Parkinson’s Disease Update

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Disclosures

• GE Speaker, DaTSCAN
Outline

PD diagnosis
- Motor and nonmotor symptoms
- Differential diagnosis

Treatment
- Behavior/Lifestyle
- Medication
- Surgical: Deep Brain Stimulation
PD by the numbers

Prevalence 160/100,000 (1087 in 70-79 age group)
Second most common neurodegenerative disease after Alzheimer’s disease
Mean onset early 60’s
  • Early onset PD (<50): 5-10%
1st degree relatives have 2-3x greater risk
Multifactorial: hereditary predisposition, environmental toxins, and aging
  • Synergistic risk factors: head trauma + pesticides

Pringsheim et al, Mov Disord. 2014
PD pathophysiology

Degeneration of dopaminergic neurons in the brainstem substantia nigra

Appearance of Lewy bodies in brainstem and other parts of the brain

- Lewy bodies contain alpha-synuclein and ubiquitin: markers of abnormal protein folding
- Mechanism: oxidative stress, mitochondria dysfunction, abnormal protein phosphorylation?

Braak et al. Neurobiol Aging 2003;24:197-211
PD Cardinal Features

- Resting tremor
- Asymmetric rigidity
- Bradykinesia
- Postural instability
  - Later in disease course
  - Parkinsonian gait
Tremor

- Resting tremor that improves with action
- 4-6 Hz
- “Pill-rolling”
- Asymmetric
- Worsens during anxiety/excitement or walking
- Hand tremor more common than foot as presenting feature
- Chin tremor
Parkinson's tremor
Rigidity

Raised resistance during passive range of motion

Cogwheeling

- Often more noticeable when tremor present

Enhanced during mental task or contralateral limb movement
Bradykinesia

Slowness of movement
Difficulty with fine motor tasks
  • Buttoning
  • Handwriting: micrographia
  • Brushing teeth, washing hair

On exam: FFM, RAM, heel tapping, or arm swing
  • Rotator cuff injury
Postural Instability

Gradual onset of poor balance
  • Increased risk of falls

Retropulsion
  • Pull test: can the patient catch herself

Shuffling and narrow based gait

En bloc turning

Freezing
  • With initiation or when encountering obstacles
Postural Instability
PD Gait
PD Clinical Diagnosis

Queen’s Square criteria: **bradykinesia** plus 1 of:

- Rigidity
- Rest tremor
- Postural instability, AND . . .

Typical PD features:

- Unilateral onset
- Levodopa response
- Development of dyskinesia

PLUS: absence of exclusion criteria . . .

PD Exclusion criteria

- Exposure to drugs that can cause parkinsonism
- Cerebellar signs
- Corticospinal tract signs
- Eye movement abnormalities
- Severe dysautonomia
- Early moderate/severe gait disturbance or dementia
- History of encephalitis or recurrent head injury
- Evidence of severe subcortical white matter disease, hydrocephalus, or structural lesions on MRI
Non-Motor Features of Preclinical iPD

Strong evidence
- Constipation
- Olfactory deficit
- REM Sleep Behavior Disorder (RBD)
- Depression

Weaker evidence
- Restless Legs Syndrome
- Apathy
- Fatigue
- Anxiety
Dx of PD: premotor and motor phases

Diagnosis
At diagnosis, 30% of nigral cell bodies and 60% of nigral axon terminals and dopamine content have been lost.

Nonmotor Symptoms
Motor Symptoms
Dopaminergic Neurons

Increase
Decrease
Disease Onset
Premotor Phase
Motor Phase
Time (y)
Non-Motor Features in iPD

Autonomic symptoms
- Bladder disturbances: nocturia, urgency, frequency
- Sweating
- Orthostatic hypotension
- Sexual dysfunction
- Dry eyes

GI Symptoms
- Sialorrhea
- Dysphagia
- Constipation

Chauduri, Lancet Neurol. 2006
Non-Motor Features in iPD

Neuropsychiatric symptoms
- Depression, anxiety, anhedonia
- Attention deficit
- Psychosis
- Dementia
- Confusion

Sleep disorders
- RLS, periodic limb movements
- REM sleep behavior disorder
- Excessive daytime somnolence
- Insomnia
- Sleep disordered breathing

Chauduri, Lancet Neurol. 2006
Imaging: DaTSCAN

- SPECT scan (single-photon emission CT)
- DaT uptake (dopamine transporter)
  - Abnormal if decrease in striatal binding
- FDA approved in 2011 to distinguish ET vs. PD
- Useful to distinguish PD from medication induced or vascular parkinsonism, identify atypical presentations of PD
- Not useful to distinguish iPD from “PD-plus” or to stage disease severity

Catafau AM, Tolosa E. *Mov Disord* 2004;19:1175–1182
Imaging: DaTSCAN

(a) healthy age-matched control subject
(b) asymptomatic carrier of a mutation in LRRK2

PD: Differential Diagnosis

Drug-induced parkinsonism
Essential tremor
Vascular parkinsonism
Frontal gait/NPH
Dopa-responsive dystonia
Psychogenic

“Parkinson’s plus” syndrome
- Progressive supranuclear palsy (PSP)
- Corticobasal degeneration (CBD)
- Multi-system atrophy (MSA)
- Lewy Body dementia
PD: Principles of Treatment

Multidisciplinary approach

• Physical therapy
• Speech therapy
• Occupational therapy
• Psychiatry/psychology
• Social work

Non-motor issues

Caregiver support

Medical & surgical therapies
Medical therapy of motor PD symptoms

- Anticholinergics
- MAO-B inhibitors
- Dopamine agonists
- Carbidopa/Levodopa (Sinemet, Rytary, Duopa)
- COMT inhibitors
Anticholinergics

Trihexyphenidyl, cogentin, others

- Counts cholinergic overactivity in PD
- Good treatment for tremor
- Significant confusion and urinary retention
  - Avoid in patients with cognitive impairment or > 65 years old
MAO-B inhibitors

Selegiline (Eldepryl)
Rasagiline (Azilect)
Safinamide (Xadago)

Interactions:
- Tyramine-containing foods (some cheeses, processed meats) producing hypertensive crisis
- Serotonergic antidepressants and some pain meds

Disease modification: mixed results
- ADAGIO study: rasagiline 1 mg daily, delayed start study design, supported protective effect of rasagiline, but not rasagiline 2 mg daily
Dopamine agonists

- Pramipexole, ropinirole - TID and qday dosing
- Rotigotine 24hr patch
- Apomorphine injectable “rescue” med, continuous pump in Europe

Less potent than levodopa

Side effects: GI upset, fatigue, impulse control disorder

Best for milder disease, “levodopa sparing” strategy?
Levodopa

Most potent and effective medication for PD

• BUT, dyskinesia and motor fluctuations develop as disease progresses

**Sinemet**: combination pill (Carbidopa/Lvododopa)

• Levodopa – converted to dopamine by dopa-decarboxylase in the brain

• Carbidopa – inhibits dopa-decarboxylase outside the brain, does not cross blood brain barrier
New formulations of levodopa

**Sinemet**: immediate release “IR” and extended release “CR” formulations

**Rytary**: newer extended release formulation

**Duopa**: intestinal gel formulation of carbidopa/levodopa

- Continuously delivered via J-PEG, pt wears cartridge of med in a “fanny pack”
Levodopa: dyskinesia
Which therapy first?

Minimally affected: PT and exercise!

Tremor only: consider trihexyphenidil

Younger patients (<60)
  • Mildly affected: MAO-B inhibitor, dopamine agonist

“Typical” iPD (mid 60’s and up)
  • Sinemet (carbidopa/levodopa), rytary?
  • Agonist? We may be shifting towards using agonists as adjunctive therapy rather than first line, except in young onset pts
Surgical options

Deep Brain Stimulation (DBS)

- Subthalamic nucleus: most directly mimics levodopa effect
- Globus Pallidus interna: antidyskinetic effect
  - Also for generalized dystonia, FDA humanitarian approval
- Thalamus (essential tremor)

Ultrasound thalamotomy

Stem cell, gene therapy: not there yet!
When to refer for surgery?

Med side effects become disabling – “the end of the honeymoon"

- Motor fluctuations, unpredictable “OFF’s”
- Dyskinesia

Pt has a clear response to levodopa

No/minimal cognitive impairment

Patient selection (and education) is key!

- Red flags: postural instability and freezing, dysarthria/dysphagia, cognitive impairment, depression
DBS Eval: OFF med
DBS Eval: ON med
Jack
post-DBS
60 day visit,
before
programming
Jack
Post-DBS
60 day visit, after programming
Thank you!

• Questions?