Parkinson Disease: Pathophysiology, Diagnosis, DaTscan & Differential Diagnosis

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Objectives

• To understand the genetic causes of Parkinson disease (PD)
• To learn the current knowledge regarding the pathophysiology of PD
• To learn how the DaTscan can be useful in the diagnosis of parkinsonism
• To increase knowledge of the DDx of PD
“Primary PD”

- Resting tremor
- Bradykinesia
- Rigidity
- Postural Instability

- Asymmetric
- Levodopa response
- Levodopa - induced motor complications

- Lewy body pathology
Parkinson Syndrome

- **Incidence**
  - Incidence of PS/PD rising slowly with aging population

- **Prevalence**
  - 1% over age 65
  - 4% over age 80
  - 57-371/10^5 worldwide (USA/Canada 300/10^5)

- **Onset**
  - mean PD 62.4 years
  - 4-10% cases before age 40
  - rare before age 30

[www.wemove.org](http://www.wemove.org)
Pathology of Parkinson Disease
Main Biochemical Abnormality

• Marked striatal DA depletion

• ~70% DA loss for symptom manifestations
Etiology of PD

- Genetics
- Environment
- Aging brain
Nongenetic PDs Risks

- Aging
- Male gender
- Caucasian
- FH PD
- Personality traits
- Well water
- Pulp mills
- Farming
- MPTP like compounds
- Pesticides
- Industrial agents
- CO
- Metals
- Rural residence
- Dietary lipid & milk
- ↑ caloric intake
- Encephalitis
- Chronic inflammation
- Head trauma
- Stress

Nongenetic Factors that \(\downarrow\) PDs Risk

- Smoking
- Caffeine
- NSAIDs
- \(\uparrow\) Uric Acid

Genetics of PDs

• Rare single gene mutations (monogenic forms of PD)  
  \textit{SNCA, LRRK2, PRKN, DJ1, PINK1, and ATP13A2}

• Susceptibility genes  
  \textit{MAPT, LRRK2 and SNCA}
# Monogenic PD

<table>
<thead>
<tr>
<th>Locus</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Inheritance</th>
<th>Probable function</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARK1 &amp; PARK4</td>
<td>α-synuclein</td>
<td>4q21</td>
<td>Dominant</td>
<td>Presynaptic protein, Lewy body, lipid and vesicle dynamics</td>
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<tr>
<td>PARK2</td>
<td>parkin</td>
<td>6q25.2-27</td>
<td>Recessive</td>
<td>Ubiquitin E3 ligase, mitophagy</td>
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<tr>
<td>PARK3</td>
<td>Unknown</td>
<td>2p13</td>
<td>Dominant</td>
<td>Unknown</td>
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<tr>
<td>PARK5</td>
<td>UCHL1</td>
<td>4p14</td>
<td>Dominant</td>
<td>Ubiquitin C-terminal hydrolase</td>
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<tr>
<td>PARK6</td>
<td>PINK1</td>
<td>1p35-36</td>
<td>Recessive</td>
<td>Mitochondrial kinase</td>
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<tr>
<td>PARK7</td>
<td>Dj-1</td>
<td>1p36</td>
<td>Recessive</td>
<td>Oxidative stress</td>
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<tr>
<td>PARK8</td>
<td>LRRK2</td>
<td>12p11.2</td>
<td>Dominant</td>
<td>Kinase signaling, cytoskeletal dynamics, protein translation</td>
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<td>PARK9</td>
<td>ATP13A2</td>
<td>1p36</td>
<td>Recessive</td>
<td>Unknown</td>
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<td>PARK10</td>
<td>Unknown</td>
<td>1p32</td>
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<tr>
<td>PARK11</td>
<td>GIGYF2</td>
<td>2p37</td>
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<td>IGF-1 signaling</td>
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<td>PARK12</td>
<td>Unknown</td>
<td>Xq21-q25</td>
<td>X-linked</td>
<td>Unknown</td>
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<tr>
<td>PARK13</td>
<td>Omi/Htra2</td>
<td>2p13</td>
<td>Unknown</td>
<td>Mitochondrial serine protease</td>
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<tr>
<td>PARK14</td>
<td>PLA2G6</td>
<td>22q13</td>
<td>Recessive</td>
<td>Phospholipase enzyme</td>
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<tr>
<td>PARK15</td>
<td>FBX07</td>
<td>22q11</td>
<td>Recessive</td>
<td>Ubiquitin E3 ligase</td>
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<td>PARK16</td>
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<td>1q32</td>
<td>Unknown</td>
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<table>
<thead>
<tr>
<th>Gene/protein</th>
<th>Pattern</th>
<th>Prevalence</th>
<th>Pathology</th>
<th>Common Features</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>α-Synuclein</strong></td>
<td>AD</td>
<td>Very rare</td>
<td>Lewy bodies</td>
<td>Early-onset dementia; presentation variable with mutation type</td>
<td>Aggregation of protein in Lewy bodies from genetic and sporadic forms of PD</td>
</tr>
<tr>
<td><strong>Parkin</strong></td>
<td>AR (mostly)</td>
<td>18% EOPD (50% with family history)</td>
<td>Rare Lewy bodies, if any</td>
<td>Early onset, slow progression</td>
<td>Protein is involved in ubiquination</td>
</tr>
<tr>
<td><strong>DJ-1</strong></td>
<td>AR</td>
<td>&lt;1% EOPD</td>
<td>Unknown</td>
<td>Early onset, slow, progression</td>
<td>Protein is involved in the cellular stress response</td>
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<tr>
<td><strong>PINK-1</strong></td>
<td>AR (carriers may be at increased risk)</td>
<td>2-3% EOPD</td>
<td>Unknown</td>
<td>Early onset, slow progression</td>
<td>Protein is a mitochondrial kinase</td>
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<tr>
<td><strong>LRRK2</strong></td>
<td>AD</td>
<td>Highly variable</td>
<td>Lewy bodies</td>
<td>Typical PD (mostly)</td>
<td>Protein is a kinase with multiple putative domains</td>
</tr>
</tbody>
</table>
α-synuclein
PD pathophysiology

• Aggregated protein may
  – Form pores in cell membrane
  – Interfere with axonal transport
  – Impair proteasomal system
  – Interfere with chaperone role in autophagy
  – Selectively damage DA neurons
α-synuclein Fibrillogenesis

- Monomer: Natively unfolded
- Protofibril: β-sheet rich oligomer
- Fibril: Amyloid-like
- Lewy body: Fibrillar
DEATH OR DAMAGE OF DOPAMINE NEURONS

The hallmark pathology of Parkinson’s disease is the damage and death of dopamine producing neurons in the brain. Dopamine plays a role in controlling movement, cognition, learning, and mood, explaining the dementia and difficulty with motor control exhibited by patients with deficits in the production of this key neurotransmitter. The α-synuclein gene was one of the first to be implicated in this disease. It produces a protein that, in certain circumstances, aggregates to form bundles that are a major component of Lewy bodies—fibers that disrupt normal cell processes. Recently researchers have discovered other mechanisms by which this protein damages or kills dopamine-producing neurons, as well as other genes that may also play a role in driving the disease.

PUNCTURING THE MEMBRANE

Some researchers propose that single α-synuclein molecules bind together in a doughnut shape that inserts into the plasma membrane and forms a pore. The hole allows calcium ions—a tightly regulated ion that helps neurons propagate signals—to accumulate in the cell at toxic levels.

MITOCHONDRIAL DAMAGE

Some evidence suggests that an overabundance of α-synuclein causes mitochondrial dysfunction which can lead to neuron death. However, other researchers have shown that damaged mitochondria can initiate the formation of α-synuclein aggregates, which in turn become toxic to the cell. It’s unclear which comes first, but it appears that each feeds the aberrant production of the other.

BURIED RECYCLING

Rather than an overabundance of α-synuclein, some think that it’s a mutant form of the protein that contributes to disease. Mutant forms of the protein are not easily degraded by the cell’s recycling machinery, such as the proteasome and autophagy-lysosome pathways and thus interferes with the normal recycling of damaged organelles and proteins, creating a deadly back-up of junk proteins in the cell.

ROLES OF AUTOSOMAL RECESSIVE GENES

Mutations that render these genes inactive or less productive produce some Parkinson’s-like effects.

DJ-1 is a molecular chaperone with roles in antioxidant gene expression and possibly counters oxidative stress in mitochondria.

PARKIN normally tags proteins with ubiquitin and plays a role in mitochondrial homeostasis.

PINK1 is normally involved in maintaining normal mitochondrial function and may act in concert with PARKIN.
LRRK2

- Leucine-rich repeat kinase 2
- AD
- Most common cause of familial and sporadic PD
  - 1.5% of late-onset PD
  - 40% of Arab PD pts
  - 20% of Ashkenazi Jewish PD pts
- Late onset ‘idiopathic PD’ phenotype
  - Homozygous = heterozygous phenotype
- Pathology: Lewy bodies
Parkin, PINK-1, DJ-1

- AR, loss of fxn
- Young onset, slow progression
PD Susceptibility Genes

- LRRK2
- Microtubule associated tau protein (MAPT)
- Glucocerebrosidase (GBA)
Glucocerebrosidase (GBA)

- Lysosomal enzyme \(\rightarrow\) Gaucher’s
  - hepatosplenomegaly, anemia, thrombocytopenia, bone disease and, at times, neurologic involvement

- Screening PD
  - \(~5\%\) of non Ashkenazi Jews
  - \(~15\%\) of Ashkenazi Jews

- Variable phenotype
  - Earlier onset
  - Affected relatives
  - Atypical presentation
Pathogenesis of PD

- α-synuclein $\Rightarrow$ aggregation
- LRRK2 $\Rightarrow$ phosphorylation
- Parkin $\Rightarrow$ ubiquitin-proteasomal system
- DJ-1 $\Rightarrow$ oxidative stress
- PINK-1 $\Rightarrow$ mitochondrial dysfunction
PD Pathophysiology Puzzle

- Inflammation HLA genes (PARK18)
- ↓Protein Degradation Parkin, PINK1, GBA
- Δ Kinase PINK1, LRRK2
  - Oxidative Stress Parkin, DJ1
  - Mitochondrial Dysfunction Parkin, PINK1
  - ↓Autophagy GBA

SNCA accumulation & aggregation
SNCA, LRRK2, GBA, DJ1, others?

Neuronal Death
Stage 1: medulla
Stage 2: & pons
Stage 3: & midbrain
Stage 4: & basal prosencephal and mesocortex
Stage 5: & neocortex
Stage 6: & more neocortex

Transmission of Lewy body (α-synuclein) pathology

• Through the nervous system
  – Braak H et al. *Neurol Biol Aging* 2003
• Host cells to grafted cells
  – Fetal transplants
    • Kordower JH et al. *Nat Med* 2008
    • Li JY et al. *Nat Med* 2008
    • Desplats P et al. *PNAS* 2009

α-Synuclein is the most abundant protein found in Lewy bodies, ..., and can aggregate to form toxic oligomers and fibrillar structures. Recent studies have shown that α-syn can be transmitted between neurons and can seed the formation of toxic aggregates in recipient neurons in a prion-like manner. In addition, it is known that Lewy body pathology may spread gradually and systematically from the peripheral or enteric nervous system or olfactory bulb to specific brain regions during progression of idiopathic PD. It is therefore conceivable that α-syn species could act as seeds that drive PD progression.

Is PD a Prion Disorder?

Olanow & Prusiner PNAS 2009
As the disease progresses, disability increases through different mechanisms.

- Reduced olfaction
- Constipation
- RBD

Motor threshold:

- Pre-motor phase
- Motor phase
- Honeymoon phase

L-Dopa

Motor disability

Fluctuations
Dyskinesia

Motor complications
Incontinence
Orthostatic hypotension
Dementia

Late-stage complications

FOG
Falls

“Should I get a DaTscan or PET scan to confirm my diagnosis of PD?”

From NPF website, front page, Sept 2012
DaTscan

- Ioflupane I123 injection
  - used to visualize striatal dopamine transporter (DAT) using SPECT
- Demonstrates the integrity of dopaminergic nigrostriatal nerve terminals
- Abnormal in parkinsonian syndrome (PS)
  - PD, DLBD
  - MSA
  - PSP
DaTscan Uses

- Differentiate PD from essential tremor (ET)
- Differentiate PD from drug induced PDism
- Differentiate PDism from NPH
- Differentiate PDD/DLBD from AD
- Differentiate PD from vascular PD
- Differentiate PD from psychogenic PD
Not to be used for

- Differentiate between PD, MSA, PSP
- Confirmation of PD
- Longitudinal assessment of progression
- Quantitation, e.g., severity of PD
  - Is a qualitative test
- Replace clinical judgment
DaTscan

- **Contra-indicated:** allergy to iodone
- **Thyroid Accumulation:** The DaTscan injection may contain up to 6% of free iodide. To decrease thyroid accumulation of I-123, block the thyroid gland at least 1 hour; failure to do so may increase the long-term risk for thyroid neoplasia. Patient is given Potassium Iodide Oral Solution or Lugol’s Solution (100 mg iodide) or potassium perchlorate (400 mg)
- **Radiation safety:** To minimize radiation dose to the bladder, encourage hydration prior to and following DaTscan - to permit frequent voiding.
- **Adverse reactions:** headache, nausea, vertigo, dry mouth or dizziness of mild to moderate severity
**Drug Interactions** - Drugs that bind to the dopamine transporter with high affinity may interfere with the DaTscan image

**DC 4 half-lives before test**
(4-5 days before)

dextroamphetamine-48 hours
methamphetamine-20 hours
methylphenidate-16 hours
phentermine-32 hours
psuedoephedrine-64 hours
modafinil-60 hours
bupropion-80 hours
mazindol-51 hours

fentanyl
IV-16 hours
Patch-88 hours
Buccal-56 hours
Nasal-100 hours
Patient instructions

- Stop meds
- hydrate
- SHOW UP!
- Thyroid block, wait 1 hour
- DaTscan, wait 3-6 hours
- Scan (30 min)
- Hydrate x 2 days
Normal
- Comma shape
- Symmetric

Abnormal
- Oval or round (loss of putamen)
- Asymmetric

For a abnormal scan neither side should be the normal full comma shape
Differential Diagnosis of Primary PD

Secondary Parkinsonism

- Drug-induced (Reglan)
- Toxin-induced
- Metabolic
- Structural lesions (vascular parkinsonism, etc.)
- Hydrocephalus
- Infections

Neurodegenerative Syndromes with PDism
Classification of parkinsonism

I. Primary (idiopathic) Parkinsonism
   - Parkinson disease
   - Juvenile parkinsonism

II. Multisystem Degenerations (Parkinsonism-Plus)
   - Progressive supranuclear palsy (PSP)
   - Steele-Richardson-Olszewski disease (SRO)
   - Multiple-system atrophy (MSA)
   - Striatonigral degeneration (SND or MSA-P)
   - Olivopontocerebellar atrophy (OPCA or MSA-C)
   - Shy-Drager syndrome (SDS)
   - Lytico-Bodig or parkinsonism-dementia-ALS complex of Guam (PDACG)
   - Cortical-basal ganglionic degeneration (CBGD)
   - Progressive pallidal atrophy
   - Parkinsonism-dementia complex
   - Pallidopyramidal disease

III. Heredodegenerative Parkinsonism
   - Hereditary juvenile dystonia-parkinsonism
   - Autosomal dominant Lewy body disease
   - Huntington disease
   - Wilson disease
   - Hereditary ceruloplasmin deficiency
   - Hallervorden-Spatz disease
   - Olivopontocerebellar and spinocerebellar degenerations
   - Machado-Joseph disease
   - Familial amyotrophy-dementia-parkinsonism
   - Disinhibition-dementia-parkinsonism-amyotrophy-complex
   - Gerstmann-Strausler-Scheinker disease
   - Familial progressive subcortical gliosis
   - Lubag (x-linked dystonia-parkinsonism)
   - Familial basal ganglia calcification
   - Mitochondrial cytopathies with striatal necrosis
   - Ceroid lipofuscinosis
   - Familial Parkinsonism with peripheral neuropathy
   - Parkinsonism-pyramidal syndrome
   - Neuroacanthocytosis
   - Hereditary hemochromatosis

IV. Secondary (Acquired, Symptomatic) Parkinsonism
   - Infectious: postencephalitic, AIDS, SSPE, Creutzfeldt-Jakob disease, prion diseases
   - Drugs: dopamine receptor - blocking drugs (antipsychotic, antiemetic drugs), reserpine, tetrabenazine, alpha-methyl-dopa, lithium, flunarizine, cinnarizine
   - Toxins: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
   - Vascular: multi-infarct, Binswanger disease
   - Trauma: pugilistic encephalopathy
   - Other: parathyroid abnormalities, hypothyroidism, hepatocerebral degeneration, brain tumor, paraneoplastic, normal pressure hydrocephalus, noncom-municating hydrocephalus, syringomesencephalia, hemiatrophy-hemiparkinsonism, peripherally induced tremor and parkinsonism, and psychogenic
Classification of Parkinsonism in a Community

- Primary PD ~ 85%
- Drug-induced PDism 7% - 9%
- MSA ~ 2.5%
- PSP ~ 1.5%
- Vascular PDism ~ 3%
- PS due to MPTP, CO, Mn, recurrent head trauma is extremely rare
- No new cases of postencephalitic parkinsonism since 1960s
Clues Suggesting PD+

- Early onset of, or rapidly progressing, dementia
- Rapidly progressive course
- Supranuclear gaze palsy
- Upper motor neuron signs
- Cerebellar signs - dysmetria, ataxia
- Urinary incontinence
- Early symptomatic postural hypotension
• Progressive supranuclear palsy
  – Supranuclear downgaze palsy, square wave jerks
  – Upright posture/frequent falls
  – Pseudobulbar emotionality
  – Furrowed brow/stare

• Corticobasal degeneration
  – Unilateral, coarse tremor
  – Limb apraxia/limb dystonia/alien limb
PSP facial mask
PD+

• Multiple system atrophy
  – MSA – A (Shy-Drager syndrome: SDS)
    • Autonomic insufficiency—orthostasis, ↓ B&B
  – MSA – P (Striatonigral degeneration: SND)
    • Tremor less prominent
  – MSA-C (Olivopontocerebellar atrophy: OPCA)
    • Cerebellar signs

• Fragile X-associated tremor/ataxia syndrome (FXTAS)
Clinical usefulness of magnetic resonance imaging in multiple system atrophy.

Schrag A, Kingsley D, Phatouros C, Mathias CJ, Lees AJ, Daniel SE, Quinn NP
Natural History of MSA

Median survival 9.5 years
PD+

- Diffuse Lewy body disease
  - Early onset of dementia
  - Delusions and hallucinations
  - Agitation
- Alzheimer’s disease
  - Dementia is the primary clinical syndrome
  - Rest tremor is rare
Vascular Parkinsonism

• Abrupt onset, usually unilateral
• Step-wise or no progression
• Other signs—hemiparesis, aphasia, hyperreflexia
• Infarcts on neuroimaging helpful in confirming diagnosis
Hydrocephalus-induced Parkinsonism

- Can be communicating or obstructive
- Normal pressure hydrocephalus—idiopathic
- Clinical triad:
  - parkinsonism/gait disorder
  - urinary/fecal incontinence
  - dementia
Normopressure Hydrocephalus (NPH)
Clinical Characteristics of FXTAS

Most Common

- Male
- Onset in 50’s or 60’s
- Cerebellar gait ataxia
- Intention tremor
- Frontal executive dysfunction
- Parkinsonism
- Sensory peripheral neuropathy

Less Common

Fragile X mental retardation 1 (FMR1) gene

- X chromosome
- Mutation is CGG repeat expansion
- Lack of FMRP => FXS
- FXS: common cause of MR
- M affected > F
**FMR1** gene CGG repeat size & resultant clinical signs

<table>
<thead>
<tr>
<th>Genotype</th>
<th>CGG Repeat Size</th>
<th>Neurological Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>6 - 40</td>
<td>None</td>
</tr>
<tr>
<td>Premutation</td>
<td>56 - 199</td>
<td>POF, FXTAS</td>
</tr>
<tr>
<td>Full mutation</td>
<td>&gt;200</td>
<td>FXS: Mental retardation, learning disabilities, autism</td>
</tr>
</tbody>
</table>
FXTAS Patients
FXTAS Misdiagnoses Categories (n = 98)

- Tremor: 20%
- PDism: 24%
- Dementia: 12%
- Misc: 16%
- Cerebro-vascular: 11%
- Ataxia: 17%
- PDism: 24%
FXTAS MCP sign

Also: Global atrophy
↑T2 white matter