Cardiac Amyloid

May 11, 2019
Vikranth Gongidi, DO FACC
Cardiology
Cleveland Clinic Indian River Hospital
Vero Beach, FL
Vikranth Gongidi, DO FACC

I Have No Disclosures
OBJECTIVES

• Understand differences between Transthyretin (ATTR) and Light Chain (AL)
• Understand role of imaging in establishing the diagnosis
• Discuss treatment options
Introduction

• First described by Rudolf Virchos (1853) as deposits in tissues noted with iodine and sulfuric acid stains.
• Derived from “amylum” latin for starch
• 1922 Congo red stain was discovered
• 1927 apple green birefringence noted in brains of patients with Alzheimer’s dx
Introduction

• Extracellular space of the heart is expanded by amorphous, proteinaceous material known as amyloid

• composed of fragments of precursor protein, proteoglycans and serum amyloid P (SAP)

• Extremely resistant to degradation
Introduction

• Systemic amyloidosis:
  1. AL Amyloidosis—>monoclonal plasmacytoma in the bone marrow
  2. AA Amyloidosis—>deposits of amyloid protein due to chronic inflammation (RA, Tuberculosis)
  3. Senile or wild type (ATTR subtype)
  4. Familial AF amyloid (ATTR subtype)
  5. AH amyloid—>B2-microglobulin deposits in dialysis patients
Introduction

- Cardiac amyloid is systemic disease
- Most common Cardiac amyloid types:
  - Transthyretin (ATTR)
  - Light chain (AL)
<table>
<thead>
<tr>
<th>Amyloid Nomenclature</th>
<th>Precursor Protein</th>
<th>Age Range, yrs</th>
<th>Sex</th>
<th>Clinical Clues</th>
<th>Laboratory Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL</td>
<td>Light chains</td>
<td>50+</td>
<td>Either</td>
<td>Multiorgan involvement. Periorbital bruising or macroglossia are almost pathognomonic of AL in setting of typical MRI or electrocardiogram. Severe hypotension with ACE inhibitors.</td>
<td>Elevated serum free lambda or kappa, with abnormal ratio. Monoclonal spike in serum and/or urine. Suppressed immunoglobulins. Proteinuria.</td>
</tr>
<tr>
<td>ATTRwt</td>
<td>Wild-type (normal) transthyretin</td>
<td>65+</td>
<td>Marked male predominance, &gt;15:1</td>
<td>History of carpal tunnel syndrome 5-10 yrs earlier, with no other organ involvement.</td>
<td>No specific abnormalities. (Normal free light chain values, no proteinuria)</td>
</tr>
<tr>
<td>ATTRm</td>
<td>Mutant transthyretin</td>
<td>40+ (mutation dependent). In V122I, the common African-American variant, usual age of clinical onset is 60-65 yrs.</td>
<td>Either, slight male predominance.</td>
<td>African-American/Caribbean origin (for V122I TTR variant).</td>
<td>No specific abnormalities on routine testing. Genetic testing reveals mutation in TTR molecule</td>
</tr>
<tr>
<td>AA (Secondary)</td>
<td>Serum amyloid A (an acute phase protein)</td>
<td>May occur in 20s-30s upward with severe inflammatory disease.</td>
<td>Either</td>
<td>Underlying chronic inflammatory disease. Hepatomegaly, splenomegaly. Usually no cardiac involvement, but in rare cases may be severe</td>
<td>High ESR/CRP. Proteinuria.</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; CMR = cardiac magnetic resonance; CRP = C-reactive protein; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; LBBB = left bundle branch block; TTR = transthyretin.
Cardiac Amyloid (ATTR)

• Transthyretin (ATTR)
  • tetrameric protein rich in beta strands present in all human serum
  • functions to transport thyroxine and retinol-binding protein (TTR)
  • synthesized mostly by liver
  • important for behavior, cognition, and nerve regeneration and axonal growth
  • TTR aggregate into insoluble amyloid fibers
Cardiac Amyloid (ATTR)

- Tranthyretin (ATTR)
  - Single point mutation increases likelihood of misfolding to beta-pleated sheets
  - More than 80 mutations described
  - V30M mutation is most common in world but in USA its second most common
  - Cluster common in Portugal, Japan and Sweden
  - T60A mutation most common in USA originated in Northwest Ireland (Appalichian amyloidosis)
  - V122I mutation originated in West Africa
Cardiac Amyloid (AL)

• Wild type (wt) TTR can also occur.
  • sporadic
  • called senile cardiac or senile systemic
  • protein deposits occur exclusively in men >60
General Characteristics

• Predominately men (80% of ATTR cases)
  • Mutant ATTR (72% male)
  • wt ATTR (99% male)
  • Mutant and wt ATTR better prognosis than AL amyloidosis
• Median survival of wt ATTR is over 60 months versus 5.4 months in AL amyloidosis
Clinical characteristics

• Amyloid infiltrating results in poor diastolic relaxation (poor filling, low end-diastolic volume, restrictive physiology)
• Right-side heart failure predominates (lower-extremity edema, hepatomegaly, ascites and elevated JVP)
• Severe atrial and ventricular infiltration results mechanical standstill and thrombus formation (even in sinus rhythm)
• EKG shows low voltage in QRS complex (useful but not reliable)
• Associated with carpal tunnel syndrome (precede cardiac manifestation 8-10yrs)
Clinical characteristic

- Peripheral neuropathy noted in over 60%
- Suspect amyloidosis if heart failure with preserved ejection fraction or infiltrative cardiomyopathy noted on imaging
- Orthostatic hypotension, sweat abnormalities, urinary incontinence often present
- Prevalence of wt ATTR was 25% in one autopsy study of patient over 85yrs old. (clinical significance was not known)
- True prevalence is not known
Diagnosis

• Echocardiogram
  • most common used modality when amyloid cardiomyopathy is suspected.
  • thickening of the left ventricular free wall and the septum
  • often misdiagnosed at hypertrophic cardiomyopathy or hypertensive cardiomyopathy
  • usually biventricular hypertrophy
  • left atrial enlargement
Diagnosis

• Low tissue doppler velocities
• High E/e ratio
• Restrictive physiology
• Longitudial strain is severely impaired for both (worse in AL amyloidosis)
• Strain and tissue doppler is picking up early amyloidosis compared to traditional echo
• Strain demonstrates “apical sparing”
Others tests

- Right-side cauterization shows restrictive filling pattern, median PCWP 21mmHg
- ECG low-voltage (only 36%) and pseudo infarction complex with poor R-wave progression (65%)
- Cardiac MRI
- Radionuclide scan
Cardiac MRI

• Cardiac MRI demonstrates late gadolinium enhancement over the entire subendocardial circumferencne
• Sensitivity 80% specificity 94% PPV 92% NPV 85%
• Useful in distinguishing between hypertrophic cardiomyopathy and hypertensive heart disease
• 90% ATTR have transmural LGE vs 37% AL
Radionuclide imaging

• First noted 30 years ago
• DPD (Tc-3,3-diphosphono-1,2-propanodicarboxylic acid) first used.
• Higher uptake in ATTR versus AL amyloidosis.
• Earlier uptake noted than CMR
Radionuclide imaging

• Tc-pyrophosphate (more commonly available in USA) uptake showed 97% sensitivity and 100% specificity for ATTR
• Tc-hydroxyxymethylene diphosphonate can detect ATTR
• Negative SPECT can exclude cardiac involvement
Other testing

• Labs: elevated troponin and BNP are elevated (ATTR appears to be less toxic than AL amyloid)
• Biopsy verification is essential but not necessary (especially in elderly or debilitated pt with neuropathy)
• Noncardiac biopsies usually show amyloidosis (AL greater than ATTR) in patient with positive echo or CMR finding;
  • skin biopsy from abdominal wall (73% sensitivity)
  • bone marrow biopsy (41%)
  • rectal or sural nerve biopsy (81%)
  • minor salivary glands (61%)
• Negative biopsy of unaffected organs does not exclude diagnosis
• Confirmation of amyloid type made on immunostaining and mass spectroscopy (gold standard)
**CENTRAL ILLUSTRATION:** Diagnosing and Typing Cardiac Amyloidosis in a Patient With Unexplained Heart Failure

- Echocardiogram or MRI suggestive of cardiac amyloidosis
- Clinical and laboratory evaluation including: NTproBNP, troponin I, SPEP, serum immunofixation and free light chain assay
- Is plasma-cell dyscrasia present?*

Myocardial uptake of \[^{99m}Tc\text{CPYP/DPD}\] assessment

- None or trace
- Strongly positive

Bone marrow biopsy +/- cardiac or non-cardiac biopsy

- Immunohistochemistry strongly positive for light chains and negative for transthyretin in amyloid deposits
- Immunohistochemistry shows ambiguous results
- Mass spectrometry confirms light chains in amyloid deposits

Cardiac amyloidosis is unlikely. IMPORTANTLY, proceed with endomyocardial biopsy if clinical suspicion of amyloidosis is still high.

- ATTRwt (non-hereditary form caused by wild-type TTR)
- ATTRm (hereditary form caused by a genetic mutation of TTR)

Light-chain (AL) amyloidosis


Rodney H. Falk et al. JACC 2016;68:1323-1341
ATTR Therapies

• Supportive care
  • Diuretic agents should be cautiously used
    • since there is usually low end-diastolic volumes and high filling pressures needed to distend a stiff ventricle
    • reduce stroke volume and SBP results in cerebral hypo perfusion
  • Digoxin binds to amyloid fibers and increase toxicity
  • Beta blockers, ACE and ARB are poorly tolerated
ATTR Therapies

- Liver transplant
  - considered first-line
  - bulk TTR is produced in liver
  - mutant ATTR is removed but wt ATTR is present and cardiac deposits still occur
  - quality of life is stable for first 4 years then declines
- Heart and Liver transplant do better (5 year survival 80%, 10 year survival 28-78% depending on mutation involved, V30M better prognosis)
ATTR Therapies

- Pharmacologic therapy
  - Several on going trial
  - Catechin (present in green tea) inhibits amyloid fibril formation
  - Diflunisal binds to TTR and stabilizes monomers thru prevent misfolding
  - Tafamidis approved in Europe and Japan for mutant ATTR, prevents dissociation of native TTR
  - RNA inhibition technology is used to knock down disease causing TTR tissue deposits
  - Doxycycline can disrupt fibrils and in mouse models results in amyloid disaggregation
<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>TTR Type</th>
<th>Organs</th>
<th>Study Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline + tauroursodeoxycholic acid</td>
<td>II</td>
<td>Wild type and mutant</td>
<td>Cardiac, nerve</td>
<td>NCT01171859</td>
</tr>
<tr>
<td>Revusiran (ALN-TTRsc), Alnylam Pharmaceuticals Cambridge (Cambridge, Massachusetts)</td>
<td>III</td>
<td>Mutant</td>
<td>Cardiac</td>
<td>NCT02319005</td>
</tr>
<tr>
<td>Tafamidis</td>
<td>III</td>
<td>Wild type and mutant</td>
<td>Cardiac</td>
<td>NCT01994889</td>
</tr>
<tr>
<td>Diflunisal</td>
<td>II/III</td>
<td>Mutant</td>
<td>Nerve</td>
<td>NCT01432587</td>
</tr>
<tr>
<td>Patisiran (ALN-TTR02), Alnylam Pharmaceuticals Cambridge (Cambridge, Massachusetts)</td>
<td>III</td>
<td>Mutant</td>
<td>Nerve</td>
<td>NCT01960348</td>
</tr>
<tr>
<td>ISIS-TTR_{rx} Isis Pharmaceuticals (Carlsbad, California)</td>
<td>III</td>
<td>Mutant</td>
<td>Nerve</td>
<td>NCT01737398</td>
</tr>
<tr>
<td>SOM0226, SOM Biotech SL (Barcelona, Spain)</td>
<td>I-II</td>
<td>Mutant</td>
<td>Nerve</td>
<td>NCT02191826</td>
</tr>
</tbody>
</table>

TTR = transthyretin.
AL Amyloid

- AL amyloidosis effects renal, neural and/or skin
- Hematologic disorder of plasma cells closely related to multiple myeloma
- Abnormal proliferation of plasma cells overproducing lambda and kappa (less common) light chain
- Unlike multiple myeloma AL amyloid plasma cells make up less than 20% of bone marrow
- Renal involvement most common, Cardiac is second
- Cardiac AL amyloid is rarely by itself
AL Amyloid

- Clinical aspect of AL
  - Severity of heart failure is worse
  - AL amyloid infiltration into heart is necessary before
  - Light chains cause increase in cellular reactive oxygen species and up-regulation of heme oxygenate which induces apoptosis
AL Amyloid

- Clinical Manifestations
  - Dyspnea on exertion is most common manifestation (likely from LV diastolic dysfunction)
  - Peripheral edema (likely related to hypoalbuminemia for nephrotic syndrome)
  - Ascites also common
  - Prominent V waves noted in absence of mitral regurgitation
  - Amyloid deposits in atrium results in dysfunction and thrombus formation even in sinus rhythm
  - Exertion syncope likely form low or fixed cardiac output
AL Amyloid

• Clinical Manifestation
  • Jaw claudication, leg claudication or angina due to small vessel amyloid deposits
  • 10% have macroglossia
  • Periorbital bruising in setting of heart failure (pathognomonic for AL)
  • Enlarged liver due to hepatic infiltration
  • Low blood pressure (decrease CO and low peripheral tone)
  • Early sensory neuropathy
AL Amyloid Tests

• Diagnostic tests
  • ECG shows low voltage with unusual axis (extreme right axis). QRS low voltage but P wave is often normal size
  • Echo shows LV wall thickness exceeds 15mm;
    • Hypetensive heart rarely has >15mm thickness
    • E/e exceeds 15
    • Restrictive pattern with short deceleration time
    • Pericardial effusion is common but rarely large and tamponade is rare.
AL Amyloid Tests

- Cardiac MRI features:
  - difficulty in nulling the myocardium following gadolinium injection
  - noncoronary usually subendocardial pattern of delayed gadolinium enhancement
AL Amyloid Tests

• SPECT
  • 1980s Tc-PYP was noted as marker for cardiac amyloid but fell out of favor due to low sensitivity
  • However, recently it was noted that Tc-PYP and DPD are avidly taken up by hearts infiltrated by TTR amyloid but none or minimal uptake in AL amyloid
AL Amyloid

• SPECT
  • If Tc-PYP or DPD is positive and there is absence of plasma cell dyscrasia, it has been deemed acceptable as specific enough for TTR amyloidosis without cardia biopsy
  • Positive Tc-PYP is helpful if to identify TTR amyloidosis with unrelated MUGS (~20% of TTR pts)
AL Amyloid

- Labs:
  - Usually unrevealing but often have
    - hypoalbuminemia,
    - hypercholesterolemia,
    - low troponin elevation
  - Free light chain kappa/lambda ratio is >90% in untreated AL
  - All patient with suspected AL should have bone marrow biopsy to determine percentage of plasma cells involved to rule out both multiple myeloma
AL Amyloid

- Therapy for AL:
  - Optimize heart failure
  - Chemotherapy aimed at getting rid of amyloidogenic plasma cell dysuria
AL Amyloid

• Therapy:
  • atrial tachycardia and arrhythmia common
  • treat with amiodarone and sometimes dofetilide;
  • anticoagulation should be given (even if pt in sinus rhythm)
  • no proven benefit of pacing or prophylactic ICD
AL Amyloid

- Therapy
  - high dose melphalan and stem cell transplant was tried but high treatment related mortality
  - bortezomib with dexamethasone and low-dose cyclophosphamide has some success
  - cardiac transplant has been tried with concomitant chemotherapy
    - high mortality rate
CENTRAL ILLUSTRATION: Diagnosing and Typing Cardiac Amyloidosis in a Patient With Unexplained Heart Failure

Echocardiogram or MRI suggestive of cardiac amyloidosis

Clinical and laboratory evaluation including: NTproBNP, troponin T, SPEP; serum immunofixation and free light chain assay

Is plasma-cell dyscrasia present?*

Myocardial uptake of $^{99m}$TcPYP/DPD assessment

Bone marrow biopsy +/- cardiac or non-cardiac biopsy

None or trace

Strongly positive

Is there a transthyretin protein (TTR) mutation present?

Cardiac amyloidosis is unlikely. IMPORTANTLY, proceed with endomyocardial biopsy if clinical suspicion of amyloidosis is still high.

ATTRwt (non-hereditary form caused by wild-type TTR)

ATTRm (hereditary form caused by a genetic mutation of TTR)

Light-chain (AL) amyloidosis

Immunohistochemistry shows ambiguous results

Mass spectrometry confirms light chains in amyloid deposits

ATTRm


Rodney H. Falk et al. JACC 2016;68:1323-1341
Conclusion

• Amyloidosis is a condition where the extracellular space of the heart is expanded by amorphous, proteinaceous material which is extremely difficult to degrade.
• The source of these proteins are the liver (ATTR) or plasma cells (AL).
• Amyloidosis leads to restrictive cardiac physiology
Conclusion

• Speckled echocardiogram and strain analysis have advanced the ability to detect early changes from amyloidosis

• Cardiac MRI and SPECT Tc-PYP images can help differentiate between ATTR and AL amyloidosis.
References

Falk RM et al. AL (Light-chain) cardiac amyloidosis. J AM Coll Cardiol 2016; 68: 1323-41


Pai RG, Varadarajan P. Deeper into cardiac amyloid. J AM Coll Cardiol: Cardiovascular imaging, 2017; Vol 10, No 4:408-10

Maurer M, Castano, A. Prognosticating in Cardiac Amyloidosis. J AM Coll Cardiol: Cardiovascular imaging, 2018; in press

ASNC Practice points: 99mTechnetium-Pyrophosphate imaging for transthyretin cardiac amyloidosis.
Cleveland Clinic

Every life deserves world class care.