Update on Parkinson’s Disease
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Origins

• First described in 1817 by James Parkinson: “Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.”

• Charcot, 1872: “even a cursory exam demonstrates that their problem relates more to slowness in execution of movement rather than to real weakness. In spite of tremor, a patient is still able to do most things, but he performs them with remarkable slowness. Between the thought and the action there is a considerable time lapse.”

• Gowers, 1888: “The movement of the fingers at the metacarpal-phalangeal joints is similar to that by which Orientals beat their small drums.”
Stats

• Age of onset:
  • <4% less than 50
  • Likelihood increases with age
• Male to female ratio: 1.5:1
  • 50 to 59 years old: 3:1
• US prevalence:
  • 680,000 individuals in the US aged ≥45 years with PD in 2010
  • This is 572 per 100,000 over 45
  • Predicted 930,000 in US by 2020
  • Approaching the number of people with Type I Diabetes in the US
• US incidence: 60,000 new cases a year

Nebraska Parkinson’s disease registry

• Report PD patients within 60 days of diagnosis
  • Demographics
  • Date of diagnosis
• Estimated prevalence of 329.3 per 100,000 in 2004, about 6000 people, highest per-capita of any state at that time
Theregistry began collecting data in 1997. Diagnosis of PD based on physician office confirmation or death certificate. Registry was terminated from Oct. 2004 - Feb. 2006 due to lack of funding.
Pathophysiology of PD
Predictors of PD

- Dream enactment
  - 50% of those with RBD will get PD or dementia within 10 years
- Anosmia
- Constipation
- Depression/Anxiety
- PD personality
  - Low novelty seeking: secondary to low dopamine?
  - High harm avoidance: secondary to depression?
  - Higher levels of Neuroticism, but lower levels of Openness and Extraversion

Poop

- Gut microbiome is all the rage
- Hot poster in 2018:
  - Overall, PD patients had increased Verrucomicrobia, Christensenellaceae, Lactobacillaceae, and decreased Lachnospiraceae and Ruminococcaceae than healthy controls.
  - Reduced level of Lachnospiraceae was significant in all PD duration strata, while many of these differences were associated with disease progression.
  - De novo PD differed from healthy controls only by lower abundance in Lachnospiraceae.
Risk Factors: Appendectomy

- Study of 1.6 million Swedes found that people who had an appendectomy were 20 percent less likely than those with an appendix to develop Parkinson’s.
- Another study showed appendectomy was associated with an 3.6 year delay in disease onset among people who had the surgery and later developed Parkinson’s.
- More evidence that Parkinson’s may start outside the CNS.

Diagnosing PD

- Rizzo et al, 2016:
  - Accuracy of clinical diagnosis performed by movement disorders experts rose from 79.6% on initial assessment to 83.9% of refined diagnosis after follow-up.
  - Using UK Parkinson’s Disease Society Brain Bank Research Center criteria, the pooled diagnostic accuracy was 82.7%.
Diagnosing PD

- Clinical diagnosis with a levodopa trial
- DAT scan
  - FDA approved to distinguish between ET and PD
  - Might be helpful in sorting drug-induced parkinsonism from PD
MIBG Cardiac SPECT
Measures cardiac sympathetic denervation
80-95% sensitive and specific for PD/DLB
Transcranial ultrasound

- Li et al: Overall diagnostic accuracy of TCS in differentiating PD from normal controls: pooled sensitivity of 0.83 and a pooled specificity of 0.87

Normal

PD

Treatment of PD

- Levodopa
  - First tried in 1961
  - FDA approved in 1968
  - Carbidopa/levodopa (Sinemet) became available in 1973
    - Carbidopa is a dopa decarboxylase inhibitor
  - Remains the strongest drug for PD 45 years after inception
My treatment approach

• Titration begins at 0.5 tablets TID
• Empty stomach = 1 hour before or 2 hours after meals
• Sinemet CR for nighttime symptoms: 70% bioavailable
• I add entacapone and/or dopamine agonists once early-wearing off or motor fluctuations develop
• I treat dyskinesias with amantadine or levodopa reduction
• THERE IS NO UPPER LIMIT ON LEVODOPA DOSE PER DAY NO MATTER WHAT EPIC OR THE INSURANCE COMPANIES TELL YOU

Homocysteine

• Levodopa therapy causes elevated homocysteine
• Homocysteine is associated with heart attack and stroke
• Lowering homocysteine in PD with folate/B6/B12 combo supplements may decrease complications such as:
  • Cognitive decline (those with high Hcy levels decline faster)
  • Peripheral neuropathy:
    • “In a comparison between patients with and without neuropathy, the levodopa dose was higher, serum vitamin B12 levels were lower, and homocysteine levels were higher in the patients with neuropathy”
New therapy: Almost the same as old therapy

- **Rytary (C/L ER)**
- Compared with CL + E, IPX066 demonstrated a lower percent "off" time (24.0% vs. 32.5), lower "off" time (3.8 vs. 5.2 h/day), and higher "on" time without troublesome dyskinesia (11.4 vs. 10.0 h/day)
- So **1.4 hours more on time/day** than Stalevo
Dyskinesias

- The 5-year risk of dyskinesias was **50% in patients with disease onset between 40–59** years of age as compared to **16% in those with disease onset after 70 years**.

- Dyskinesias develop at a mean daily dose of 387 mg.

- Genetic polymorphism of the dopamine receptor D$_2$ gene → reduced risk of dyskinesias.

- Reduced by:
  - Reducing daily levodopa dose
  - Amantadine reduces the duration of LID by 60%
  - Dopamine agonists/COMT inhibitors
  - DBS
New therapy: Almost the same as old therapy

- Amantadine CR (Gocovri)
- Amantadine ER reduced on-time with troublesome dyskinesias by about 1.5 hours per day, from a baseline of about 4.6 hours.

Future therapy

- Dyskinesias involve the serotonergic system and mGluR5 glutamate receptors
- Eltoprazine
  - partial 5-HT1A/5-HT1B receptor agonist
- Buspirone
  - a 5HT1A agonist
- Dipraglurant (although a relative, mavoglurant, failed)
  - mGluR5 negative allosteric modulator
- IRL790
  - “Psychomotor stabilizer” targeting D3 receptors; may treat dyskinesias and psychosis
Neuroprotection in PD

- BDNF or GDNF
  - Multiple failed trials:
    - Recombinant protein administration into the brain (infusion, injection)
    - Adeno-associated virus vector delivery
    - Stem cells most promising recent attempt

Forced exercise

1 hour
3 times a week
8 weeks

30%
Neuroprotection in PD

**Nilotinib (Tasigna)**
Tyrosine kinase inhibitor similar to Gleevec (imatinib), treatment for CML
Modulates dopamine levels and metabolism, as well as prevents the formation of toxic alpha-synuclein aggregates
In Phase II trials

**Uric acid**
May affect inflammation and oxidative stress
33% reduction in PD incidence among persons with high serum urate level

Neuroprotection in PD

- Calcium channel blockers
  - **Isradipine (Dynacirc),** L-type calcium channel blocker, is in Phase III for neuroprotection
  - Inhibits up-regulation of L-type calcium channels → decreases iron accumulation in substantia nigra → less oxidative stress?
Thank You!