Uncommon Etiologies of Heart Failure: Cardiac Amyloidosis

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Objectives

- Describe cardiac amyloidosis as one of the uncommon etiologies of cardiomyopathy
- Discuss clinical presentation, incidence, and treatment of cardiac amyloidosis
- Discuss the application of guideline-directed medical therapy, including recent research findings, in the setting of cardiac amyloidosis

Disclosures: NONE

A 44 yo man with no previous medical history presented with a three year history of progressive exertional dyspnea. During the past year he developed edema and increasing abdominal girth.

Family History: Father died of a stroke at age 45, siblings all younger and alive and well.

Social History: Married with children, works as a banker.

PE: BP 113/74↓, 100/62↑, HR 88, no ∆. Remarkable for ↑↑JVD, bibasilar rales, sustained and diffuse PMI, +S4. Liver span 12 cm, 2+ bilat. pedal edema.

Labs: NT-proBNP 8760 pg/ml. Troponin-T 0.02 ng/ml
Case Presentation

Echocardiography


Definition and Pathogenesis

- Misfolding of proteins
- Oligomers, pre-fibrillar protein aggregation
- Local cellular toxicity, complex pathophysiology
- Multi-organ dysfunction, fatal disorder
- Relatively rare, often misdiagnosed or confused with other forms of infiltrative and hypertrophic cardiomyopathy
Major Amyloid Types & Causative Proteins

<table>
<thead>
<tr>
<th>Amyloid Types</th>
<th>Constituent Protein Subunits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light chain (AL) [Primary]</td>
<td>Immunoglobulin Light Chains</td>
</tr>
<tr>
<td>Wildtype Transthyretin (ATTRwt) [“Senile”]</td>
<td>Transthyretin - Wildtype</td>
</tr>
<tr>
<td>Familial Transthyretin (FAC/FAP)</td>
<td>Transthyretin with Mutation</td>
</tr>
<tr>
<td>Hereditary Transthyretin (ATTRm)</td>
<td>Transthyretin with Mutation</td>
</tr>
<tr>
<td>Hereditary Apolipoprotein (AApoA1)</td>
<td>Apolipoprotein A1 mutations</td>
</tr>
<tr>
<td>Hereditary Fibrinogen (AFib)</td>
<td>Fibrinogen mutations</td>
</tr>
<tr>
<td>Isolated Atrial Amyloid (IAA)</td>
<td>Atrial Natriuretic Peptide</td>
</tr>
<tr>
<td>Secondary Amyloidosis (AA)</td>
<td>Amyloid Protein A</td>
</tr>
</tbody>
</table>

*FAC = Familial Amyloid Cardiomyopathy  FAP = Familial Amyloid Polyneuropathy

Cardiac Amyloidosis

<table>
<thead>
<tr>
<th>Type</th>
<th>Incidence/Prevalence</th>
</tr>
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</table>
| Primary AL Amyloid (Ig Light Chain) | ~ 2500 cases per year 50% have cardiac involvement  
Protein factory: Plasma cells in bone marrow |
| ATTR Mutant (Transthyretin)  | 4% of African American are carriers 25,000 – 120,000 US patients  
Hereditary  
Protein factory: Liver |
| ATTRwt (Senile) (Transthyretin) | ~ 10-25% of male adults  ~1 million  
No mutation  
Protein factory: Liver |

ATTR Geographic Distribution & Age

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mutation</th>
<th>Clinical Classification</th>
<th>Population and Age of Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Senile systemic amyloidosis (SSA)</td>
<td>WT</td>
<td>Cardiomyopathy</td>
<td>10-25% of males worldwide &gt; 60 years of age</td>
</tr>
</tbody>
</table>
| Familial amyloid cardiomyopathy (FAC)| V122     | Cardiomyopathy          | 3-4% African Americans (~1.3 Million)  
5% West Africans  
High penetrance > 66 years of age |
| Familial amyloid polyneuropathy (FAP)| V30M     | Peripheral Neuropathy   | Europe and Japan (~12,000 worldwide)  
High penetrance  
early and late onset 30-80 years of age |

Sravan C. Pendhale et al. (PNAS 2013;110:9992-9997)
Prevalence of Variant TTR Amyloid

<table>
<thead>
<tr>
<th>Mutation</th>
<th>ORIGIN</th>
<th>Decade of Presentation/ Prevalence</th>
<th>M : F Ratio</th>
<th>Involved Organs</th>
</tr>
</thead>
<tbody>
<tr>
<td>V122I</td>
<td>United States, Caribbean, Africa</td>
<td>50-55 y, highly prevalent among African Americans and Africans; variable clinical penetrance 0.4% of Caucasians</td>
<td>3 : 1 (Gene +)</td>
<td>Heart more common (majority of cases)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 : 1</td>
<td></td>
<td>Peripheral nerves, ANS</td>
</tr>
<tr>
<td>T60A</td>
<td>United Kingdom, Ireland</td>
<td>30-60 y, 1% Northwest Ireland</td>
<td>2 : 1</td>
<td>Heart common up to 90% by diagnosis</td>
</tr>
<tr>
<td>V30M</td>
<td>Most common and found worldwide</td>
<td>40-50 y (geographic variation)</td>
<td>2 : 1</td>
<td>Heart less common (Peripheral nerves, Autonomic nervous system)</td>
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<td>Portugal, Sweden, Japan</td>
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Survival

Among 24 patients with familial amyloid cardiomypathy, the 24 with familial amyloidosis have a better survival free of death or the need for cardiac transplantation than those with primary (AL) amyloidosis.

Revised prognostic staging system for AL cardiac amyloidosis

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<tr>
<th>Revised Mayo Clinic stage</th>
<th>Proportion of patients in primary cohort (%)</th>
<th>Median Overall Survival, months</th>
<th>5-year Survival rate (%)</th>
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<tbody>
<tr>
<td>I</td>
<td>25</td>
<td>94.1</td>
<td>59</td>
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<td>27</td>
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<td>23</td>
<td>5.8</td>
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A score of 1 is assigned for each of three variables: cardiac troponin T ≥0.025 ng/ml, NT-ProBNP ≥1800 pg/ml, and dFLC ≥18 mg/dl.

Revised Mayo Clinic staging system for cardiac AL amyloidosis

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Common Presenting Symptoms

- Parasthesias and dysesthesias with or without pain.
- Reflected in an advanced phase and can manifest first in the lower limbs and impair walking.
- Carpal tunnel syndrome is frequent.
- Generalized weakness.
- Autonomic nervous system involvement may be present.
- Bowel dysfunction.
- Orthostasis.
- Urinary retention or incontinence.

Extra-cardiac Manifestations

- Sensorimotor polynearopathy may be present.
- Parasthesias and dysesthesias with or without pain.
- Reflected in an advanced phase and can manifest first in the lower limbs and impair walking.
- Carpal tunnel syndrome is frequent.
- Generalized weakness.
- Autonomic nervous system involvement may be present.
- Bowel dysfunction.
- Orthostasis.
- Urinary retention or incontinence.

Online Survey – Amyloidosisline.com

Cardiac MRI

- CMR provides a "second opinion" on cardiac structure and systolic function.
  - Echocardiography remains the mainstay of current cardiac imaging, by defining cardiac structure and function.
- Advantages
  - Tomographic technique provides the most accurate measure of structure and systolic function.
  - Evaluation of myocardial tissue characterization with gadolinium.
  - Phase-sensitive inversion recovery sequence is highly sensitive and specific with images virtually pathognomonic for amyloidosis.
  - CMR with T1 mapping, a relatively new CMR technique, can measure the amyloid burden.
- Disadvantages
  - Contrast contraindicated if eGFR < 30
  - Can't be performed routinely in patients with pacemakers/ICDs
  - Unable to assess diastolic function
  - Not widely available
  - Not able to distinguish type of cardiac amyloid
  - Delayed enhancement not specific for cardiac amyloid
    - Also seen in HCM and other disorders

Non-invasive approach to work-up

Tc-99 PYP can Distinguish AL and ATTR Cardiac Amyloidosis

171 patients, Tc 99m PYP cardiac imaging showed 91% sensitivity & 92% specificity for ATTR cardiac amyloidosis
**Invasive approach to work-up**

- Lab Studies for AL amyloid screen
  - Serum Ig free light chain (FLC) assay
    - Comparing the ratio of κ FLCs to λ FLCs in serum against reference ranges (0.26-1.65)
    - Elevated ratio may indicate that person may have a plasma cell dyscrasia or multiple myeloma. Renal failure can increase FLCs.
    - Kappa/lambda ratio between 0.5 and 5.0 accurately distinguishes AL amyloidosis from non-AL amyloidosis in setting of cardiac amyloidosis.
  - Serum Immunofixation
  - Urine Immunofixation
  - SPEP / UPEP (Not useful in initial screen)

**Management Considerations**

- Mostly symptom management
  - ACEI/ARB and beta blocker not well tolerated
  - Congestion: Bioavailable diuretics (aldosterone antagonists?) salt and fluid restriction, daily weights
  - Atrial fibrillation
    - Digoxin and non-dihydropyridine calcium channel blockers should be avoided due to possible binding to amyloid fibrils and risk of toxicity
    - Amiodarone (with caution)
  - Anticoagulation
  - AVN ablation/pacemaker
  - Heart Block: Pacemaker
  - AICD/CRT-ICD?
Time for Genetic Testing

- Clinical Suspicion for Cardiac Amyloidosis
- Imaging Highly Suggestive of Cardiac Amyloidosis (Positive CMRI or 99mTc-PyP Spect MPI)
- Serum Free Light Chain Assay, Serum and Urine Immunofixation Testing Results
- Marrow and Fat Aspirate or Endomyocardial Biopsy (Exclude AL Amyloidosis)
- Order TTR Mutation Testing (TTR Mutant or Wild Type) and Consider EMB

2016 ISHLT Listing Criteria for Heart Transplantation: 10-Year Update

2.2.2 Patients with transthyretin related (TTR) amyloidosis involving the heart may be considered for heart transplantation (HT). Familial TTR cardiac amyloidosis patients should be considered for combined heart and liver transplantation in experienced centers with established collaboration between cardiology, hepatology, and neurology teams. (Class IIA, Level of Evidence B)

2.2.3 Amyloid involvement of extra-cardiac organs must be carefully evaluated when considering AL amyloid patients for sequential HT/ASCT or TTR amyloid patients for HT or combined HT with liver transplantation (LT). Severe extracardiac amyloid organ dysfunction should be considered as a contraindication to proceeding with HT. (Class IIA, Level of Evidence B)

Treatment Targets for TTR Amyloid

Diflunisal - Tafamidis

Diflunisal:
• Non-steroidal Anti-inflammatory (NSAID caution)
• Non-selective stabilizer of TTR tetramer
  ○ RCT in FAP showed significant reduction in rate of neurological deterioration and improvement in QOL\(^1\)
  ○ Japanese observational study in FAP reported sustained effects on neurological & cardiac function

Tafamidis (available in Europe)
• Kinetic stabilizer to prevent TTR amyloidogenesis
• Reduced neurological impairment over 30 months

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EGCG – “Green Tea”

• Epigallocatechin-3-gallate (EGCG) – “Green Tea”
  ○ Inhibits fibril formation
  ○ Disrupts fibrils
  ○ Stabilizes circulating TTR tetramers
  ○ AL pts - ↓ IVS thickening
    ○ ↑ EF
  ○ ↑ NYHA (Mereles D et al Clin Res Cardiol 2010)
  ○ TTR pts - ↓ IVS (14 pts: Kirsten et al. Clin Res Cardiol 2012)
  ○ ↓ LV mass

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Doxycycline and TUDCA

• Doxycycline 100 mg po BID
  ○ Disrupts amyloid fibrils

• Tauroursodeoxycholic Acid (TUDCA)
  ○ ↓ prefibrillar aggregates
  ○ Phase 2 Doxy 100mg bid + TUDCA 40 pts 12 months
  ○ Stabilization of cardiomyopathy and neuropathy (Obici et al. Amyloid 2012)
Treatment of AL Amyloidosis

- In collaboration with Hematology
- Effective drug targeting clones
  - Chemotherapy: (used in MM)
    - Melphalan, Dexamethasone, Cyclophosphamide, Bortezomib, Lenalidomide, etc
  - Autologous stem cell transplantation (ASCT)
- New drugs targeting amyloid are in trials
- Heart Transplant should not be excluded

Summary

- Amyloid cardiomyopathy should be suspected in HFpEF
- Better survival when diagnosed early
- Proven therapies are limited but available
- Investigational therapies are in progress (siRNA)
- Resources clinicians: HFSA Online CME for Cardiac Amyloidosis
- Resources for Patients and Providers