Understanding Parkinson's Disease

Irene Oh, MD
Neurologist, Movement Disorders Specialist
The Neurology Center of Southern California,
Encinitas & Escondido

Introduction

- PD was first described in 1817 by Dr. James Parkinson, a British physician, in "An Essay on the Shaking Palsy."

- It is a chronic, progressive neurological disorder, affecting primarily movement. It is the second most common neurodegenerative disorder.

Epidemiology

- Average age of onset is 60 yrs old. However, 5-10% of patients start with symptoms at <50 yrs old.
- Affects 1 in 100 people over age 60 yrs. At least 1 million people in the U.S. and 7-10 million people worldwide have PD.
- In the U.S., an estimated 600,000 new cases are diagnosed each year.

Risk Factors

- The single largest risk factor is advancing age.
- People with one or more close relatives with PD have a small increased risk of developing PD compared to the general population.
- PD affects more males than females.

Overview

- Diagnosis and Clinical Course
- Pathology and Etiology
- Treatment
- Updates and Research

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Parkinsonism: Motor Features

Parkinson's disease is a clinical diagnosis, based on the history and examination.

- Bradykinesia = slowness of movements
- Rigidity = stiffness
- Rest tremor
- Postural instability = gait imbalance

Signs of Early PD

- Rest tremor affecting one side
- Reduced arm swing
- Pain in one shoulder
- Loss of dexterity in one hand
- Loss of facial expression
- Involuntary muscle contractions of one of the feet (dystonia)

Clinical Course of PD

- Early signs and symptoms are typically mild and limited to one side of the body.
- As the disease progresses, symptoms may begin to interfere with everyday activities and eventually affect both sides of the body.
- Generally, the rate of progression is gradual. It is difficult to predict the likely course of the disease – rate of progression or resulting level of disability – in an individual patient.
- PD is not a fatal disease.

Potential Mimics of PD

- Essential tremor
- Atypical parkinsonism
- Drug-induced parkinsonism
- Lower-half parkinsonism
  - NPH, vascular parkinsonism, cervical myelopathy
- Parkinsonism of “normal” aging

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Essential Tremor vs. PD

	Parkinson's Disease	Essential Tremor
Age at onset	Mean ~60 yrs	Any age, mean ~40 yrs
Duration of sxs prior to medical contact	6-12 months	Usually several yrs or more
Gender	Males > females	Males = females
Tremor type	Occurs when hands are at rest	Occurs when hands are in use
Distribution	Hands, legs, chin	Hands, legs, head, voice
Family history	Usually no family history	+Family history in >60%
Alcohol effect	Unaffected or minimal	Improvement

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Neurodegenerative Disorders Causing Parkinsonism

- Parkinson's disease

- *Atypical parkinsonism, or Parkinson-Plus syndromes*
  - Multiple system atrophy
  - Diffuse Lewy body disease
  - Progressive supranuclear palsy
  - Corticobasal ganglionic degeneration

Clues of Atypical Parkinsonism

- Limited or no response to levodopa
- Rapid progression
- Early falls/postural instability
- Early dementia/hallucinations
- Early and prominent speech or swallowing changes
- Early and prominent positional blood pressure changes
- Symmetric onset
- Impaired eye movements, including down gaze

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Drug-induced Parkinsonism

ANTIPSYCHOTICS

- promethazine
- fluphenazine
- haloperidol
- Triavil® (amitriptyline + perphenazine)
- risperidone
- olanzapine

ANTIEMETICS

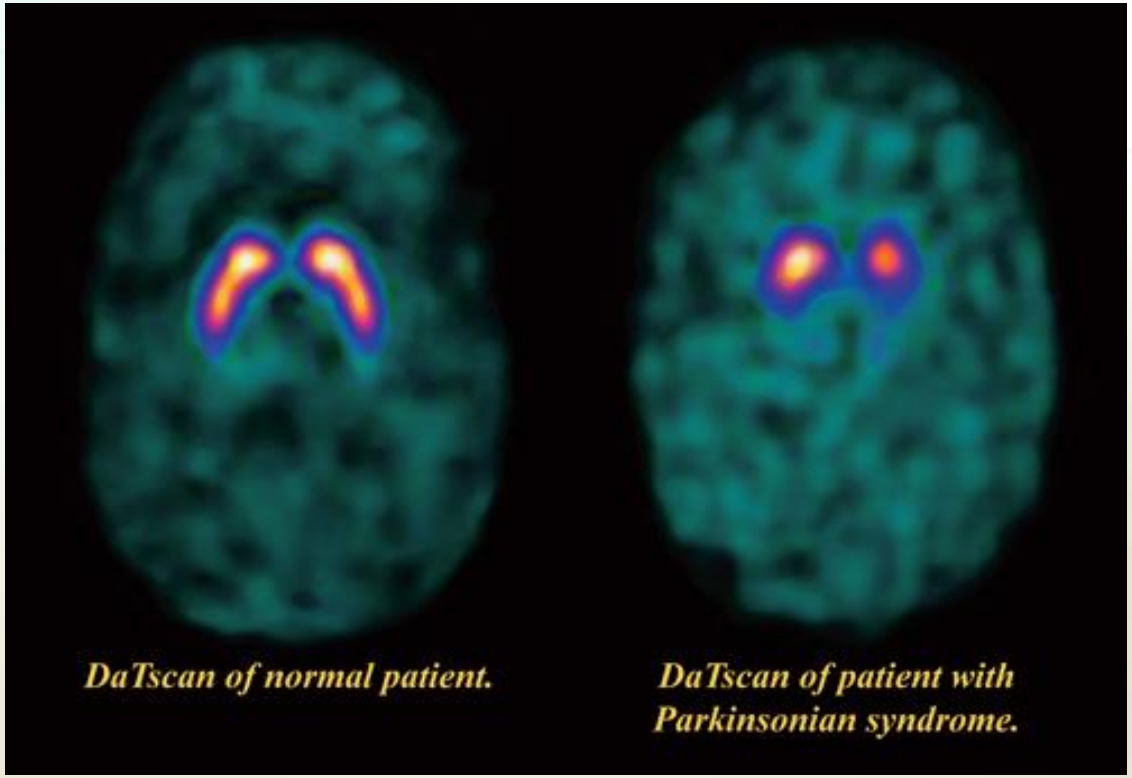
- compazine
- metoclopramide

MISCELLANEOUS

- valproic acid
- amiodarone
- reserpine
- tetrabenazine
- lithium
- calcium channel blockers

Tests

- CT or MRI of the brain
- Bloodwork
- Cognitive screening, neuropsychological testing
- Dopamine transporter scan of the brain



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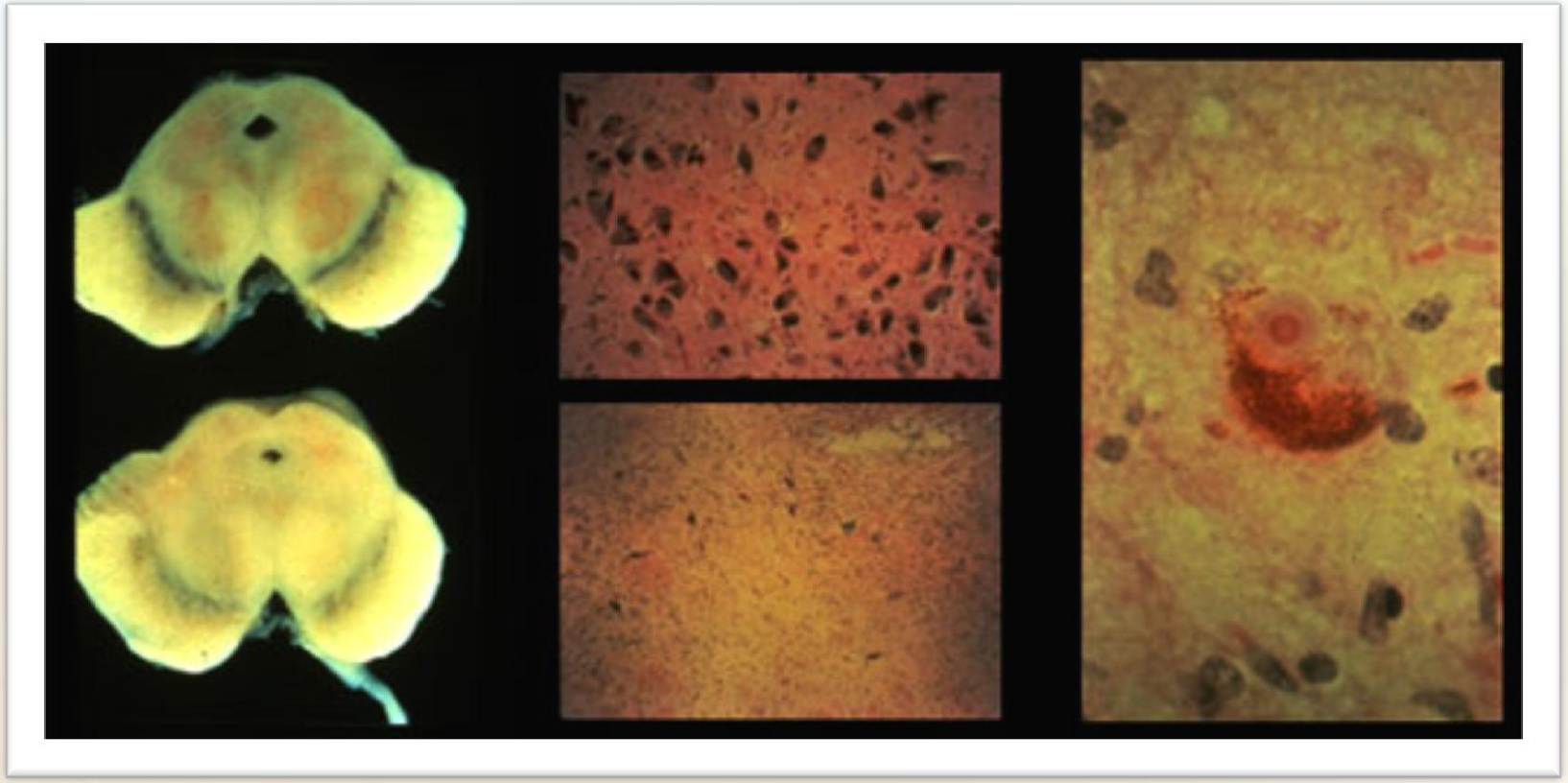
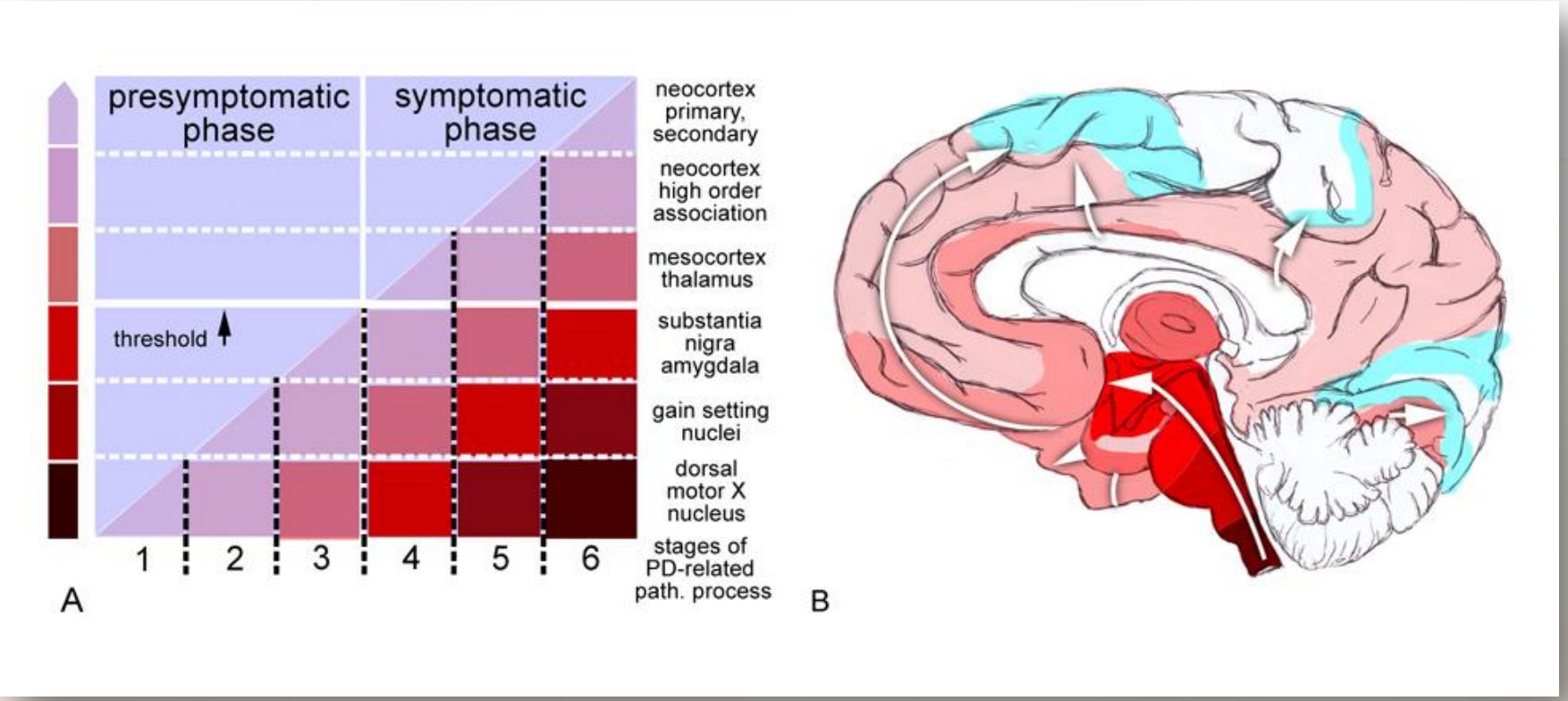
Pathology – Substantia Nigra

- In the traditional view, the pathologic process of PD was thought to start with degeneration of dopaminergic neurons in the *substantia nigra*.



Pathology - …and More



Now, we know that other parts of the brain are involved, accounting for symptoms aside from changes in movement.

Non-Motor Features of PD

- Decreased sense of smell
- Acting out of dreams (REM sleep behavior disorder)
- Constipation
- Fatigue
- Depression/anxiety
- Swallowing problems

Environmental Factors and Increased PD Risk

- Rural residency, herbicides/pesticides, consumption of well water
- Wood preservatives, heavy metals, exhaust fumes, head trauma, general anesthesia; dietary factors – high iron + high manganese, milk consumption; excess body weight
- Occupations: teachers, healthcare workers, farmers.

Genetic Revolution

- Single gene mutations as causes of familial PD, 5-10% of all cases.

GENE	INHERITANCE PATTERN	PROTEIN	LOCUS
PARK 1	AD	α-synuclein	4q21
PARK 2	AR	Parkin	6q25.2-q27
PARK 4	AD	α-synuclein	4q21
PARK 6	AR	PINK1	1p35-36
PARK 7	AR	DJ-1	1p36
PARK 8	AD	LRRK2	12q12
PARK 9	AR	ATP13A2	1p36

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Medications

Levodopa compounds	carbidopa/levodopa (Sinemet®), carbidopa/levodopa sustained release (Sinemet CR®), carbidopa/levodopa/entacopone (Stalevo®)
Dopamine agonists	pramipexole (Mirapex®), ropinirole (Requip®), rotigotine (Neupro patch®).
Enzyme inhibitors	COMT inhibitors: entacapone (Comtan®), tolcapone (Tasmar®). MAO-B inhibitors: rasagiline (Azilect®), selegiline (Eldepryl®, Zelapar®). DOPA decarboxylase inhibitor: carbidopa (Lodosyn®)
Others	amantadine (Symmetrel®); anticholinergics: trihexyphenidyl (Artane®), benztroprine (Cogentin®)

Potential Adverse Effects of Dopamine Agents

- Nausea/vomiting
- Dizziness/lightheadedness
- Drowsiness/sleep attacks
- Hallucinations/paranoia
- Compulsive behavior

Factors to Consider When Initiating Therapy

- Age of patient
- Severity of symptoms
- Cognitive status
- Comorbidities/concomitant medications

Surgical Options – Deep Brain Stimulation

- FDA-approved for the treatment of PD in 2002.
- Involves chronic electrical stimulation to specific brain nuclei through electrodes implanted deep in the brain.

Advantages of DBS Over Ablative Surgery

- Reversibility
- Programmability
  - DBS settings can be adjusted for better efficacy even when the disease advances.
- Ability to perform procedures on both sides of the brain safely.

DBS vs. Best Medical Management

Weaver M et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease. JAMA 2009;301(1):63-73.

- CONCLUSION: "In this randomized controlled trial of patients with advanced PD, deep brain stimulation was more effective than best medical therapy in improving on time without troubling dyskinesias, motor function, and quality of life at 6 months, but was associated with an increased risk of serious adverse events."

Non-Pharmacologic Interventions

- Exercise!
- Therapies – physical therapy, occupational therapy, speech therapy.
- Self-education
- Support groups – Parkinson's Association of San Diego
- Nutrition – fiber, staying well-hydrated.

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Areas of Interest for the Future

- Understanding disease pathogenesis.
- Finding a neuroprotective or disease-modifying therapy that can slow or stop disease progression.
- Finding biomarkers that will allow early, preferably preclinical, detection of disease.
- Discovering new treatments to reduce symptoms and disability.