Parkinson’s Disease: Tuning the Brain

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The Ohio State University College of Optometry
~Nothing to Disclose~
Outline

I. Introduction
   – Basic presentation
   – Who is at risk

II. What is happening at the cellular level?

III. Stages of Disease
   – Stage 1
   – Stage 2
   – Stage 3
Parkinson’s Disease

- Second most common neurodegenerative disease
  - Chronically progressive
- Affects up to 1 Million people in the US
  - Expected to double within 20 years
- ~60,000 new diagnoses/year
- Male 2:1 Female
- Average age of onset 60
- No cure

Willis et. al., *Neuroepidemiology*. 2010
History

- 1817 Description of Shaking Palsy (Paralysis Agitans)
  James Parkinson

AN ESSAY
ON THE
SHAKING PALSY.

CHAPTER I.
DEFINITION—HISTORY—ILLUSTRATIVE CASES.

SHAKING PALSY. (Paralysis Agitans.)
Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace; the senses and intellects being uninjured.
History

- 1895 Substancia Nigra cell loss E. Brissaud
- 1912 Lewy Bodies F.H. Lewy
- 1958 Dopamine main substance in Substancia Nigra A. Carlsson
- 1968 L-Dopa treatment G. Cotzias
- 1997 Alpha synuclein mutation in familial Parkinson’s Polymeropoulos et. al.
- 1998 Alpha synuclein primary component of Lewy Bodies Spillantini et. al. and Baba M. et. al.
Epidemiology

- Diabetes and obesity
- Lack of exercise
- Genetic predisposition
  - Alpha synuclein
  - Aldehyde dehydrogenase 2
- Pesticides
  - 11 different
- Herbicides

Epidemiology

Willis et. al., *Neuroepidemiology*. 2010
What have we known about PD?

Substancia nigra
Involves death of dopaminergic cells
  – Bradykinesia
  – Rigidity
  – Resting tremor
  – Dyskinesia (with Rx)

Truth?
  Dynamic Disease = Spreads
  Autonomic dysfunction

http://www.puhuahospital.com/diagnoses/parkinson-s-disease
Paradigm shift in Neurodegenerative Diseases

A pathological pathway leading from soluble proteins to insoluble filaments.

Alpha Synuclein Travels from Synapse to Synapse

Alpha Synuclein found:
– Cortex
– Thalamus
– Retina
  • Bodis-Wollner et al, Brain 2014
  • Beach et al, Neurosci Letters 2014
Spreading Nature

Human Fetal Cell Transplants Do Not Work!

Angot et al. *The Lancet Neurology*, 9(11) 2010
Where does Parkinson’s Start?

**Dual Hit Theory**

_Starts_

– Olfactory Bulb
– Enteric Nervous System

_Spreads to Dorsal Motor Vagus (DMX)

Lewy Bodies in Stomach Wall

- Prefers long/mid length neurons
- Little or no myelination
- Dopamine

Braak et al, Neuroscience Letters, 396(1), 2014
## Clinical Presentation

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Armstrong RA, *Parkinson’s Disease* (V 2011) 2011  
Early Parkinson’s Disease: Stage 1

Adapted from Mal Horne, Florey Institute
Treatments for PD: Bradykinesia

Levodopa:
- Madopar
- Sinemet
- Kinson

D2 Agonists:
- Sifrol
- Neupro

Inhibition of Clearance Enzymes:
- ComTan
- Azilect
- Anipryl

https://transmed-parkinsons.wikispaces.com/file/view/d-transmsisn.jpg/31673601/553x270/d-transmsisn.jpg
Stage 1

- Normal
- Early PD (fewer cells)
- Early PD + Therapy
- Rx
Effect of Rx on Stage 1

Dyskinesia

Early PD + Rx

Normal Movement

Bradykinesia ("Off")

6 hrs

Adapted from Mal Horne, Florey Institute
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Armstrong RA, *Parkinson’s Disease* (V 2011) 2011
What is meant by Bradykinesia?

- Difficulty getting up from sitting position
- Difficulty getting out of bed
- Walking without swinging arms
- Reptilian stare
What is meant by Dyskinesia?

Unwanted involuntary movements
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Armstrong RA, *Parkinson’s Disease* (V 2011) 2011
Stage 2: Fewer Cells

Middle PD
“Wearing off”

Middle PD
With Rx
Dyskinesia
Effect of Rx on Stage 2

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6 hrs
2 hrs

Adapted from Mal Horne, Florey Institute
Effect of Rx on Stage 2

Dyskinesia & Poor Impulse Control

Anxiety/Depression

“Wearing Off” Bradykinesia
Slow thinking
Fall Risk

Even out Fluctuations with:
1. Carbidopa
   • Mydriatic followed by miosis
   • Blepharospasm
   • Saccades
2. Anticholinergics (benzhexol or diphenhydramine)
   • Mydriatic
   • Glaucoma
Disease Fluctuation

Fluctuation Score (Bradykinesia and Dyskinesia)

- Normal
- Early PD
- Non-Fluctuators
- Fluctuators

Adapted from Mal Horne, Florey Institute
Clinical Window for Advanced Therapies

Stage 1

DuoDopa

Stage 2

Apomorphine

Stage 3

Deep Brain Stimulation
DuoDopa Gel

- Same as oral
- Dopamine oxidizes = gel
- Constant administration
Apomorphine

- Not dopamine but very similar
- Pump
Deep Brain Stimulation

• Advantages:
  – Very Effective!
  – No Digestive issues
  – No pumps
  – Can be turned off

• Disadvantages:
  – Needs Surgery
  – Postsurgical infections
  – Other functional losses
  – Does not work in Stage 3

http://www.webmd.com/parkinsons-disease/guide/dbs-parkinsons
Deep Brain Stimulation
Clinical Window for Advanced Therapies

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Stage 3

Prefrontal Cortex (cognition and dementia)

Autonomic Severely impaired

Visual cortex

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Armstrong RA, *Parkinson’s Disease* (V 2011) 2011
Freezing Gait

Asmus et al, Neurology 2008
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