Introduction to Parkinson’s Disease (PD)

Overview of Current Knowledge

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Introduction to PD

• A chronic neurological condition that develops slowly over many years.

• Currently incurable, but good symptomatic therapies are available.

• More than 1 million Americans live with PD, 60,000 new cases each year.

• More than 10 million people with PD worldwide.

• Reported that number of people with PD will double by year 2040.
Who Gets Parkinson’s Disease

Average age of onset 60, 10% diagnosed before age 50.
Symptoms of Parkinson’s Disease

Classic motor symptoms
- Tremor of the limbs when at rest
- Slow movement (bradykinesia)
- Muscular stiffness (rigidity)
- Change in walking and balance

- Loss of facial expression
- Low volume or hoarse voice
- Small handwriting
- Problems swallowing
- Trouble getting out of a chair
- Stooped posture
- Loss of arm swing
- Short, shuffled steps
- Freezing when walking
- Problems with balance
Non Motor Symptoms of Parkinson’s disease

- Loss of smell
- Fatigue, excessive daytime sleepiness
- Apathy
- Depression/ Anxiety
- Problems with memory, concentration
- Acting out dreams while asleep
- Lightheadedness when standing
- Constipation
- Urinary frequency or urgency
- Oily skin and dandruff

* The collection of and intensity of symptoms varies from person to person.
How is Parkinson’s disease diagnosed?

- No specific blood or imaging test available to diagnose PD.

- Diagnosis based on medical history, a neurological examination and response to dopamine-based medications.

- Sometimes blood test, brain MRI or DAT scan may be performed to rule out other conditions that have similar symptoms.
Is Parkinson’s disease hereditary?

- Less than 10% of cases of Parkinson’s disease are directly inherited (due to specific gene mutations).
- Directly inherited genes - Alpha-synuclein, Parkin and LRRK2 genes
- In most inherited cases, there is a strong family history (more than one family member) and most start at a young age (under age 40).
Genetic Susceptibility in PD

• Genome-wide association studies (GWAS) – compare genome of large groups of people with PD to those without.

• To date >90 variations in the humane genome identified in PD as compared to those without PD.

• Individually, genetic variations have very low contribution as risk factor.

• Genetic variations give clues as to impaired cellular processes.
Environmental Exposures and PD

• Head Injury – repeated or associated with altered consciousness

• Heavy metals exposure – higher incidence of PD in welders

• Chronic amphetamine use

• Solvents

• Long term pesticide/herbicide exposure

**Based on studies that show an association and have not proven causality.**
What causes PD

**Risk Factors**
- Aging
- Genetic Susceptibility
- Environmental exposures
- Low vitamin D

**Protective Factors**
- *Exercise*
- Caffeine
- Nicotine
- Education
- Dietary factors
• Slow loss of dopamine producing cells in the brain.

• Dopamine deficiency leads to classic motor (physical) symptoms:
  - Tremor with limbs at rest
  - Muscular rigidity
  - Slow movements
  - Changes in walking and balance
What’s happening in the brain

- Lewy Bodies - accumulations of abnormally folded proteins

- Alpha synuclein = main protein

- Lewy bodies also found in other affected brain areas. Other brain centers affected, alterations in other brain chemicals that may affect:
  - Serotonin – mood, motivation
  - Acetylcholine – memory
  - Norepinephrine – cardiovascular control, gait and attention
Where Does PD start?

- Evidence has suggested that PD may start in the little nerves of the gut or the nose then spread to the brain.

- Constipation and loss of smell may predate the diagnosis of PD by 10 years or more.

- The brain-gut axis – bidirectional communication regulated by neural, hormonal and immunological factors.

- Abnormal gut bacterial environment (microbiome) may alter communication with the brain.

- Gut-first vs. brain-first
Symptomatic therapies 55% (35% motor, 20% non motor symptoms)

Therapies for advanced stage complications (fluctuations and dyskinesias) 5%

Disease modifying therapies 40%
Disease modifying therapies (DMT)

• Aim to slow or halt the progression of PD.
• No current DMT available at this time.
• Current research targets for disease modification:

- **Alpha synuclein and Lewy Bodies**
  - Prevent mis-folding
  - Prevent protein clumping
  - Vaccinations

- **Neurotrophic factors**
  - Enhance natural protective factors i.e. BDNF, GDNF

- **Genetic targets**
  - Correct abnormal function

- **Lifestyle modification**
  - Diet
  - Exercise
  - Cognitive training
  - Mind-body practices
Parkinson’s Disease Vaccines

◆ Active immunization – introduces man-made molecule similar to alpha-synuclein to trigger body to produce antibodies.
  ▪ 2 antibodies being studied
  ▪ AFFITOPE PD01A - Phase I study – safe and well tolerated, did produce antibodies

◆ Passive immunization – pre-formed antibodies given that target alpha-synuclein.
  ▪ 4 antibodies being studied
  ▪ PASADENA study – phase II, placebo controlled, 316 patients. Did not meet the defined combined clinical endpoints. But did meet secondary endpoints – clinician rating of improved motor function.
  ▪ SPARK study – phase II
Insulin Resistance an the Brain

• Patients with type 2 diabetes have a higher risk (1.5 times) of developing PD.
• Risk of PD up to 60% lower in diabetic patients on certain medications (GLP1 agonists).
• GLP1 agonists shown in animal models to improve brain glucose use and decrease inflammation
• Exenatide trial
  – 60 people, treated for 48 week, 1x/week injection exenatide versus placebo
  – In off state, treated group had improved motor function as compared to placebo group had worsened since start of trial
  – Phase II trial underway
• Others in trials - Liraglutide, Lixisenatide
Nilotinib

- Currently used for treatment of leukemia
- In animal models – reduces abnormal, mis-folded proteins and improves motor function
- 2016 small open label study
  - 12 PDD and DLBD, no placebo group, treated for 24 weeks
  - Positive changes dopamine production and reduction of toxic alpha synuclein in CSF
  - Mild improvement in motor and cognitive symptoms, worsened once nilotinib stopped
- 2 recent Phase II studies (Georgetown and PSG) yielded conflicting results
  - Georgetown – 75 PD patient x 12 months treatment – mild improvement in CSF markers and clinical scores in low dose but not high dose group
  - Parkinson study group – 76 patient x 6 months. No effect in CSF markers and worsening clinical scores when off medication

**Current black warning of increased cardiovascular effects and death**
Exercise and Parkinson’s disease

- Growing evidence over > 10 years that exercise, specifically vigorous exercise, provides neuroprotection and enhances brain plasticity.

- Exercise:
  - enhance dopamine transmission
  - increase release of neurotrophic factors
  - increase blood flow
  - reduce inflammation
  - promotes new brain cell growth

- Goal-directed or dual tasking may provide additional benefits

Courtesy of APDA
In Summary

• Parkinson’s disease is a chronic and slowly progressive neurological conditions that spans decades.

• Most cases are not directly inherited by likely due to a combination of genetic and environmental risk factors.

• Loss of dopamine causes classic motor symptoms but other brainc centers and brain chemical can explain the non motor symptoms.

• Parkinson’s disease may start outside of the brain in some people.

• Extensive research looking at different possible mechanisms for disease modifying therapies.