Historical Perspective and Future Trends of Brain Imaging

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Disclosure: Dr. Seibyl has equity interest in Molecular NeuroImaging, LLC

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Overview

1. Understand current clinical indications and application of brain imaging

2. Know basic differences between brain blood and metabolism tracers and receptor tracers

3. Describe potential future directions and clinical applications of brain receptor agents
Brain Imaging 2004: Where are we now?

• Limited types of radiopharmaceuticals largely brain metabolism and blood flow assessment
• Fairly wide range of applications, but not widely used in many nuclear medicine clinics
• Generally visual, qualitative interpretation of images
# Properties of radiotracers commonly used in brain imaging

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Modality</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>99mTc-HM-PAO</td>
<td>SPECT</td>
<td>Blood flow</td>
</tr>
<tr>
<td>99mTc-ECD</td>
<td>SPECT</td>
<td>Blood flow</td>
</tr>
<tr>
<td>18F-FDG</td>
<td>PET</td>
<td>Glucose metabolism</td>
</tr>
<tr>
<td>201 Thallium</td>
<td>SPECT</td>
<td>Tumors</td>
</tr>
<tr>
<td>123-I Iodoamphetamine (Japan)</td>
<td>SPECT</td>
<td>Blood flow</td>
</tr>
<tr>
<td>99m-DTPA</td>
<td>planar</td>
<td>Blood flow</td>
</tr>
<tr>
<td>123-I FP-CIT (Europe)</td>
<td>SPECT</td>
<td>Dopamine transporters</td>
</tr>
<tr>
<td>123-I Iomazenil (Japan)</td>
<td>SPECT</td>
<td>Benzodiazepine receptors</td>
</tr>
</tbody>
</table>
## Clinical application of radiotracers commonly used in brain scintigraphy

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Clinical Use</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>99mTc-HM-PAO</td>
<td>Cerebrovascular dz, dementia, epilepsy, brain death</td>
<td>Can also be used to label WBC's</td>
</tr>
<tr>
<td>99mTc-ECD</td>
<td>Cerebrovascular dz, dementia, epilepsy, brain death</td>
<td>Better signal:noise than HMPAO</td>
</tr>
<tr>
<td>18F-FDG</td>
<td>Epilepsy, dementia, CNS tumor recurrence</td>
<td>Can't be used for ictal studies</td>
</tr>
<tr>
<td>201 Thallium</td>
<td>CNS tumors, e.g. CNS lymphoma vs infection</td>
<td></td>
</tr>
<tr>
<td>123-I Iodoamphetamine</td>
<td>Cerebrovascular dz, dementia, epilepsy, brain death</td>
<td>Difficult to use due to washout,redistribution</td>
</tr>
<tr>
<td>99m-DTPA</td>
<td>Brain death</td>
<td>Inexpensive</td>
</tr>
</tbody>
</table>
Brain Death
Normal brain SPECT perfusion study in 65 year old female
New aphasia, prior left aneurysm repair
Alzheimer’s Dementia - moderate severity
Multi-infarct dementia transaxial slices
18-F FDG PET in Dementia, Alzheimer’s type

Serial imaging over 4 years
Identification of an astrocytoma and subsequent recurrence
During Total Balloon Occlusion

Baseline
Diamox activation study: transaxial slices

BASELINE

RT

DIAMOX ACTIVATED

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SPECT-Diff and MRI

interictal  ictal  hyperperfusion  hypoperfusion
Targets Sites on Neurons for Molecular Imaging
Normal brain SPECT perfusion study in 65 year old fem
123-I Iomazenil SPECT Scan - Binding to the Benzodiazepine ("Valium") Receptor in the Brain
Some Examples Where Brain Imaging has Contributed to Better Understanding and Treatment of Psychiatric Illness

**Schizophrenia**
Better understanding of dopamine neurochemical changes in the brain- more dopamine available for release may contribute to symptoms.

**Depression, Anxiety Disorders, and Schizophrenia**
Improving the development of new treatments- properties and brain target sites of atypical antipsychotics determined in living human brain- guiding dosing, minimizing side effects.
Midbrain SERT displacement by antidepressants in healthy humans

- Citalopram 20 mg BID (n=9)
- CP-607,366 150 mg QD (n=10)
- Venlafaxine XR 150 mg QD (n=8)

% Occupancy

Go/No-Go Criteria

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Parkinson’s disease

- Dr. James Parkinson, a physician, described the disease while observing people walking outside his office in London in 1817.
What is wrong with Parkinson’s patients?

Patients may have the following symptoms:

- Stiffness (rigidity)
- Tremor
- Slowed movements (bradykinesia)
- Disturbed pattern of walking/ trouble standing (postural instability)
- Symptoms slowly get worse over time - the disease progresses
Parkinson’s Disease: A Model Neurodegenerative Disease

• Diagnosis based on clinical evaluation over time and response to medications which augment dopamine function

• Treatments based on the loss of dopamine neurons in brain

• Factors responsible for the initiation and maintenance of on-going dopamine cell loss are poorly understood
Imaging in the brain: Molecular targets of radioligands.⁷

- DOPA → dopamine
- Neuronal dopamine metabolism (fluorodopa)
- Dopamine transporter (β-CIT, others)

Adapted from Science 2000; 289: 409-411.
Radiopharmaceuticals used for imaging PD

<table>
<thead>
<tr>
<th>Presynaptic Target</th>
<th>DA transporter</th>
<th>Vesicular transporter</th>
<th>DA turnover</th>
</tr>
</thead>
<tbody>
<tr>
<td>123-I FP-CIT</td>
<td>11-C VMAT2</td>
<td>18F-DOPA</td>
<td></td>
</tr>
<tr>
<td>123-I β-CIT</td>
<td>123-I Altropane</td>
<td></td>
<td></td>
</tr>
<tr>
<td>123-I Altropane</td>
<td>99mTc TRODAT</td>
<td></td>
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<tr>
<td>99mTc TRODAT</td>
<td>18F CFT</td>
<td></td>
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</tr>
<tr>
<td>18F CFT</td>
<td>123-I IPT</td>
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</table>
Dopamine Transporter Imaging

Normal Scan

Parkinson Patient Scan
Clinical Case 1

• 63 year old male with right-hand incoordination

• Twelve months after onset of symptoms, diagnosis of PD, trial of l-dopa/carbidopa

• Serial evaluation over 4 years demonstrated progressive symptoms with involvement of left side
Case Study #1

Healthy subject

PD patient – Hoehn-Yahr
Stage 1
Parkinson’s Disease Progression

Scan 1  Scan 2

PD Patient imaged 36 months apart
Serial SPECT in a PD Subject

Striatal uptake ratio

Months
Teaching Points

• DAT SPECT is sensitive to changes occurring in PD even before symptoms are manifest- diagnostic indication

• Progression is insidious and difficult to evaluate due to medication effects, SPECT may be helpful- monitoring indication
Clinical Case 2

- 39 year old female, 11 years earlier had a left thalamic and anterior midbrain AVM treated with proton beam radiation and subsequent gamma knife irradiation to the left midbrain for recurrent hemorrhage.

- Presents with a one year history of hemiparkinson symptoms including right upper and lower extremity bradykinesia and gait disturbance.
Healthy control  AVM and bradykinesia  Hoehn-Yahr Stage 2 Parkinson’s disease
Teaching Points

• Profound asymmetric alterations of DA nigral function may produce mild symptoms, but not immediately- perhaps there is a threshold effect for symptom expression.

• This is not a simple threshold however, as aging healthy subjects demonstrate alterations in lower DAT density than younger PD patients.
Requirements of the radiopharmaceuticals for different applications in PD imaging

**Diagnosis**
- Good target:background
- Qualitative assessments adequate

**Monitor disease progression**
- Need valid signal quantitation
- Good reproducibility of imaging measure

**Evaluate potential neuroprotective/neurorestorative treatment**
- Need valid signal quantitation
- Robust reproducibility of imaging measure
Longitudinal DAT Imaging in PD
Dopamine Transporter Brain Imaging to Assess the Effects of Pramipexole vs Levodopa on Parkinson Disease Progression

Parkinson Study Group

**Context**

Parkinson disease (PD) is a slow but relentlessly progressive neurodegenerative disorder characterized clinically by bradykinesia, tremor, rigidity, and gait dysfunction. The clinical decline reflects ongoing nigrostriatal dopaminergic degeneration. Dopaminergic replacement therapy with the precursor levodopa or agonists that stimulate the dopamine receptor is effective in ameliorating many symptoms and signs of early PD. However, progressive neurodegeneration ultimately results in severe motor, mental, and functional disability.

Increasing evidence from laboratory and animal studies suggests that in addition to their symptomatic effects, levodopa and dopamine receptor agonists may either accelerate or slow the dopaminergic degeneration of PD. Recent data regarding the effects of levodopa have been controversial with in vitro data supporting both a potential toxic and protective effect on dopaminergic neurons. Studies have demonstrated that dopamine receptor agonists protect cultured dopaminergic neurons from potential levodopa toxicity and may exert direct antioxidant and receptor-mediated antitoxic effects. The putative neuroprotective actions of levodopa or dopamine receptor agonists have provided the rationale for assessing the progression of dopamine neuronal degeneration in patients with PD after treatment with these drugs.

**Objective**

To compare rates of dopamine neuron degeneration after initial treatment with pramipexole or levodopa in early PD by means of dopamine transporter imaging using single-photon emission computed tomography (SPECT) with (123)iodoamphetamine (I-123) iodoamphetamine (I-123)/benzamide (I-123/IBZM) or (6-OHDA) iodoamphetamine (I-123)/benzamide (I-123/IBZM) labeled with iodine 123.

**Setting and Patients**

Eighty-two patients with early PD who were recruited at 17 clinical sites in the United States and Canada and required dopaminergic therapy to treat emerging disability, enrolled between November 1996 and August 1997.

**Interventions**

Patients were randomly assigned to receive pramipexole, 0.5 mg 3 times per day with levodopa placebo (n=42), or carbidopa/levodopa, 25/100 mg 3 times per day with pramipexole placebo (n=40). For patients with residual disability, the dosage was escalated during the first 10 weeks, and subsequently, open-label levodopa could be added. After 12 months of follow-up, the dosage of study drug could be further modified.

**Main Outcome Measures**

The primary outcome variable was the percentage change from baseline in striatal [123]I/IBZM-SPECT uptake after 12 months. The percentage changes and absolute changes in striatal putamen, caudate, and thalamus [123]I/IBZM-SPECT uptake after 12 and 24 months were also assessed. Clinical severity of PD was assessed using the Unified Parkinson Disease Rating Scale (UPDRS) 12 hours after anti-PD medications.

**Results**

SPECT imaging showed a decline in mean (SD) [123]I/IBZM-SPECT uptake from baseline of 10.3% (9.8%) at 22 months, 19.3% (15.3%) at 34 months, and 20.7% (14.4%) at 46 months—approximately 5.2% per year. The mean (SD) percentage loss in striatal [123]I/IBZM-SPECT uptake from baseline was significantly reduced in the pramipexole group compared with the levodopa group: 7.1% (9.0%) vs 13.5% (9.6%) at 22 months (P=.004); 10.9% (11.8%) vs 19.6% (12.4%) at 34 months (P=.009); and 14.0% (13.3%) vs 25.8% (14.1%) at 46 months (P<.001). The percentage loss from baseline in striatal [123]I/IBZM-SPECT uptake was correlated with the change from baseline in UPDRS at the 46-month evaluation (r = -0.40; P = .001).

**Conclusions**

Patients initially treated with pramipexole demonstrated a reduction in loss of striatal [123]I/IBZM-SPECT uptake, a marker of dopamine neuron degeneration, compared with those initially treated with levodopa, during a 46-month period. These imaging data highlight the need to further compare imaging and clinical end points of PD progression in long-term studies.

JAMA 2002;287:1658-1667

**Members of the Parkinson Study Group and Financial Disclosures**

For a list of the members of the Parkinson Study Group and financial disclosures, see the end of this article.

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Percentage Change in Striatal $\beta$-CIT Uptake from Baseline by Treatment
Brain Imaging 2004: Where are we now?

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What is the Future of Brain Imaging?

1. Expanded armamentarium of more specific tracers to expand the diagnostic and disease monitoring roles of nuclear medicine.

2. More sophisticated image processing - with possible development of automated processing algorithms to extract more information from the scans - ? Use of normal databases and voxel-wise quantitative approaches.

3. Imaging is in vivo phenotyping - coupled with genomic revolution may be possible to use imaging to identify those patients best suited to selected treatments.
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3. Describe potential future directions and clinical applications of brain receptor agents
I THINK WE'RE MAKING PROGRESS...

RUNNING AROUND LIKE A
WITH ITS HEAD
CUT OFF.

GOAT PIGEON
FISH MIME
SNAKE CHICKEN
RAT PORCUPINE