Parkinson's Disease:

Update on emerging pathophysiological theories and treatment

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Faces of Parkinson’s Disease
Key Terms

• **Bradykinesia**
  – Slowness of movement

• **Bradyphrenia**
  – Slowness of speech

• **Dystonia**
  – Contorted posture, often with twisting component
  • “spasms” “cramps” “posture”

• **Dyskinesias**
  – Involuntary random movements
  • “irregular jerking” “wiggling” “twitching”

• **Motor v. Nom Motor Symptoms**
PD

Pathophysiological features

• Loss of dopaminergic cells in Substantia Nigra: ↓ dopamine

ALSO

• Locus ceruleus:
  – Norepinephrine
• Raphe Nuclei:
  – Serotonin
  – Involved before Substantia Nigra
• Nucleus Basalis:
  – Acetylcholine
  – Larger cholinergic deficits than seen in AD
Histology/Pathophysiology

• Alpha-synuclein aggregates including Lewy Bodies (LBs)
  – LBs: protein bodies aggregate in the neurons and axons; “Protein mis-folding”
    • “Synaptopathy”
  – Unknown if LBs are cell toxins
    • Are LBs the “garbage can?”
  – Exact role of cells in disease and pathogenesis unknown
    • > # of LBs → greater burden of disease
Emerging theories

• *Similar to prion disease spread?*
  – Starts in periphery and spread is ascending through brain
  – Transynaptic spread?
  – Heiko Braak Theory
    • Starts in GI tract and olfactory bulb
    • Spreads
Braak Theory

Figure 1
Staging of Lewy pathology according to the Braak model. Schematic summarizing the progression of Parkinson’s disease as proposed by Braak and colleagues [1]. According to the Braak model, α-syn deposits in specific brain regions and neuronal types giving rise to Lewy pathology in a stereotypic, temporal pattern that ascends caudo-rostrally from the lower brainstem (including the dorsal motor nucleus of the vagus nerve in the medulla then the coeruleus-subcoeruleus complex, raphe nuclei, gigantocellular reticular nucleus in the medulla and pons) through susceptible regions of the midbrain (substantia nigra and the pedunculopontine tegmental nucleus) and forebrain (e.g., amygdala) and into the cerebral cortex (e.g., anteromedial temporal mesocortex, cingulate cortex and later neocortical structures). It is hypothesized that the disease initiates in the periphery, gaining access to the CNS through retrograde transport along projection neurons from the gastrointestinal tract. As the disease progresses, the severity of lesions in the susceptible regions increases.

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Risk Factors for PD:

Theorized

- ↑age: most important
- Excess dairy intake
- Bacterial or viral infections
- Occupational:
  - HCW, teachers
- Rural environment
  - ? insecticides
- Agent Orange: + association
- Solvent exposures
- Well water in California
- ? head injury
PD and Genetics

• Genetic links in young onset PD
  – Mutations: Parkin, LRRK-2, PINK-1, DJ1

• More common in 1st degree relatives

• Both genetic susceptibility and environmental factors contribute
Factors *thought to be protective against PD*

- Physical activity
- Cigarette smoking
  - *Night shade plants*
- Flavonoids?
- Coffee/tea drinking
- Anti-inflammatory drugs (ibuprofen)
- High serum urate (strong antioxidant)
- Higher Vitamin D level
- Female gender (? estrogen)
PD Diagnosis

• Largely clinical

• History
  – Preclinical clues:
    • Neuropsychiatric symptoms, depression, anxiety, insomnia, autonomic symptoms (2015: 14:57)
  – Hyposmia/anosmia
  – REM sleep behavior disorder
    • Acting out dreams, very restless/physical
  – Non-motor symptoms present long before motor symptoms evident
Parkinsonism: PD’s DDX

• Atypical Parkinson’s
  – Synucleinopathies
    • Multi-system Atrophy (MSA)
    • Dementia- Lewy Body (DLB)
  – Tauopathies
    • Progressive Supranuclear Palsy (PSP)
    • Corticobasilar Degeneration (CBD)
    • Frontal Temporal Dementia (FTD)/ Pick’s Disease
Secondary Parkinsonism

• Vascular dz risk factors
• Drug exposures: Neuroleptics, anti-emetics
• Others:
  – Normopressure hydrocephalus (NPH)
  – Calcification, infection, post infection
  – Trauma, tumor, PKAN, Wilson’s Dz, Juvenile Huntington’s Dz
Parkinsonism Red Flags

• Rapid progression: 3-4 years
• *Early prominence of:*
  – Automonic sx: MSA
  – Cerebellar signs: MSA-C
  – Falls: MSA, PSP
  – Dysphagia: PSP
  – EOM/Gaze Palsies: PSP
  – “Alien Limb,” cortical sensory sx: CBD
  – Dementia: DLB, AD
Not Parkinson’s

• Essential tremor (ET)
• Stiffness: Stiff-Person Syndrome
• Spasticity: Upper motor neuron diseases
PD: Dx Supporting Criteria
UK Brain Bank

• Unilateral sx onset
• Persistent asymmetry
• Rest tremor present
• Progressive
• Excellent response to levodopa
  – *At adequate dose*: 70-100% improvement
• Levodopa-induced dyskinesias
• Levodopa response > 5 years
• Clinical course > 10 years
Diagnostic Tests

• *Not usually needed*

• Available tests (not commonly done)
  – MRI
  
  – DaT-SPECT Scan
    • Shows dopamine activity
    • FDA approved
    • Helps differentiate between PD and Essential Tremor
PD Symptoms

• **Motor Symptoms**
  - Tremor
  - Slowed movements (bradykinesias)
  - Stiffness (rigidity)
  - Swallow dysfunction
  - Speech difficulty (hypophonia/ dysarthria)
  - Sx fluctuate
Key Terms

- **Motor fluctuations**: Variable responses to medication
- **“OFF”**: Meds wearing OFF or no meds
  - “low time” “bad time” “shaking time” “slow time” “time when my medication doesn’t work”
- **“ON”**: Typical functional state when meds are working
  - “good time” “walking time” “time when my medications work”
PD Symptoms: Non motor

- **Cognitive Sx:**
  - Memory, visuospatial, attention
  - Language sx

- **Psychiatric:**
  - Depression
  - Anxiety
  - Visual hallucinations/illusions
  - Behavioral (apathy, agitation, impulsivity)

- **Autonomic Sx:**
  - Constipation
  - Urinary frequency/urgency/incontinence
  - Orthostatsis
  - Sexual dysfunction
  - Impaired thermoregulation
  - Sensory abnormalities
  - Sialorrhea
PD Symptoms

- **Sleep:**
  - Sleep onset/maintenance
  - REM Behavior Disorder (RBD): dream enactment
  - Restless Leg Syndrome
  - OFF sx at night

- **Pain:**
  - Location severity/ type
  - Correlation with meds
  - Painful dystonia in feet

- **ADL function and need for support**

- **Psychiatric**

- **Anosmia**
PD Symptoms

• Motor complications:
  – Wearing OFF
  – Feels OFF (% of time)
  – Bothersome dyskinesias
Dopamine Dysregulation Sx

- Excessive gambling
- Atypical or excessive sexual drive
  - Repetitive activities hobbies
  - Dismantling objects
  - Sorting, collecting
- Addictive behavior
- Assess: impact of behaviors on life and family
Mechanism of dopamine

• Basal ganglia: 2 intrinsic pathways
  – Direct: facilitates movement
  – Indirect: inhibits movement
  – Striatal dopamine excites the direct pathway, suppresses the indirect pathway
Carbidopa/Levodopa

• Most effective for PD sx
  – 70-100% improvement
• Requires active transport across gut-blood and blood-brain barriers
  – BBB: transported through large amino acid transport system
• Drug half-life: 60-90 minutes!
• Rapid peripheral breakdown of dopamine, need carbidopa to slow breakdown and reduce nausea
• Regular dosing is critical
Carbidopa/Levodopa

• Key factors:
  – Gastric emptying
  – Protein rich food competes with transfer in small intestine
    • Take 30 minutes before or 60 minutes after protein

• SE:
  – Nausea
  – Postural hypotension
  – Sedation
  – Neuropsychiatric effects
  – Dyskinesias
Carbidopa/Levodopa: Formulations

• Immediate release:
  – Onset: 20-40 min; duration 2-4 hours
  – Sinemet®

• Controlled release:
  – Onset 30-60 min; duration 3-6 hours

• Liquid levodopa:
  – Dissolved tablets:
    • Parcopa®
    • Onset 10-20 minutes
    • Less nausea

• Longer-acting capsules:
  – Rytary®

• Duopa®:
  – Continuous intestinal infusion
Dopamine Agonists

• *Tricks brain* into thinking it is dopamine

• Act directly on post-synaptic dopamine receptors
  – Independent from metabolic conversion, storage and release
  – ? may delay need for *Sinemet®*
    • “Dopamine sparing”

• Pramipexole: *Mirapex®*
  – *More potent than ropinerole*

• Ropinerole: *Requip®*

• Less robust than *Sinemet®*

• Not as associated with dyskinesias (c/t *Sinemet®*)

• Not affected by protein meal
Dopamine Agonists

- **Adverse effects:**
  - Nausea
  - Vomiting
  - Dizziness
  - Postural hypotension
  - LE edema
  - Drowsiness/somnolence, “sleep attacks”
  - *Compulsive behaviors*
  - Confusion
  - Hallucinations
  - Paranoia
  - Sleep disturbances
  - Pulmonary and retroperitoneal fibrosis
  - Pleural effusion and thickening
  - Raynaud’s phenomenon
  - Vascular disease
COMT Inhibitors:
Inhibit breakdown of levodopa in the periphery

• Entacapone (Comtan®)
  – 200 mg taken with each dose of Sinemet®
  – Does not cross BBB; only works in periphery
  – SE: diarrhea, dopaminergic symptoms, discolored urine

• Tolcapone (Tasmar®)
  – Crosses BBB, acts in periphery and in CNS
  – SE: diarrhea, orthostatic hypotension, dyskinesia, confusion
  – Acute fulminant hepatic necrosis: restricted use through FDA only
Carbidopa/levodopa/entacapone

• *Stalevo®*
  – Combination med
  – Three dose formulations
    • 1:4 ratio (carbi/levo to entacopne)
MAO-B Inhibitors

• Blocks the breakdown of dopamine in the brain
  – Selegiline (Elderpryl®): 50 cents per dose
  – Rasagline (Azilect®): $7.43/dose

• ? neuroprotective

• Theoretical drug interaction with serotonergic drugs

• SE: Mild nausea, dry mouth, lightheadedness, constipation, confusion, hallucinations
Anticholinergics

• In PD: dopamine depletion and cholinergic over activity

• Used for rigidity and tremors primarily
  – Trihexyphenidyl (Artane®)
  – Benztropine (Cogentin®)

• SE: dry mouth, sedation, delirium, confusion, hallucinations, constipation, urinary retention
Antivirals

• Discovered by accident!
• Helps with tremor, bradykinesia, rigidity, dyskinesias
• Mechanism of action: not clear
• SE: autonomic, blurred vision, psychiatric, dry mouth, constipation
• Amantadine (Symmetrel®)
Management of med “ON-OFF”

• Deliver more dopamine to brain in constant state
  – Increase total dosage of PD meds; increase frequency
  – Add controlled release
  – Add COMT inhibitor
  – Add dopamine agonist
  – Add apomorphine
Rx of Dyskinesias

• Many PD patients experience dyskiniesias

• Add dopamine agonist and reduce dopamine
• Add amantidine
• Consider Deep Brain Stimulation (DBS) surgery
Unified PD Rating Scale (UPDRS)

Non-motor Aspects of Experiences of Daily Living

- Cognitive Impairment
- Hallucinations and Psychosis
- Depressed mood
- Anxious mood
- Apathy
- Features of dopamine dysregulation

- Rated on 0-4 scale
- Time frame: past week
Unified PD Rating Scale (UPDRS)
Non-motor Aspects of Experiences of Daily Living

- Sleep problems
- Daytime sleepiness
- Pain/other sensations
- Urinary problems
- Constipation
- Light headedness on standing
- Fatigue
UPDRS: Motor Aspects of Experiences of Daily Living
Rated 0-4 Scale

• Speech
• Saliva and drooling
• Chewing and swallowing
• Eating tasks
• Dressing
• Hygiene
• Handwriting

• Hobbies/activities
• Turning in bed
• Tremor
• Getting out of bed, car or deep chair?
• Walking and balance
• Freezing
UPDRS Motor Examination

Note if done “OFF” or “ON” meds

0-4 Scale

• Speech
• Facial expression
• Rigidity
• Finger tapping
• Hand movements
  – Open and close
• Pronation-supination of hand
  – Arms extended, palms down to start
• Toe tapping
• Leg agility
  – Stomping
• Arising from chair
• Gait (30 feet)
• Freezing of gait
• Postural stability
• Posture
• Global spontaneity of movement
UPDRS Motor Examination

Note if done “OFF” or “ON” meds

0-4 Scale

- **Postural tremor of hands**
  - Arms out stretched, palms down
  - Size of tremor (> 1 cm, up to 10 cm or more)

- **Kinetic tremor of the hands**
  - Finger to examiners finger (reaching)

- **Resting tremor amplitude**
  - Extremities
  - Lip/jaw

- **Constancy of resting tremor**
  - Presence of tremor throughout exam

- +/- dyskinesias
  - Interfere?

- **Hoen & Yahr Stage**
https://www.youtube.com/watch?v=91BZnsm4oHY

https://www.youtube.com/watch?v=EnS4SMQJPKg
UPDRS: Motor complications

- Time spent with dyskinesias
- Functional impact of dyskinesias

- Time spent in “OFF” state
  - None
  - Slight: < 25% of waking day
  - Mild: 26-50% of waking day
  - Mod: 51-75% of waking day
  - Severe: > 75% of waking time
UPDRS: Motor complications

• Time spent in “OFF” state
  – None
  – Slight: < 25% of waking day
  – Mild: 26-50% of waking day
  – Mod: 51-75% of waking day
  – Severe: > 75% of waking time

• Functional impact of fluctuations:
  – Normal: No impact
  – Slight
  – Mild
  – Moderate
  – Severe
UPDRS: Motor complications

• Complexities of motor fluctuations

• Functional impact of fluctuations

• Painful OFF-State Dystonia
DDx of PD

• **Essential Tremor**
  – Only feature, no response to PD meds

• **Progressive Supranuclear Palsy (PSP)**
  – ↓gaze palsy, square wave jerks, upright posture, pseudobulbar affect; early gait instability, dysphagia

• **Multi System Atrophy (MSA)**
  – Autonomic disturbance; cerebellar signs, relative absence of tremor, early gait instability, dysphagia

• **Corticobasilar Degeneration (CBD):**
  – Limb apraxia, cortical sensory abnormalities, coarse unilateral tremor, early dementia
DDx of PD

• **Diffuse Lewy Body Dementia (LBD):**
  – Early dementia, psychosis, agitation

• **Alzheimer’s Disease:**
  – Dementia is primary symptom

• **Drug-induced parkinsonism:**
  – Lack of rest tremor and asymmetry

• **Vascular parkinsonism:**
  – Hx of chronic HTN; stepwise progression (if any); unilateral; imaging
Physical Assessment

- UPDRS
- Postural instability
  - Testing
- Olfactory function
- Gait
- Micrographia
PD Staging:
Hoehn and Yahr

• **Stage One**: S/Sx *one side only* and mild, may be inconvenient, not recognized by indiv.
  – Others may notice changes in posture, locomotion and facial expression

• **Stage Two**: Sx are mild, bilat, minimal disability; no axial involvement
PD Staging:
Hoehn and Yahr

• **Stage Three**: Significant slowing of body movements
  – Mild to moderate bilateral disease with deteriorating balance
  – Impairment of balance on walking, standing or pull test +

• **Stage Four**: Severe symptoms
  – Needs assist with ADLs; walking may be greatly impaired or limited
PD Staging:
Hoehn and Yahr

• **Stage Five**: Cachectic stage
  
  – *May need feeding tube or tracheostomy*
  
  – Cannot stand or walk, confined to bed or wheelchair
  
  – Requires assist with all activities
Depression in PD

• Common in PD
  – Due to combo of:
    • Psych factors, pathophysiology of dz, PD-induced treatment effects
• Neurotransmitter deficits
• Depression precede onset of motor sx
• Variability

• Optimal meds
  – SSRI
  – SNRI
  – Dopamine agonists
Anxiety in PD

• Occurs in 20-40%
• Often present before motor sx
• Can be associated with autonomic symptoms of PD
• Frequently occurs during OFF times
• Associated with changes across neurotransmitters:
  – Dopamine, norepinephrine, 5HT, acetylcholine
Impulse Control Disorder in PD

• Occurs typically with Dopamine Agonists
  – Can occur with high doses of levodopa/carbidopa
  – Excessive spending, gambling, binge eating, punding (excessive hobbies)
  – May be exacerbation of previous tendencies

• Usually responsive to DA reduction or discontinuation
Cognitive Impairment in PD

• Cog deficits occur early in dz

• Mild Cognitive Impairment-PD:
  – Usually with executive dysfunction, visual-spatial deficits, associated with ↑ risk of dementia

• Parkinson’s Disease Dementia (PDD)
  – Cog and behavioral impairment
  – Functional impairments

• Cog deficits are multifactorial:
  – Dopamine and acetylcholine signaling
  – Basal ganglia and cortical atrophy
  – Meds
  – PD sx (depression, sleep disturbances)
Hospitalized PD Patient

• Hospital = House of Horrors

• How should PD meds be managed?
• Which meds should be avoided?
Aware in Care Kit
National Parkinson Foundation

- Hospital Action Plan
- ID Bracelet
- Medical Alert Card
- Medication Form
- PD Fact Sheet
- “I have Parkinsons” Reminder Slips
- Magnet
Interventions/Tips

• **Bed immobility**
  – Satin sheets

• **Freezing**: *Feet stuck to floor*
  – Stepping over imaginary line
  – Counting when walking
  – Marching (lifting legs)

• **Hypophonia**:  
  – “Lee Silverman LOUD”

• **Gait and balance**
  – BIG Program
  – PD specific exercise programs
U-Step Walker

- Heavier
- More supportive
- Moves only when hand grips activated
- Can add laser for visual cueing
Deep Brain Stimulation

• Mechanisms of why/how it works unknown

• Carefully selected:
  – Only benefits motor symptoms
  – Considered when max doses of dopamine are not working or causes intolerable dyskinesias
Deep Brain Stimulation (DBS)

Surgery done awake or asleep

Can be done with MRI (asleep)

Targets used: Globus Pallidus or Subthalamic Nucleus

May have one or two stimulators inserted

Programming occurs over several weeks
In summary, PD... 

- is a progressive neurodegenerative disease
- sx have major physical, functional, emotional and psychosocial impacts
- cause is largely unknown
- pharmacotherapeutics are limited
- surgery (DBS) is an option for some
- requires special care and attention when hospitalized
- patients benefit from exercise at all stages
- patients benefit from PT/OT/Nursing/Peer/Family Support
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