Role of imaging in parkinsonism

Dr. Santhosh Gaddikeri M.D
Nuclear Medicine Resident
• **Recommended reading:**

  • The role of functional dopamine-transporter SPECT imaging in parkinsonian syndromes, part 1. 
  Booth TC, Nathan M, Waldman AD, Quigley AM, Schapira AH, Buscombe J. AJNR Am J Neuroradiol part 1 and 2
I, Dr. Santhosh Gaddikeri have no financial relationships to disclose.

Planning Committee:

Dr. Hubert Vesselle has disclosed his financial relationship with MIM Software for consulting.

Dr. Lewis has no financial relationships to disclose.

*If there is a financial relationship to disclose, please replace “no financial relationships” with the name of any commercial entity and the type of relationship with which you or your spouse/partner have an affiliation. Otherwise, delete this smaller print before including as the first slide in your case conference presentation.
Introduction

• Definition: Clinical syndrome characterized by bradykinesia and at-least one of the following symptoms: resting tremor, muscular rigidity, and postural instability

• First described by James Parkinson in 1817

• Progressive neurologic degenerative disease, usually begin between the age of 45 and 70 years. Peak in sixth decade

• Exact cause not well known. Multifactorial including trauma (Punch-Drunk syndrome), toxins (MPTP), genetic disorders

• Smoking and coffee drinking may have mild protective effects

• Slight predominance in white males
# Introduction

## Table 39.2 Genetic Defects Associated with Parkinson Disease

<table>
<thead>
<tr>
<th>Notation</th>
<th>Chromosome</th>
<th>Gene</th>
<th>Genetics</th>
<th>Age of Onset</th>
<th>Lewy Bodies</th>
<th>Special Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park1</td>
<td>4q21</td>
<td>α-synuclein</td>
<td>AD</td>
<td>30–40 years</td>
<td>+</td>
<td>Two main mutations—A53T, A30P—promote oligomerization of α-synuclein.</td>
</tr>
<tr>
<td>Park2</td>
<td>6q25</td>
<td>parkin</td>
<td>AR</td>
<td>20–40 years</td>
<td>−</td>
<td>Accounts for 50% of early onset inherited PD; 20% of “sporadic” early onset cases.</td>
</tr>
<tr>
<td>Park3</td>
<td>2p13</td>
<td></td>
<td>AD</td>
<td>Late onset</td>
<td>−</td>
<td>Resembles idiopathic PD.</td>
</tr>
<tr>
<td>Park5</td>
<td>4p14</td>
<td>UCH-L1</td>
<td>AD</td>
<td>50’s</td>
<td>+</td>
<td>Gene is ubiquitin carboxyterminal hydrolase L1. Mutations decreased recycling of ubiquitin monomers.</td>
</tr>
<tr>
<td>Park6</td>
<td>1p35-36</td>
<td>PINK1</td>
<td>AR</td>
<td>varies</td>
<td>?</td>
<td>Mitochondrial gene.</td>
</tr>
<tr>
<td>Park7</td>
<td>1p36</td>
<td>DJ-1</td>
<td>AR</td>
<td>30’s</td>
<td>?</td>
<td>Slow progression; gene plays role in cellular response to oxidative stress.</td>
</tr>
<tr>
<td>Park8</td>
<td>12 cent</td>
<td>LRRK2</td>
<td>AD</td>
<td>late</td>
<td>±</td>
<td>Ashkenazi Jews. Protein is dardarin, a novel kinase.</td>
</tr>
<tr>
<td>NR4A2</td>
<td>2q22</td>
<td>NURR1</td>
<td>AD</td>
<td>?</td>
<td></td>
<td>Gene is implicated in the formation and identity of dopaminergic neurons.</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive; PD, Parkinson disease.
Table 38-1 Initial Symptoms in Patients with Parkinson Disease

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
<td>70%</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>11%</td>
</tr>
<tr>
<td>Stiffness</td>
<td>10%</td>
</tr>
<tr>
<td>Slowness</td>
<td>10%</td>
</tr>
<tr>
<td>Muscle aches</td>
<td>8%</td>
</tr>
<tr>
<td>Loss of dexterity</td>
<td>7%</td>
</tr>
<tr>
<td>Handwriting disturbance</td>
<td>5%</td>
</tr>
<tr>
<td>Depression, nervousness, other psychiatric disturbance</td>
<td>4%</td>
</tr>
<tr>
<td>Speech disturbance</td>
<td>3%</td>
</tr>
</tbody>
</table>

Source: Adapted from Hoerrn and Yahr's study of 183 idiopathic cases, 1967.
introduction

Tremor:

• Resting tremor
• Pill-rolling tremor
• Alternating activity in the agonist and antagonist muscle groups on EMG (alternating tremor)
• Around 4/Sec
• One side of the body is always involved by tremor and rigidity before the other. Tremor always remain asymmetrical as the disease advance
questions

1. What is diagnostic accuracy of clinical criteria in the diagnosis of PD
2. Potential role of DAT SPECT
3. Potential role of 18F-FDOPA PET
4. Role of MRI
5. Appropriate imaging as per the ACR-AC for
   • PD with typical features and levodopa responsive
   • PD with atypical features and levodopa resistant
pathophysiology

CORTEX

LENTIFORM NUCLEUS

SUBSTANTIA NIGRA

P GPe GPi

INTERNAL CAPSULE

THALAMUS

STN

SNc

SNr
pathophysiology

DIRECT PATHWAY: Stimulatory pathway (Activates the agonists)
- Excitatory neuron (Glutaminergic pathway)
- Inhibitory neuron (GABAergic pathway)
pathophysiology

INDIRECT PATHWAY: Inhibitory pathway
(Inhibits the antagonists)

- Excitatory neuron (Glutaminergic pathway)
- Inhibitory neuron (GABAergic pathway)
pathophysiology

CORTEX

LENTIFORM NUCLEUS

SUBSTANTIA NIGRA

INTERNAL CAPSULE

THALAMUS

STN

D1

D2

P

GPe

GPi

SNc

SNr
pathophysiology

• Parkinsonism is divided into two categories:
  1. With nigro-striatal dopaminergic cell loss: PD and APD (including MSA-P, PSP, CBD (corticobasilar degeneration) and DLB (Diffuse Lewi body) disease
  2. Without nigro-striatal dopaminergic cell loss: Psychogenic parkinsonism, dystonic tremor, dopa-responsive dystonia and drug induced parkinsonism
• Parkinson disease (PD) is the most common cause of Parkinsonism. It is a neurodegenerative process and is idiopathic
How do we make a diagnosis of parkinsonism?
Accuracy of clinical diagnosis in parkinsonism—a prospective study.

Rahut A\textsuperscript{1}, Rozdilsky B, Rahut A.

\textbf{Author information}

\textbf{Abstract}

Clinical diagnosis of Parkinson’s syndrome (PS) is reasonably easy in most cases but the distinction between different variants of PS may be difficult in early cases. The correct diagnosis is not only important for counselling and management of patients but also in conducting pharmacological and epidemiological studies. There is very little critical literature on the pathological verification of the clinical diagnosis in PS. We report our 22 years experience to address that issue. Between 1968 and 1990, 65 PS patients came to autopsy. Complete data are available in 59 (M=50, F=19) cases. The initial diagnosis made by a qualified neurologist was idiopathic Parkinson’s disease (IPD) in 41 cases. Of those 28 (65\%) had Lewy body pathology. After a mean duration of 12 years the final diagnosis was IPD in 41 cases which was confirmed in 31 (76\%). The IPD could not be clinically distinguished from cases with severe substantia nigra neuronal loss without inclusions or from those with neurofibrillary tangle inclusions and neuronal loss at the anatomical sites typically involved in IPD. All progressive supranuclear palsy, olivopontocerebellar atrophy, Jakob-Creutzfeldt’s disease and the majority of the multiple system atrophy cases were diagnosed correctly during life. The correct clinical diagnosis in most non-IPD variants of PS was possible within 5 years of onset (range: 2 months to 18 years). We recommend that studies aimed at including only the IPD cases restrict the enrollment to those cases that have had PS motor manifestations for five years or longer duration.

\textbf{PMID: 103360} (PubMed - indexed for MEDLINE)

<table>
<thead>
<tr>
<th>Reference</th>
<th>PD cases/all cases</th>
<th>Diagnostic criteria</th>
<th>Sens.</th>
<th>Spec.</th>
<th>PPV</th>
<th>NPV</th>
<th>Comments and recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ward and Gibb\textsuperscript{2}</td>
<td>24/34</td>
<td>2 of 3 of T, B, R</td>
<td>75</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 of 3 of T, B, R</td>
<td>67</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hughes et al.\textsuperscript{3}</td>
<td>76/100</td>
<td>2 of 3 of T, B, R</td>
<td>99</td>
<td>8</td>
<td>77</td>
<td>67</td>
<td>Retrospective</td>
</tr>
<tr>
<td>3 of 3 of T, B, R</td>
<td>65</td>
<td>71</td>
<td>88</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Superscript numbers correspond to the list of References. Validity values are given as percentages.

T, tremor; B, bradykinesia; R, rigidity; Sens., sensitivity; Spec., specificity; PPV, positive predictive value; NPV, negative predictive value; dx, diagnosis.
Why do we care to differentiate parkinsonism from other mimics

Because they differ in

1. Molecular pathogenesis
2. Treatment response and
3. Prognosis

This is where imaging plays a role
Dopamine transporter spect (dat spect)

- DAT SPECT is used to detect nigrostriatal dopaminergic cell loss
- Helps in distinguishing parkinsonism that results due to loss of nigrostriatal cells (e.g; PD, MSA-P, PSP, CBD and DLB disease) from similar clinical mimics without nigrostriatal cell loss (e.g; psychogenic parkinsonism, dystonic tremor, dopa-responsive dystonia and drug induced parkinsonism)
- When clinical symptoms occur there is already loss of at-least 50% to 80% of the nigro-striatal dopaminergic neurons
- On average there is 5.5-7.1% loss of dopaminergic neurons in PD annually. The rate is much higher in APD
Dopamine transporter spect (DAT spect)

• Radiotracers target D2/D3 receptors
• Radiotracers used include:
  ❖ $^{123}$I FP-CIT [fluoroprpyl-carbomethoxy-3β-4-iodoprophenyltropane]
  ❖ $^{123}$I Iodobenzamide
  ❖ $^{123}$I Iodobenzofuran
Dopamine transporter spect (DAT spect)

- Current reference standard (or gold standard) for detection of nigrostriatal cell loss is pathological evaluation, which is not a practical for evaluation of new diagnostic tools for early diagnosis
- Many believe DAT SPECT is a most suitable to act as a reference standard in detection of early nigrostriatal cell loss in patients with early stage parkinsonism
Dopamine transporter spect (dat spect)

Axial DAT SPECT (I-123 FP-CIT) images of healthy control (left) and a patient with PD (right) at the level of striatum. Intense symmetrical DAT binding in the striatum of healthy control and asymmetrical DAT binding bilaterally in PD patient

Suwijn et al; EJNMMI Research, 2015
According this literature review the sensitivity and specificity of DAT SPECT for differentiating parkinsonism due to NS cell loss from mimics without cell loss is 98%
Fluorodopa f-18 PET

- Useful in detecting nigrostriatal dopaminergic cell loss and hence in the diagnosis of neurodegenerative parkinsonism
- L-Dihydroxyphenylamine (l-DOPA) labelled with Flurine-18 transported into the presynaptic neurons by LAT (large amino acid transporter)
- L-DOPA converted to flurodopamine by AADC (aromatic acid decarboxylase)
- Flurodopamine is stored in to presynaptic vescicles by VMAT2 (type 2 vesicular monoamine transporter)
- Therefore F18-FDOPA uptake reflect the presynaptic vesicular storage capacity of nigrostriatal neurons

Fluorodopa f-18 PET

- Previous estimates of the rate of progression of the nigral pathology underlying idiopathic parkinsonism (IP) have been derived mainly from pathological studies that have an inherent selection bias. Fluorodopa positron emission tomography (PET) is a reliable tool for assessing nigrostriatal dopaminergic function in vivo. We performed fluorodopa PET on two occasions, 7 years apart, on 16 patients with IP (age at the time of the first scan: 51 +/- 14 yr [mean +/- SD]) and 10 normal controls (age: 54 +/- 16 yr). For the patients with IP, the average duration of symptoms from the time of diagnosis to the first scan was 4.5 years (range: 1-12 yr), their PET index (striatal-occipital)/occipital ratio, dropped by 1.7% per year, from 0.49 +/- 0.08 to 0.43 +/- 0.08 (p < 0.001). The normals' ratio decreased by 0.3% per year from 0.77 +/- 0.05 to 0.75 +/- 0.10 (p = 0.33). The ratios in the IP group progressed significantly faster than the controls (p = 0.036). The rate of decline in IP represents 7.8% per decade, expressed as a fraction of the normals' initial mean value at 54 years of age. These results also permit power analysis for the design of future studies assessing the effect of treatment on the underlying pathology in IP.

- 18F-FDOPA-PET cannot differentiate between IPA and APD
Fluorodopa $^{18}$PET

In Parkinson patients there is preferential reduction in uptake in the region of posterior putamen early in the disease

A: Healthy control
B: PD patient with decreased FDOPA uptake in the posterior putamen

MRI

• Conventional MRI (T₁WI, T₂WI and PD)
• Advanced MR imaging:
  1. Susceptibility weighted imaging (SWI)
  2. MR volumetry
  3. Diffusion weighted imaging (DWI)
  4. Diffusion tensor imaging (DTI)
  5. MR spectroscopy (MRS)
Conventional mri

• Routine T1WI, T2WI and proton density imaging
• For most part it is going to be normal in early PD
• Role is to exclude other causes like vascular lesions, MS, tumor, NPH, striopallidodental calcinosis or NBIA
• Late in the disease process (PD) there may be smudgy appearance of SNC from lateral to medial
• Sometimes may help identify features pointing to specific type of APD
• Presence of at-least two abnormalities on conventional MRI has a reasonable sensitivity of 78% and specificity of 76% to identify patients with APD
Conventional MRI

Structural changes of the substantia nigra in Parkinson's disease as revealed by MR imaging.

Hutcheson M, Raff U.

Imaging degeneration of the substantia nigra in Parkinson disease with inversion-recovery MR imaging.

Minati L, Grisoli M, Carella F, De Simone T, Bruzzone MG, Savoiardo M

Abstract

BACKGROUND AND PURPOSE: Visualizing with MR imaging and obtaining quantitative indexes of degeneration of the substantia nigra in Parkinson disease have been long-sought goals. We investigated the potential role of area and T1 contrast measurements in differentiating patients from controls and their age-related changes.

METHODS: Eight patients with Parkinson disease, 8 age-matched controls, and 8 young controls were imaged. We obtained the pixel-wise difference between 2 sets of inversion-recovery images, acquired parallel to the biocommissural plane, with different inversion times. Pixel-intensity ratios between lateral and medial nigral regions, and nigral area and substantia-nigra/midbrain area ratios were computed.

RESULTS: Compared with that of controls, loss of substantia nigra was evident in patients, its borders taking a smoother and more irregular appearance. Patients were characterized by a lateral-to-medial gradient, due to reduced hypointensity of the lateral portion of the substantia nigra and relative sparing of its medial portion. The visible nigral area was significantly smaller in patients compared with matched controls (P = .04). The substantia nigra/midbrain area ratio enabled considerably better separation (P = .001). The lateral/medial pixel-intensity ratio was significantly higher in patients compared with matched controls (P = .01) and in young controls compared with age-matched controls (P = .01).

CONCLUSION: Inversion-recovery sequences may provide a convenient way to visualize nigral degeneration. Relative area and pixel-intensity measurements may integrate other techniques (such as diffusion-tensor imaging on nigrostriatal pathways) in the neuroradiologic diagnosis and follow-up of Parkinson disease by quantitatively assessing the degeneration of the substantia nigra.
Upper row displays an example of axial WMS and GMS MR acquisition images of the mesencephalon in a control participant.

Conventional MRI

MSA-P

- Hypointensity of the dorsal putamen
- Hyperintense putaminal rim
- Pontine atrophy
- “Hot-cross bun” sign
- Cerebellar atrophy
- Hyperintensity in the middle cerebellar peduncle (MCP sign)
Brain magnetic resonance imaging techniques in the diagnosis of parkinsonian syndromes.

Segpi K', Poewe W.'
12/47 MSA-C and 2/21 MSA-P patients had clear ‘cross sign’ [grade 3]
Conventional MRI

PSP

- Midbrain atrophy (penguin silhouette or humming bird sign), reduced AP diameter of midbrain or decreased midbrain to pons ratio
- Atrophy of inferior olives
- Superior cerebellar peduncle atrophy and increased T2 signal
SCP atrophy has a sensitivity of 74% and a specificity of 94% in identifying PSP cases.
Scheme for measurement of the area of the midbrain and pons on mid-sagittal MRI. On the workstation, mid-sagittal MR images were magnified fourfold. Two straight lines were drawn. The first line was drawn to pass through the superior pontine notch and inferior edge of the quadrigeminal plate. The second line was drawn parallel to the first line so as to pass through the inferior pontine notch. The area of the midbrain (illustrated by boxes in A) was traced around the edges of line 1 and the delta-shaped midbrain tegmentum above it. The area of the pons (illustrated by boxes in B) was the area inside the line traced along the anterior and posterior margins of the pons and along lines 1 and 2.

- **Midbrain tegmentum area** cut off at 70 mm² the sensitivity was 100% and specificity 91.3%
- **Midbrain/pons ratio** cut off at 0.15, the diagnostic sensitivity and specificity were 100%
New radiographic sign for the diagnosis of progressive supranuclear palsy (PSP). Midsagittal MR image of a patient with Parkinson disease (PD) does not show any apparent abnormality (A), while that of a patient with PSP shows marked atrophy of midbrain tegmentum (B), and a patient with multiple-system atrophy of the Parkinson type (MSA-P) shows marked atrophy of pons (C). The midbrain to pons ratio is always small in the patients with PSP. In patients with PSP, the shapes of midbrain tegmentum (bird's head) and pons (bird's body) on midsagittal MR images look like a lateral view of a standing penguin (especially the king penguin) with a small head and big body. Recognition of this penguin silhouette sign should strongly raise suspicion for the diagnosis of PSP.
CBD

- Not many studies available
- Cortical atrophy predominantly in the frontal and parietal lobes
- Mild increased T2 signal along the cortex an subcortical white matter
Susceptibility-weighted imaging improves the diagnostic accuracy of 3T brain MRI in the work-up of parkinsonism.

Meijer F1, van Rijn A2, Fasen BA3, Jutte UA1, Aerts IA2, Esselinck R2, Bloem BR2, Vemeer MM4, Gorga R5

Abstract

BACKGROUND AND PURPOSE: The differentiation between Parkinson disease and atypical parkinsonian syndromes can be challenging in clinical practice, especially in early disease stages. Brain MR imaging can help to increase certainty about the diagnosis. Our goal was to evaluate the added value of SWI in relation to conventional 3T brain MR imaging for the diagnostic work-up of early-stage parkinsonism.

MATERIALS AND METHODS: This was a prospective observational cohort study of 65 patients presenting with parkinsonism but with an uncertain initial clinical diagnosis. At baseline, 3T brain MR imaging with conventional and SWI sequences was performed. After clinical follow-up, probable diagnoses could be made in 55 patients, 38 patients diagnosed with Parkinson disease and 18 patients diagnosed with atypical parkinsonian syndromes, including 12 patients diagnosed with multiple system atrophy-parkinsonian form. In addition, 13 healthy controls were evaluated with SWI. Abnormal findings on conventional brain MR imaging were grouped into disease-specific scores. SWI was analyzed by a region-of-interest method of different brain structures. One-way ANOVA was performed to analyze group differences. Receiver operating characteristic analyses were performed to evaluate the diagnostic accuracy of conventional brain MR imaging separately and combined with SWI.

RESULTS: Disease-specific scores of conventional brain MR imaging had a high specificity for atypical parkinsonian syndromes (80%-90%), but sensitivity was limited (50%-80%). The mean SWI signal intensity of the putamen was significantly lower for multiple system atrophy-parkinsonian form than for Parkinson disease and controls (P < 0.01). The presence of severe dorsal putaminal hypointensity improved the accuracy of brain MR imaging. The area under the curve was increased from 0.75 to 0.85 for identifying multiple system atrophy-parkinsonian form, and it was increased from 0.76 to 0.82 for identifying atypical parkinsonian syndromes as a group.

CONCLUSIONS: SWI improves the diagnostic accuracy of 3T brain MR imaging in the work-up of parkinsonism by identifying severe putaminal hypointensity as a sign indicative of multiple system atrophy-parkinsonian form.
A–D, SWI with a circular region of interest in the left dorsal putamen.
Dorsolateral nigral hyperintensity on 3.0 T susceptibility-weighted imaging in neurodegenerative Parkinsonism.

Reiter F1, Mueller C1, Pinter B1, Krismer F1, Scherll T1,2, Esterhammer B3,2, Kremser C3,2, Schacke M3,2, Wenning GK1, Poewe W1,2, Seppi K1,2.

Abstract

BACKGROUND: Absence of a hyperintense, ovoid area within the dorsolateral border of the otherwise hypointense pars compacta of the substantia nigra (referred to as dorsolateral nigral hyperintensity) on iron-sensitive high-field magnetic resonance imaging sequences seems to be a typical finding for patients with Parkinson’s disease (PD).

OBJECTIVE: This study was undertaken to evaluate the diagnostic value of the dorsolateral nigral hyperintensity in a cohort of patients with neurodegenerative parkinsonism including PD, multiple system atrophy (MSA), and progressive supranuclear palsy (PSP) as well as healthy controls using high-field susceptibility-weighted imaging (SWI) at 3.0 Tesla (T).

METHODS: Absence of dorsolateral nigral hyperintensity was assessed on visual inspection of anonymized 3.0 T SWI scans in a case-control study including 148 patients with neurodegenerative parkinsonism (PD: n = 104, MSA: n = 22, PSP: n = 22) and 42 healthy controls.

RESULTS: Dorsolateral nigral hyperintensity was absent unilaterally in all patients with MSA or PSP in 83 of 90 patients with PD, but only in one of the healthy controls resulting in an overall correct classification of 95.2% in discriminating neurodegenerative parkinsonism from controls in the per-protocol analysis. Overall correct classification was 93.2% in the intent-to-diagnose analysis, including also SWI scans with poor quality (12.1% of all scans) for nigral evaluation.

CONCLUSION: Visual assessment of dorsolateral nigral hyperintensity on high-field SWI scans may serve as a new simple diagnostic imaging marker for neurodegenerative parkinsonian disorders. © 2015 International Parkinson and Movement Disorder Society.

© 2015 International Parkinson and Movement Disorder Society.
Dorsolateral nigral hyperintensity on 3.0T susceptibility-weighted imaging in neurodegenerative Parkinsonism

Healthy controls
Dorsolateral nigral hyperintensity on 3.0T susceptibility-weighted imaging in neurodegenerative Parkinsonism

Looks like volume averaging??
MRI volumetry

- **MSA-P**: Predominant atrophy involving pons with PSP and others (PD and MSA-P)

  Sensitivity and specificity were 100%
Diffusion weighted and diffusion tensor imaging

• Diffusivity in midbrain SN not very helpful in differentiating PD from healthy controls
• Decreased FA in SN can help distinguish PD from healthy controls
• Decreased FA values can be seen in frontal lobes in PD patients
• Increased putaminal diffusivity (ADC value) can help differentiate MSA-P from PD in early stage of the disease
• Increased putaminal diffusivity failed to differentiate MSA-P from PSP
Proton MRS

• Decreased NAA/Cr and NAA/Cho ratios in putamen and at the pontine base on a 3 T MRI scanner, can help differentiate MSA-C/MSA-P from PD and healthy controls.
question

- What is diagnostic accuracy of clinical criteria in the diagnosis of PD ~75%
- Potential role of DAT SPECT

Early diagnosis of parkinsonism due to nigro-striatal cell loss and hence differentiating it from mimics

Potential role of 18F-FDOPA PET

Assess IPD progression

- Role of MRI

To differentiate IPD from APD

- may help differentiate parkinsonism from mimics

- Appropriate imaging as per the ACR-AC for

  - PD with typical features and levodopa responsive: MRI head without contrast (7)
  - PD with atypical features and levodopa resistant: MRI head without contrast (8)
Thank you for your attention
Dopaminergic Receptor Studies for Parkinson Syndromes

Yuyang Zhang
NM UW
9/2/2010
Definition:

- A neurological syndrome characterized by tremor, hypokinesia, rigidity and postural instability
The neurodegenerative condition parkinson’s disease (PD) is the most common cause of parkinsonism. A wide-range of other etiologies can lead to a similar symptoms. Like:

- AIDS
- Corticobasal degeneration
- Diffuse lewy body disease
- Medication, such as antipsychotics, metoclopramide, MPTP
- Encephalitis lethargical
- Multiple system atrophy
- Pantothenate kinase-associated neurodegeneration
- Progressive supranuclear palsy
- Toxicity, such as CO, carbon disulfide, manganese, paraquat, mercury, hexane, ---totenone and toluene
- Vascular parkinsonism
- Wilson’s
- Pareneoplastic syndrome
- Genetic
cell death in the substantia nigra result in the greatly reduced activity of pigmented dopamine-secreting cells in the substantia nigra (black substance). These neurons project to the striatum and their loss leads to alterations in the activity of the neural circuits within the basal ganglia that regulate movement. In essence, GABA/ Substance P of the direct pathways diminish, leading to less inhibition of the pars reticulata and an inhibition of the indirect pathway by way of GABA.
Dilemma of Diagnosis:

• Typically, the diagnosis is based on medical history and neurological examination. The physician interviews and observes the patient in the search of the cardinal motor symptoms of the disease, while also attending to other symptoms that would exclude the diagnosis of PD. Response to levodopa is another sign pointing towards PD. However, there is no definitive test for diagnosis although finding Lewy bodies during autopsy has been traditionally considered the gold standard for diagnosis.

• CT and MRI brain scans of people with PD usually appear normal, but useful for diagnosis to rule out other diseases which can be secondary causes of parkinsonism such as basal ganglia tumors, vascular pathology and hydrocephalus.
PD vs benign process like essential tremor vs neurodegenerative diseases

Need to differentiate
Presynaptic radiotracers for PD studies:

1. Dopamine transporter (DAT): Most common ones are TRODAT-1, FP-CIT, beta-CIT for SPECT and beta-CFT, FE-CIT for PET
   ↑(+): underlying degenerative mechanism; (-): o degenerative PD
   ↓: no info. On postsynaptic level of the nigro-striatal circuitry
   **: studies with DAT tracers discriminate PD patients from healthy subjects with high sensitivity and specificity.

** A DAT called DATscan has been approved by FDA recently.

2. Vesicular monoamine transporters (VMAT): DTBZ for PET
3. Dopa-decarboxylase (DDC): F18-dopa to estimate dopamine synthesis
DATscan: 1. for use with SPECT imaging; 2. contains I-123 labeled ioflupane.
Images DaT in the striatum of the brain.
Approved in Europe since 2000 and other 31 countries.
Estimated exposure of 216,000 patients as of June, 2009.
Rationale of D2 receptor binding tracer research

• **Presynaptic tracers** is a reliable criterion to distinguish PD from healthy subjects or essential tremor or other forms not characterized by loss of presynaptic DA cells.

• For therapeutic and prognostic reasons it is necessary to differentiate between PD and atypical PD due to other neurodegenerative diseases. Post-mortem shows 20% of clinical dx PD have atypical syndrome.

• Presynaptic tracer can not differentiate PD and atypical PD syndrome.

• Patients with PD show a normal or upregulated postsynaptic D2 receptor, whereas patients with atypical PD show reduced binding indicating decreased receptor density.
<table>
<thead>
<tr>
<th>Imaging techniques</th>
<th>Radiotracers</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET</td>
<td>D1 receptor probes</td>
</tr>
<tr>
<td></td>
<td>$[^{11}C]\cdot R(\cdot)+8\cdot-chloro\cdot2,3,4,5\cdot-tetrahydro\cdot3\cdot-methyl\cdot5\cdot-phenyl\cdot1H\cdot3\cdot-benzazepine\cdot7\cdot-ol\ (^{11}C\cdot\text{SCH-23390})$</td>
</tr>
<tr>
<td></td>
<td>$[^{11}C]\cdot(\cdot)+8\cdot-chloro\cdot5\cdot(7\cdot-benzofuranyl)\cdot7\cdot-hydroxy\cdot3\cdot-methyl\cdot2,3,4,5\cdot-tetra-hydro\cdot1H\cdot3\cdot-benzazepine\ (^{11}C\cdot\text{NNC-112})$</td>
</tr>
<tr>
<td></td>
<td>D2/3 receptor probes</td>
</tr>
<tr>
<td></td>
<td>$[^{11}C]\cdot\text{raclopride}$</td>
</tr>
<tr>
<td></td>
<td>$[^{18}F]\cdot\text{fallypride}$</td>
</tr>
<tr>
<td></td>
<td>$[^{18}F]\cdot\text{desmethoxyfallypride}$</td>
</tr>
<tr>
<td></td>
<td>$[^{11}C]\cdot\text{N-methylspiperone}$</td>
</tr>
<tr>
<td></td>
<td>$[^{18}F]\cdot\text{benperidol}$</td>
</tr>
<tr>
<td></td>
<td>$[^{11}C]\cdot\text{FLB-457}$</td>
</tr>
<tr>
<td></td>
<td>$[^{11}C]\cdot\text{norphyrilnorphine (NPA)}$</td>
</tr>
<tr>
<td></td>
<td>$[^{11}C]\cdot(\cdot)+propyl\cdot9\cdot-hydroxynaphthoxazine (PHNO)$</td>
</tr>
<tr>
<td></td>
<td>$[^{11}C]\cdot\text{epidepride}$</td>
</tr>
<tr>
<td>SPECT</td>
<td>D2/3 receptor probes</td>
</tr>
<tr>
<td></td>
<td>$[^{123}I]\cdot\text{IBZM}$</td>
</tr>
<tr>
<td></td>
<td>$[^{123}I]\cdot\text{epidepride}$</td>
</tr>
</tbody>
</table>

Nandhagopal, R. et al. Neurology 2008;70:1478-1488
4. D2 dopamine receptors: on clinical research IBZM for SPECT and raclopride for PET

postsynaptic, dopaminergic involvement, help with unclear PD (PD vs atypical parkinsonism)

-a class of metabotropic G protein-coupled receptors that are prominent in the vertebrate central nervous system (CNS). The neurotransmitter dopamine is the primary endogenous ligand.

-dopamine receptors are common neurologic drug targets; antipsychotics are often dopamine receptor antagonists while psychostimulants are typically indirect agonists of dopamine receptors.

-Activation of D2-like family receptors is coupled to the G protein Gαi, which directly inhibits the formation of cAMP by inhibiting the enzyme adenylate cyclase.
D2 receptor binding radiotracers

- **Raclopride** is a synthetic compound that acts as an antagonist on D2 dopamine receptors. It can be radiolabelled with the carbon-11 radioisotope and used in positron emission tomography (PET) scanning to assess the degree of dopamine binding to the D2 neuroreceptor.

- **IBZM** (abbreviation for *iodobenzamide*) is a chemical substance. Pharmaceutically it is a dopamine antagonist and it can be used by as a radioactive tracer for SPECT where the radioactive isotope is iodine-123.
<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Integrity Nigrostriatal Pathway</th>
<th>Binding to $D_2$ Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAT SPECT</td>
<td>[$^{123}I$]IBZM SPECT</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>loss</td>
<td>normal/increased</td>
</tr>
<tr>
<td>MSA</td>
<td>loss</td>
<td>reduced</td>
</tr>
<tr>
<td>PSP</td>
<td>loss</td>
<td>reduced</td>
</tr>
<tr>
<td>ES</td>
<td>no loss</td>
<td>normal</td>
</tr>
</tbody>
</table>
Comparison of SPECT IBZM and PET Raclopride

• $^{123}$-IBZM: widespread clinical use; favorable half life (13.2 hr); comparably lower sensitivity and image quality

• $^{11}$-Raclopride: higher sensitivity and image quality; a spatial resolution of 3-5 mm; brief half life (20 min) need local cyclotron; a similar product $^{18}$-DMFP with half life of 110 min may be more favorable
Simultaneous assessment of the pre- and postsynaptic dopaminergic system: IPS

$[^{99m}Tc]{\text{TRODAT-1}}$

rt: 0.72  
lt: 0.48

$[^{123}I]{\text{IBZM}}$

rt: 0.86  
lt: 0.89
What is the next??

- functional imaging can be enormously useful in detecting preclinical disease. Functional imaging studies will continue to provide substantial insights into the mechanisms that underlie both motor and neuropsychiatric complications of advanced disease and of therapy. Studies of natural history and using markers of aberrant cell function may shed light on disease pathogenesis. Perhaps most excitingly, functional imaging studies conducted in patients with PD provide an unparalleled opportunity to assess the multiple roles of dopamine in the brain,. Future advances in molecular imaging, perhaps allowing quantitative in vivo visualization of gene and protein expression, will result in even richer rewards.

- One of the major challenges facing all investigators interested in neurodegenerative diseases is the capacity to assess the effects of disease-modifying therapies, including neuroprotection and cell-based treatments designed to reverse disease. While functional imaging should be an ideal means by which to do this, existing methods have, for reasons that are not fully understood, proved highly unsatisfactory. Development and characterization of novel imaging markers to assess disease progression and the effects of therapeutic interventions is likely to form a major focus of research in the next decade.

- The benefits of imaging studies must be considered in the context of challenges that are both potential and already very real. PET is expensive and studies of dopaminergic function are available at only a minority of centers. Presymptomatic detection of disease, while potentially very useful in a research setting, is fraught with considerations of how one will use the resulting information, particularly as there is currently no established therapy to prevent the emergence or progression of disease.
Thank you!
Parkinson’s Disease
Parkinson’s Disease (PD)

- PD is a neurodegenerative disorder
- Characteristic findings: resting tremor, rigidity, slowed movement, decreased dexterity, small handwriting, flexed posture, gait disorder, imbalance, dementia.
- Mean age of onset 57 years
- Affects 1-2% of population over age 60
- Highly varied collection of symptoms and pace of progression
Pathogenesis of PD

• 11 genetic forms identified (LRRK2)
• 10-15% affected have suggestive family history
• Unknown cause for sporadic cases (oxidative stress, Nrf2)
PD is neurodegenerative

- Motor impairments arise from loss of dopaminergic neurons arising from substantia nigra
- Nerve loss of ~50% required for symptoms

Treatments

1. Levodopa
2. Dopaminergic agents (ropinirole, pramipexole)
3. Inhibitors of peripheral metabolism (by AAAD, COMT)
4. Inhibitors of CNS metabolism (by MAO-B)
Clinical Use of Levodopa

1. Diagnostic tool
2. Almost always combined with carbidopa
3. Does not always help all symptoms
4. Can have blunted response over time
   (use alternative monotherapy or use as polytherapy)
5. Significant side effects (dyskinesias)
Clinical Evidence for Levodopa

• Earlier versus Later Levodopa Therapy in Parkinson Disease (ELLDOPA NEJM 2004)
• Concern about levodopa hastening neurodegeneration despite symptomatic control.
• Randomized 361 patients with early PD to placebo or one of three doses of levodopa (with carbidopa)
ELLDOPA
ELLDOPA Conclusions

1. Levodopa improves signs and symptoms in dose-dependent manner
2. Levodopa does not hasten progression of underlying disease
3. As part of study, subjects underwent B-CIT SPECT at baseline and week 40:
   slower decline in striatal uptake in placebo group compared with 3 treatment groups
Results

Change in dopaminergic binding from 0 to 40 weeks on B-CIT SPECT imaging:

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Levodopa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>150mg/d</td>
</tr>
<tr>
<td>Change (%)</td>
<td>-1.4</td>
<td>-6.0</td>
</tr>
</tbody>
</table>

- Does levodopa accelerate the loss of nigrostriatal dopamine nerve terminals?
- Does levodopa modify binding of β-CIT or down-regulate DAT?
- Does falling dopamine in placebo group lead to compensatory increase in DAT (hence increased β-CIT binding)?
Disparity between clinical outcomes and radiotracer imaging in PD

• ELLDOPA: levodopa controls symptoms and does not promote neurodegeneration, but B-CIT imaging shows less loss in binding with placebo groups.

• Two smaller studies comparing
  (1) Whone AL, et al. REAL-PET. Ann Neurol 2003
    levodopa vs. ropinirole
  (2) Parkinson Study Group. CALM-PD. JAMA 2002
    levodopa vs. pramipexole
Surrogate endpoints

• Clinical endpoint (CE) – how a patient feels, functions, or survives
  Unified Parkinson’s Disease Rating Scale (UPDRS)
• Surrogate endpoint (SE) – a biomarker substitute for a CE cholesterol (death from heart disease)
  PSA (survival in prostate cancer)
  ? Radiotracer imaging in PD
Surrogate endpoint failures

Advantage of SE’s: save time and money, shorten clinical trial
Disadvantage of SE’s – one example
- CE= cardiacvascular mortality in post-MI patients
- SE = Ventricular arrhythmias
- Encainide and flecainide approved on basis of reducing SE
- Subsequently shown to increase mortality (CAST Trial. NEJM. 1992).

Multiple trials needed to establish relationship between a SE and a CE.
Dopaminergic nerve terminal
Targets of radiotracers in PD imaging

- **18F-dopa**
- **11C-DTBZ**
- **123I-B-CIT**
- **123I-IBZM**

Diagram showing the targets and mechanisms of action of the radiotracers: L-dopa, dopamine, AAAD, MAO, VMAT2, DAT, D1-D5, FDG-PET.
Uses of radiotracers imaging in PD

1. Exploring the biologic process (upregulation of D2 receptor)
2. Study diagnosis and prognosis (PD versus ET)
3. Therapy development and evaluation (early, late)
4. Primary outcome in clinical trials
5. Assisting in choosing and monitoring response to therapy
DAT imaging in PD

Radiotracers:

123I beta-CIT tropane (B-CIT)
123I FP-CIT ioflupane (DATSCAN)  
Approved 1/20/11
99mTc-TRODAT-1 altropane (TRODAT)
18F FP-CIT

Findings:

1. Markedly reduced DAT density
2. Putamen > caudate
3. Asymmetric
4. Correlates with clinical severity
123I-β-CIT SPECT in PD progression over 3-year period

Dopaminergic decline:
PD: ~10%/year
HC: ~0.1%/year

Marek K et al. Neurology 2001;57:2089-2094
Tc-99m-TRODAT-1 SPECT reflects symptom severity/side.
I-123-B-CIT SPECT in Hemiparkinsonism


Seibyl J. Institute for Neurodegenerative Disorders.
123I-B-CIT SPECT in may distinguish PD versus MSA subtypes via symmetry index

Varrone A. Movement Disorders, 16: 1023–1032
FP-CIT SPECT in PD versus AD and DLB

FP-CIT in PD vs Essential Tremor

ET

PD

Tc-99m TRODAT SPECT in PD plus anxiety/depression
$^{18}$F]fluorodopa (F-dopa) PET and (+)-$^{11}$C]dihydrotetrabenazine (DTBZ) PET

- Generally same findings as DAT imaging
VMAT2 imaging confirms olfactory deficit mechanism

- Previously: PD odor dysfunction correlated with hippocampal dopamine loss
- Observed: Hyposmia in AD is related to hippocampal cholinergic loss
- Hypothesis: olfactory dysfunction in PD related to hippocampal cholinergic loss.
- PD diagnosis confirmed by VMAT2 PET (¹¹C-DTBZ).
- AchE imaging with ¹¹C-PMP (methyl-4-piperidinyl propionate) PET
- Dynamic imaging with kinetics models

Robust correlation between hippocampal cholinergic activity and odor identification scores in non-demented PD patients.

Bohnen NI. Brain. 2010 Jun;133(Pt 6):1747-54
[¹⁸F]fluorodeoxyglucose (FDG) PET

Disease-related pattern in PD:
**hypermetabolism:** pallidothalmalic, pontocerebellar
**hypometabolism:** lateral premotor cortex, supplementary motor area, parietooccipital association region
Red = increased metabolism
Blue = decreased metabolism
FDG-PET and PD vs MSA and PSP

- Disease-related pattern of FDG uptake in idiopathic PD, MSA, and PSP
- Developed automated classification procedure
- Diagnosed 3 diseases with Sn 84-88%, Sp 94-97%, PPV 91-98%, NPV 82-92%
Can radiotracer imaging serve as surrogate endpoint in PD?

- ELLDOPA: levodopa controls symptoms and does not promote neurodegeneration, but B-CIT imaging shows less loss in binding with placebo groups.
- Two smaller studies comparing
     levodopa vs. ropinirole
  2. Parkinson Study Group. CALM-PD. JAMA 2002
     levodopa vs. pramipexole
CALM-PD

A. Striatal β-CIT Uptake

B. Putamen β-CIT Uptake

C. Caudate β-CIT Uptake

Mean Change From Baseline, %

Scan Time, mo

No. of Patients

Pramipexole

Levodopa

39
39
39
35
36
36
33
33
33
32
32
32
<table>
<thead>
<tr>
<th></th>
<th>REAL-PET (Levodopa vs Ropinirole)</th>
<th>CALM-PD (Levodopa vs Pramipexole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear imaging</td>
<td>18F-DOPA PET (all)</td>
<td>123I-B-CIT SPECT (subset)</td>
</tr>
<tr>
<td>Group with better UPDRS scores</td>
<td>Levodopa</td>
<td>Levodopa</td>
</tr>
<tr>
<td>Group with fewer motor complications</td>
<td>Ropinirole</td>
<td>Pramipexole</td>
</tr>
<tr>
<td>Nuclear Imaging findings</td>
<td>1/3 less decline in uptake in Ropinirole group (at 24 months)</td>
<td>1/3 less decline in uptake in Pramipexole group (at 48 months, but not at 24 months)</td>
</tr>
<tr>
<td>Drug</td>
<td>n</td>
<td>Duration</td>
</tr>
<tr>
<td>----------------------</td>
<td>----</td>
<td>----------</td>
</tr>
<tr>
<td>L-dopa 750 mg/d</td>
<td>8</td>
<td>4–6 wk</td>
</tr>
<tr>
<td>Selegiline 10 mg/d</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Pramipexole 1.5–4.5 mg/d</td>
<td>7</td>
<td>10 wk</td>
</tr>
<tr>
<td>L-dopa 300–600 mg/d</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>L-dopa 200–400 mg/d</td>
<td>7</td>
<td>2–3 mo</td>
</tr>
<tr>
<td>Pergolide 2.75 mg</td>
<td>12</td>
<td>4–6 wk</td>
</tr>
<tr>
<td>L-dopa 300 mg/d</td>
<td>10</td>
<td>6 wk</td>
</tr>
<tr>
<td>Pramipexole 1.5 mg</td>
<td>10</td>
<td></td>
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<tr>
<td>Placebo</td>
<td>10</td>
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</tbody>
</table>

DAT = dopamine transporter; RTI = radiotracer imaging.
Summary

- Each of these neuroimaging techniques (except FDG-PET) measures one or more functions of dopaminergic neurons.
- They do not directly assess the # of dopaminergic neurons.
- Helpful in diagnosis, studying biology of disease, drug development.
- There are non-dopaminergic processes in PD (such as olfactory dysfunction) which will not be captured by dopamine-related tracers.
References

(22) Varonne A, et al. (123I)beta-CIT SPECT imaging demonstrates reduced density of striatal dopamine transporters in Parkinson’s disease and multiple system atrophy. Mov Disord 2001 Nov;16(6):1023-1032.