Parkinson’s Disease
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Potential Conflicts of Interest

• Speaker programs
  – Teva Pharmaceuticals
  – Boehringer and Ingelheim

• Consultant
  – Advanced Neuromodulation Systems
  – Advanced Bionics

• Grants
  – Medtronic Neuromodulation
“Off label”, Experimental and Investigational Uses

• I may discuss uses of drugs and/or devices for indications not approved by the FDA

• The role of the FDA is to regulate interstate commerce in drugs and devices, not to determine the practice of medicine
Disclaimer

• I do not guarantee the correct spelling of any word on any slide
Epidemiology

- Prevalence 150/100,000 population
- Age of greatest risk 57 – 63 years
- Baby boom generation entering age of greatest risk
- Current 1.5 million will increase to nearly 3 million by 2015
Diagnosis

• No laboratory diagnostic test
  – PET and SPECT poor positive and negative predictive value
• Genetic tests not relevant to 97% of cases in North America
• No biomarkers
Clinical Features

- Motoric
  - 3 of 4 cardinal signs
    - Slowness and poverty of movement = bradykinesia and akinesia
    - Tremor at rest
    - Rigidity to passive movement
      - Cogwheel or lead-pipe
    - Gait and postural abnormalities
Bradykinesia and Akinesia

- Of limb movement
- Of gait and postural reflexes
- Swallowing
  - Contributes to malnutrition
Tremor

- Typically but not exclusively at rest
- 4 – 6 Hz oscillations
- Any part of the body although distal upper extremity most common
- Variable
  - ~30% without tremor
  - Variable within a subject
- Affected by stress
Increased Muscle Tone

- Rigidity
- Resistance to passive movement
  - Cogwheel
  - Lead-pipe
- Highly variable
Gait and Postural Abnormalities

- Flexed posture
- Loss of postural reflexes
- Slow gait
  - Short step length
  - Decreased cadence
  - Decreased arm swing
Non-Motoric Symptoms

- Decreased sense of smell
- Depression
  - May antedate motoric symptoms and disability
- Autonomic problems
  - Orthostatic hypotension
  - Urinary bladder problems
  - GI motility problems
  - Abnormal sweating
Non-Motoric Symptoms

• Obsessive-compulsive traits
• Cognitive problems
  – Impaired executive functions
  – Dementia
Parkinson’s Syndrome

- Idiopathic Parkinson’s disease
- Parkinson-Plus syndromes
- Lower Body Parkinsonism
- Parkinsonism/Dementia
- Others
Idiopathic Parkinson’s disease

- Associated with Lewy Bodies
- Degeneration of substantia nigra pars compacta
- New staging
  - Begins in the caudal brainstem and olfactory tubercle then ascends upwards in the brain
Parkinson’s Disease
Parkinson-Plus syndromes

Tauopathies

• Multi-Systems Atrophy
  – Parkinsonism plus cerebellar and severe autonomic dysfunction
  – May have specific MRI abnormalities
  – Neurofibrillary tangles on post-mortem specimen
Parkinson-Plus syndromes

Tauopathies

- Progressive Supranuclear Palsy
  - Supranuclear gaze palsy
  - Neurofibrillary tangles on post-mortem specimen
Lower Body Parkinsonism

- Vascular
  - Infarcts particularly of the globus pallidus intern or externa

- Normal Pressure Hydrocephalus
  - Expansion of the ventricular system
Parkinsonism/Dementia

- Diffuse Lewy Body Disease
- Alzheimer's disease
- Creutzfeldt-Jakob Disease
- Cortico-Basal Ganglia Degeneration
Others

• Drug Induced
  – Metoclopramide
  – Traditional neuroleptics
  – Some atypical neuroleptics
    • Risperdal
    • Geodon
    • Abilify
Others

- Wilson’s disease
- Carbon monoxide poisoning
- Kuft’s disease
- Machado-Joseph’s disease (SCA 3)
- Environmental toxins
  - MPTP
  - Ecstasy
  - Rotenone
What Causes Parkinson’s Disease?

• Genetic?
• Environmental?
• Both?
• Not contagious
Genetic Causes of Parkinson’s disease

- Eleven different mutations have been identified
  - The first alpha-synuclein
  - Most not relevant to typical Parkinson’s disease in North America
Importance of Genetic Causes

• May have a common mechanism
• This mechanism may be relevant to those with Parkinson’s disease not related to known genetic causes
  – Involvement of the Ubiquitin system
  – Process of getting rid of “old” proteins before they “gum up” the works
Ubiquitin and Old Proteins

• The Levy body
  – Hallmark of idiopathic Parkinson’s disease
  – Made up of ubiquitin and alpha-synuclein
Environmental Causes

- MTPT story
  - MPTP toxicity prevented by selegiline
    - Inhibits Monoamine Oxidase (MAO) in the brain
  - Neuroprotection
    - Selegiline
    - Rasagiline
Environmental Causes

- Herbicides and pesticides
  - Rotenone
    - Damages mitochondria
    - Mitochondria energy plant in the cell
Both Genetic and Environmental

- Inherit the risk
  - No disease unless also exposed to environmental agent
- Prone to oxidative stress
Therapy

- Neuroprotection
- Symptomatic medications
- Rehabilitation
- Exercise
- Counseling
Opportunities to Slow Disease Progression

• MAO-B inhibition
  – Protective in the MPTP animal model of Parkinson’s disease
  – DataTop study
  – TEMPO study
Anti-Oxidants

- Blueberries
- Co-enzyme Q10
- Brain fertilizer
  - Glial Derived Nerve Growth Factor
  - Immunophylins
  - Exercise
Symptomatic Treatment
Dopamine Replacement Therapies

- Carbidopa/levodopa (Sinemet)
- Entacapone/carbidopa/levodopa (Stalevo)
- Dopamine agonists
  - Ropinirole (Ropinirole)
  - Pramipexole (Mirapex)
- Fetal cell transplantation
- Porcine retinal neuroepithelial transplant
- Stem cell transplant
Non-dopaminergic

- Anti-cholinergics
  - Trihexyphenidyl (Artane)
  - Amantadine (Symmetrel)
- Adenosine A2 antagonists
- GDNF
Symptomatic Treatment: Prevention of iatrogenic Disease

Preventing or delaying Dyskinesia
Nutritional Issues

• Levodopa therapy
  – Dopamine does not cross the blood brain barrier

• Complicated pharmacokinetics and pharmacodynamics

• Short plasma half-life
Levodopa pharmacokinetics and pharmacodynamics

• Absorption by enzyme mediated facilitated transport
  – Both across the gut endothelium and blood brain barrier
  – Displays saturable kinetics
  – Competition with large neutral amino acids
Affect of Dietary Protein on Levodopa pharmacokinetics

• Large protein meal increases GI and plasma large neutral amino acids that compete with levodopa transport across the gut endothelium and blood brain barrier

• <5% of patients will display a “protein effect”
Managing the “Protein Effect”

• Minimize protein intake
  – 60 gm protein diet
  – Divide protein intake into multiple small meals

• Saving protein intake to late evening meal to be discouraged
Issue of Dietary Supplements

- Parkinson cachexia
- Supplements low in protein
Meals, GI Kinetics and Levodopa

• Levodopa absorbed only in the distal jejunum
• Taking levodopa with meals will delay gastric emptying and delay absorption
• Absorption will be erratic
• CAUTION – pharmacies often affix label instructions to take levodopa with meals
Special Cases - NPO

- No parental form of levodopa or other medications for Parkinson’s disease
- 4% risk of neuroleptic malignant-like syndrome with sudden discontinuation of anti-Parkinson medications
  - Fever
  - Muscle spasms and breakdown
  - Renal failure
  - Delirium
- Do not routinely hold anti-Parkinson medications for surgery
Special Cases – NG feedings and Levodopa

• Issue of controlled (extended) release carbidopa/levodopa versus immediate (regular) carbidopa/levodopa

• Grinding up or pulverizing either controlled release preparation converts to immediate release

• Controlled release preparations
  – 50/200 or 25/100 carbidopa/levodopa
Special Cases – NG feedings and Levodopa

- 125 mg (as levodopa) of controlled release carbidopa/levodopa = 100 mg (as levodopa) immediate release carbidopa/levodopa

- Breaking a controlled release 25/100 tablet makes it effectively immediate release but 25% more
Special Cases – NG feedings and Levodopa

- Straight conversion of controlled release to immediate release risks overdose
- Straight conversion of immediate release to controlled release risks underdose
Special Cases – Nausea and Levodopa

- Carbidopa blocks peripheral dopamine receptors to block nausea
- May require supplemental carbidopa (25 mg tablets called Lodosyn)
- Domperidone (Motilium) from Canada
Dopamine Agonists

- Ropinirole (Requip)
- Pramipexole (Mirapex)
- Less nutritional issues other than higher risk of nausea
COMT Inhibitors

- Entacapone (Comtan)
- Entacapone/carbidopa/levodopa (Stalevo)
- Risk of diarrhea
New Surgical Approaches
Electric Ray

(c) Sue Daly
Who Should Do DBS Surgery?

- Importance of a team
  - Neurosurgeon
  - Neurologist
  - Intra-operative Neurophysiologist
- Microelectrode recordings
- Nurse programmer
Before implantation (bilateral STN)

- Asleep: 29%
- "On" with dyskinesia: 35%
- "On" without dyskinesia: 16%
- "Off": 20%

After implantation (bilateral STN)

- Asleep: 34%
- "On" with dyskinesia: 13%
- "On" without dyskinesia: 49%
- "Off": 4%
STN Stimulation: Outcome

- Deep brain stimulation (DBS) is safe and effective

Limousin et al., NEJM, 1988
DBS Remarkable Benefit

• Succeeds when all manner of pharmacological flogging fails
• Succeeds when brain transplant fails
• Better than best medical therapy
• Estimated that 15% of patients are candidates though less than 1% are referred
DBS of the Pedunculopontine Nucleus for Gait and Postural Abnormalities

Standard and Accepted “Off-label” Use
Epidural Motor Cortex Stimulation (EMCS) for Movement Disorders. Standard and Accepted “Off-label” Use.
A Nater-Potater Production

Nate
Montgomery
Future Neuroscientist
• “Teacher, may I go now? My brain is full.” - Gary Larson

• Questions?
  – So long as they are not too hard