Functional Imaging of Neuroblastoma

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Neuroblastoma

- 7.2% of cancers in children < 15 y/o in US
- Most common extracranial solid tumor of childhood
- ~ 650 new cases per year in US
The Plan

• Clinical Features
• Tracers
  – Conventional
    • mIBG
    • Bone
    • Somatostatin receptor
  – Positron emitting
    • FDG
    • HED
    • EPI
    • F-DMN
    • F-DOPA
Diagnosis of Neuroblastoma

- Unequivocal pathologic diagnosis from tumor tissue based on light microscopy
  OR
- Bone marrow aspirate or biopsy with unequivocal tumor cells AND increased urine or serum catecholamine metabolites
Clinical Presentation of Neuroblastoma

- Abdominal distention
- Bone pain
- Incidental
- Occasional
  - Opsomyoclonus-ataxia (dancing eyes)
  - Horner’s syndrome
    - Ptosis – drooping eye lid
    - Myosis – contraction of the pupil
    - Endophthalmos – sunken in globe
  - Treatment resistant diarrhea (VIP production)
  - Hypertension
    - Renal artery compression
    - Catecholamines

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Where is the Primary Tumor

• Anywhere along the sympathetic paravertebral chain
  – Adrenal medulla ~50%
  – Abdomen including adrenal ~80%
  – Chest ~15%
  – Neck, other, undetected ~5%
Where Does It Metastasize

- Bone
- Bone Marrow
- Lymph Nodes
The Plan

• Clinical Features

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    • FDG
    • HED
    • EPI
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    • F-DOPA
Tracer pathophysiology

- **hNET uptake**
  - mIBG
  - HED
  - EPI

- **Glucose metabolism**
  - FDG

- Somatostatin receptor

A positron emitting tracer of hNET is inherently better than the single photon agent mIBG.
Approaches to Imaging of Neuroblastoma

- **Less specific functional imaging agents (not nonspecific)**
  - Glucose metabolism
  - Bone turnover
  - Amino acid uptake and protein synthesis
  - DNA synthesis
  - Membrane synthesis
  - Membrane permeability
  - Blood flow
  - Hypoxia
Fig. 1. A diagrammatic representation of the topology of the human norepinephrine transporter (hNET) protein. Indicated are the positions of the amino acids which are mutated in the naturally occurring hNET variants and examined in this study. *From:* Runkel: Pharmacogenetics, Volume 10(5). July 2000. 397-405
hNET

- member of the Na+- and Cl--dependent family of neurotransmitter transporters
- highly homologous to other members of this family, such as
  - serotonin transporter (SERT)
  - dopamine transporter (DAT)
- 617 amino acids with 12 transmembrane domains
  - cytoplasmatic NH2 and COOH termini
  - hNET gene on long arm of chromosome 16
Function of hNET

- Responsible for the rapid reuptake of the neurotransmitter norepinephrine into the presynaptic nerve terminals

- Leads to the rapid termination of neurotransmission
MIBG
meta-iodobenzylguanidine

- Developed by Wieland and colleagues at University of Michigan late 1970s for imaging the adrenal medulla
- Pheochromocytoma localization reported by Sisson - NEJM 1981
- Neuroblastoma localization reported by Treuner - Lancet 1984

MIBG

Norepinephrine
meta-iodobenzylguanidine (MIBG)

meta-hydroxyephedrine (HED)

[^11C]epinephrine (EPI)
sympathetic nerve varicosity

neuronal axoplasm

vesicles

interstitium

NET

HED

MIBG

*MA

EPI

MAO
## Properties of Radionuclides That May Be Used To Label MIBG And Its Analogs

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Mode of Decay</th>
<th>$T_{1/2}$</th>
<th>Principal Photon Energy</th>
<th>Principal Particulate Emissions</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{123}$I</td>
<td>Gamma, EC$^a$</td>
<td>13.2h</td>
<td>159 KeV</td>
<td>Low energy Auger electrons</td>
<td>Near ideal gamma camera imaging agent; various accelerator routes of production; supply and cost remain problems. Permits SPECT.</td>
</tr>
<tr>
<td>$^{125}$I</td>
<td>Gamma, EC$^a$</td>
<td>60d</td>
<td>35KeV</td>
<td>Multiple low energy Auger electrons</td>
<td>Widely used for animal and in vitro studies. May have utility for the therapy of micrometastases and intra-operative tumor location with probe detectors.</td>
</tr>
<tr>
<td>$^{131}$I</td>
<td>Gamma, $\beta^-$</td>
<td>8.05d</td>
<td>$364(637)^b (723)^b$ KeV</td>
<td>Multiple $\beta^-$ (69-190KeV)</td>
<td>Less than optimal for gamma camera imaging. Suitable for therapy of larger tumor deposits. Convenient compromise agent, approved by FDA.</td>
</tr>
<tr>
<td>$^{18}$F</td>
<td>$\beta^+$</td>
<td>110m</td>
<td>511$^c$ KeV</td>
<td>$\beta^+$</td>
<td>Label for MFBG and FIBG.</td>
</tr>
<tr>
<td>$^{11}$C</td>
<td>$\beta^+$</td>
<td>20m</td>
<td>511$^c$ KeV</td>
<td>$\beta^+$</td>
<td>Label for HED and epinephrine.</td>
</tr>
<tr>
<td>$^{76}$Br</td>
<td>$\beta^+$</td>
<td>16.2h</td>
<td>511$^c$ KeV</td>
<td>$\beta^+$</td>
<td>Label for MBrBG which has been used for PET of cardiac autonomic innervation.</td>
</tr>
<tr>
<td>$^{211}$At</td>
<td>$\alpha$</td>
<td>7.2h</td>
<td>77-92$^d$ KeV</td>
<td>$\alpha$</td>
<td>Label for MABG which has potential for $\alpha$ therapy.</td>
</tr>
</tbody>
</table>

$^a$ = electron capture  
$^b$ = minor but still significant emission  
$^c$ = Annihilation photon  
$^d$ = Gamma rays from $\alpha$ decay  
$^e$ = Gamma rays from $\alpha$ decay  

EC$^a$ = electron capture  
MIBG = Meta-iodobenzylguanidine  
FIBG = Fluoro-iodobenzylguanidine  
HED = Hydroxyephedrine  
MBBrBG = Meta-bromobenzylguanidine  
MABG = Meta-astatobenzylguanidine  

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I-131 mIBG study of a 2 y/o with newly diagnosed neuroblastoma
I-131 mIBG study of a 2 y/o with newly diagnosed neuroblastoma

it is not possible to obtain high quality images with I-131 mIBG.
9 year old boy with recurrent neuroblastoma
9 y/o boy with recurrent neuroblastoma - MIBG
Some Tracers of Tumor hNET

- I-MIBG
- C-11 HED
- C-11 epinephrine
- F-18 dopamine
Carbon-11 HED (Hydroxyephedrine)

• Synthesized by Wieland and colleagues for imaging the sympathetic innervation of the heart
sympathetic nerve varicosity

neuronal axoplasm

vesicles

HED
MIBG
EPI

NET

MAO

interstitium

vesiculars
PET Scanning with Hydroxyephedrine: An Approach to the Localization of Pheochromocytoma

- Ten patients
  - Pheochromocytomas were localized by PET scanning in 9 of the 10 patients
  - Uptake of 11C-HED into pheochromocytomas was rapid
  - Image quality superior to 131I-mIBG, and 123I-mIBG planar and SPECT studies
HED Pheochromocytomas

42 year old with malignant pheochromocytoma
Conclusion: HED PET is a promising functional imaging method for the study of pheochromocytomas.
PET Hydroxyephedrine Imaging of Neuroblastoma

- 6/6 true positive
- Complete concordance with MIBG
- Tumor/nontumor ratios < MIBG SPECT
FIGURE 5. Patient 4. (A) HED-PET scan of the midabdomen 30 min postinjection. There is accumulation of HED (arrow) to the left of the liver as well as excretion of HED through the right kidney. (B) MIBGSPECT scan at 24 hr shows excellent uptake within the neuroblastoma. There is little remaining liver and kidney activity, and thus the tumor appears quite prominent.
FIGURE 3. Tumor accumulation (Patients 1–6) as a function of time. The x-axis value is minutes postinjection of HED. The majority of uptake of HED occurs within 2 min of injection. Retention of activity was high, with the exception of the tumor of Patient 4, whose activity declined substantially from peak levels.
Tracer and Technology

- I-123 mIBG
- C-11 HED
- SPECT CT
- PET CT
• Whole-Body PET/CT with 11C-Meta-Hydroxyephrine in Tumors of the Sympathetic Nervous System: Feasibility Study and Comparison with 123I-MIBG SPECT/CT

• Christiane Franzius, Klaudia Hermann, Matthias Weckesser, Klaus Kopka, Kai Uwe Juergens, Josef Vormoor and Otmar Schober

• Journal of Nuclear Medicine Vol. 47 No. 10 1635-1642
HED in Neuroendocrine Tumors

- 19 consecutive patients, 9 mo to 68 y old
- whole-body 11C-HED PET/CT compared with attenuation-corrected 123I-MIBG SPECT/CT scans
- 6 neuroblastomas, 5 pheochromocytomas, 1 ganglioneuroblastoma, and 2 paragangliomas, 5 no tumor diagnosis
Findings

- 11C-HED PET/CT detected 80 of 81 totally depicted tumor lesions
- 123I-MIBG SPECT/CT detected 75 of 81 lesions
- Tumor-to-background contrast
  - HED > MIBG uptake in 26 lesions
  - HED = MIBG uptake in 39 lesions
  - HED < MIBG uptake in 16 lesions
FIGURE 4. A 5-y-old girl (patient EN) who had neuroblastoma stage IV 3 y ago. Large local relapse in left upper abdomen does not demonstrate increased 11C-HED uptake above surrounding tissue in PET/CT: (A) PET, coronal slice; (B) PET/CT fusion, coronal slice; (C) PET, transversal slice; (D) CT, transversal slice; (E) gadolinium-enhanced T1-weighted MRI with fat saturation, transversal slice. Osseous metastasis (solid arrows in A and B) in left hemipelvis is visible with faintly increased tracer uptake. 123I-MIBG SPECT/CT: (F) SPECT, coronal slice; (G) SPECT/CT fusion, coronal slice. Local relapse (open arrows) and osseous metastasis (solid arrows) show highly increased 123I-MIBG accumulation. Neuroblastoma was confirmed histologically at first diagnosis 3 y ago. In relapse situation, osseous involvement was confirmed by bone marrow puncture. Additionally, patient showed increased urinary catecholamines at first diagnosis and in relapse situation.
Conclusions

- Whole-body imaging using 11C-HED PET/CT is feasible in the clinical setting of patients with tumors of the sympathetic nervous system.
- 11C-HED PET/CT detected more tumor lesions than 123I-MIBG SPECT/CT.
- However, tumor-to-background contrast of 11C-HED in lesions can be higher, equal, or lower compared with 123I-MIBG.

- BLS comment (mIBG is really good, that’s why GE is trying to get NDA approved)
Some Tracers of Tumor hNET

- I-MIBG
- C-11 HED
- C-11 epinephrine
- F-18 dopamine
C-11 Epinephrine

- Synthesized by Wieland and colleagues for imaging the sympathetic innervation of the heart
- A true tracer, endogenous compound
sympathetic nerve varicosity

neuronal axoplasm

vesicles

interstitium

sympathetic nerve varicosity
University of Michigan
PET EPI

- 15-30 sec
- 30-45 sec
- 45-60 sec
- 60-90 sec
- 90-120 sec
- 2-3 min
- 3-4 min
- 4-5 min
- 5-7.5 min
- 7.5-10 min
- 10-20 min
- 20-30 min
- 30-40 min
C-11 Epinephrine in Pheochromocytoma and Neuroblastoma

- A true tracer
- High quality images
- Uptake not related to plasma catecholamine levels
- Less sensitive than mIBG
- Unlikely to reach clinical relevance
Some Tracers of Tumor hNET

- I-MIBG
- C-11 HED
- C-11 epinephrine
- F-18 dopamine
- F-18 dopa?
The Plan

• Clinical Features

• Tracers
  – Specific
    • mIBG
    • HED
    • EPI
  – Less specific
    • Somatostatin receptor
    • FDG
Less Specific Agents

- Target specific physiologic processes
- Processes common to many tumors
  - **Glucose metabolism**
    - Bone turnover
    - Amino acid uptake and protein synthesis
    - DNA synthesis
    - Membrane synthesis
    - Membrane permeability
    - Blood flow
    - Hypoxia
• Neuroblastoma: positron emission tomography with 2-[fluorine-18]-fluoro- 2-deoxy-D-glucose compared with metaiodobenzylguanidine scintigraphy

• BL Shulkin, RJ Hutchinson, VP Castle, GA Yanik, B Shapiro and JC Sisson
Radiology, Vol 199, 743-750
GR – 2 y/o with newly diagnosed neuroblastoma

I-123 mIBG SPECT 9/14/05

FDG PET 9/21/05
Seventeen patients with known or suspected neuroblastoma underwent FDG positron emission tomography (PET) (20 scans) and MIBG scintigraphy.

- Tumor uptake of FDG was detected in 16 of 17 patients (18 of 20 scans).
- Neuroblastomas and their metastases avidly concentrated FDG prior to chemotherapy or radiation therapy.
- Uptake after therapy was variable.
- Uptake of FDG was intense in one patient with neuroblastoma that failed to accumulate MIBG.
Results continued

• In 13 of the 20 scans, however, MIBG was rated superior to FDG for delineation of tumor compared with background and normal organs.

• MIBG uptake is more intense prior to therapy

• FDG PET most useful for neuroblastomas that fail to concentrate MIBG
$^{123}$I-MIBG Scintigraphy and [$^{18}$F]FDG PET CT in Neuroblastoma

Susan E. Sharp MD, Barry L. Shulkin MD, Wayne L. Furman MD, & Michael J. Gelfand MD
MIBG Statics_E
MIBG Statics_F
MIBG Statics_E.01
MIBG Statics_F.01
mIBG SPECT
mIBG SPECT CT: Zvi Bar-Sever

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5 y/o with hx of stage 3 NB; post auto BMT

Feb 9 2007
Feb 13 2007

NTFP

Not Truly False Positive
Extending Positron Emission Tomography Scan Utility to High-Risk Neuroblastoma: Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography as Sole Imaging Modality in Follow-Up of Patients

- J Clin Oncol 2001;19:3397-3405
- MSKCC
Findings

• 51 pts high risk NB: 92 FDG PET scans – comparison with MIBG scans, bone scans, CT and/or MRI, urine catecholamines, bone marrow

• 40 pts not in CR

  – Only 1 had disease that would have been missed if staged only by FDG and bone marrow
  – 13 had disease detected by PET but no by bone marrow and urine catecholamines
  – “PET equal to or superior to MIBG for identifying NB in soft tissue and extracranial skeleton, for revealing small lesions, and for delineating the extent and localizing sites of disease.
• Fantastic tumor imaging agent
• For clinical purposes, other general purpose tumor imaging agents will need to show incremental value
• Expression of glucose transporters is affected by many upstream cellular processes. FDG can thus be used to evaluate the effect of an intervention
  – Imatinib mesylate inhibition of the activating mutation of the KIT tyrosine kinase receptor in GIST
Approaches to Imaging of Neuroblastoma

- Less specific functional imaging agents
  - Glucose metabolism
  - Amino acid uptake and protein synthesis
  - DNA synthesis
  - Membrane synthesis
  - Membrane permeability
  - Blood flow
  - Hypoxia
Uptake of Various Compounds in SH-SY5Y

<table>
<thead>
<tr>
<th>Compound</th>
<th>Picomoles Compound/mg Protein/120 Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methionine (C-14)</td>
<td>90</td>
</tr>
<tr>
<td>Threonine (C-14)</td>
<td>10</td>
</tr>
<tr>
<td>Thymidine (3-H)</td>
<td>1</td>
</tr>
<tr>
<td>L-DOPA (3-H)</td>
<td>0.1</td>
</tr>
<tr>
<td>Uridine (3-H)</td>
<td>100</td>
</tr>
<tr>
<td>L-phenylalanine (3-H)</td>
<td>100</td>
</tr>
<tr>
<td>MIBG (I-125)</td>
<td>100</td>
</tr>
</tbody>
</table>

SH-SY5Y
Observations

• For clinical purposes, new imaging agents will need to demonstrate incremental value to those already available: principally MIBG and FDG

• Specialized tracers that probe specific aspects of cellular pathophysiology may be critical in providing an early indication of drug efficacy
  – May require highly technical facilities and support
  – May not be suitable for broad based trials
Summary of New Imaging Approaches in Neuroblastoma

- Many new agents to probe pathophysiology
- MIBG is the standard for cellular viability
- FDG may be useful for probing the effects of particular interventions which ultimately result in alterations of glucose transporter
Summary of New Imaging Approaches in Pheochromocytoma and Neuroblastoma

• The choice of imaging agent will depend on which pathophysiologic process you want to investigate
• Many agents are short lived, enabling repeat studies with rapid feedback on the likely efficacy of an agent
• Imaging could become surrogate end point
Summary of New Imaging Approaches in Pheochromocytoma and Neuroblastoma

• The choice of imaging agent will depend on which pathophysiologic process you want to investigate
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• For you attention I