Overview of Parkinson Disease
Diagnosis, Cause, Treatment

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Disclosures

- I receive research grant funding from the following commercial entities for research on new Parkinson Disease Therapies
  - Insightec: Makers of equipment for focused ultrasound, now FDA approved to treat tremor dominant PD
  - Neuroderm: Makers of infusible carbidopa/levodopa, not yet approved by the FDA to treat PD
- I will point out any off-label uses
Impact of Parkinson Disease:

- 1-3% people > 65
- 7-10 million people have PD
- 725,000 US citizens with PD
- 60,000 people diagnosed/year in US
- 4-10% diagnosed < 50 y.o.
Parkinson Disease: Diagnosis

What is PD?
- Slowly progressive disease without a cure
- So far there is no imaging or blood test that positively identifies Parkinson disease
- Diagnosis is made clinically in life, and **pathologically** after death
- Blocq and Marinesco (1893)
  - Midbrain TB led to PD symptoms
  - Contradicts Parkinsons who said medulla
- Brussaud implicated SN (1895)
Pathology of PD

- Tretiakoff (1919)
  - Black pigment loss in the substantia nigra led to PD
  - Saw Lewy Bodies
- Spillantini (1997)
  - Synuclein is a major constituent of Lewy bodies.
Role of Dopamine

- Arvid Carlsson (1957)
  - Reserpine and Rabbits
  - Dopa reduced bunny PD
- Ehringer and Hornkiewicz (1961)
  - Low dopamine in PD
  - Give dopa IV, eased symptoms
- Cotzius (1967)
  - High dose oral dopa worked
- Carbidopa was added and Sinemet was approved in 1972.

“Bed-ridden patients who were unable to sit up, patients who could not stand up when seated, and patients who when standing could not start walking performed all these activities with ease after L-dopa [levodopa]. They walked around with normal associated movements and they could even run and jump. The voiceless, aphonie speech, blurred by pallilalia and unclear articulation, became forceful and clear as in a normal person” (Birkmayer and Hornykiewicz 1961).
PD Pathology

- Loss of pigmented area in the midbrain
- Remaining cells have Lewy bodies
- Lewy bodies have abnormal synuclein
- Loss of cells reduces dopamine
Staging PD Pre-symptomatic and Symptomatic Phases

Braak et al Cell Tissue Res. 2004;318:121
PD: Clinical Diagnosis

- Kampavata:
  - Sanskrit ~ 2500/1400 BC.
  - Tremor, drool, stare, stammer, low mood.
  - Mucuna pruriens (Kapikachhu)

- James Parkinson described 6 and examined 2 “patients” in 1817. Paralysis Agitans

- Charcot refined the symptoms and named it late in the 19th century
  - Tremor at rest (1 in 5 had no tremor)
  - Rigidity
  - Akinetic/Bradykinesia
  - Postural instability
  - Added masked face and small writing

PD: Diagnosis/ Features

- TRAP
- Onset 60 yrs
- Male > Female
- Asymmetric onset
- Anxiety, depression, constipation, hyposmia, masked face, reduced arm swing, soft voice, small writing
- REM Behavioral disorder
- Medication responsive
- Accuracy 76-90%.


- US approved (PD vs ET) in 2011.
Motor and non motor features of PD

Poewe et al 2017
What Causes PD

- Up through 1980s-90:
  - Environment
    - Post-encephalitic PDism after viral epidemic 1916-1926.
    - Markey and Langston’s discovery of MPTP effects
    - 1 Marylander (1976) and 6 (1982) Californians

Constantin von Economo

Encephalitis lethargica

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\text{Chemical structure of MPTP}
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Environmental Risks

Solvents
- Carbon disulfide in French Rayon industry workers linked to Pdism.
- **Painters** exposed to TCE, n-Hexane and other solvents may have greater a PD risk Reis et al 2016.

Chemicals
- **Pesticides** can lead to oxidative stress, mitochondrial toxicity, synuclein fibrillation, neuronal death Yan et al 2018. *Well water*
  - Paraquat: Dopamine cell death in culture
  - Rotenone causes PD like pathology in rodents
  - Organochlorine disrupt proteasome function, increase and aggregate synuclein
- Meta-analysis: pesticide exposure of 5 years increased PD risk by 5% and 10 years by 11%
- Atrazine, simazine, alachlor and metachlor, permethrin, beta-hexachlorocyclohexane, 2,4-dichlorophenoxyacetic acid, Paraquat (especially in those who genetically have reduced ability to metabolize)
- Ziram, maneb and paraquat exposure triples risk
- **Agent Orange.**
- Benomyyl (fungicide) exposure increases PD risk and is toxic in fish models of PD and in dopamine cell culture. Fitzmaurice et al PNAS 2013.
Environmental Risks

- Infections
  - PD rates higher after Hep B and C infection. Pakpoor et al 2017
  - Case control study found OR 7.42 for lifetime Influenza risk. Vlajinac et al Int. J. Neurosci 2013
  - Pro-inflammatory, reduced butyrate-producing, fecal microbiome may increase risk (cause or effect?). Keshavarzian et al Mov dis 2015.
  - Severe flu within 10 years of PD onset doubles PD risk. Increased risk after cat and cattle exposure too. Harris et al Mov. Dis., 2012.

- Head Trauma
  - Consensus statement says little evidence of a link. (LOC > 5 minutes) with exposure to paraquat triples risk of PD. Marras et al Arch. Phys. Med Rehabil 2014
  - Head trauma in those 55 and older increased PD risk 44% over those with other trauma over the next 5-7 yrs. Synuclein levels are elevated after head trauma. Gardner et al Ann. Neurol 2015.
  - Mild TBI in Vets increases PD risk by 56% Gardener et al Neurol. 2018

- Protection:
  - Caffeine: Coffee and tea, NSAID (Ibuprofen), CCBs, albuterol, tobacco. Role of GI bacteria?
  - Exercise: 60% reduced risk for 10 months of strenuous exercise/year vs 2 months/year
  - Mediterranean diet
What Causes PD? Genetics?

- 5-25% of patients have an affected family member.
- 2-5% higher risk of PD with a family history.
- Young onset more genetic.
  - Identical twins concordance: <51 yr onset 100%
  - Later onset risk; identical twins = non-identical twins (5-11%)

Tanner et al. JAMA 1999
Genetics: α-Synuclein


- Polymorphisms/duplications / triplications increase PD risk.
Synuclein Prion Hypothesis

- Synuclein Prions
- Syn monomer $\rightarrow$ $\beta$-sheet aggregate that is toxic
  - Fetal cells transplant
  - Synuclein (preformed fibrils) injection or into Gut of mice.
  - Truncal vagotomy delays PD risk in Danes and Swedes.

Tome et al. Molecular Neurobiology 47(2), 2012
More Genes

- Common gene changes in 30% of PD. *Mata et al. Mov. Dis. 2012*
- GBA mutation is greatest genetic factor
  - Lysosomal enzyme
  - 2.3-10% of PD patients
  - sPD patients have reduced GBA activity
  - 30% of 80 yo w/ mutation get PD
- LRRK-2 present in 1-2% of all PD and > 4% of familial cases.
  - May respond to kinase inhibitors
- EOPD more strongly genetic
  - Parkin accounts for 8.6%, PINK-1 3.7%
    - Involved in mitochondrial maintenance.
    - Mitochondrial biogenesis (Parkin-Paris)
  - DJ-1 0.4% of EOPD.
    - Regulates oxidant defenses in mitochondria and cells
  - Onset under 40, 9.5% genetic, 29% if a person has an affected sibling, 50% if parents are related.
So What Causes PD?

- Genes
- Synuclein
- Abnormal transport and signaling
- Oxidative stress
- Inflammation
  - T cells recognizing synuclein
- Impaired protein clearance
  - Lysosomal enzymes (5 so far) implicated in PD
- Mitochondrial damage

Treatment of Parkinson Disease
PD Treatment: Exercise

- Evidence for weightlifting, Tai-Chi, rowing, dancing too.
- Treadmill 85% max HR > 65% max HR= Controls in PD progression. Schenkman et al 2017 JAMA Neurol.
Carbidopa/Levodopa

- Utility proved in 1969
- Sinemet launched 1972, CR 1991
- Levodopa is converted to dopamine
- Carbidopa prevents the peripheral inactivation of levodopa.
- Most effective medication

351(24):2498-2508
L-dopa is not perfect....

- State of relative mobility
- Medication is "working"
- Reduction in tremor, rigidity and slowness
- Improved mood

- State of relative immobility
- Tremor
- Rigidity and slowness
- Sensory and behavioral phenomena
Types of Motor Complications

- Complications
  - Wearing off
  - Delayed on
  - Dose failures
  - Sudden off
  - Hallucinations/ delusions
  - Dyskinesia
L-dopa Complications

- Risks
  - Longer disease duration
  - Higher l-dopa dose
  - Lower weight (dyskinesia)
  - N. American > European
  - Youth
  - More pulses of drug
  - Genetics
  - Tremor is protective
  - GI bacteria
- Not a risk
  - Time on l-dopa
  - Cilia et al Brain 2014.
Treat Complications

- Wearing off
  - Move doses closer
  - COMT-I
    - Entacapone
    - Tolcapone
  - MAOb-I
    - Selegilne
    - Rasagilne
    - Safinamide
  - Longer acting L-dopa
  - Dopamine Agonists
Rytary, ER C/L

- Approved 1/2015
- Reduces off time
- Fewer doses/day
- Reduces dyskinesia

Duopa: C/L Enteral Susp 4.63mg/20 mg/mL

- In Europe since 2004
- Improves off by 4 hrs vs 2hrs from baseline
- Reduces dyskinesia
- Sleep, mood and fatigue improve (GLORIA)
- Concerns about polyneuropathy and device-related complications

Approx 100 mg/hr, Nyholm et al AAPS 2013
Inhaled Levodopa Rescue

- Acorda-CVT-301 AKA Imbria
  - Inhaled 42mg x 2 l-dopa
  - Onset 5-15 minutes
  - Risk bronchospasm
  - Cough
Dopamine Agonists

- **Choices**
  - Pramipexole (Mirapex), ER available
  - Ropinirole (Requip), XL available
  - Apomorphine (Apokyn) injection (rescue)
  - Rotigotine patch (Neupro)

- **Side Effects**
  - Nausea / vomiting, drowsiness, edema, orthostasis, hallucinations, dyskinesias, constipation
  - Compulsive behaviors
  - DAWS

Adapted from Rascol et al 2000 NEJM
Apomorphine

- Apomorphine
  - Used in US (Apokyn), for rescue of off.
  - Used elsewhere as a continuous infusion (> 30 years)
  - US trials (Infus-On) recruiting
- Cynapsus/Sunovion, APL-130277
  - Thin film apomorphine, five dose strengths
  - 1/30/19: FDA delays approval
Treating Dyskinesia

- **Dyskinesia**
  - Reduce PD medication
  - Amantadine
    - Prophylactic for Asian flu approved in 1966
    - Improved PD symptoms found by Schwab in 1969
    - Used for dyskinesia, effectiveness has been controversial
  - ADS-5102, Gocovri (8/2017)
    - 274 mg (340 mg amantadine) at bedtime
    - 46% less dyskinesia, 48% less off time
  - Osmolex (Amantadine ER)
    - Four doses: 129, 193, 258, 322 mg
    - Once a day in the morning.

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Elmer et al. CNS Drugs 2018, Oertel et al. Mov. Dis. 2017

Osmolex commercial
Therapy for Resistant Symptoms

- Tremor
  - Trihexyphenidyl
  - Benztropine
- Memory loss
  - Donepezil
  - Rivastigmine
  - Galantamine
  - Memantine
- Hallucinations/Delusions
  - Pimavanserin
  - Quetiapine
  - Clozapine
- REM behavior disorder
  - Melatonin
  - Clonazepam
- Constipation
  - Fluids, Fiber
  - Miralax
  - Other drugs
- Depression/Anxiety
  - Anti-depressants
- Urinary Symptoms
  - Pills
  - Botox
Therapies for Resistant Symptoms

- High frequency, pulsatile, electrical stimulation (Configuration, amplitude, frequency, pulse width).
- Placed into target nucleus (STN, GPi, ViM)
- Improves good on-time
- Reduces refractory tremor
- Using earlier and earlier
- Three companies competing
  - Medtronic
  - Abbott
  - Boston Scientific

Okun et al NEJM 2012
MRI Guided Focused Ultrasound (FUS)

- **PD**
  - No scalpel
  - > 1000 emitters to head
  - Transient weakness/tingling
  - Approved for PD tremor
  - Target Pallidum
  - Target STN
    - Asymmetric STN in Madrid, 50% UPDRS motor improvement
Thanks

Questions?