Overview of FDG-PET’s Role in Epilepsy Management

Jacob G. Dubroff, MD PhD
Chief Resident, Nuclear Medicine
Hospital of the University of Pennsylvania
Disclosure of Commercial Support

With respect to my presentation I DO NOT have any financial arrangement or affiliation with any corporate organization associated with the manufacture, distribution or promotion of a drug or devise which is related to the topic of my presentation.
Objectives

- Basic knowledge of Epilepsy including its epidemiology, spectrum of presentations, patho-physiology, treatments and clinical outcomes
- Understand the physiological basis for using FDG-PET in Epilepsy Imaging
- Understand the technique and goals of FDG-PET imaging for Epilepsy
Presentation Outline

**Epilepsy**
- Definition
- Epidemiology
- Classification
- Causes
- Diagnosis
- Outcomes

**FDG PET**
- Background
- Technique
- Cases
- MR Fusion
- Quantification
- Future Targets/Radiotracers
Definitions

- **Epilepsy**: chronic neurological condition characterized by recurrent (2 or more) unprovoked* seizures
- **Seizure**: transient symptom of excessive or synchronous neuronal activity in the brain

http://www.epilepsyfoundation.org
Famous Epileptics

Socrates
Julius Caesar
Napoleon Bonaparte
Harriet Tubman
Vladimir Lenin
Sir Walter Scott
Jonathan Swift
Lord Byron
Percy Bysshe Shelley
Fyodor Dostoyevsky
Joan of Arc
Soren Kierkegaard
George Frederick Handel
Neil Young
Lindsey Buckingham
Budd Abott (and Costello)
Florence Griffith Joyner
George Inness
George Gershwin

Ludwig van Beethoven
Isaac Newton
Dante
Peter Tchaikovsky
Niccolo Paganini
Edgar Allan Poe
Lewis Carroll
Alfred Nobel
Truman Capote
Vincent van Gogh
Alexander the Great

http://www.epilepsy.com
Epilepsy Epidemiology

- Approximately 50 million worldwide
- Approximately 3 million in US
- 200,000 diagnosed annually in US

http://www.epilepsyfoundation.org
http://www.who.int
Recent studies in both developed and developing countries have shown that up to 70% of newly diagnosed children and adults with epilepsy can be successfully treated (i.e. their seizures completely controlled) with anti-epileptic drugs. After two to five years of successful treatment, drugs can be withdrawn in about 70% of children and 60% of adults without relapses.
Root Causes of Epilepsy

- Genetic
- Congenital
- Developmental
- Head Trauma
- CNS Infection
Diversity of Epilepsy

Epilepsy Classification

- Etiology
- Semiology (Observable Manifestations)
- CNS Location of Onset
- Medical Syndrome
- Triggering Event
  - Primary reading epilepsy
  - Musicogenic epilepsy
Epilepsy Classification (ILAE)

- Ictal Phenomena
- Seizure Type
- Syndrome
- Etiology
- Impairment

http://www.ilae-epilepsy.org
Seizure Spectrum

- Generalized
  - Absence
  - Atonic
  - Tonic-clonic
  - Myoclonic
- Partial
  - Simple
  - Complex
- Non-epileptic
- Status Epilepticus (Medical Emergency!!)

http://www.epilepsyfoundation.org
Epilepsy Treatments

- Medications (AED’s: Anti Epileptic Drugs)
- Vagal Nerve Stimulator
- Ketogenic Diet
- Complementary Strategies
- Surgery
Epilepsy Treatment Outcome

Goal: Freedom from seizures (Class I)

Engel Class System

- I: Free of disabling seizures
- II: Rare disabling seizures
- III: Worthwhile Improvement
- IV: No worthwhile improvement
Epilepsy Treatment: Medications

Excitation/Inhibition Balance in the CNS

Decrease Excitation

- Dilantin/Phenytoin, Lamictal/Lamotrigine, Trileptal/Oxcarbazepine, Tegretol/Carbamazepine (Na+)
- Keppra/Levetiracetam (SV2A)

Increase Inhibition (GABA-A)

- Benzodiazepines (e.g. Klonopin/Clonazepam), Barbituates (e.g. Phenobarbital), Neurontin/Lyrica
Epilepsy Treatment: Vagal Nerve Stimulator

www.medgear.org
MRI status post Vagal Nerve Stimulator Implantation?
Epilepsy Treatment: Ketogenic Diet

- Metabolic Pseudo-Starvation
- Switch metabolic fuel from glucose to fat
- 80% Caloric Intake from Fat
- Inconsistent Efficacy
- Compliance
- Side Effects
  - Dehydration, Constipation, Renal/Gall Stones, Vitamin Deficiencies, Menstrual Irregularities, Pancreatitis, Osteoporosis, Elevated Cholesterol Levels
The ultimate goal of PET and SPECT epilepsy imaging is to identify and/or confirm the location of a seizure focus which may be invisible (completely or partially) to other diagnostic techniques (EEG, MRI).
Epilepsy Surgery for Pharmacoresistant Temporal Lobe Epilepsy: A Decision Analysis


**Results** Compared with medical management, anterior temporal lobe resection for a 35-year-old patient with an epileptogenic zone identified in the anterior temporal lobe would *increase survival by 5.0 years* (95% CI, 2.1-9.2) with surgery preferred in 100% of the simulations. Anterior temporal lobe resection would *increase quality adjusted life expectancy by 7.5 quality-adjusted life-years* (95%, CI, −0.8 to 17.4) with surgery preferred in 96.5% of the simulations, primarily due to increased years spent without disabling seizures, thereby reducing seizure-related excess mortality and improving quality of life. The results were robust to sensitivity analyses.
SPECT Perfusion Epilepsy Imaging

- Subtraction of Interictal from Ictal States
- Technical Challenges of Ictal Imaging
  - Timely Injection
  - Access to scanner
- Cost
Drug Resistant Epilepsy Testing Battery

- MRI (Anatomy)
- Epilepsy Monitoring Unit (EMU)
  - Continuous EEG, Continuous Video
- Neuropsychological Testing
- Wada Testing
What should been done if a patient seize?

A. Nothing
B. Call 911
C. Prop patient’s mouth open so airway is not compromised
D. Move sharp objects away from patient
E. Put a pillow under patient’s head
F. Flick lights on and off
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FDG-PET

- FDG is metabolized by hexokinase bound to the outer mitochondrial membrane
- **BUT** it is metabolized to 18F-FDG-6-phosphate (18F-FDG-6-P) not 2-Deoxy-D-glucose
- Therefore 18F-FDG-6-phosphate becomes trapped in the mitochondria but continues to emit positrons (then e).
Mitochondria

http://www.mansfield.ohio-state.edu/~sabedon/campbl09_files/image004.gif
Compartments and Glycolysis

http://www.metabolic-database.com/assets/images/glycolysis.jpg
PET Physics

http://depts.washington.edu/nucmed/IRL/pet_intro/intro_src/section2.html
PET Physics (cont)

http://depts.washington.edu/nucmed/IRL/pet_intro/intro_src/section2.html
Pet Physics (cont)

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Preparation

- Limit Strenuous Exercise
- Drink Fluids
- No sugar, caffeine
- High protein, low carbs meals day before
- 4-6 hours fasting
- Remove all metal objects
- Check glucose levels (150 vs. 200)

*Patient sits in a dim, quiet, WARM room without reading or talking, singing or talking.*
FDG-PET Case 1

27 yo, right handed female

PMHx:
- 2 febrile infant seizure
- “typical” seizures began at 14
- 2-5 seizures/month
FDG-PET Case 1:  
Seizure Semiology

The patient and observers report: panic and déjà vu feeling prior to event. She may have mild rocking back and forth, automatisms (manual and lip-smacking), and appears to lose awareness (she presently denies LOC). She may have limbs stiffening and clonic movements. She appears to have difficulty speaking but appears to comprehend some of the time. She has occasional urinary incontinence and tongue biting. The event will last ~1 minute. Sometimes, the episodes are lesser and without generalization.
FDG-PET Case 1: EEG (EMU)

11.5 Hz posterior dominant rhythm; mild intermittent left temporal slowing; rare left temporal spikes of low amplitude with maximal phase reversal at F7/F9; rare focal spike-and-wave complexes (towards the end of the recording) maximal over T3; normal sleep architecture.
FDG-PET Case 1: Neuropsychological Assessment

- FSIQ 83 (13 %ile); Verbal Comprehension Index VCI 81 (10%ile), Perceptual Reasoning Index PRI 90 (25 %ile), Working Memory Index WMI 80 (9 %ile), Processing Speed Index PSI 94 (34 %ile).
- Boston Naming Test 14%ile. Language function is impaired (naming 14%, comprehension 5%, repetition 3%) Memory scores are significantly worse for visual rather than language components (geometric designs 9%, Doors & People Visual 10-25% vs. 90-95% Verbal).
- Official impression is variability in cognitive profile that did not strongly lateralize.
- Conference assessment is language (left hemisphere) is significantly more impaired than perception (right hemisphere). However, memory scores are worse for non-verbal than verbal components.
FDG-PET: Case 1
27 year old woman with febrile history seizure and subsequent 13 year history of medically-intractable complex partial seizures, some with secondary motor generalization. Her syndrome and data are suggestive of left mesial temporal lobe sclerosis and left temporal lobe epilepsy.

1. Obtain Wada.
2. Consider left temporal lobectomy (including mesial and anterior structures) after review of the Wada data.
3. Chance of 1-2 year seizure freedom with a left temporal lobectomy is estimated to be 60-80%.

<table>
<thead>
<tr>
<th>Element</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semiology</td>
<td>Temporal, mild suggestion of left.</td>
</tr>
<tr>
<td>Interictal EEG</td>
<td>Left frontotemporal</td>
</tr>
<tr>
<td>EEG Ictal</td>
<td>Left temporal.</td>
</tr>
<tr>
<td>MRI</td>
<td>Left MTS, left temporal atrophy</td>
</tr>
<tr>
<td>PET</td>
<td>Left anterior temporal lobe</td>
</tr>
<tr>
<td>Neuropsychology</td>
<td>More overall left hemispheric than right dysfunction. However, nonverbal memory is worse than verbal memory.</td>
</tr>
</tbody>
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FDG-PET Case 2

- 21 yo, left-handed female
- PMHx
  - congenital-heart disease-related stroke at 4 years old with hemiparesis and aphasia. Her first seizure in the following year (3/1993) was a generalized tonic-clonic seizure.
FDG-PET Case 2: Seizure Semiology

Complex partial seizure: These start with a strange feeling in the chest (“tickling”, “like on a roller coaster”) for several seconds followed by amnesia and aphasia (worse in production). She has diffuse hypermotor features and brief yelling. Her right arm stiffens and the head will deviate to one side with the eyes open. There is at times right-sided clonic jerking, moaning, and automatisms (oral, manual – left-handed facewiping). She is unresponsive during these events and they last approximately 1 minute. They occur more frequently in the morning, during menses and during periods of stress. She is sleepy postictally.
FDG-PET Case 2: EEG

The onset is likely left temporal region but unclear precisely often due to motion artifact and interictal/ictal common overlap. Left posterior temporal (T5) rhythmic 4-6 Hz theta or sharp waves is seen at onset in a few. Sometimes, broadly distributed left temporal 3 Hz PLEDS or rhythmic delta (interictal findings) lead into the seizures. One seizure (2/28/09, 07:18) demonstrates left temporal PLEDs dropout and left hemisphere low voltage theta-alpha just before clinical onset followed by T5 small repetitive sharp waves.
FDG-PET Case 2: Neuropsychological Assessment

FSIQ 80 (9th %); VCI 74 (4th%); PRI 92 (30th%), WMI 83 (13th%); verbal and nonverbal abilities were significantly discrepant, with an average performance on perceptual reasoning skills and a borderline performance on verbal abilities (both receptive and expressive impaired), suggestive of left hemisphere dysfunction. Executive function is also impaired. Processing speed index (PSI) 86 (18th%). BNT 2nd%. Boston Facial Recognition Test 33rd-59th%. BDI-II 19 (mild); BAI 2 (mild).
There are at several small foci of magnetic susceptibility involving the gray and white matter of the left cerebral hemisphere more than the right hemisphere, consistent with old blood products or calcification. Decrease in the size of the left hippocampus compared to the right, which is compatible with left MTS.
FDG-PET Case 2
Case 2: Summary

The patient is a 21-year old woman with medical refractory left temporal-frontal epilepsy (symptomatic). There is a catamenial component. Seizures began within 1 year after a perioperative stroke (likely afflicting the left anterior region).

<table>
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<th>Result</th>
</tr>
</thead>
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<tr>
<td>Historical Insult</td>
<td>Left anterior</td>
</tr>
<tr>
<td>Semiology</td>
<td>Left frontal-temporal</td>
</tr>
<tr>
<td>Neurologic Exam</td>
<td>Left anterior region</td>
</tr>
<tr>
<td>Interictal EEG</td>
<td>Left temporal and posterior temporal.</td>
</tr>
<tr>
<td>EEG Ictal</td>
<td>Left temporal region early involvement</td>
</tr>
<tr>
<td>MRI</td>
<td>Mild left hippocampal atrophy.</td>
</tr>
<tr>
<td>PET</td>
<td>Left hemisphere hypometabolism</td>
</tr>
<tr>
<td>Neuropsychology</td>
<td>Left hemisphere dysfunction</td>
</tr>
</tbody>
</table>

1. Obtain Wada. Rediscuss in conference after Wada.
2. If language on left, do intracranial monitoring for seizure localization and functional mapping.
3. If language on right, do 8 cm left temporal lobe resection.
4. A resective surgery is palliative. Her lack of a clear MRI lesion, diffuse left hemisphere hypometabolism on PET, and frequent epileptiform discharges contribute to decreased chance of seizure freedom after resective surgery.
5. Consider trial of perimenses benzodiazepine or Diamox.
6. VNS is an option. SANTE or RNS may be options.
FDG PET Case 3

- 36 yo, female
  - generalized tonic-clonic seizures since the age of 12
- PMHx
  - Depression and question of Bipolar Disorder: requiring hospitalization in approximately 2002 and treated with Zoloft, VPA, Neurontin in the past
- EEG: frontal, poor lateralization
- Neuropsychological Assessment: temporal lobe dysfunction and executive memory problems
- Poor Overall Lateralization
FDG-PET Case 3
FDG-PET: Case 3

T1                         T2                         FLAIR
Case 3
FDG-PET Case 3

http://www.downstate.edu
FDG-PET Case 3
PET/MRI: Fusion
PET: Serotonin Receptor (5HT-1A)

FDG-PET: Response Assessment
PET: C11-Methionine

Epilepsy represents a significant public health problem.
Epilepsy has a broad spectrum of clinical presentations.
Goal of treatment is freedom from disabling seizures.
Current treatments include diet, medications, vagal nerve stimulators and surgical resection.
FDG-PET can reveal and/or confirm surgical targets and, therefore, can play a critical role in diagnosis and management of intractable epilepsy.
References and Resources

- World Health Organization (www.who.int)
- Centers for Disease Control, CDC (http://www.cdc.gov/epilepsy)
- International League Against Epilepsy ILAE (http://www.epilepsy.org)
- Epilepsy Foundation (www.epilepsyfoundation.org)
Thank You

Kate Davis MD
Ram Mani MD
Brian Litt MD
Peter Crino MD, PhD
John Pollard MD
Gordon Baltuch MD, PhD