Parkinson’s Disease

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No Conflict of Interest

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

- 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
  - Decreasing in amplitude and speed (fatiguing)
  - Tested by rapid alternative movements (finger taps, hand opening, foot taps)
  - Distinguish from upper & lower motor neuron weakness, ataxia
- 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, an bloc turns
  - Instability at onset & doorways, freezing/instability
  - Decreased arm swing, stooped posture
  - Postural instability often develops later, truncal sway, impaired post ut;

Diagnosis of Parkinson’s disease

- United Kingdom PD Society Brain Bank Criteria:
  - Bradykinesia
  - Plus one other cardinal feature:
    - Rest tremor
    - Rigidity
    - Postural instability
  - 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>
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<th>TABLE 1. MDS Clinical Diagnostic Criteria for PD—Executive Summary/Compliance Form</th>
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Diagnosis of Parkinson’s disease: New MDS criteria

| Movement Disorders, 2015 |

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

The first essential criteria is parkinsonism, which is defined as traditional, is combined with at least 1 of rest tremor or rigidity. Examination of all clinical features (including tremor) is mandatory. The diagnosis of Parkinson’s disease (PD) is made on clinical grounds by a clinician experienced in the diagnosis of PD (MDS) Clinical Diagnostic Criteria Task Force). They are based on the MDS Clinical Diagnostic Criteria Task Force, which provided a detailed description of the clinical features of PD in the 2015 MDS Clinical Diagnostic Criteria Task Force. The criteria are intended to facilitate the diagnosis of PD in clinical practice. The diagnostic criteria are based on the clinical features of PD and are designed to be used in the evaluation of patients with PD. The criteria include both clinical and pathological features, and they are intended to be used in combination. The criteria are intended to be used in combination with other clinical and pathological features, and they are intended to be used in combination with other clinical and pathological features. The criteria are intended to be used in combination with other clinical and pathological features, and they are intended to be used in combination with other clinical and pathological features. The criteria are intended to be used in combination with other clinical and pathological features, and they are intended to be used in combination with other clinical and pathological features. The criteria are intended to be used in combination with other clinical and pathological features, and they are intended to be used in combination with other clinical and pathological features. The criteria are intended to be used in combination with other clinical and pathological features, and they are intended to be used in combination with other clinical and pathological features.
Non-motor symptoms of Parkinson’s disease

- Cognitive impairment
  - 50% 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)
  - Hydropseudus (including idiopathic pseudosubcortical)
  - Treatment of dementia, gait impairment, urinary incontinence (but not always)
  - 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)

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
  - 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 SNpc 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

Basal ganglia motor channel

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

Blumenfeld, “Neuroanatomy through Clinical Cases” 2002

SNpc
Glu
GABA

“Direct” Pathway
DA (D1) +
DA (D2) -

GPe
STN
Ventral Thalamus
Cortical Motor Areas

“Indirect” Pathway
Inhibitory
Stimulatory
DA = Dopamine
Glu = Glutamic acid
GABA = Gamma amino butyric acid

Striatum (Putamen)
GABA
GABA
GABA
Glu
GABA
GABA
GABA
GABA
**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.

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
- 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

- Levodopa
  - Always used with carbidopa to block peripheral breakdown

Olanow et al., Neurology, 2001

Treatment “Stages” of PD

- 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

- Parkison’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

- Other symptomatic medications
  - Monoamine Oxidase B inhibitors (selegiline, rasagiline, safinamide)
  - COMT inhibitors (entacapone, tolcapone)
  - Weak NMDA antagonist (amantadine)
  - Anticholinergic agents (Benztropine, Trihexyphenidyl)
Wearing-off phenomenon develops with disease progression

Extended 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

Deep brain stimulation (DBS) also normalizes PD motor neurophysiology

<table>
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<tr>
<th>Structure</th>
<th>Function</th>
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<tbody>
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<td>Striatum (Putamen)</td>
</tr>
<tr>
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<td>STN</td>
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"Direct" Pathway

DA (D1) \(\rightarrow\) GABA

"Indirect" Pathway

DA (D2) \(\rightarrow\) Glu

Inhibitory \(\rightarrow\) Stimulatory

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

Parkinson's Disease: DBS

Deep brain stimulation (DBS) also normalizes PD motor neurophysiology

-机制未知，但可能减少或归一化STN神经元和输出基底神经节回路的活动
- 有证据表明，STN / GPi在PD中STN / GPi的异常活动得以正常化
- DBS效应可能直接通过STN，或通过GPe刺激STN，甚至通过附近白质纤维
- 患者通常在DBS放置后需要更少的药物，有些人可能根本不需要
- 好处可能持续数年
- 没有明确的证据表明DBS是神经保护性的
- DBS可以在PD持续超过4年的患者中改善生活质量