Disease Modification in Parkinson’s Disease

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Parkinson’s Disease (PD)

- Peak onset around 60 years of age
- Approximately 850,000 people in the US have PD
- 2% of the population will have PD at age 80
- Cardinal Motor Symptoms
  - Tremors
  - Rigidity
  - Akinesia (slowness)
  - Postural instability
“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 unimpaired.”
Linda Ronstadt

_Lead singer of 1960’s band the Stone Poneys_
Brian Grant
NBA star who played for the Sacramento Kings, the Portland Trail Blazers, the Miami Heat, the Los Angeles Lakers, and the Phoenix Suns
Risk factors for PD

- **Genetics**
  - ~20% of patients with PD report someone else in the family
  - First gene mutation discovered: SNCA – causes younger age of onset (40’s) and rapidly worsening course
  - Other gene mutations
    - Parkin: mutations in both genes cause juvenile PD but has been in individuals over 50
    - LRRK2: seen in 2% of sporadic North American PD patients and has typical age of onset
    - GBA: most common genetic risk factor for PD
Risk factors for PD

- **Environmental toxic factors**
  - Pesticides: maneb and paraquat

- No consistent evidence for other environmental factors
Treatment of Parkinson’s

• Currently, there is only treatment for the symptoms and no proven restorative therapy

• Potentially protective drug therapies are under investigation
NO MORE FUN OF ANY KIND!!!
‘Disease Modification’

- Refers to an intervention that modifies the natural clinical course of the disease

- In Parkinson’s, an unmet need is a treatment that slows or halts disease progression, i.e. “neuroprotection”

- To date, all trials that have attempted to demonstrate disease modification have failed
Reasons for Failure

• **Precise cause unknown**
• Animal models may be poorly reflective of human Parkinson’s disease
• Lack of reliable biomarkers
• Not clear if outcome measures are able to detect disease modification
• “Early” Parkinson’s already has extensive loss of brain cells
What Biological Mechanism Leads to Parkinson’s?

- Studies treat Parkinson’s disease as a single disorder but it is heterogeneous
  - For example, genetic types may have different mechanisms from ‘sporadic’ PD
  - The clinical presentations of Parkinson’s disease are varied, from mainly tremor to mainly postural and gait abnormalities

- There may not be just a single mechanism and therefore combinations of therapy may be more likely to succeed
Some Proposed Disease Causing Mechanisms in Parkinson’s
α-Synuclein targeted therapies

• Antibodies to parts of the α-synuclein protein
  – 2 clinical trials currently underway: Roche’s PASADENA and Biogen’s SPARK

• Block clumping and misfolding of α-synuclein
  – Nilotinib, a leukemia drug is being studied
Other Targeted Therapies

- Increasing GCase activity reduces α-synuclein levels
  - **Ambroxol** is currently being studied in 2 clinical trials

- Reduce synthesis of glucosylceramides
  - The Parkinson’s Institute is a site for Sanofi’s **venglustat**

- Reduce activity of LRRK2 kinase
  - Undergoing clinical testing by Denali Therapeutics
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Biomarkers

- There is a lack of reliable markers that reflect disease presence and severity as well as impact of the therapy.
- For example, it is not currently possible to assess the level of α-Synuclein in the brain and clinical trials must rely instead on clinical endpoints.
- The Parkinson’s Institute is a site for the Parkinson’s Progression Markers Initiative, funded by the Michael J Fox Foundation.
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- Not clear if outcome measures are sensitive in capturing disease modification
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‘Pre-motor’ Parkinson’s Disease

- Characterized by loss of smell, REM sleep disorder, problems with ‘autonomic nervous system’
- $\alpha$-Synuclein accumulates years before motor symptoms
- The Parkinson’s Institute is the site for the GI Natural History study
Questions?