this intervention in slowing down the course of PD remains under investigation

- Symptomatic therapies
  - Medications
  - Surgical
  - Rehabilitative
Parkinson’s disease Medical Treatment

- Effective **symptomatic therapies** are available for a range of motor symptoms:
  - Dopamine receptor agonists (D2/D3 receptors)
    - Ropinirole
    - Pramipexole
    - Rotigotine patch
  - Dopamine substrate (levodopa)
    - Most effective treatment and mainstay of symptomatic therapy
    - Used in combination with carbidopa to prevent side effects
    - Includes oral immediate release, sustained release (CR) and extended release (Rytary), orally disintegrating (Parcopa), & Enteral suspension gel (Duopa)
  - Other symptomatic medications
    - Monoamine Oxidase B inhibitors (selegiline, rasagiline, safinamide)
    - COMT inhibitors (entacapone, tolcapone)
    - Weak NMDA antagonist (amantadine)
    - Anticholinergic agents (Benztropine, Trihexyphenidyl)
Parkinson’s disease Treatment

- Dopamine agonists
  - Ropinirole (6-24 mg per day)
  - Pramipexole (1.5-4.5 mg per day)
  - Rotigotine patch (2-12 mg daily)
  - Effective as monotherapy
  - Equivalent in terms of efficacy
  - Can be considered as starting treatment in younger patients (< 70)
  - Main benefit is lower rate of motor complications associated with levodopa (wearing off and dyskinesia)
  - Side effects include nausea, ankle edema, sleepiness & sleep attacks, orthostatic symptoms, hallucinations, confusion & impulse control disorder (excessive shopping, gambling, hypersexuality)
  - Cognitive and psychotic side effects higher in older patients
Parkinson’s disease Treatment

- Levodopa
  - Always used with carbidopa to block peripheral breakdown

Olanow et al., Neurology, 2001
Treatment “Stages” of PD

- **Birth**
- **Pre-clinical onset**
- **Clinical Onset**
- **Death**

- Treat?
- “Honeymoon”
- Motor Fluctuations/Dyskinesias
- Failure

- Consider Medical Therapy
- Consider Surgery
Levodopa: The downside

- Not effective for gait imbalance, postural instability, and many non-motor symptoms

- Side effects: fatigue/somnolence, confusion, delusions, hallucinations, hypotension, orthostasis, choreiform dyskinesias, cramps (< agonists)

- Absorption adversely affected by food presence and poor GI motility

- Clinical effect becomes less robust and long-lived with disease progression

- May cause “on/off ” motor fluctuations and dyskinesia
Levodopa-related motor complications

- Motor fluctuations
  - Benefit of levodopa (ON state) wears off before next dose (Off state)
    - Early morning akinesia
    - Nocturnal akinesia
    - End of dose fluctuations
    - Paradoxical fluctuations
  - *Cause:* Progressive loss of capacity to store dopamine and changes in the pattern of gene expression

- Levodopa-induced dyskinesia
  - Involuntary choreiform movements
  - Mostly during peak effect of levodopa
  - *Cause:* Increased sensitivity of dopamine receptors over time, leading to excessive uncontrolled movements
  - Pulsatile stimulation of dopamine receptors likely to play a key role in development of dyskinesia and motor fluctuations
Wearing-off phenomenon develops with disease progression
Extending the benefit of levodopa

- Increase the dose per administration, the dosing frequency, and/or the total number of doses given
- Add a dopamine agonist
- Add a monoamine oxidase B inhibitor
- Add a catechol-O-methyl transferase inhibitor

- Consider use of long acting formulations of levodopa
- In more advanced cases consider surgical treatments
Advanced Medical Therapy in Parkinson’s disease

- Extended release levodopa (Rytary)
  - This formulation achieves fast and prolonged stable dose
  - More sustained stimulation of receptors may reduce motor fluctuations and improve non-dyskinetic ON time

Hsu et al., J Clin Pharmacol, 2015
Advanced Medical Therapy in Parkinson’s disease

- Enteral levodopa suspension (Duopa)
  - A more reliable way to provide sustained levodopa
  - Requires intra-duodenal tube placement
  - Works with a pump, Cartridge should be changed daily
  - GI side effects common, central non-motor side effects unchanged
  - May reduce off time
Surgical Therapy: Ablative Lesions

- Targets: Globus pallidus (arrow) or thalamus
- Irreversible
- More prone to side effects
- Not commonly used anymore (replaced by DBS)

Pallidotomy: GPi lesion (MRI)
Surgical Therapy: Deep Brain Stimulation

- Targets: **Globus pallidus interna** (Gpi) or **subthalamic nucleus** (STN)
- Thalamus target can control only tremor, often not used in PD
- Reversible and programmable
Optimal Candidates for Surgical Therapies

- Diagnosis is clearly PD
- Levodopa responsive
- Motor fluctuations / dyskinesia/ medication-side effects
- Refractory tremor
- Age < 75 y, > 4 y since Diagnosis
- Absent of marked cognitive deficit or unstable mood disorder
STN deep brain stimulation

MRI of bilateral DBS STN electrodes

Deep brain stimulation (DBS) also normalizes PD motor neurophysiology.

- **SNpc**: Striatum (Putamen)
- **GPe**: GABAergic output nuclei (GPe, GPi/SNpr)
- **Ventral Thalamus**: Inhibitory to Cortical Motor Areas
- **Cortical Motor Areas**: Stimulatory to GPe
- **STN**: GABAergic output to GPe

**Pathways**:
- **Direct Pathway**
  - DA (D1) action
- **Indirect Pathway**
  - DA (D2) action

**Chemicals**:
- **DA**: Dopamine
- **Glu**: Glutamic acid
- **GABA**: Gamma amino butyric acid

**Parkinson’s Disease**: DBS
STN Deep Brain Stimulation

- Mechanism unknown, but *may* reduce and/or normalize activity of STN neurons and output noise from basal ganglia circuit
  - Some evidence of normalization of excessive oscillatory activity of STN / GPi in PD
  - DBS effect can be mediated directly via STN, or by stimulation of GPe efferent to STN, or even via nearby white matter tracts

- Patients usually require less medication after DBS placed, and some require none at all
- The beneficial effect can last for years

- There is no clear evidence that DBS is neuroprotective
- DBS can improve quality of life in patients with PD of > 4 years duration