PARKINSON’S DISEASE 101

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• Parkinson’s Disease affects 1-2% population over age 60. More men than women.
• Genes account for <10-15%
• Several different genes.
• Commonest gene LRRK2 most common in Ashkenazi Jews
History of Parkinson’s Disease

• 1817 James Parkinson wrote essay “The Shaking Palsy”

• 1919 Charcot elucidated neural pathways between brainstem Substantia Nigra and Basal Ganglia

• 1960s role of neurotransmitter dopamine in PD.

• Dramatized in the movie Awakenings starring Robin Williams
WHAT IS PARKINSON’S DISEASE?

• Parkinson’s Disease is a disease of dopamine deficiency (other neurotransmitters also)
• Lewy Body/Alpha-Synuclein deposits in brain
• What is the function of Alpha-synuclein?
• Today’s truths will be replaced
CAUSE OF PRIMARY PD?

• Complex interaction among multiple genetic and environmental factors.

• Environmental factors: herbicides, pollutants, heavy metals

• Cellular factors: oxidative stress, cellular inflammation, mitochondrial dysfunction, protein mishandling.

• All of these are contributors to neurodegeneration.

• For now we know that there is a positive correlation with herbicides, rural residence and head injuries.

• And a negative correlation with anti-inflammatory drugs like ibuprofen, coffee drinking, prior smoking history
Braak Hypothesis Cartoon

- Olfactory Nerve & Brainstem – Embryologically most ancient & primitive cells which are below the cerebral cortex but above spinal cord and govern automatic neural function, smelling, blinking, breathing, postural reflexes, heartbeat.
- Dopaminergic cells in the Midbrain’s Substantia Nigra travel to Basal Ganglia. Midbrain takes care of a lot of basic motor function including eye movements, upright locomotor function, basic use of limbs.
- Cerebral Cortex – (The Neocortex) Seat of consciousness. Neurons that control conscious movements, executive function, interpretation of all sensory, visual, and olfactory and auditory stimuli and have veto power over lower motor functions.
- Kinisie Paradoxale.
Braak Hypothesis

Stage 1 + 2
Brainstem

Stage 3 + 4
Brainstem
Basal Ganglia

Stage 5 + 6
Brainstem
Basal Ganglia
Cerebrum
Tip Of The Iceberg

• Average diagnosis of PD by early 60s
• Diagnosis by the physician is usually connected to recognition of motor symptoms that are due to loss of the neurotransmitter dopamine
• But we now know that non-dopaminergic neurons are also involved. Particularly affecting NON MOTOR aspects of PD
• Complex disease. Though our treatments are related to giving the patient dopamine, there are other neurotransmitters involved: acetylcholine, serotonin, norepinephrine, glutamate
Neuroprotection

- Drugs are not yet proven to modify the course of Parkinson’s Disease
- A lot of research is still happening on this subject
Is Parkinson’s Disease a Movement Disorder?

• There are 4 traditional things all doctors are taught to look for:
  
  – Resting tremor (on one side)
  – Slowness
  – Stiffness
  – Loss of postural stability
One Way of Describing Stages of PD

• LONG LATENT PRECLINICAL PARKINSON’S PHASE (patient is asymptomatic but dopaminergic neurons are dropping out)
• EARLY NON-MOTOR PARKINSON’S PHASE
  Loss of smell, REM Behavioral symptoms and other non-motor symptoms. Often recognized in retrospect after diagnosis.
• MOTOR PARKINSON’S DISEASE (see 4 traditional motor features of last slide)
Non-Motor Features of PD

• Neuropsychiatric (depression, anxiety, hallucinations, obsessions, slow thinking)
• Sleep (restless legs in sleep, rapid eye movement behavioral problems, vivid dreams, daytime sleepiness, insomnia)
• Autonomic nervous system (night time urination, sweating, falls due to postural low BP, sexuality issues, dry eyes)
• Stomach/intestinal problems (too much saliva, swallowing/choking, slow food absorption, constipation)
More Non-Motor Features of PD

• Abnormal sensations, tingling
• Decreased sense of smell
• Fatigue unexplained by sleepiness or sadness
• Weight loss
• Blurred or double vision
• Problems with sexuality
• Frontal lobe problems
• I would like to give a whole talk on this
• Non-motor problems get more prominent later in the course of the disease
• Non-motor problems do not have satisfactory treatment
THE DIAGNOSIS

• So how does a doctor determine whether it is Parkinson’s Disease or another brain disease?
• Taking a detailed history, doing a detailed physical examination, and doing tests to rule out other diseases.
• Early non-motor symptoms not easily recognized as Parkinson’s Disease because they are non-specific and hard to describe. A unilateral resting tremor is something a doctor can see, touch and describe.
• Non-motor problems become more important as the disease progresses.
Parkinson’s Disease Vs Parkinsonism

-Primary Parkinson’s Disease

-Atypical “parkinsonism:”
  ABNORMAL BRAIN DOPAMINE BUT NOT PARKINSON’S DISEASE
different brain pathology, rapid progression, less responsive to levodopa
Examples of atypical parkinsonism:
  -Multiple System’s Atrophy (MSA)
  -Progressive Supranuclear Palsy (PSP)
  -Corticobasal Degeneration (CBD)

-Secondary “parkinsonism”
  NOT EVEN RELATED TO PD. No dopamine connection at all
  -Examples of secondary parkinsonism:
  -Normal pressure hydrocephalus
  -Cumulative brain disease from many small strokes, tumors or other
ASSESSMENT of Parkinson’s Disease

Unified Parkinson’s Disease Rating Scale
(activities of daily living a long questionnaire)
   motor and non-motor
   reflect overall functioning

Symptoms: What the patient complains of:
   Motor complaints:
      tremor, trouble turning over in bed, slow walking, small handwriting, falls, difficulty cutting meat, change in voice, freezing (late)
   Non motor complaints:
      fatigue, depression, anxiety, sleepiness, loss of drive
Assessment of Parkinson’s Disease

• Examples of signs (the physician sees)
  – Motor:
    • stiff gait
    • one sided resting tremor more noticeable when walking
    • decreased facial expression
    • decreased blinking
    • stooped
    • voice soft
    • reduced finger dexterity
    • lies on exam table crooked
    • more than one try rising from chair
    • limbs stiff
    • doesn’t put head down when lies on exam table
    • freezing (late)
    • falls like a block (late)
    • cannot walk (late)
Assessment of Parkinson’s Disease

• Examples of signs the physician sees
  – Non-motor:
    • sweating
    • dandruff, skin on forehead flaking
    • difficulty concentrating (late)
    • paranoid delusions (due to drugs, late)
    • appears anxious (late)
    • appears hopeless (late)
PD is still a Clinical Diagnosis

• The diagnosis is often very easy to make just by looking at a patient.
• But sometimes very difficult.
• There may be a brain disease, but is it Primary Parkinson’s Disease?
• Or is it parkinson”ism”
• Or is it secondary parkinsonism
• There is a scan
DAT Scan

- Will help differentiate tremor vs primary PD
- Will help differentiate primary vs secondary parkinsonism
- But WILL NOT distinguish between Parkinson’s Disease and atypical parkinsonism due to rare diseases of Basal Ganglia such as Progressive Supranuclear Palsy and Multiple Systems Atrophy, Dementia with Lewy Bodies, or Corticobasilar Degeneration
Neuroprotection

- Active research.
- But no drug has been conclusively demonstrated to be neuro-protective.
- Many agents seem promising in labs but haven’t been determined to have a disease-modifying effect in clinical trials even if shown to be superior to placebo.
Drugs Treat Dopamine Deficiency

• Drugs mainly treat the motor features of Parkinson’s Disease.
• With epilepsy we try to use one drug
• In Parkinson’s disease: we start with one drug
• But as the condition progresses we add other drugs to help neurons function by more than one mechanisms
• Synergism at the level of the synapse
• Example: carbidopa/levodopa vs direct acting agonists
List of Drugs

- Carbidopa/Levodopa (Sinemet) (pre-synaptic dopamine)
  - Carbidopa slows breakdown (in gut)
  - Levodopa becomes dopamine (in brain)
- Dopamine Agonists (post-synaptic dopamine) rotigotine (Neupro) patch, ropinirole (Requip), pramipexole (Mirapex)
- Rasagiline (Azilect) and selegiline (Eldepryl), both are Monoamine B Oxidase Inhibitors (increase extra-cellular dopamine in the Basal Ganglia)
- Entacapone (catechol 0-methyltransferase inhibitor) Brand name Comtan. Entacapone is part of the branded drug Stalevo
  - COMT inhibitor leads to more “on” time from levodopa
- Amantadine (Symmetrel) increases CNS dopamine, unknown mechanism
Direction of Nerve Impulse

Axon
Sending message

Dopamine is in storage in nerve terminal, waiting to cross synapse.

The Synapse (the crossing)
The "docks", AKA receptors

POW! Muscle Fires!

to Firing Muscle

Drug Actions

Carbidopa/Levodopa is pre-synaptic, works before the synapse

Ropinirole, Pramipexole, Rotigotine Patch

Direct Acting Agonists

Post-synaptic, they work after the synapse
CARBIDOPA/LEVODOPA

• Support brain’s need for dopamine, helps motor symptoms presynaptically.
• Carbidopa lets levodopa become dopamine in brain
• Eventual motor complications: drug wears off too soon, there is more off time, drug wears off suddenly, drug doesn’t kick in at all, dyskinesia
• Non-motor symptoms are not helped with CDLD
One In The Brain
Worth Two in the Gut

• Carbidopa lets Levodopa become dopamine in brain not gut.
• Take CDLD on empty stomach, at least ½ hr before or 2 hours after protein meal.
• Why? Because dietary proteins compete with levodopa for entrance to brain.
• Entacapone as Comtan or in combo drug Stalevo slows the breakdown of levodopa in the brain.
• More “on” time
• But also potentially more dyskinesia.
Levodopa Advantages

• Most efficacious anti-parkinson drug
• Virtually all PD patients respond
• Improves activities of daily living, disability, independence, employability, lifespan
Levodopa, Disadvantages

• Dyskinesias
• Motor complications
• Neuropsychiatric problems (psychosis)
• Sedation
• Does not treat non-motor effects of Parkinson’s Disease
Levodopa Effect

• In early disease the drug last 4+ hours
• As disease progresses the therapeutic window narrows and it gets complicated.
• Recent studies have shown that giving levodopa intermittently destabilizes an already unstable parkinsonian basal ganglia
• We await a good once/day formulation of levodopa
Concerns About Long-term Toxicity from Levodopa

• Concern that levodopa might accelerate neuronal degeneration due to generation of free radicals.
• Elldopa study: Raised more questions than it answered.
• Experts argue about results but seem to agree that levodopa should not be withheld.
• And that dyskinesias are more common in patients receiving higher doses of levodopa.
• Motor fluctuations in advanced PD were thought related to decreased dopamine storage due to loss of dopaminergic terminals but now we understand that there is also some postsynaptic component to motor complications.
Levodopa-induced Dyskinesia

- Inevitable over time.
- Related to output neurons from Basal Ganglia to brainstem and cerebral cortex
- We try to manage by reducing drugs but if we cut down levodopa patient gets more parkinsonism
- Deep Brain Stimulation to the rescue!
- DBS decreases miscoded neuronal firing from Basal Ganglia
Levodopa-Induced Dyskinesias
A Complicated Motor Complication

• Any part of the body can be affected: head, neck, torso, limbs and breathing muscles.
• Often bothers the family more than it does the patient.
• Disturbance of the basal ganglia to automatically choose and carry out motor tasks.
• If dyskinesias occur when the patient starts to turn on, involves lower body, goes away for awhile, then comes back when the patient starts to turn off they are called diphasic. And might improve with a higher dose.
• But if they occur with peaking of drug, the dose should be lowered. Which is why we need patient diaries.
Practical Recommendations With Carbidopa/Levodopa

- Keep a diary: Record actual time of taking drug and actual time of onset of dyskinesia. Very important information to help your doctor decide what to do next.
- Be aware: Some people have delayed emptying of the stomach and this delays the effect of levodopa. Caffeine may help in this case.
- It is hard to get accurate information about duration of effect of drug from patient.
- Bring an observant care-giver to doctor’s office.
- It is not safe to withdraw this drug without supervision.
DRUG MANAGEMENT (MOTOR)
Direct-Acting Agonists

• Increase dopamine at receptor. Can be used instead of or with CDLD

• Benefits:
  – Synergism with levodopa.
  – Less likely to cause dyskinesia in future.
  – Can be taken with a meal.

• Side effects variable: nausea, dizziness when standing up, leg swelling, constipation, day-time sleepiness, increased dopamine drive which could be beneficial (or not), nightmares, hallucinations
Dopamine Agonists

- Help parkinsonism symptoms with fewer motor complications.
- Used to be used late in the course of disease after onset of motor complications.
- Current practice is to use early in course of disease to prevent motor complications.
- And sometimes added after motor complications in order to cut back on levodopa.
Dopamine Agonists, Advantages

Levodopa sparing. Fewer motor complications
Can be used alone or with levodopa
Potential though unproven: neuroprotective
Available in long-acting formulations
Dopamine Agonists, Disadvantages

• Some are similar to levodopa: nausea, hypotension with standing up, psychosis

• Some are different:
  – ankle edema
  – excess dopamine drive (leading to poorly controlled gambling, spending, staying up late, sexual obsessions, hallucinations in older patients, compulsive eating)
  – sedation which could lead to car accidents
Mao-B Inhibitors-Advantages

• Block oxidation of dopamine and increase dopamine levels in synapse.
• Advantages of rasagiline or selegiline: antiparkinsonian as monotherapy. Early drug
• Also late drug: Reduces motor fluctuations, increases “on” time
• Levodopa sparing
• Rasagiline is once/day and generally well-tolerated
• Early start of rasagiline gives potential long-term benefits not seen with delayed start
• Neuroprotective in lab animals (rasagiline)
MAO-B Inhibitors, Disadvantages

• Modest anti-Parkinsonian effect
• Neuroprotection not proven
• Selegiline has amphetamine and methamphetamine metabolites
• Theoretical cheese effect and serotonin syndrome.
• Avoid some drugs due to interaction
Amantadine

- Advantages: helps tremor, said to be energizing, said to help with motor complications
- Disadvantages: confusion in elderly or those with renal impairment, potential balance problems, more useful early (when all drugs work well)
Deep Brain Stimulation

• Usually used when dyskinesias bothersome and on-time is delayed or short-lasting
• Levodopa sparing
• One study reported 60% improvement UPDRS
• Disadvantages: It does not stop the disease. Potential problems with speech
• Potential though rare complications of surgery (infection, problems with implant, hemorrhage)
• Potential though rare neurobehavioral side effects.