

12:45 - 1:30 pm

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

SPEAKER Jennifer G. Goldman, MD, MS

primed

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.

Off-Label/Investigational Discussion

► In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

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

Jennifer G. Goldman, M.D., M.S.
Associate Professor, Department of Neurological Sciences
Section of Parkinson Disease and Movement Disorders
Rush University Medical Center

Pri-Med's Annual Conference Midwest program

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

- - 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

Motor

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

Non-motor

- 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/psyc hosis
 - Autonomic features
 - Drooling
 - Dysphagia

Impact of PD non-motor symptoms

- Non-motor (and nonlevodopa responsive) symptoms predominate at 15 years (holy, et al., 2005)
- Associated with increased morbidity, nursing home placement, fall risk, and mortality (Loude et al., 1997; Levy et al., 2002; Hughes et al., 2004; Welfshald 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

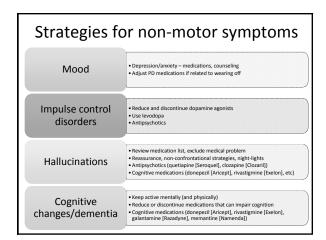
- More frequent doses
- Longer acting medications (dopamine agonists, rasagiline)
- Combined medications (above, COMT inhibitors)
 Monitor diet protein intake
- Take levodopa on empty stomach
- Dyskinesias
- Discontinue medications (selegiline, entacapone, anticholinergics)
- Smaller (more frequent) doses
- Add agonist, reduce levodopa
- Add amantadine
- Surgery

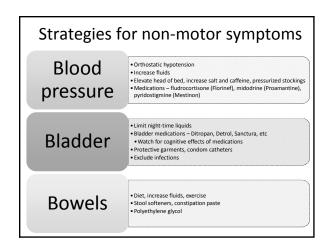
Surgery for PD

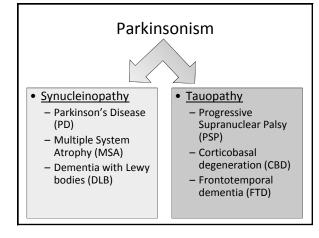
- Types of procedures
 - Ablative procedures
 - Deep brain stimulation
 - Experimental

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







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
 - Dvsarthria
 - 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 > 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