Introduction to Parkinson's Disease (PD)

Overview of Current Knowledge

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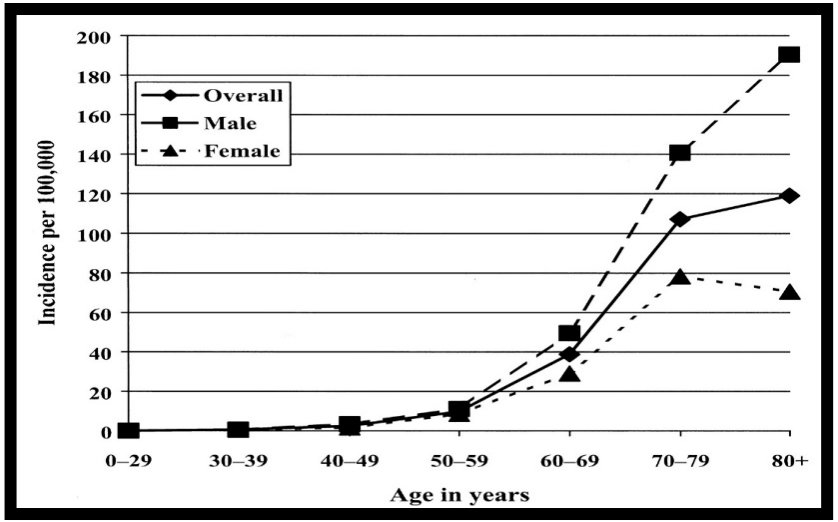
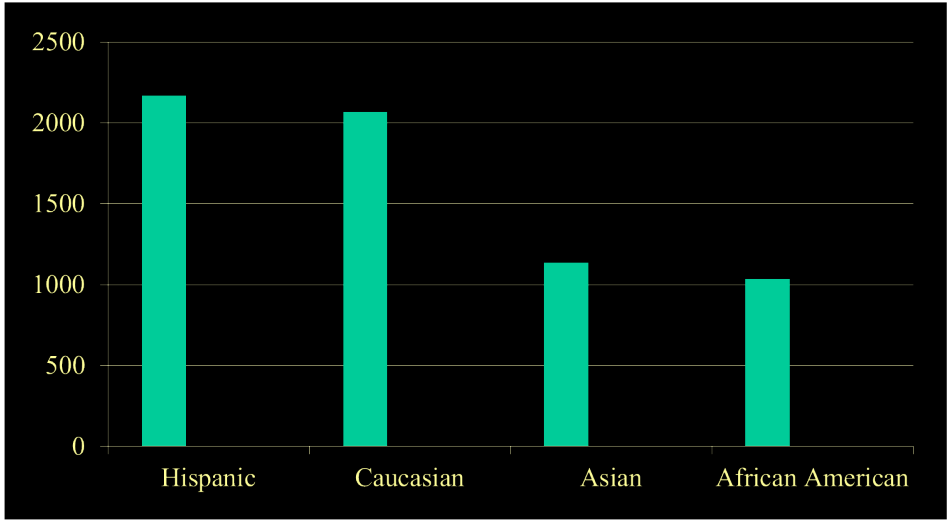
Introduction to PD

- 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

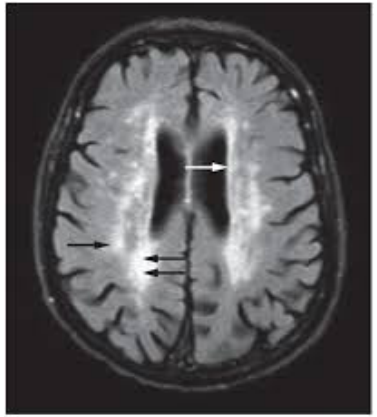
Non Motor Symptoms of Parkinson's disease

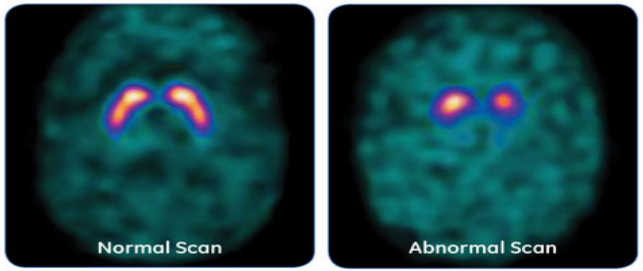
- Loss of smell
- Fatigue, excessive daytime sleepiness
- Apathy
- Depression/ Anxiety
- Problems with memory, concentration
- Acting out dreams while asleep
- Lightheadedness when standing
- Constipation
- Urinary frequency or urgency
- Oily skin and dandruff

*** 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.





"Comma"-shaped
Possible essential tremor

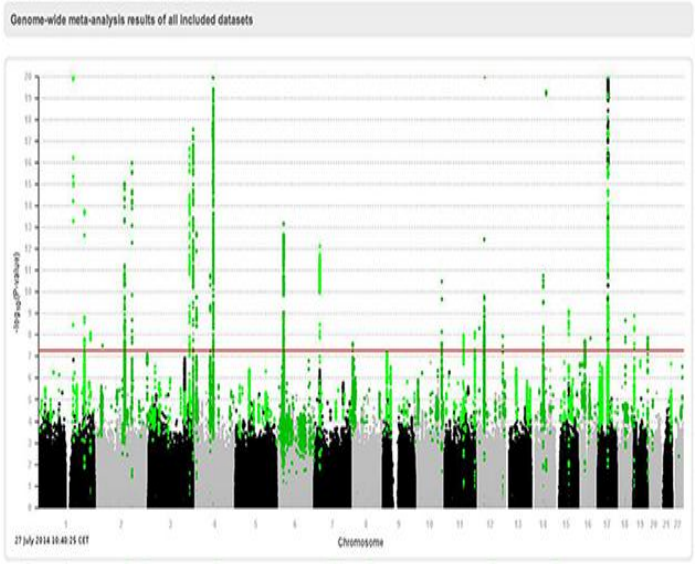
"Period"-shaped
Possible parkinsonian syndrome

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.

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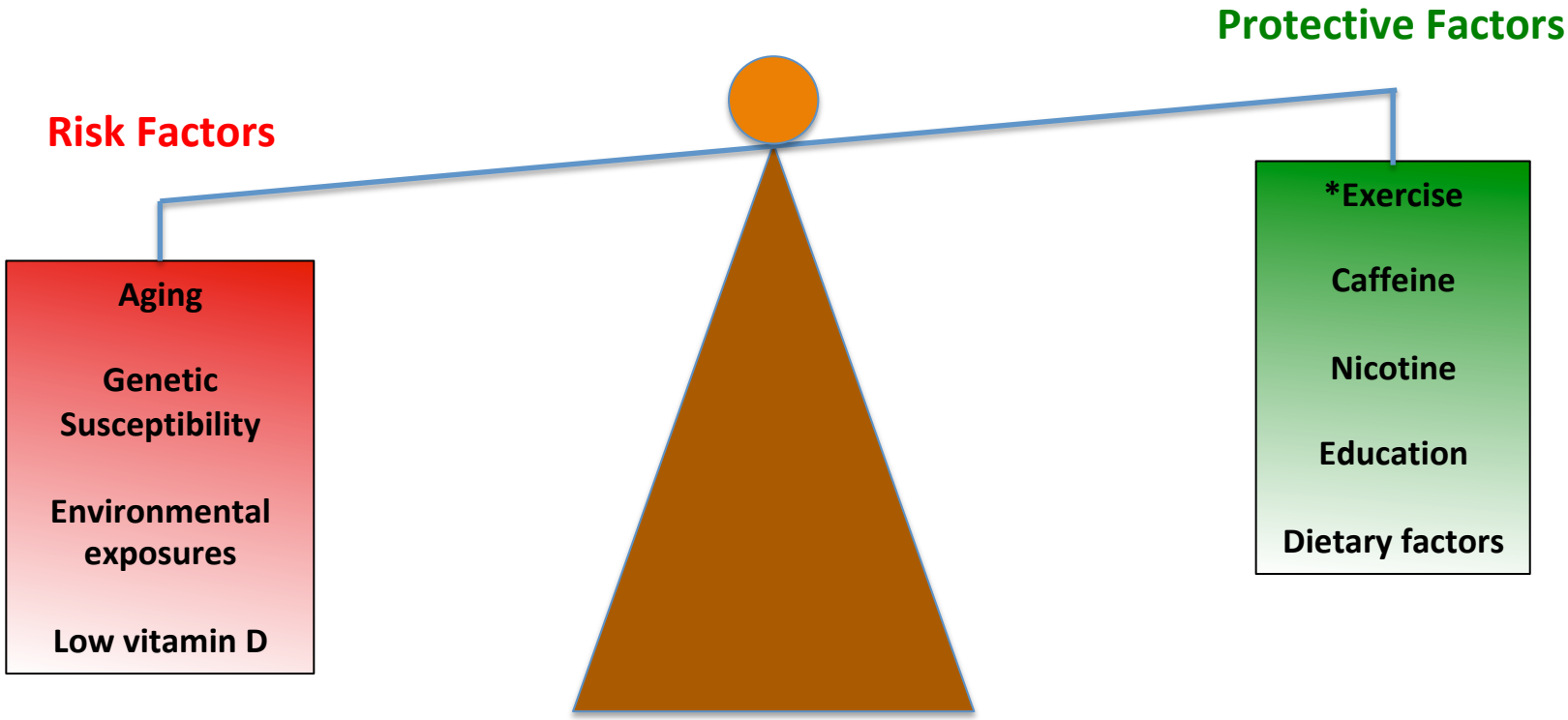
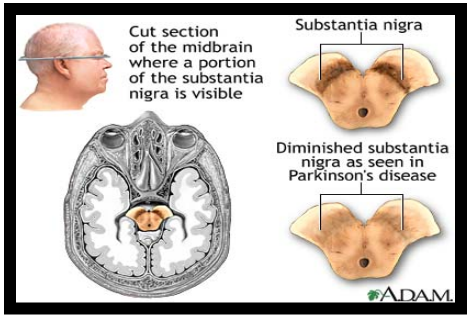
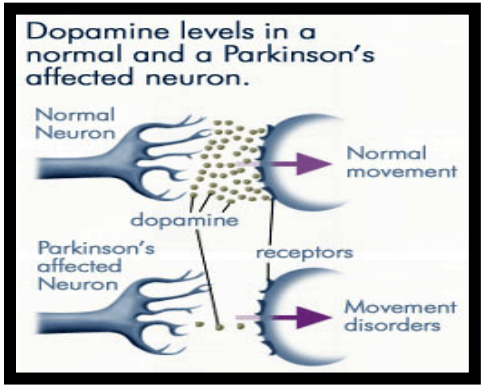
What causes PD



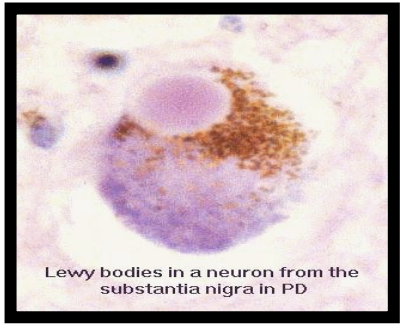
What's happening in the brain

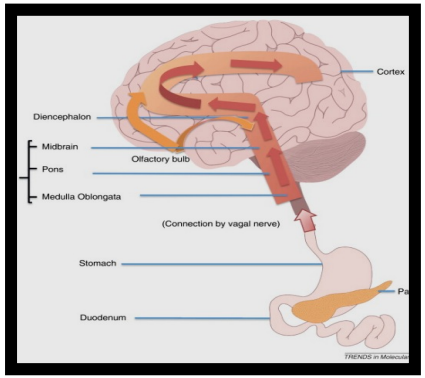




- Slow loss of dopamine producing cells in the brain.
- Dopamine deficiency leads to classic motor (physical)symptoms:
  - Tremor with limbs at rest
  - Muscular rigidity
  - Slow movements
  - Changes in walking and balance

What's happening in the brain

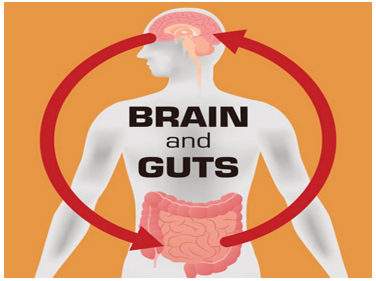




- Lewy Bodies - accumulations of abnormally folded proteins
- Alpha synuclein = main protein
- Lewy bodies also found in other affected brain areas. Other brain centers affected, alterations in other brain chemicals that may affect:
  - Serotonin – mood, motivation
  - Acetylcholine – memory
  - Norepinephrine – 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



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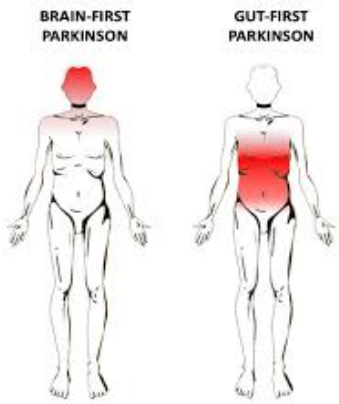
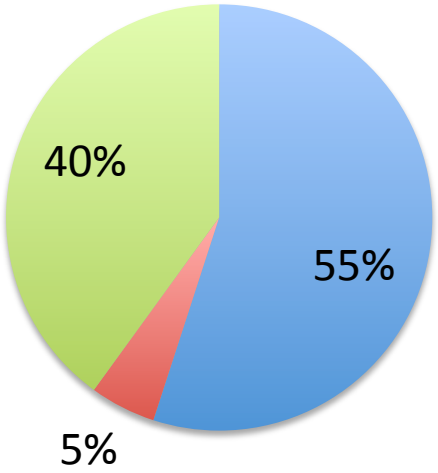


PD Therapies in the Pipeline - early2020

- 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

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Prevent mis-folding

Prevent protein clumping

Vaccinations

Neurotrophic factors

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Enhance natural protective factors i.e. BDNF, GDNF

Genetic targets

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Correct abnormal function

Lifestyle modification

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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 24weeks
  - 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 x12 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

Courtesy of APDA

- 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

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.

Courtesy of SharonSpence.com