Parkinson’s Disease – An Introduction

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Disclosures

• Some brand names will be used, none are specifically endorsed
• Some illustrations and videos are either public domain or provided for teaching activities
• Reference is made to confidential work in progress
• All patients appearing in videos and photos have provided informed consent
• Some public figures appear for illustrative purposes; all the discussions related to these persons are hypothetical and for illustration only
• I have active research collaborations with Medtronic, Inc., BCN Peptides, Inc., the Kinetics Foundation, Convergent Medical Devices.
Outline

- Definition, features, diagnosis and pathology
- Genes, environment, or both?
- Symptomatic therapy, practical approaches and examples
- What basic research teaches us and gene-targeted therapy
- Functional surgery and its role
Outline

• **Definition, features, diagnosis and pathology**
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Parkinson Disease

- Progressive degenerative neurological disorder, characterized by a large number of motor and non-motor features.
- The classic cardinal features are tremor, bradykinesia, rigidity and loss of postural reflexes.
- Parkinson’s is the earliest detailed description, features present in the literature before, the entity was subsequently refined.
Cardinal Features:
Tremor
Cardinal Features:
Bradykinesia
Cardinal Features:
Gait and Postural Impairment
Cardinal Features:
Masked Face
Clinical Manifestations (Abbreviated Selection)

**Cardinal Features:**
- Tremor
- Bradykinesia
- Rigidity
- Postural instability

**Non-motor Features:**
- Cognitive dysfunction
- Psychosis
- Mood disorders: depression
- Anxiety
- Apathy/abulia
- Sleep disturbances: RBD
- PLMS
- Fatigue
- Autonomic dysfunction: urinary urgency/frequency
- Constipation
- Orthostasis
- Erectile dysfunction
- Olfactory dysfunction
- Pain and sensory disturbances
- Dermatologic findings: seborrhea
- Seborrheic dermatitis

**Complications of Therapy:**
- Dyskinesia
- Motor fluctuations
- Sudden off states
- Failed doses
- Impulse control disorders
- Psychosis

**Other motor features**
- Craniofacial
- Hypomimia (masked facial expression)
- Decreased eye blinking
- Speech disturbances: hypokinetic dysarthria, hypophonia
- Dysphagia
- Sialorrhea
- Visual
- Blurred vision
- Impaired contrast sensitivity
- Impaired color discrimination
- Hypometric saccades
- Impaired vestibuloocular reflex
- Impaired upward gaze and convergence
- Lid apraxia
- Musculoskeletal
- Micrographia
- Dystonia
- Myoclonus
- Stooped posture
- Kyphosis
- Scoliosis
- Difficulty turning in bed
- Gait
- Shuffling, short-stepped gait
- Freezing
- Festination
UK Brain Bank Criteria
(Hughes et al JNNP 1992)

• Bradykinesia
• At least one of:
  • Rigidity
  • 4-6Hz resting tremor
  • Postural instability

• No other cause of parkinsonism present
• At least 3 of:
  • Unilateral onset
  • Rest tremor
  • Progressive
  • Persistent asymmetry
  • Excellent response to L-DOPA
  • Severe dyskinesia
  • L-DOPA response 5 years or more
  • Clinical course 10 years or more
Pathophysiology and Possible Targets

Helmich et al., Ann Neurol 2011

Cozzens, Dis Mon 2007
Pathology: Braak Stages

Braak H et al, J Neurol 2002
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Historic note

• In the modern era, traditionally considered predominantly due to environmental factors
  – Absence of family history in most cases
  – Link to infectious etiology - 1918 flu pandemic (Poskanzer DC et al, J Chronic Dis 1963)
  – Link to toxins - MPTP etc. (Langston JW et al, Science 1983)

• Leroux & Lhirondel, 1880: regarding the etiology of PD, “a true cause of paralysis agitans, and may be the only cause, is heredity”. (Leroux PD, Thesis, Paris 1880)

• Mjones, 1949: AD transmission with reduced penetrance (Mjones H, Acta Psych Neurol Scand Suppl 1949)


• Recently, LRRK2 mutations found in both AD PD (Paisan-Ruiz C et al, Neuron 2004), and “sporadic” PD (Gilks WP et al, Lancet 2005), pointing to a possible false dichotomy of “genetic” and “sporadic”
Most Relevant Putative Environmental Factors

Raising susceptibility or potential of causing distinct parkinsonian syndrome:

- Well water
- Rural residence and farming
- Pesticides
- Infection - post-encephalitic parkinsonism
- Trauma - traumatic parkinsonism, dementia pugilistica

Protective from sporadic PD:

- Caffeine
- Smoking
- Some NSAIDS
<table>
<thead>
<tr>
<th>Gene / Product</th>
<th>Proposed Role</th>
<th>Typical Onset</th>
<th>Clinical Features</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-synuclein</td>
<td>Synaptic vesicle traffic</td>
<td>YOPD</td>
<td>Rapid progression; high rate of dementia</td>
<td>Lewy bodies, Tau pathology</td>
</tr>
<tr>
<td>PARK 1/4</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>LRRK2</td>
<td>Cytoplasmic kinase / signaling</td>
<td>LOPD</td>
<td>Similar to sporadic, less severe, less dementia</td>
<td>Variable, with/without Lewy bodies</td>
</tr>
<tr>
<td>PARK 8</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Parkin</td>
<td>Ubiquitin ligase; mitochondrial integrity</td>
<td>YOPD</td>
<td>Slow progression, severe motor complications, non-motor features rare</td>
<td>Nigral degeneration without Lewy bodies</td>
</tr>
<tr>
<td>PARK 2</td>
<td></td>
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</tr>
<tr>
<td>PINK1</td>
<td>Mitochondrial protein</td>
<td>YOPD</td>
<td>Slow progression, severe motor complications, non-motor features rare</td>
<td>Nigral degeneration without Lewy bodies</td>
</tr>
<tr>
<td>PARK 6</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>DJ1</td>
<td>RNA binding / oxidation</td>
<td>YOPD</td>
<td>Same as Parkin and PINK1</td>
<td>Unknown</td>
</tr>
<tr>
<td>PARK 7</td>
<td></td>
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</tbody>
</table>
Where This Leaves us

- Calne, 1989 (JNNP): “It is remarkably difficult to find a clear statement of what constitutes Parkinson’s disease”
- Weiner, 2008 (Arch Neurol): “There is no Parkinson disease”
- Fahn, 1989 (Mov Disord): “Parkinson’s disease, although of unknown etiology today, undoubtedly will be subdivided in the future into different varieties and etiologies”.

Klein and Schlossmacher, Neurology 2007
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Basis for Symptomatic Therapy

Hurtig H et al. Medscape Neurology 2010
Treatment

• Levodopa: Carbidopa/Levodopa; Sinemet®: Provides the missing dopamine; can be combined with COMT inhibition. Short half-life. Side effects: dyskinesia; nausea

• DA agonists: Pramipexole – Mirapex®; Ropinirole – Requip® etc. Mimic the effects of dopamine by activating the same receptors. Longer half-life. Side-effects: psychiatric; sleep-related
Treatment

• Anticholinergics: Trihexyphenidyl – Artane® etc: Act on the cholinergic system, for tremor. Side-effects: cognitive slowing
• MAO-inhibitors: Rasagiline – Azilect®; Selegiline – Zelapar® etc.: prevent break-down of dopamine. Studied for disease-modifying effect. Side-effects: concern for interaction with anti-depressants
Non-dopaminergic Symptomatic Therapy

Rascol O et al. Mov Disord 2011
Different Patients, Different Diseases, Different Approaches

Young patient, tremor dominant

Start treatment with DA agonists, tremor agents; MAO-inhibitors; Consider DBS surgery early; Discussion of genetic causes
Different Patients, Different Diseases, Different Approaches

Middle age patient, tremor and postural problems; possible question about atypical parkinsonism.

Treatment with agonists or levodopa; physical therapy; likely avoid DBS surgery
Different Patients, Different Diseases, Different Approaches

Elderly patient, slowness and stiffness dominant.

Treat with levodopa; physical therapy; investigate cognitive function and treat; watch for complications; support structure; likely avoid surgery
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Relevant PD Pathogenic Pathways Including Symptomatic Approaches

Berry and Foltynie, J Neurol 2011
Relevant PD Pathogenic Pathways
Neurogenesis/Survival Approaches

Various genes linked to PD
Misfolded protein accumulation (i.e. α synuclein)
Microglial activation & inflammation
Degeneration of dopaminergic neurons, related structures and their connections
Motor symptoms of PD

Mitochondria dysfunction
Iron

Courtesy of Dr Pritha Ghosh
Gene-Targeted Therapy

Systemic DJ-1 induction

C-ABL inhibition

PGC-1α induction

LRRK2 inhibition

GDNF transfection

Martin I et al. Annu Rev Genomics Hum Genet. 2010
Gene-Targeted Therapy

Autosomal recessive
- DJ-1
- PINK1
- Parkin

Sporadic PD
- Mitochondrial dysfunction
- Oxidative stress
- LRRK2 mutations
- α-synuclein mutations
- LRRK2
- POLG

Autosomal dominant
- GABA
- α-synuclein aggregation
- Kinase-dependent cell death
- GDNF transfection

Martin I et al. Annu Rev Genomics Hum Genet. 2010
GDNF Early Clinical Data and Next Steps

• 4 GDNF and 2 NTN trials conducted so far
• Variable efficacy, limited primarily by the efficacy of drug delivery

• New trial in preparation at the NIH, intramural – extramural collaboration
• Convention-enhanced delivery of AAV2-GDNF allows much better distribution of the gene product to the striatum
• 4 sequential dosing cohorts planned
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• **Functional surgery and its role**
Deep Brain Stimulation Therapy
For Whom?

- Confirmed PD diagnosis
- Clear response to L-DOPA: at least 30% improvement in UPDRS with L-DOPA induced transition from off to on, by in-office evaluation
- Exclusion for severe medical conditions
- Exclusion for untreated depression, psychosis or dementia
- Failed medical therapy: appears superior to medical therapy in patients with motor complications
- Age: not a strict criterion
Deep Brain Stimulation Therapy
When?

JAMA

Bilateral Deep Brain Stimulation vs Best Medical Therapy for Patients With Advanced Parkinson Disease: A Randomized Controlled Trial
Frances M. Weaver, PhD; Kenneth Follett, MD, PhD; Matthew Stern, MD; Kwan Hur, PhD; Crystal Harris, PharmD; William J. Marks Jr, MD; Johannes Rothlind, PhD; Oren Sagher, MD; Domenic Reda, PhD; Claudia S. Moy, PhD; Rajesh Pahwa, MD; Kim Burchiel, MD; Penelope Hogarth, MD; Eugene C. Lai, MD, PhD; John E. Duda, MD; Kathryn Holloway, MD; Ali Samii, MD; Stacy Horn, DO; Jeff Bronstein, MD, PhD; Gatana Stoner, RN, CCRC; Jill Heemskerk, PhD; Grant D. Huang, PhD; for the CSP 468 Study Group

Enough Is Enough
Moving on to Deep Brain Stimulation in Patients With Fluctuating Parkinson Disease
Michael S. Okun, MD
Kelly D. Foote, MD

The time to refer to DBS is the time of fluctuations and dyskinesia
Deep Brain Stimulation Therapy

How?

• See Dr Zaghloul’s lecture
Thank You

"Mr. Osborne, may I be excused? My brain is full."
Thank you!

- NIH Parkinson Clinic
  - Dr Pritha Ghosh
  - Beverly McElroy
  - Mae Brooks
  - All our staff

- NIH OCD
  - Dr Avi Nath
  - Support staff

- Patients and families

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