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PD or not PD? Distinguishing Parkinson's Disease From Other Parkinsonian and Tremor Syndromes

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Presenter Disclosure Information

The following relationships exist related to this presentation:

- Jennifer G. Goldman, MD, MS: Consultant for Acadia; Pfizer, Inc.; and Teva Pharmaceutical Industries Ltd.. Speaker for American Academy of Neurology and Movement Disorder Society. Reviewer for Michael J. Fox Foundation.

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PD or not PD? Distinguishing Parkinson's disease from other parkinsonian and tremor syndromes

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Objectives

- Differentiate Parkinson's Disease (PD) from atypical parkinsonian disorders
- Distinguish PD from other tremor disorders
- Outline management strategies for parkinsonian movement disorders

Characteristics

- Involuntary movements
- Interrupted or poor coordination of volitional movements
- Abnormalities of posture and muscle tone
- Absence of motor weakness
- Tremor

Basal Ganglia Structures

- Caudate nucleus
- Putamen
- Striatum
- Globus pallidum
- Subthalamic nucleus
- Substantia nigra

Neurotransmitters

- Dopamine
- Acetylcholine
- Norepinepherine
- Serotonin
- GABA
- Glutamate

Phenomenology

Hypokinetic
- Too little movement

- Akinesia-rigidity
- Parkinsonism

Hyperkinetic
- Excessive movement

- Chorea
- Dystonia
- Ballism
- Tremor
- Tics
- Myoclonus

Parkinsonism - hallmarks

- Akinesia
  - Impairment in the initiation of movement
  - Difficulty planning and generating programmed movements
- Bradykinesia
  - Reduction in velocity and amplitude of movement
- Rigidity
  - Increase in muscle tone to passive motion
    - Velocity-independent
    - Lead-pipe, Cogwheel
  - Differs from spasticity
    - Clasp-knife

Parkinsonism - features

- Resting tremor
- Bradykinesia (akinesia)
- Rigidity
- Impaired postural reflexes

Parkinsonism - categories

- Primary
  - Idiopathic Parkinson's disease (PD)
- Atypical parkinsonian syndromes
  - Multiple System Atrophy, Progressive Supranuclear Palsy, Corticobasal degeneration, Dementia with Lewy Bodies
- Secondary
  - Drugs and toxins, MPTP, cerebrovascular, metabolic
- Heredodegenerative disorders
  - Wilson's, Huntington's Disease (juvenile)

Parkinson's Disease (PD)

- 1,000,000 affected in US
  - Incidence 16-19/100,000
  - Prevalence 360/1,000,000
  - Increasing with 2-3 million in US by 2050
- 1-2% of persons > 65
- In 2000, total estimated annual cost $26 billion

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

Red flags -- atypical parkinsonism

- Rapid progression
- Early and prominent…
  - Balance problems and/or falls (within first year)
  - Memory loss
  - Hallucinations
  - Autonomic symptoms (BP, potency or urinary symptoms)
- Additional neurological findings
- Lack of levodopa response
- Symmetry of symptoms
- Treatment with dopamine receptor antagonists

Etiology of PD

- Aging
- Environmental
- Genetics

- Multi-factorial

	Gene	Inheritance	Onset
Park 1	α-synuclein	AD	All
Park 2	PARKIN	AR	Early
Park 3	unknown	AD	Late
Park 4	SNCA triplication	AD	Early
Park 5	UCH-L1	AD	Late
Park 6	PINK 1	AR	All
Park 7	DJ-1	AR	Early
Park 8	LRRK 2	AD	Late
Park 9	unknown	AR	Early
Park 10	unknown	AD	Late
Park 11	unknown	AD	Late
GBA	Glucocerebro-sidase	AR	Early

DaT scan

- Approved by FDA (2011)
- DaT scan (Ioflupane I 123 injection) SPECT
- Distinguish PD from ET
- Does not differentiate PD from atypical parkinsonian disorders (PSP, MSA)
- Qualitative interpretations

PD Clinical features

<u>Motor</u>

- Tremor
- Bradykinesia
- Rigidity
- Gait
- Postural impairment
- Cramps/dystonia

<u>Non-motor</u>

- Cognitive
- Dementia
- Mood – depression, anxiety, apathy
- Autonomic – BP, bladder/bowel
- Sleep disturbance

Early PD – signs and symptoms

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

Complications of advanced PD

- Motor
  - Increased motor severity
  - Wearing off
  - Unpredictable responses
  - Dyskinesias
  - Freezing of gait
  - Postural reflex impairment
- Non-motor
  - Dementia
  - Hallucinations/psychosis
  - Autonomic features
  - Drooling
  - Dysphagia

Impact of PD non-motor symptoms

- Non-motor (and non-levodopa responsive) symptoms predominate at 15 years (Hely et al., 2005)
- Associated with increased morbidity, nursing home placement, fall risk, and mortality (Louis et al., 1997; Levy et al., 2002; Hughes et al., 2004; Wielinski et al., 2005)

Symptom	%
Depression	50%
Hallucinations	50%
Cognitive decline	84%
Dementia	48%
Urinary incontinence	41%
Orthostatic hypotension	35%
Dysphagia	50%

Symptomatic treatment

- Carbidopa/levodopa (Sinemet)
- Dopamine agonists:
  - Ergot (pergolide) – *no longer used*
  - Non-ergot (pramipexole, ropinirole, rotigotine)
- MAO B inhibitors: selegiline, rasagiline
- COMT inhibitors: entacapone, tolcapone
- NMDA antagonists: amantadine
- Anticholinergics: trihexyphenidyl, benztropine

Strategies for treating early PD

- Single dopaminergic drug with mild effects
  - Amantadine, selegiline, rasagiline, pramipexole, ropinirole
  - Low dose levodopa
- Anticholinergics for tremor (young pts)
- Non-pharmacological therapies
- Research trials for potential neuroproteective agents

Strategies for treating advanced PD

- Define the motor complication
- Motor fluctuation
  - Wearing off of doses
  - Early morning akinesia
  - Night-time “off”
- Dyskinesias
  - Peak dose dyskinesia
  - Diphasic dyskinesia
  - “Off” period dystonia

Motor fluctuations

Wearing off

- More frequent doses
- Longer acting medications (dopamine agonists, rasagiline)
- Combined medications (above, COMT inhibitors)
- Monitor diet – protein intake
- Take levodopa on empty stomach

Dyskinesias

- Discontinue medications (selegiline, entacapone, anticholinergics)
- Smaller (more frequent) doses
- Add agonist, reduce levodopa
- Add amantadine
- Surgery

Surgery for PD

- Types of procedures
  - Ablative procedures
  - Deep brain stimulation
  - Experimental

Surgery for PD – Good candidates

- Age <= 75 yr
- Advanced PD
- Good response to levodopa
- Motor complications or marked tremor
- Medical treatment not satisfactory
- No psychiatric illness (psychosis, mood)
- No cognitive impairment
- No major medical problems
- Good support system
- Realistic goals and expectations

Strategies for non-motor symptoms

Mood	• Depression/anxiety – medications, counseling • Adjust PD medications if related to wearing off
Impulse control disorders	• Reduce and discontinue dopamine agonists • Use levodopa • Antipsychotics
Hallucinations	• Review medication list, exclude medical problem • Reassurance, non-confrontational strategies, night-lights • Antipsychotics (quetiapine [Seroquel], clozapine [Clozaril]) • Cognitive medications (donepezil [Aricept], rivastigmine [Exelon], etc)
Cognitive changes/dementia	• Keep active mentally (and physically) • Reduce or discontinue medications that can impair cognition • Cognitive medications (donepezil [Aricept], rivastigmine [Exelon], galantamine [Razadyne], memantine [Namenda])

Strategies for non-motor symptoms

Blood pressure	• Orthostatic hypotension • Increase fluids • Elevate head of bed, increase salt and caffeine, pressurized stockings • Medications – fludrocortisone (Florinef), midodrine (Proamantine), pyridostigmine (Mestinon)
Bladder	• Limit night-time liquids • Bladder medications – Ditropan, Detrol, Sanctura, etc • Watch for cognitive effects of medications • Protective garments, condom catheters • Exclude infections
Bowels	• Diet, increase fluids, exercise • Stool softeners, constipation paste • Polyethylene glycol

Parkinsonism

- Synucleinopathy
  - Parkinson's Disease (PD)
  - Multiple System Atrophy (MSA)
  - Dementia with Lewy bodies (DLB)
- Tauopathy
  - Progressive Supranuclear Palsy (PSP)
  - Corticobasal degeneration (CBD)
  - Frontotemporal dementia (FTD)

Multiple system atrophy (MSA)

OLD

- Striatonigral degeneration (SND)
- Olivopontocerebellar atrophy (OPCA)
- Shy-drager syndrome (SDS)

NEW

- MSA-parkinsonism (MSA-P)
- MSA-cerebellar (MSA-C)

MSA - Core Features

- Autonomic dysfunction
  - Orthostatic hypotension
  - Urinary incontinence
  - Erectile dysfunction
- Parkinsonism
  - Poor levodopa response
- Cerebellar dysfunction
  - Gait ataxia/limb ataxia
  - Dysarthria
  - Gaze evoked nystagmus
- Corticospinal abnormalities
  - Hyperreflexia
  - Extensor plantar responses
- Other
  - REM behavior disorder
  - Inspiratory stridor
  - Antecollis

Litvan I (2003), Mov Disord 18(5):467-486; Weiner WJ (2005), Rev Neurol Dis 2(3):124-131

MSA

- Imaging
  - Cerebellar atrophy
  - Hot cross buns sign
  - Putaminal hyperintense rim
- Pathology
  - Cerebellar/pontine atrophy
  - Cell loss of IML column of spinal cord
  - Glial cytoplasmic inclusions

Progressive Supranuclear Palsy (PSP) - Core Findings

- Progressive disorder
- Age onset $\geq$ 40
- Often symmetric at onset
- Falls in the first year
- Vertical supranuclear gaze palsy
- Dysarthria
- Minimal levodopa response
- Cognitive and behavioral problems

Litvan, Mov Disord 2003;5:467-486

PSP features and pathology

- Other clinical features
  - Axial > appendicular rigidity
  - Neck hyperextension
  - Blepharospasm or apraxia of eyelid opening
  - Dry eyes, light sensitivity
  - Frontal lobe dysfunction
- Pathology
  - Midbrain atrophy, neurofibrillary tangles and phosphorylated tau

Corticobasal degeneration (CBD) – Core features

- Gradual onset
- Age ≈ 60 years
- Marked asymmetry
- Parkinsonism
- Apraxia
- Alien limb
- Cortical sensory loss
- Myoclonus
- Dementia
- Aphasia

CBD imaging and pathology

- Imaging
  - Asymmetric fronto-parietal atrophy
  - Often seen on MRI or SPECT
- Pathology
  - Asymmetric fronto-parietal atrophy
  - Ballooned, achromatic neurons
  - Astrocytic plaques
  - Tau

Dementia with Lewy bodies (DLB)

- Core clinical features
  - Dementia
  - Parkinsonism
  - Hallucinations
  - Fluctuating cognition
- Supportive features
  - Neuroleptic sensitivity
  - Delusions
  - Visual spatial impairment
  - REM behavior disorder
- Pathology
  - Cortical and limbic Lewy bodies
  - Decreased ACh

Vascular parkinsonism

- Lower body parkinsonism
- Early gait impairment
- Corticospinal tract signs (hyperreflexia, extensor plantar response)
- Urinary incontinence
- Pseudobulbar signs
- "Lacunar" infarcts or white matter hyperintensities

Drug induced parkinsonism

- May be similar to PD in presentation
- 6-7% of parkinsonism
  - Increases with advanced age
  - F > M
- Blockade of D2 receptors
  - Typical and atypical neuroleptics
  - Anti-emetics
  - DA depletors (tetrabenazine, reserpine)
- Treatment
  - Discontinuation of causative agent
  - Dopaminergic or anticholinergic medications

Tremor

- Definition: to & fro oscillation around a joint
- Classifications:
  - Rest (parkinsonism)
  - Postural
  - Action or kinetic (essential tremor, increased noradrenergic states)
  - Cerebellar or intention
  - Rubral (multiple sclerosis, stroke)

Essential Tremor

- AD or sporadic
- Affects 10% of people > 65 yrs
- Alcohol responsive
- Hands, head/neck, voice
- Posture and action
- Frequency 4-10 Hz
- Interferes with ADLs
- Treatment
  - Nonpharmacologic
  - Medications: βblockers, primidone, benzodiazepines
  - Surgery: thalamotomy, thalamic VIM DBS

Summary

- Parkinsonism is a clinically defined syndrome
- PD is the most frequent cause of parkinsonism
- Red flags, atypical features, history, examination, and biomarker studies may help differentiate parkinsonian syndromes
- History, examination, and evidence of dopaminergic deficiency can help distinguish PD and ET