Parkinson’s Disease and the Silver Tsunami

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Parkinson's Disease

- 0.5-1.5 million people
- 50,000 USA new cases are reported annually

Treatments: Drug therapy and deep-brain stimulation to alleviate symptoms, but not causes.

- Appears to be slightly more common in men than women
- Expectation of a doubling of Parkinson's patients and costs by 2040
- Average age of onset: 60 years
- Onset as early as 2 years
- Both prevalence and incidence increase with advancing age
- Cost exceeds $14.4 billion each year
1. Billy Connolly (b. 1942)  
Scottish comedian, musician, presenter and actor  

American politician  
By Unknown. This work is free and may be used by anyone for any purpose.

3. Brian Grant (b. 1972-)  
American basketball player  
(Nov. 20, 2009 - Source: Theo Wargo/Getty Images North America)

4. Alex Hill (b. 1994-)  
Diagnosed with Parkinson's disease at just 11-years-old  

English actor  

American evangelist  
By Warren K. Leffler - This image is available from the United States Library of Congress's Prints and Photographs division under the digital ID ppmsc.03261

7. Keegan Mclellan (b. 2014-)  
Diagnosed with Parkinson's disease at just 2-years-old  

8. Estelle Getty (1923-2008)(LBD)  
American actress and comedian  
By Alan Light, CC BY 2.0, https://commons.wikimedia.org/w/index.php?curid=2142952

9. Gunther von Hagens (b. 1945-)  
German anatomist who invented the technique for preserving biological tissue specimens called plastination  

10. Linda Ronstadt (b. 1946-)  
Grammy award-winning singer  
By Carl Lender, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=5906167

Polish cleric, Pope of the Catholic Church and sovereign of Vatican City 1978-2005  
By Uncredited; retouch of Image:JohannesPauuli.jpg - Public Papers of the Presidents of the United States - Photographic Portfolio --1993 Vol II Public Domain

12. Michael J Fox (b. 1961-)  
Canadian/American actor, author, producer, and activist
Intracytoplasmic inclusions termed Lewy bodies containing α-synuclein.

Substantia nigra not first site of injury in PD, Lewy neurites found in olfactory bulb & autonomic nervous system.

Widespread neuropathology through multiple neuronal systems.

- REM Sleep BD
- Anxiety
- Depression
- Dementia

Stooped posture

- Slow movement (bradykinesia)
- Inability to move (akinesia)
- Postural instability, loss of balance
- Sexual difficulties
- Shuffling gait

Often, the first diagnosed symptom of Parkinson's disease is tremor (trembling or shaking) of a limb.

Severity progresses over time

- Hyposmia
- REM Sleep BD
- Anxiety
- Depression
- Dementia

Heart Rate Variability

- Constipation

Rigid limbs, Reduced facial expressions

Speech impairments

Sexual difficulties
Propagation and Transmission of Pathogenic Proteins

Donor

- Amyloid aggregates
- α-syn fibrils
- Exosomes
- MDV

Recipient

- Direct penetration
- Endocytosis
- Receptor-mediated internalization (LAG3)
- Pathogenic α-syn seeds
- Tunneling nanotube
- Amyloid aggregates

Reciprocal transmission of pathogenic protein aggregates between donor and recipient cells.
Scientific Approach

- Patient
- Sporadic
- Familial – Gene mutations

- CSF
- Postmortem Brain Tissue
- Dermal Fibroblasts

- Human Cortical Cultures
- Human Dopaminergic Cultures
- Human Microglia
- Human Astrocytes

- PFF Mouse Models (Sporadic)
  - Intrastriatal
  - Gut to Brain
  - Genetically Engineered Mice (Familial)

- Mouse Neuronal Cultures
- Drosophila
- Cell lines

- Genomics
- Proteomics
- Cell Biology
- Behavior

- Define Pathways
- Identify Targets
  - Primary versus Secondary

- Identify New Therapeutic Approaches to Test
- Assay Development and Target Engagement

- Develop Biomarkers
- Develop Imaging Tools
Pathways of Neurodegeneration in Parkinson’s Disease

**Parkinson’s Disease**
- Age
- Nitrative Oxidative Stress
- Cell to Cell Transmission

**α-syn**
- Aggregation

**Mitochondrial Dysfunction**
- TNF-α
- IL-1β
- C1q
- Microglia Activation
- A1 activated Astrocytes
- Cell Death

**Pathways**
- Inhibitors of Microglia Activation
- PARP Inhibitors
- MIF Inhibitors
- AIF
- MIF
- Cell Death

**Autosomal Recessive Parkinson’s Disease**
- PINK1
- PARIS
- Defects Mitophagy Transport Fission/Fusion
- P-S613
- P-S322

**DJ-1**
- PARIS
- PARIS Inhibitors

**PARKIN**
- P-Y143
- α-syn
- c-Ab1
- c-Ab1 Inhibitors

**LAG3 Inhibitors**
- Mutations

**LAG3**
- Immune System Activation

**Pathway Diagram**
- α-synuclein
- Parkin
- PARIS
- PGC-1α
- NRF-1
- Mitochondrial Dysfunction

**AIF**
- PAR
- MIF
- Cell Death
In Development

- Neuroimaging
- Biomarkers
- LAG3 Inhibitors
- c-Abl Inhibitors
- Inhibitors of Microglia Activation
- PARP Inhibitors
- PARIS Inhibitors
- MIF Inhibitors