Update in Nuclear Imaging of Amyloidosis and Sarcoidosis

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Outline

• Amyloidosis
  – General considerations
  – Nuclear imaging methods
  – Role of MRI
  – Diagnostic algorithm

• Sarcoidosis
  – General concepts
  – Nuclear imaging methods
  – Complementary imaging with MRI
  – Diagnostic algorithm
Cardiac Amyloid

- Amyloidosis-major types: ATTR and Light Chain
- How do we distinguish between the subtypes with nuclear imaging?
  - Tc-99m-Pyrophosphate (Tc-99m-PYP) scanning
- Significance of assessment of Tc99m-PYP uptake
- SPECT
  - Improved localization over planar
  - Dual isotope imaging
Cardiac Amyloid

- **ATTR**
  - ATTR includes senile ("Wild-type") (95%) and hereditary/familial types (5%)
  - Senile type: tends to be an older male with LVH
  - 25% of men over 85 have it (may include patients with AS-low flow low gradient or patients with HFPEF)
  - Biopsy:
    - Congo red stain positive
    - Immunohistochemistry stain positive for kappa or lambda light chains
  - Medical therapy (tafamidis, Diflunisal, small interfering RNA)
Median overall survival for ATTR WT is 3.6y

Tafamidis improves survival compared to non-treatment
Cardiac Amyloid

- AL is a systemic disorder
  - Characterized by monoclonal gammopathy
  - Immunoglobulin light chain produced by a clonal cell population
  - Lambda chain predominant
- Biopsy
  - Congo red staining with infiltration
  - Bone marrow biopsy and presence of circulating light chains
- Treatment
  - consists of chemotherapy and stem cell transplantation
  - Cardiac transplantation
AL Survival with SCT

Cardiac AL

Non-cardiac AL

D’Souza et al. Journal of Clinical Oncology 33, 2015 3741-3749
CMR: Usual initial imaging test

Diffuse late gadolinium enhancement (LGE): high sensitivity

Does not distinguish between ATTR and AL
Nuclear Medicine for Cardiac Amyloid

Tc-99m pyrophosphate
- Bone imaging tracer since 1970’s
- High specificity for ATTR
- SPECT increasing utilization

F-18 Florbetapir
- FDA approved 2012 (brain)
- Images the amyloid protein itself
- AL>ATTR uptake

\[^{99m}\text{Tc-PYP in Cardiac Amyloidosis}\]

\(^{18}\text{F}\text{AV-45}\) (Florbetapir, Amyvid)
We propose that the scintigraphic pattern of intense, diffuse, biventricular uptake of Tc-99m PYP may be highly specific for the diagnosis of amyloid cardiomyopathy.
"We propose that the scintigraphic pattern of intense, diffuse, biventricular uptake of Tc-99m PYP may be highly specific for the diagnosis of amyloid cardiomyopathy."
Planar Imaging

Standard approach:
Recommended by ASNC guidelines
Can distinguish patients with strong uptake and absence of uptake

$^{99m}$Tc-PYP in Cardiac Amyloidosis

Planar and SPECT acquisition (30min)

$^{99m}$Tc-PYP 20mci

0

3h
Semiquantitative Assessment of PYP Uptake

$^{99m}$Tc-PYP in Cardiac Amyloidosis

Tc-99m-PYP SPECT

Semiquantitative Assessment of PYP Uptake
Quantification of Tc99m PYP Uptake

**Biopsy proven ATTR with H/CL = 2.08**
Limitation of Planar Imaging

$^{99m}$Tc-PYP in Cardiac Amyloidosis
Simultaneous Dual Isotope Imaging with TI-201/Tc99m-PYP SPECT
$^{99m}$Tc-PYP in Cardiac Amyloidosis

Tc-99m-PYP SPECT  
TI-201 SPECT
Simultaneous Dual Isotope Imaging with TI-201/Tc99m-PYP SPECT

TI-201 allows unequivocal demonstration of the absence of myocardial Tc99m-PYP uptake
Myocardial Tc99m-PYP counts with and without the use of TI-201 for processing of raw images and for quantification.

- **Single isotope**
  - P=0.83

- **Dual isotope with coregistration**
  - P=0.007
  - P=0.0001
Prediction of ATTR by Tc-99m PYP SPECT with and without the use of Ti-201
Clinical Approach to the Use of Imaging in Diagnosis of Cardiac Amyloidosis

Clinical Suspicion

CMR for myocardial infiltration

YES

NO

Light chains in serum and urine + plasma cells in bone marrow

YES

NO

Systemic Amyloidosis -AL

Tc99m-PYP SPECT

YES

NO

ATTR WT Or Mutation

Alternate etiology
Summary

- ATTR best diagnosed by Tc-99m-PYP SPECT
- Myocardial Tc-99m-PYP uptake is usually absent in AL
- Quantification may be important for assessment of progression/effects of therapy
- Quantification is improved by simultaneous dual isotope imaging with TI-201
Sarcoidosis

• Clinical features
• Nuclear imaging for inflammation (F18-FDG)
• Quantification of FDG uptake
• Potential benefits of quantitative assessment
Sarcoidosis

• Systemic disease of unknown cause
  – Pulmonary > skin > eye > bone
  – Cardiac involvement recognized in only a small % of cases
  – Nearly 25% of patients with extracardiac sarcoid have cardiac involvement (autopsy findings)

• Cardiac sarcoid
  – Heart block
  – VT
  – Heart failure
  – Atrial arrhythmias
Diagnosis of Cardiac Sarcoid
HRS Criteria

Cardiac biopsy positive
OR
Extracardiac biopsy positive
AND

- Steroid +/- immunosuppressant responsive cardiomyopathy or heart block
- Unexplained reduced LVEF (<40%)
- Unexplained sustained (spontaneous or induced) VT
- Mobitz type II 2nd degree heart block or 3rd degree heart block
- Patchy uptake on dedicated cardiac PET (in a pattern consistent with CS)
- Late Gadolinium Enhancement on CMR (in a pattern consistent with CS)
- Positive gallium uptake (in a pattern consistent with CS)
Diagnostic and Therapeutic Strategy in Cardiac Sarcoidosis

• Indications for screening
  – Diagnosed extracardiac sarcoidosis
  – Unexplained 2° or 3° AV block age <55 y
  – Unexplained monomorphous VT
  – Non ischemic dilated cardiomyopathy

• Routine screening
  – Physical, ECG, Echo, Holter

• Advanced screening
  – CMR
  – PET (F18-FDG has replaced Ga67)
  – Invasive EP study
Post-contrast cine image shows difference in signal intensity.

Delayed gadolinium image dark myocardium (without fibrosis) and enhancement (in regions of fibrosis).

Assessment of inflammation for treatment decisions is made with PET imaging.
## F18-FDG PET Imaging for Inflammation

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>Uptake Pattern</th>
<th>Perfusion</th>
<th>Metabolism</th>
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<tbody>
<tr>
<td>Normal</td>
<td>Perfusion: Normal</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
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<tr>
<td></td>
<td>Metabolism: No FDG Uptake</td>
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<tr>
<td>Mild or Early Disease</td>
<td>“Focal Mismatch Pattern”</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
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<tr>
<td></td>
<td>Perfusion: No or mild defect</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
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<tr>
<td></td>
<td>Metabolism: FDG uptake in area of defect</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
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<tr>
<td>Moderate or Progressive</td>
<td>“Focal Mismatch Pattern”</td>
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<td><img src="image10.png" alt="Image" /></td>
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<tr>
<td>Disease</td>
<td>Perfusion: Moderate</td>
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<td><img src="image12.png" alt="Image" /></td>
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<tr>
<td></td>
<td>defect</td>
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<tr>
<td></td>
<td>Metabolism: FDG uptake in area of defect</td>
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<td><img src="image14.png" alt="Image" /></td>
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<tr>
<td>Severe or Fibrous Disease</td>
<td>Perfusion: Severe</td>
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<tr>
<td></td>
<td>defect</td>
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<tr>
<td></td>
<td>Metabolism: No or minimal FDG uptake</td>
<td><img src="image17.png" alt="Image" /></td>
<td><img src="image18.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Bokhari et al., FDG-PET is a Superior Tool in the Diagnosis and Management of Cardiac Sarcoidosis, ACC Expert analysis Apr 10, 2017
Practical Concerns

F18-FDG for detection of myocardial inflammation

• Myocardial glucose uptake suppression is the goal
  – F18-FDG uptake indicates inflammation

• CSMC pre- test preparation protocol:
  – HFLC dietary preparation 24-48hr
  – Prolonged fast 12-16 hours
  – Heparin iv at 45 min and 15 min pre F18-FDG*

• Diabetic patients
  – Early morning zero carbohydrate meal

* There is evolving consensus regarding the use of heparin.
Perfusion and FDG PET

Key concept:
FDG uptake in inflamed myocardium but suppressed in healthy tissue which utilizes free fatty acid

How do you measure disease burden?

Rest Rb82 and F18-FDG cardiac PET
Is There a Need to Measure FDG Uptake and How to Quantify?

SUV (standard uptake value): Uptake of FDG activity in a lesion normalized on the basis of a distribution volume.

Useful to measure disease activity and monitor treatment
FDG Uptake and Response to Treatment

Yokoyama et al., Quantitative analysis of myocardial 18F-fluorodeoxyglucose uptake by PET/CT for detection of cardiac sarcoidosis
63 patients out of 203 suffered adverse events over a mean followup of 1.8y

Sperry et al., Prognostic Impact of Extent, Severity, and Heterogeneity of Abnormalities on 18F-FDG PET Scans for Suspected Cardiac Sarcoidosis JACC Imag 2017
Diagnostic Imaging in Sarcoidosis

Extracardiac Sarcoidosis, Abnormal heart rhythm or Sudden death

ECG and Echocardiography

CMR with T1 and T2 and DE imaging

FDG PET

Sarcoidosis

Assessment of Inflammation

Positive

Equivocal

Positive

Steroid

No Steroids

Positive

Negative

No Steroids

Abnormal

Abnormal

Steroid
PET-MRI for Sarcoid Imaging

MRI | PET Perfusion | PET FDG

18F-FDG PET in Cardiac Sarcoidosis

Eur Heart J. 2013;35(5):312
Cardiac Imaging in Sarcoidosis

- Diagnosis: MRI/PET
- Prognosis: MRI/PET
- Quantification of FDG uptake can be useful for guiding therapy and monitoring response
- PET-MRI combines the best of both modalities