WHEN IS LVH NOT JUST LVH?

PRACTICAL CLINICAL ALGORITHMS WHEN YOU SUSPECT CARDIAC AMYLOID

Mazen Hanna, MD
Co-Director, Amyloidosis Center
Section of Heart Failure and Cardiac Transplant
Cleveland Clinic
Disclosures

• **Grants/research support:** Term chair for Amyloid Heart Disease, Philanthropic donation

• **Consulting fees:** Pfizer, Alnylam, Akcea, Eidos (served on an advisory board)

• **Speaker fees:** Alnylam, Akcea

• **Other:**

• I will not be discussing names of medications for treatment during this lecture.
HCM

Amyloid

HTN heart w/ renal failure

Lysosomal storage disease
Two Main Types of Amyloid That Affect the Heart

**AL**
Light chain amyloidosis

**ATTR**
Transthyretin amyloidosis

Wild type
Hereditary
AL Amyloidosis (Light Chain amyloidosis)

- Plasma cell disorder
- IgG light chain (κ:λ)
- 3000-4000 cases annually
- Median age 63
- Untreated 6 mo survival if CHF

Kyle RA & Rajkumar V Immunological Reviews 194: 112–139; 2003
Transthyretin (TTR)
“Prealbumin”

Transport protein: thyroxine and retinol
Homotetramer: 127 amino acids monomers
130 mutations described in monomer
Wild Type Transthyretin Amyloidosis (wtATTR)

“Senile systemic amyloidosis” (SSA)

Median age at dx 74 years

Cardiomyopathy/ Atrial fibrillation/ Conduction disease

Bilateral carpal tunnel syndrome/ Spinal Stenosis *

The most common type of amyloidosis!!

Median survival 3-4 years
Hereditary TTR amyloidosis (hATTR)

> 130 point mutations
Autosomal dominant inheritance

Familial amyloid polyneuropathy (FAP)  Familial amyloid cardiomyopathy (FAC)
Mixed Phenotype Common

Phenotype:
- V30M
- S77Y
- E89L
- F64L
- G47A
- E89Q
- V30M (late onset)
- I107V
- T49A
- T60A
- L111M
- I68L
- V122I

"Neurologic" Phenotype
- V30M

"Cardiac" Phenotype
- 3.5% African-Americans
- Irish Descent

Early onset

Late onset
Pathology: Diffuse involvement

- Increase in LV mass w/out dilatation
- Atrial infiltration impairing atrial contraction
- Conduction system / valves
- Microvascular ischemia
Echocardiogram: Prompts Suspicion

Normal

Amyloid

• Classic Low-Voltage Electrocardiogram in Cardiac Amyloidosis\textsuperscript{1,2}

81 year old white male with biopsy proven ATTR cardiac amyloidosis

55 year old male with nephrotic syndrome and HF

LV &RV Thickening, Atrial Dilation, Thickened Valves, Pericardial Effusion
55 year old male
Nephrotic syndrome and heart failure

AL Amyloid

1.7 cm
1.6 cm
Clinical Presentation

**Cardiac**
- HFpEF ("right sided")
- "Hypertrophic cardiomyopathy"
- Low-flow low-gradient AS
- Afib/cardioembolic stroke
- Pacemaker/Heart Block
- Angina with normal course

**Non-Cardiac**
- Orthostasis
- Neuropathy
- Peripheral
- Autonomic
- Bilateral CTS (TTR > AL)
- Spinal stenosis (TTR)

References:
Physical Exam Findings Specific to AL Amyloidosis

Macroglossia

Periorbital Purpura
• Diagnosing Cardiac Amyloid

• Endomyocardial biopsy used to be the first option
MUST SUBTYPE THE AMYLOID

Determines further testing
Prognosis
Treatment

Immunohistochemistry

Mass Spectrometry
Diagnostic Approach

**IMAGING**
- Cardiac MRI
- Echo w/ Strain
- Tc PYP Scan

**Clinical + Echo + ECG**

**BIOPSY**

**Transthyretin**
- Genetic testing
  - Wild Type
  - Mutant TTR

**κ or ι light chains**
- Heme/Onc Consult

**Labs**
- Serum free light chains
- Serum immunofixation
- Urine immunofixation
- NTproBNP
- Troponin T
Laboratory Testing for work up of AL

- SPEP and UPEP

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kappa Free, Serum</td>
<td>3.30 - 19.40 mg/L</td>
</tr>
<tr>
<td>Lambda Free, Serum</td>
<td>5.7 - 26.3 mg/L</td>
</tr>
<tr>
<td>K/L Ratio, Serum</td>
<td>0.26 - 1.65</td>
</tr>
</tbody>
</table>

* Urine immunofixation
Diagnosis Cardiac Amyloid by MRI

80% sensitivity
90% specificity
85% negative predictive value

Vogelsburg et al. JACC 2008;51:1022-30
Apical Sparing Pattern on Echo
Apical Sparing Pattern: Longitudinal Strain
99mTechnetium pyrophosphate (PYP) or dipyrophosphate (DPD) Scintigraphy:

Diagnostic of ATTR Cardiac Amyloidosis

1) Grade 2 or 3 scan
2) Negative monoclonal lab testing
3) 91% sensitivity and 100% specificity for ATTR amyloidosis

Perugini score
- 0 – absent uptake - NEGATIVE
- 1 – less than rib – INDETERMINATE
- 2 – equal to rib – LIKELY POSITIVE
- 3 – greater than rib – POSITIVE
Starts With Clinical Suspicion

Serum free light chains
Serum immunofixation
Urine immunofixation

ECG
ECHOCARDIOGRAPHY (CARDIAC MRI)

HEART BIOPSY

Technetium pyrophosphate scan

Bone marrow biopsy
Fat pad aspirate
Biopsy affected organ

Genetic testing
Wild type Hereditary

Grade 2/3 uptake (-) monoclonal
78 yo AA female  h/o HTN & EF 45%
Referred for shortness of breath
Echocardiogram
Serum free light chains
Serum immunofixation
Urine immunofixation
Technetium pyrophosphate scan
ECHO (with strain)
ECG
NORMAL fLC
No M protein

Hereditary transthyretin cardiac amyloidosis (ATTRv)
61 yo white female

- SOB and edema X 1 year
- Urine with 9 grams proteinuria
ECG: 1\textsuperscript{st} degree AV block, LAFB
<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LVPWd</td>
<td>1.0 cm</td>
<td></td>
</tr>
<tr>
<td>LV1Dd</td>
<td>4.9 cm</td>
<td></td>
</tr>
<tr>
<td>EDV(Heich)</td>
<td>110 mL</td>
<td></td>
</tr>
<tr>
<td>IVSd</td>
<td>1.3 cm</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin T</td>
<td>0.000 - 0.029 ng/mL</td>
<td>&lt;0.010</td>
</tr>
<tr>
<td>NT Pro BNP</td>
<td>&lt;125 pg/mL</td>
<td>3505 (H)</td>
</tr>
</tbody>
</table>
Global LGS – 10.5%
Serum free light chains
Serum immunofixation
Urine immunofixation

ECG
ECHO (with strain)

TcPYP scan

Kidney Biopsy
+ Kappa light chain amyloid

Bone Marrow biopsy
only 1% plasma cells,
Congo red negative

Kappa light chain AL Amyloid
81 yr old white male
Serum immunofixation
No M protein

<table>
<thead>
<tr>
<th>Component</th>
<th>Latest Ref Rng &amp; Units</th>
<th>5/24/2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kappa Free, Serum</td>
<td>3.30 - 19.40 mg/L</td>
<td>41.6 (H)</td>
</tr>
<tr>
<td>Lambda Free, Serum</td>
<td>5.7 - 26.3 mg/L</td>
<td>23.1</td>
</tr>
<tr>
<td>K/L Ratio, Serum</td>
<td>0.26 - 1.65</td>
<td>1.80 (H)</td>
</tr>
</tbody>
</table>

ECHO (with strain)

ECG

TTR cardiac amyloid
Genetic testing
No mutation

Wild type transthyretin cardiac amyloid
Teaching points

• Look at ECG and wall thickness on ECHO

• Diagnostic work up
  • **DO NOT ORDER SPEP AND UPEP!!!!!!!**
  • Rather order serum free light chains & immunofixation serum +/- urine
  • Technetium pyrophosphate scan specific for TTR

• Red flags
  • *Older white male w previous carpal tunnel and diastolic HF or “HOCM”*
  • *Older African American with “diastolic heart failure”*
  • As about both carpal tunnel and spinal stenosis in history taking