FDG-PET/CT Assessment of Inflammatory and Infectious Diseases in Children

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Almost a quarter century ago, the Surgeon General of the United States testified to Congress that it was time to "close the book on infectious diseases"....
Infection - 2008

- Major cause of worldwide illness and death in spite of significant advances in the development of potent and safe antimicrobial agents

- As new and powerful antibiotics appear, microbes develop the ability to resist these drugs and to attack with new survival strategies

- Infectious processes become more varied and more difficult to diagnose and treat, in particular in diabetic and immuno-compromised patients
Diagnosis of Infection

- Timely diagnosis: critical for appropriate management
- Conventional imaging modalities
- Advantages - High resolution imaging
  - CT: bone destruction, soft tissue changes
  - MRI: sensitive for osteomyelitis
  - US: fluid collections
- Limitations
  - limited value in early stages (insignificant/no infection-related tissue changes)
  - challenging in the presence of:
    - coexisting pathology (eg: fractures, osteo-arthropathy)
    - coexisting structural changes related to treatment and/or healing (eg: bone remodeling, post-operative edema, scar, fibrosis)
Nuclear Medicine
Clinical Indications in Infection
Functional & Metabolic Assessment

- Fever of unknown origin
- Osteomyelitis
- Lung infection
- Endocarditis
- Vascular prosthetic infection
- Abdominal infection
- Assessment of disease activity in IBD
- Kidney/transplant infection
Ideal Radiotracer for Infection

Corstens et al, Sem Nucl Med 1993

- *Tc99m* labeled
- Rapid localization at site of infection
- Low uptake & rapid clearance from non-infected sites
- Specific uptake in infection but not inflammation
- Rapid dg. within 2 hrs post-injection
- No pharmacological effect on patient
- No immunological reaction - can be safely re-used
- Can identify all focal infectious processes (bacterial, viral & fungal)
Radiotracers & Infection

SPECT Tracers
- Gallium-67
- Labeled Leucocytes (In & Tc)
- Labeled Antibodies (Human Immunoglobulin, Antigranulocyte: Tc-sulesomab, IgG, Tc-fanolesomab, IgM)
- Labeled Antibiotics (Tc-ciproflaxacin, Tc-fluconazol)
- Labeled Cytokines (Tc-interleukin 8)

PET Tracers
- F18-FDG (Fluorodeoxy-Glucose)
- FDG-labeled Leucocytes
Functional & Metabolic Imaging

Pros:

- Highly sensitive
- Whole body imaging
- Data on patho-physiological & biochemical processes
  - Locally increased blood flow
  - Locally increased vascular permeability
  - Enhanced transudation of plasma proteins
  - Enhanced influx of leucocytes
Inflammatory and infectious processes may be visualized by functional and/or metabolic imaging tests (SPECT & PET) in their early phases when anatomic lesions are not yet detectable.
Functional & Metabolic Imaging

Cons:

- Poor physical characteristics (may lead to image quality degradation)
- Lack of anatomical landmarks
- Non-specificity of tracers (diagnosis of infection vs. tumors)
SPECT or PET & CT
Complementary Role in Suspected Infection

NM – detection of a suspicious focus
CT – precise localization to specific tissue/organ

CT (or physical exam) – anatomic lesion
NM - confirmed as active infectious process

Correlation of anatomical & functional data obtained from tests performed on different devices, on different days, is difficult.
Infectious Diseases in Children

- **Neonates**
  - immature immunity
  - low sensitivity of bone scintigraphy
  - WBC scan not feasible (cumbersome blood collection)
  - high dosimetry for Ga-67 and CT (whole body)
  - seldom: incomplete response to antibiotics, need to change the therapeutic approach
  - finding the focus of infection – referral to surgery
- **Congenital/acquired immunodeficiency**
  - highly susceptible to severe infection
  - diagnosis: by histology and microbiological tests
  - need to define activity of disease & therapy monitoring
- **Older children: challenging infectious processes** (e.g. discitis)
Hybrid Imaging in Children (with Infection)  
Specific Considerations

• Radiation dosimetry
  – Weight/age adjusted dose of the tracer (FDG)
  – Correct CT parameters

Effective dose equivalent
  TcWBC: 0.25mSv/ 5MBq
  FDG: 0.56/5 MBq

Means to reduce dose of FDG:
  increase imaging time/FOV
  3D imaging protocol

Means to reduce CT radiation:
  limited examinations
  no automatic multiphase exams

• Sedation – risk consideration vs. non-optimal studies
Hybrid Imaging in Infection
The Rambam Experience

SPECT/CT:
- Ga-67: FUO, soft tissue, osteomyelitis
- In/Tc labeled leucocytes: vascular graft infection, complicated bone infection

FDG-PET/CT:
- Vascular graft infection
- Assessment of the diabetic foot
- FUO
SPECT/CT
CONTRIBUTION OF SPECT/CT USING Ga-67 FOR DIAGNOSIS & LOCALIZATION OF INFECTION


82 patients: 47 Ga-67, 35 labeled WBC

SPECT/CT– better diagnosis & localization (~50% pts)

47 pts Ga-67; SPECT/CT was contributory in 36% pts
48% with susp. osteomyelitis
23% with susp. soft-tissue infection
31% with FUO

35 pts WBC; SPECT/CT was contributory in 63% pts:
67% - suspected vascular graft infection
55% - assessed for osteomyelitis

SPECT/CT contributed significantly more WBC > Ga-67
M, 12, fever, sepsis and pelvic pain
Suspected osteomyelitis

Tc-MDP:
abnormal focus
lower sacrum & coccyx

Ga-67:
abnormal focus
lower spine & sacrum
Ga-67 SPECT/CT:
Uptake in the lower part of the sacrum - osteomyelitis

... and the adjacent soft tissue

Whole extent of infectious process
M, 11, acute lymphoblastic leukemia, fever
E-coli septicemia

$^{67}$Ga-SPECT/CT – Diagnosis of soft tissue abscess
Excludes osteomyelitis
FDG-PET/CT
FDG-PET in Infection

Inflammatory cells & granulation tissue (activated lymphocytes, neutrophils, macrophages ~ malignant cells) exhibit high intracellular levels of hexokinase & increased expression of surface glucose transporter proteins with high affinity to FDG

FDG-imaging – a good alternative for assessment of infection ("the blessing of the curse...")
FDG-PET Imaging of Infection and Inflammation

Pros:

- F-18 has good physical properties
- FDG has good tracer kinetics
- Images with high spatial & contrast resolution
- Study completed within 1.5 – 2h
- Short physical half-time: lower radiation doses
FDG-Imaging of Infection and Inflammation

Due to the FDG biodistribution:

**Cons:**
- Suspicious FDG-avid foci located in/adjacent to organs with high physiologic tracer concentration misinterpreted as FP or FN
- Lack of anatomic landmarks

*Due to PET/CT - less limiting factor (~ in cancer)*
FDG-PET/CT in Infection & Inflammation
Clinical Indications

Musculo-skeletal
- Acute/chronic osteomyelitis
- Infected implants
- Inflammatory arthritic processes

Fever of unknown origin (FUO)
- Immune compromised patients

Vascular
- Vasculitis
- Infected vascular graft
- Inflammatory vulnerable plaques

Other
- Sarcoidosis
- Inflammatory bowel disease
- Cardio/respiratory tract infections
- Foreign body reactions
PET/CT characterization of 118 FDG-avid foci in 43 children with cancer

Bar-Sever et al, EJNMMI 2006
False Positives?

A hypermetabolic FDG-avid focus is not the definite proof for the presence of cancer.
F, 15, Hodgkin Lymphoma, During CR
New FDG+ foci in Nasopharynx & Cervical LN

1/2005
Negative PET 4/2005

Upper Respiratory Tract Infection
FDG Imaging in Infectious Diseases in Children


6 children (incl. 3 neonates, 2 immunocompromised children)

- Neonates (rising biomarkers, septicemia):
  - OM distal tibia (negative US & bone scan) – to surgery
  - Infected ventriculo-peritoneal shunt (negative US & bone scan) – to removal of infected catheter
  - True negative PET/CT – no further tests
- Immuno-compromised – monitoring activity of infectious processes prior to treatment:
  - AML & pulmonary aspergillosis – before BMT
  - Neuroblastoma & pulmonary candidiasis – before restarting chemo
- Discitis confirmed (suspected by bone scan & MRI) - biopsy was cancelled
FDG Imaging & Bone Infection

- Infected joint replacement
  - No DD: aseptic loosening vs. infected joint
    similar inflammatory/immune reaction can be present
  - Potential better agent: FDG-WBC
    high accumulation of neutrophils in infection
- Spinal OM – accurate dg. Modality
- Diabetic foot
Malignant/Necrotising Otitis Externa

Involvement of soft tissues (posterior aspect of auditory canal)

Involvement of bone (sphenoid ridge & temporal bone)
F, 75, Fever, Tenderness & Swelling, Chest Wall

Osteomyelitis of Rt. Clavicle
Dorsal Soft Tissue Abscess
Septic Arthritis Lt. Shoulder

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Non-Malignant Etiology of FDG Uptake
F, 13, Hodgkin, Stage 3, End of Chemo

New FDG+ skeletal foci
Non-malignant & non-infectious
MRI: Bone infarcts
Non-Malignant Etiology of FDG Uptake
M, 10, Hodgkin Lymphoma, in CR

FDG-avid process
non-malignant & non-infectious
Synchondrosis Pubis
Fever of Unknown Origin (FUO)

Definition: fever >38.3°C, >3 weeks duration

Incidences: 7-53%

geographic factors, variable definition

Final Diagnosis:

Neoplasms ~1/3
Infection ~1/3
Collagen & granulomatous diseases ~1/3

Recent: decrease in patients with final etiology

Functional imaging approach:
WBC, Ga-67, FDG
FDG-PET/CT in FUO

- FDG imaging does not differentiate between infectious etiology and other causes for hypermetabolic states (e.g. tumor, post-operative/therapeutic changes)
- FDG imaging (PET/CT) – identifies organ/tissue likely to contain the source of fever – guiding further tests
- Very high NPV – unlikely to find a focal etiology of the FUO in the presence of a negative FDG-PET/CT
FDG imaging in Children with FUO

Sturm et al, Liver Transpl, 2006, 11 children

- FUO in children with biliary cirrhosis and terminal chronic liver failure – general contraindication for transplant
  - Systemic infection of non-hepatic origin – unsuitable for transplant
  - Infection in liver – may require resection of organ
- Based on FDG results:
  - 5 patients – hepatic infection
  - 6 patients – true negative, NED for focal infection
FUO
Looking for the source of infection in immuno-compromised patients
F, 68, Vasculitis, Fever
Prolonged Immunosuppressive Rx

Skin: Biopsy proven Herpes Zoster

Rectum: Inflamed tubular adenoma
F, 21, fever, polycystic kidneys s/p renal transplant (1 mo)
F, 21, fever, polycystic kidneys
S/a renal transplant

Pelvic abscess
Infected renal cyst
Reactive lymph node
Infection in immuno-compromised children

Chronic granulomatous disease (CGD)

Gungor et al, Arch Dis Child, 2001, 7 children
Ozsahin et al, Blood, 1998 (case rep)

• Inflammatory complications responding to systemic anti-inflammatory Rx
• High risk for infection, mainly aspergillosis
• Treatment: BMT (after identification of all active sites)
• CT – cannot differentiate active vs. inactive
• PET defined 1/3 of susp. CT sites as inactive
• PET identified 40% active sites not seen on CT

Infection post-organ transplant
Infection in children with cancer during/after Rx
M, 9 mo, Myelofibrosis, Fever, Staph bacteremia, Abdominal US – suspicious liver lesions

Multiple FDG+ pulmonary opacities, ± cavitation & ground glass halo
Consistent with Aspergillosis, confirmed by bronchoscopy
No further evidence for liver abscess
M, 9 mo, Myelofibrosis, Fever, Staph bacteremia, Abdominal US – suspicious liver lesions

FDG+ blurring of subcutaneous fat w/o sharp borders

? infectious infiltrate at site of previous biopsy
F, 13, Recurrent Hodgkin (Nodal), End of Rx

6/2004: new lung infiltrates & alveolar shadows

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F, 13, Recurrent Hodgkin (Nodal), Follow up

10/2004:
New lung infiltrates; disappearance of previous lesions
Recurrent bilateral pneumonia
Thus, the task is not so much to see what no one has seen yet, but to think what nobody has thought yet, about what everybody sees.

Spinoza
SPECT/CT & PET/CT
Promising Role in Evaluation of Infection

PET/CT: Better localization - Better image interpretation
Higher diagnostic confidence
Improved clinical decision making
  We have learned from pitfalls and “false positives” in children with cancer
  - Accurate diagnosis, localization & extent of infection
  - DD - tracer uptake unrelated to infectious processes - exclusion of disease
  - Guiding invasive procedures for diagnosis (tissue sampling) or treatment
Thank you!