MHIF Research Highlights Dashboard: MAY 2018

THANK YOU! to our physician partners who presented featured studies at Grand Rounds:

Dr. Bennett
Dr. Goessl
Dr. Titus
Dr. Mudy
Dr. Lin
Dr. Sharkey
Dr. Harris
Dr. Eckman
Dr. Schwartz
Dr. Romero
Dr. Miedema
Dr. Brilakis
Dr. Knicklebine
Dr. Traverse

We appreciate your support of MHIF Research!

MHIF is committed to making research possible that offers hope to patients and may lead to advances in care and treatment options.

FEATURED STUDY UPDATES

DREAM-HF
Scout
Roadster 2* *Enrollment complete
Expand Heart Trial
Resolute PAS* *Enrollment on track
DAPA HF
KPL
Heart FID
DEFINE-PCI* *Enrollment on track
Prelude
VENT-AVOID* *First site to enroll a patient
PACES
CASCADE
Artesia* *Just opened
CONCERT
TRANSCEND* *Just opened

200+ active studies ongoing at MHIF

17 MHIF studies featured in the Grand Rounds 2017-18 season!
Cardiac Sarcoidosis

Peter Zimbwa

Conflict Of Interest Disclosures

• None
Objectives

1. Increase awareness
2. Challenges in diagnosis
3. Challenges in management

Sarcoidosis Definition

- Dr. James Hutchinson 1869
- Multisystem inflammatory disorder
- Genetic predisposition
  - Familial clustering, HLA DQB*0601, HLA DRB1*1101, TNF -308A and -857T, BTNL2
- Antigen exposure
- Noncaseating granuloma

Crohn’s disease Pathology

Cobblestone

Intestine

Cardiac cirrhosis Pathology

Nutmeg

Liver
Sarcoidosis
Histology

Cheese

Granulomas

Sarcoidosis
Epidemiology

- 5-64/100,000 - worldwide
- 10-40/100,000 - Europe, USA
- 3.8 fold higher in African than Caucasoid Americans
- 25-60 years (70%)
Cardiac Sarcoidosis
Epidemiology

- 2-5% clinically, >25% (58% in Japanese) advanced imaging, autopsy
- 20-fold increase in Finland 1988-2012
- 5-fold increase in UNOS 1994-1997 (0.1%), 2010-2014 (0.5%)
- 3.4% in LVAD core biopsy
- Increased morbidity, mortality (85% in Japanese)


Sarcoidosis
Clinical Manifestations

- Lungs - 90%
- Skin
- Lymph node
- Liver
- Eye
- CNS
- Heart - 35%-65% isolated
- Hypercalcemia (5%), hypercalciuria (40-62%)
- 1,25 dihydroxyvitamin D3

Pulmonary Sarcoidosis

- **Stage I**: hilar or mediastinal LN enlargement only
- **Stage II**: hilar or mediastinal LN and parenchymal disease
- **Stage III**: parenchymal disease only
- **Stage IV**: pulmonary fibrosis
Acute Sarcoidosis

• Löfgren’s syndrome
  - Bilateral hilar lymphadenopathy
  - Erythema nodosum
  - Arthritis
  - Anterior uveitis
  - Fever
• Heerfordt’s syndrome
  - Uveitis
  - Parotitis
  - Fever
  - VII palsy

Cardiac Sarcoidosis

Manifestations

• Location, extend, activity
• Conduction abnormalities
• Arrhythmias
• Congestive heart failure
• Sudden death
  - LVEF
  - NYHA
  - LVEDd
  - VT
  - Inflammation (FDG PET)
  - Fibrosis (MRI)
### Sarcoidosis Diagnosis

<table>
<thead>
<tr>
<th>Extra-cardiac</th>
<th>Cardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinical</td>
<td>• Clinical</td>
</tr>
<tr>
<td>• Imaging</td>
<td>• Imaging</td>
</tr>
<tr>
<td>- XR, CT</td>
<td>- ECG, TTE, MRI, FDG-PET</td>
</tr>
<tr>
<td>• Biopsy</td>
<td>• Biopsy</td>
</tr>
<tr>
<td>- skin, LN, lung, liver</td>
<td>- endomyocardium</td>
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<tr>
<td>• Biomarkers</td>
<td>• Biomarkers</td>
</tr>
<tr>
<td>• Qveim-Siltzbach test</td>
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#### Cardiac Sarcoidosis Diagnosis - Biomarkers

- ACE
- HS Tn
- Neopterin
- IL2 receptor
- Hypercalcemia, hypercalciuria
  - Low sensitivity/specificity

Cardiac Sarcoidosis
Diagnosis - Qveim-Siltzbach Test

- Ground up sarcoid tissue intradermally
- Type IV hypersensitivity reaction in 4-6 weeks
- Noncaseating granuloma
  - Not standardized
  - Variable sensitivity/specificity
  - Not FDA approved

Cardiac Sarcoidosis
Diagnosis - ECG

- No pathognomonic finding
- ECG abnormal 3.2-8.6%
  - Conduction abnormalities – AVB, BBB
  - Arrhythmia – atrial, ventricular
  - ST-T changes
  - Pseudoinfarct
  - Epsilon

Cardiac Sarcoidosis
Diagnosis - TTE

- No pathognomonic finding
  - Reduced LVEF/RVEF
  - LV/RV enlargement
  - RWMA
  - Aneurysm
  - Thinning of the basal septum
- Pulmonary hypertension
  - ?Strain


Cardiac Sarcoidosis
Diagnosis - MRI

- No pathognomonic finding
- Late gadolinium enhancement
  - Fibrosis vs Inflammation
  - Patchy, multifocal
  - Sub-epicardial, mid-wall
  - Basal (septum, infero-lateral)
- Prognosis (death, ICD shock, pacemaker requirement)
  - Sensitivity 76%-100%
  - Specificity 78%-92%
- LV/RV size/function, RWMA, aneurysm, thinning of the basal septum

Cardiac Sarcoidosis Diagnosis – FDG-PET

- No pathognomonic finding
  - Inflammation vs Fibrosis
  - Focal
  - Focal on diffuse
- Technical constraints
- Sensitivity 89% (79-100%)
- Specificity 78% (38-100%)
- Perfusion
  - Rubidium, Ammonia


Case 1

- 62 man, hypertension, dyslipidemia, OSA, farmer
- Syncope x2
- ECG 5/12/15
Case 1

- ECG - Sinus rhythm, 1° AVB, RBBB, ?Epsilon wave
- Event monitor
  - Sinus bradycardia
  - 1° AVB, RBBB
  - 3.8 second pause awake
- Stress echocardiogram - LVEF 55-60% at rest, no RWMA
- Dual chamber permanent pacemaker 5/27/15
Case 1

- March 2016 CHF
- LVEF now 20-25% from 55-60%
- Pacemaker interrogation
  - A-paced 95.4%, V-paced 99.2%
  - 9.2% atrial arrhythmia, atrial flutter
  - No escape at VVI 30 bpm
- LHC
- Nonobstructive disease
- AHF consult

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Case 1 – FDG-PET

Top-FDG
Bottom-Rb

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Allina Health
Case 2

- 46 man, well, policeman
- New CHF
Case 2

- 40 man, well, IT
- Palpitations
- ECG – Sinus rhythm, RBBB
- 24 hour Holter – Sinus rhythm, atrial tachycardia
- TTE – Mild LVE, LVEF 15-20%, moderate RVE, moderate RV dysfunction

Case 3
Case 3 – FDG-PET
Top-FDG
Bottom-Rb

Case 3 – MRI
Case 3 – Endomyocardial Biopsy

Cardiac Sarcoidosis
Diagnosis - Biopsy
Cardiac Sarcoidosis
Diagnosis - Biopsy

• Lymph node, lung
  - Higher diagnostic yield
  - Lower procedural risk
• Heart
  - Diagnostic yield <25%
  - Image (MRI, PET) or EP guidance increases diagnostic yield ~50%


Cardiac Sarcoidosis
Diagnosis - Enhancing Yield

• Hybrid imaging
  - FDG-PET - CMR
• Targeted endomyocardial biopsy
  - EP-guided
MRI with FDG-PET

MRI with FDG-PET
RV Electroanatomic Bipolar Voltage Mapping

- 19/40 biopsy specimens from 11 patients had electrogram voltage <5 mV, all had histopathologic abnormality (100% specificity and positive predictive value).
- A voltage amplitude cutoff of 5 mV had substantially higher sensitivity (70% vs. 26%) and negative predictive value (62%) than 1.5 mV.
- Normal signals with voltage >5 mV signified normal myocardium.

Cardiac Sarcoidosis
Treatment

• Inflammatory disorder
  - Immunomodulation
    - No RCT
    - Who, when, how

• Arrhythmias
  - Anti-arrhythmics
  - Ablation
  - Implantable electronic devices
    - No RCT
    - Primary/Secondary prevention
    - Who, when, how

• Heart failure
  - Neurohormonal antagonism
  - Mechanical circulatory support
  - Heart transplantation


Cardiac Sarcoidosis
Treatment

• Evidence of myocardial inflammation and
  - Mobitz II or CHB
  - Frequent ventricular ectopy or nonsustained ventricular arrhythmias
  - Sustained ventricular arrhythmias
  - Left ventricular systolic dysfunction
Case 4

- 66 man, hypertension, dyslipidemia, A330 captain
- Syncope
- ECG/Holter – Sinus rhythm, 1° AVB, intermittent Mobitz I and II
  2°AVB, RBBB, rare PVCs, PACs
- TTE – LVEF 68%, normal RV
- LHC – nonobstructive CAD
- FDG-PET
  - Resting rubidium PET perfusion images were normal
  - Uptake in the basal anterior and anteroseptal walls, the mid anteroseptal, inferior and inferoseptal walls and in the apical inferior wall.

Case 4 – Endomyocardial Biopsy
Case 4

- Prednisone 60 mg od with 10 mg/week taper to 10 mg od
- Mycophenolate mofetil 1,000 mg bid

Pre-Rx 7/6/16

Post-Rx 12/11/17
FDG-PET

7/8/16
- Resting rubidium PET perfusion images were normal
- FDG uptake in the basal anterior and anteroseptal walls, the mid anteroseptal, inferior and inferoseptal walls and in the apical inferior wall.

6/6/17
- Resting rubidium PET perfusion images were normal
- No significant focal myocardial FDG uptake.

Japanese Ministry of Health and Welfare Criteria for Diagnosis of Cardiac Sarcoidosis (Revised 2006)

<table>
<thead>
<tr>
<th>Histological diagnosis group</th>
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<tbody>
<tr>
<td>Cardiac sarcoidosis is confirmed when endomyocardial biopsy specimens demonstrate non-caseating epithelioid granulomas with histological or clinical diagnosis of extra-cardiac sarcoidosis</td>
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<table>
<thead>
<tr>
<th>Clinical diagnosis group</th>
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<tbody>
<tr>
<td>Although endomyocardial biopsy specimens do not demonstrate non-caseating epithelioid granulomas, extra-cardiac sarcoidosis is diagnosed histologically or clinically and satisfies the following conditions and more than one in six basic diagnostic criteria</td>
</tr>
<tr>
<td>(1) Two or more of the four major criteria are satisfied</td>
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<tr>
<td>(2) One in four of the major criteria and two or more of the five minor criteria are satisfied</td>
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</tbody>
</table>

<table>
<thead>
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<th>Major criteria</th>
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<tbody>
<tr>
<td>Advanced AV block</td>
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<tr>
<td>Bilateral thinning of the interventricular septum</td>
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<tr>
<td>Positive Gallium-67 uptake in the heart</td>
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<tr>
<td>Depressed left ventricular ejection fraction &lt;50%</td>
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<table>
<thead>
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<th>Minor criteria</th>
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<td>Abnormal ECG findings (ventricular arrhythmias, V1 or multiform or frequent PVCs), complete RBBB, axis deviation, or abnormal Q waves</td>
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<tr>
<td>Abnormal Echo wall motion abnormality or morphological abnormality (aneurysm or wall thinning or ventricular dilation)</td>
</tr>
<tr>
<td>Perfusion defects on nuclear imaging, thallium-201, technetium-99m SPECT</td>
</tr>
<tr>
<td>Delayed gadolinium enhancement on CMR</td>
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<tr>
<td>Interstitial fibrosis or macrophage infiltration on cardiac biopsy</td>
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</tbody>
</table>
### Heart Rhythm Society (HRS) consensus statement for diagnosis of cardiac sarcoidosis

**Histological diagnosis of cardiac sarcoidosis**

Endomyocardial biopsy specimens with non-caseating epithelioid granulomas and no alternative cause identified

**Clinical diagnosis of probable cardiac sarcoidosis**

Histologic diagnosis of extracardiac sarcoidosis and one or more of the following is present while reasonable alternative cardiac causes other than CS have been excluded:

- Corticosteroid or immunosuppressive therapy responsive cardiomyopathy or heart block
- Unexplained reduced LVEF (<40%)
- Mobitz type two second degree heart block or third degree heart block
- Depressed left ventricular ejection fraction <50%
- Patchy uptake on cardiac FDG-PET in a pattern consistent with CS
- Late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging in a pattern consistent with CS
- Positive gallium uptake in a pattern consistent with CS

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### HRS Diagnosis and Screening

- **Patients with biopsy-proven extracardiac sarcoidosis** - history unexplained syncope/pre-syncope/significant palpitations. I
- **Patients with biopsy-proven extracardiac sarcoidosis** - 12-lead ECG. I
- **TTE can be useful in patients with biopsy-proven extracardiac sarcoidosis.** Ila
- **CMR, or FDG-PET at a center with experience in CS imaging protocols can be useful in patients with 1 or more abnormalities detected on initial screening by symptoms/ECG/echocardiogram.** Ila
- **Screening for CS in patients age <60 yrs with unexplained second-degree (Mobitz II) or third-degree atrioventricular block can be useful.** Ila
- **CMR, or FDG-PET is not recommended for patients without abnormalities on initial screening by symptoms/electrocardiogram/echocardiogram.** III
Cardiac Sarcoidosis
Treatment - Immunomodulation

- Corticosteroids
  - No RCT
  - Dose
  - Duration
  - Harm vs. Benefit
- Mycophenolate Mofetil
  - No RCT
  - Dose
  - Duration
  - Harm vs. Benefit
- Anti-CD20
  - Rituximab
- Anti-TNFα
  - Adalimumab
  - Infliximab
- Antimalarials
- Azathioprine
- Cyclosporine
- Methotrexate
- Pentoxifylline
- Thalidomide
Cardiac Sarcoidosis
Treatment – Heart Failure

- Neurohormonal antagonism
- IED
- Heart transplant
  - Heart failure
  - Ventricular tachycardia
  - Recurrence rare
- MCS
  - LVAD
  - BiVADs/TAH


HRS Consensus Recommendations for ICD
HRS Management of Conduction Abnormalities

- Device implantation can be useful in CS patients with an indication for pacing, even if the atrioventricular block reverses transiently. IIa
- Immunosuppression can be useful in CS patients with second-degree (Mobitz II) or third-degree atrioventricular block. IIa
- ICD can be useful in patients with CS and an indication for permanent pacemaker implantation. IIa

HRS Management of Ventricular Arrhythmias

- Assessment of myocardial inflammation with FDG-PET can be useful in CS patients with ventricular arrhythmias. IIa
- Immunosuppression can be useful in CS patients with ventricular arrhythmias and evidence of myocardial inflammation. IIa
- Antiarrhythmic drug therapy can be useful in patients with ventricular arrhythmias refractory to immunosuppressive therapy. IIa
- Catheter ablation can be useful in patients with CS and ventricular arrhythmias refractory to immunosuppressive AND antiarrhythmic therapy. IIa
HRS Risk Stratification for Sudden Cardiac Death

- An EP study may be considered in patients with LVEF >35%, despite optimal medical therapy and a period of immunosuppression (if there is active inflammation). IIb
- CMR may be considered. IIb

Cardiac Sarcoidosis Prognosis

- Cardiac involvement in sarcoidosis portends poorer prognosis
- Mortality due to progressive heart failure or sudden death
  - No LV systolic dysfunction at presentation 10 year survival 83%
  - LV systolic dysfunction at presentation 10 year survival 53%
- Recurrence in transplanted heart rare
- Prognosis in clinically silent cardiac sarcoidosis is uncertain

Cardiac Sarcoidosis
Conclusion

• More common than recognized
• In sarcoidosis, prognosis poorer if cardiac involvement
• Conduction abnormalities, arrhythmias, heart failure, sudden death
• Imperfect diagnostic tests
  - Layer
  - Warranty period
• Low threshold for ICD
• Immunomodulation
  - Who, When, How
Zimbabwe

A: Alligator  
B: Log  
C: Crocodile  
D: Hippopotamus  
E: None of the above  
F: All of the above

Hippopotamus
Hippopotamus

- River horse (Male 3,300-4,000 lbs; Female 2,900-3,300 lbs)
- Sub-Saharan Africa
- Semiaquatic mammal
- Largely herbivorous
- 19 mph