Practical Applications for hATTR Amyloidosis Diagnosis

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Disclosures

Served on Advisory Board for Pfizer, Alnylam, Eidos, and Akcea Therapeutics in the past

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Objectives

Brief Review of Hereditary Transthyretin Amyloidosis

Basic Algorithm to Diagnose Hereditary Transthyretin Amyloidosis

Review Common Misdiagnoses

Case Examples in Diagnosis and Management
Two Main Types of Amyloidosis That Affect the Heart

**AL**
Light chain amyloidosis

**ATTR**
Transthyretin amyloidosis

Wild Type Hereditary
Two Main Types of Amyloidosis That Affect the Heart
Transthyretin (ATTR) Amyloidosis
What is Transthyretin?
- Transport protein for Thyroxine and Retinol binding protein
- Homotetramer made up of 4 identical monomers (127 a.a)
- Used be called “Prealbumin”, still see this name on our labs
Transthyretin Amyloidosis (ATTR)

<table>
<thead>
<tr>
<th><strong>Wild Type (ATTRwt)</strong></th>
<th><strong>Variant (ATTRv)</strong></th>
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</thead>
<tbody>
<tr>
<td>- No mutation in TTR gene</td>
<td>- Mutation in TTR gene present</td>
</tr>
<tr>
<td>- Not hereditary</td>
<td>- It’s hereditary</td>
</tr>
<tr>
<td>- Median age at dx 74 years</td>
<td>- Age depends on specific mutation</td>
</tr>
<tr>
<td>- 25% of pts &gt; 85 yrs have ATTRwt on autopsy</td>
<td>- Most common in US is V122I</td>
</tr>
<tr>
<td>*</td>
<td>- Late onset cardiac amyloid</td>
</tr>
</tbody>
</table>

- Carpal Tunnel Syndrome
- Spinal Stenosis causing back pain
- Biceps Tendon Rupture (wild type)
- Shoulder pathology
- Hip/Shoulder/Knee surgeries

Hanna M, Curr Heart Fail Rep 2014, Mar;11(1):50-7
TTR Genetic Testing

• Short gene on chromosome 18

• Simple test of the blood or saliva

• Turn around 2–3 weeks

• Involve genetic counselors
### CARDIAC
- Heart Failure (HFpEF, HFmrEF, HFrEF)
- Atrial fibrillation / cardioembolic stroke
- “Hypertrophic cardiomyopathy”
- Low flow low gradient aortic stenosis
- Pacemaker / Complete heartblock
- Angina w normal cors

### NON-CARDIAC
- Autonomic Neuropathy
  - Diarrhea
  - Orthostatic hypotension
  - Erectile dysfunction
- Peripheral Neuropathy
- Vitreous Opacities (7 mutations)
- Bilateral carpal tunnel / Spinal Stenosis
- Nephrotic Syndrome (V30M)
Ask these questions in pts with Heart Failure and increased wall thickness

1. Carpal Tunnel syndrome, bilateral
2. Spinal Stenosis
3. Biceps tendon rupture
4. Shoulder pathology: rotator cuff
Peripheral Neuropathy
Sensory-Motor
Numbness and Pain
Weakness

Autonomic Neuropathy
Orthostatic hypotension
Diarrhea
Bladder
Impotence
• Diabetic Neuropathy
• Idiopathic Neuropathy
• CIDP (chronic inflammatory demyelinating polyneuropathy)
• Alcoholic/Toxic (chemo, etc)
• Paraneoplastic Neuropathy
• Carpal Tunnel Syndrome
• ALS
• Motor Polyradiculoneuropathy
• AL Amyloidosis
Mixed Phenotype Common

- V122I
- I68L
- L111M
- T60A
- S77Y
- E89L
- V30M
- E89Q
- I107V
- F64L
- G47A

20 amino acid signal peptide on monomer
So now p.V142I instead of V122I

Phenotype: "Neurologic" vs. "Cardiac"

Japan, Sweden, Miscellaneous
Irish Descent
3.5% African-Americans
Portugal

Rapezzi et al. EHJ (2013) 34,520-528.
Genotype and Phenotype of Transthyretin Cardiac Amyloidosis
THAOS (Transthyretin Amyloid Outcome Survey)

Maurer et al. JACC 2016
Transthyretin V122I Allele Frequencies in Africa

Senegal 0.008 (132)
Gambia 0.013 (636)
Guinea 0.036 (56)
Sierra Leone 0.026 (1124)
Ivory Coast 0.037 (82)
Malawi 0.008 (130)
Nigeria 0.021 (570)
Cameroon 0.013 (230)
Ghana 0.025 (2424)
Mali 0.008 (130)
Tanzania 0.012 (254)
South Africa 0.008 (360)

Courtesy of Joel Buxbaum, Scripps Clinic
V122I (p.V142I)

• First described in 1988 in an African-American man
• Unique – predominantly in patients with African descent
• Age-dependent autosomal dominant, median age 68–70 yrs
• Males 70%, female 30%
• Median survival worse than wild type (2.5 years)
• Prevalence of ~3.5% of African Americans (44 million in US)
  • ~1.5 Million carriers*
  • ~200,000 aged ≥65 years*

*Estimation based on US Census.

Gorevic et. al, J Clin Invest. 1989;83(3):836-843
Kittleson et. al, Circulation 2020; 142: e7-e22
Ruberg et. al, Circulation 2012; 126: 1286-1300
U.S. Census Bureau
T60A (pT80A) ("Ala60")

Mixed phenotype

Cardiomyopathy
- Severe LV thickening, HF
- high rates heart block

Neuropathy
- Sensory-Motor
- Autonomic (can be severe)

Hewitt et. al, Journal of Cardiac Failure 2020; 26(10): 533
## Table 1. Characteristics of Wild-Type and Common Variant Transthyretin Cardiac Amyloidosis

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Origin</th>
<th>Prevalence</th>
<th>Male:Female Ratio</th>
<th>Onset</th>
<th>Organs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSA</td>
<td>Worldwide</td>
<td>25% &gt;65 y</td>
<td>25:1 to 50:1</td>
<td>&gt;80 y</td>
<td>Heart, ST</td>
</tr>
<tr>
<td>V122I</td>
<td>United States, Caribbean, Africa</td>
<td>4% Black</td>
<td>1:1 Gene (+) 3:1 Disease</td>
<td>&gt;65 y</td>
<td>Heart, PNS, ST</td>
</tr>
<tr>
<td>V30M</td>
<td>Portugal, Sweden, Japan</td>
<td>1:1000</td>
<td>2:1</td>
<td>&gt;50 y</td>
<td>PN/ANS, heart</td>
</tr>
<tr>
<td>T60A</td>
<td>United Kingdom, Ireland</td>
<td>1% Northwest Ireland</td>
<td>2:1</td>
<td>&gt;45 y</td>
<td>Heart, PNS/ANS</td>
</tr>
</tbody>
</table>

SSA indicates senile systemic amyloidosis, wild-type (no mutation); ST, soft tissue; PNS, peripheral nervous system; and ANS, autonomic nervous system.
Age Dependent Penetrance

Cumulative incidence (%) vs. Age (years) at onset

- ATTRwt gene
- Leu111Met mutation
- Thr60Ala mutation
- Val122Ile mutation

THAOS Registry

N=19 for ATTRwt gene
N=20 for Val122Ile mutation
N=8 for Thr60Ala mutation
N=5 for Leu111Met mutation
**Important Points**

- Classic low voltage only about 30% in ATTR-CM, 50% AL
- LVH criteria seen in about 10% of biopsy proven CA
- Discordance between ECG voltage and LV wall thickness
- Conduction disease common
  - PR interval increase
  - IVCD, RBBB, LBBB
  - Left axis deviation
Lab Testing for AL Amyloidosis

- Serum free light chain assay (kappa/lambda)
- Serum immunofixation (SIFE)
- Urine immunofixation (UFIE)

Chen et al, Current Cardiology Reports 2018
Banypersad et al, Journal of the American Heart Association 2012
Starts With Clinical Suspicion

AL Amyloidosis Labs

- Serum free light chains
- Serum immunofixation
- Urine immunofixation

ECG

ECHO

CARDIAC MRI

Technetium pyrophosphate scan

Grade 2/3 uptake
Confirmed by SPECT/CT
(-) AL amyloidosis labs

Bone marrow bx
Fat pad aspirate/bx

HEART BIOPSY

Genetic testing

Wild type
Hereditary

25
Hypertension versus Cardiac Amyloidosis?

THEY CAN COEXIST!!
Case Examples
78 yo AA female  h/o HTN & EF 45%  
Referred for shortness of breath
Echocardiogram
Diagnostic Work Up

**AL**
- Serum free light chains
- Serum immunofixation
- Urine immunofixation

**ECG**

**ECHO** (with strain)

**TTR**
- TcPYP scan
- TTR Genetic testing
  - + V122I mutation
Diagnostic Work Up

- AL
- Serum free light chains
- Serum immunofixation
- Urine immunofixation
- TcPYP scan
- ECHO (with strain)
- ECG

NORMAL fLC
No M protein

- ATTR-CM
- TTR Genetic testing
+ V122I mutation
Diagnostic Work Up

AL

NORMAL fLC
No M protein

ECG

ECHo (with strain)
Diagnostic Work Up

AL

NORMAL fLC
No M protein

ECG

ECHO
(with strain)

TTR

ATTR-CM

TTR Genetic testing

+ V122I mutation

Hereditary ATTR cardiac amyloidosis
73 yo AA male h/o Kappa MGUS

NT pro BNP 3100
Trop T 0.042
Diagnostic Work Up

AL Amyloidosis Labs

- Serum free light chains
- Serum immunofixation
- Urine immunofixation

ECG

ECHO (with strain)

TTR

TcPYP scan
Diagnostic Work Up

AL Amyloidosis Labs

Kappa 382  Lambda 27
K/L ratio 14  (0.26-1.65)
Kappa M protein on serum immunofixation

ECG

ECHO (with strain)

TTR

Diagnostic Work Up
Diagnostic Work Up

- **AL Amyloidosis Labs**
  - Kappa 382
  - Lambda 27
  - K/L ratio 14 (0.26-1.65)
  - Kappa M protein on serum immunofixation

- **ECG**
- **ECHO (with strain)**
- **TTR**
**Diagnostic Work Up**

**AL Amyloidosis Labs**

- Kappa 382
- Lambda 27
- K/L ratio 14 (0.26-1.65)
- Kappa M protein on serum immunofixation

**ECG**

**ECHO** (with strain)

**TTR**

**ATTR-CM?**

- TTR Genetic testing
- + V122I mutation

**HEART BIOPSY**

**Hereditary ATTR amyloidosis + Kappa MGUS**
77 yr old AA female w/ CHF and aortic stenosis
Severe concentric thickening of the LV
AND..... 78 yr old African American ♀
Genetic testing positive for V122I mutation
55 yr old white male of Irish descent

- Hypertension
- Unexplained mild neuropathy in feet and hands
- 2007: Complete heart block → Dual chamber pacemaker
- 2008: Recurrent ascites, SOB
Subsequent Course

- On further history, mother has h/o amyloidosis
- Endomyocardial biopsy: TTR amyloid
- TTR genetic testing: T60A (p.Thr80Ala)
- Combined heart and liver transplant 2009
Hereditary Implications

Sister age 60 tested following year (2009)
  • T60A mutation

Surveillance for symptoms and for imaging evidence of cardiac amyloid
  • CMRI 2016 patchy LGE (age 67)
  • TcPYP 2017 grade 3 uptake, H/CL ratio 1.9
Technetium pyrophosphate (TcPYP) scan
Hereditary Implications

- 41 yr old son tested positive this year
  - T60A mutation
- Mild dyspnea on exertion
  - NT pro BNP 115
- Bilateral carpal tunnel syndrome
Technetium Pyrophosphate Scan

Grade 2 uptake
Technetium Pyrophosphate Scan

Grade 2 uptake
76-year-old man referred for refractory CIDP

• The patient developed numbness in the feet at age 67.

• At 70, he started having difficulty buttoning his shirt.

• At age 73, his symptoms progressed more rapidly with numbness spreading up to the knees on both sides and mid forearm. His balance became affected, and he started to fall.

• At the age of 76 he started using a stick for balance.
76-year-old man referred for refractory CIDP

- No autonomic or GI symptoms. No dyspnea. He lost about 60 pounds since the onset of his symptoms unintentionally.

- No family history of neuropathy.

- Outside work up showed elevated CSF protein at 91, elevated B6 level at 351, and positive serum GD1a antibody.

- Genetic testing revealed mutation in TTR gene c.148G.A (p.Val50Met), a known pathogenic mutation causing hereditary transthyretin amyloidosis.

- A skin biopsy showed amyloid deposition. The patient was started on disease modifying therapy.
73-year-old African-American Male with Progressive HF Over 5 Years

• Medical history
  • Hypertension, CKD, BPH
  • Carpal tunnel release 2012
  • Lumbar spine surgery 2014

• Presents December 2014 with dyspnea on exertion / ? angina
  • Cath with distal LAD stenosis (PCI done), 60% diagonal
  • Echo EF 40%, global dysfunction
  • LVEDD 4.2 cm, “moderate LVH” sept 2.3, PW 2.1 cm
  • NT pro BNP 1720, Trop T 0.053
  • Diagnosed w/“Ischemic CM” → BB, ACE(-), also on amlodipine for BP
73-year-old African-American Male with Progressive HF Over 5 Years

- Persistently positive Trop T over follow-up period 2014-2019
- Increasing diuretic requirements by 2017-2019, BP decreasing
- 3 hospitalizations for HF, repeat ECHO EF 30%, “severe LVH”
- August 2019 consult CCF:
  - High JVP, low output symptoms
  - ECG low voltage
  - RHC: RA 27 mm Hg, PA 41/27, PCWP 29 (V 32), MVO2 48%, CI 1.2
  - NT pro BNP 8200, Trop T 0.075
12-Lead Electrocardiogram
Echo – Parasternal Long Axis View

IV septum 1.9 cm
Posterior wall 2.1 cm
AL Amyloidosis Lab Testing (Cr 2.4)

Kappa 88 (3.3 – 19)
Lambda 29 (5.7 – 26)
Ratio = 3 (0.26-1.65)

+ kappa M protein on serum IFE

Technetium Pyrophosphate Scan

Grade 3 planar uptake

+ SPECT CT

Diffuse uptake in LV myocardium

HEART BIOPSY

Transthyretin (ATTR) Amyloid Deposits
73-year-old African-American Male with Progressive HF Over 5 Years

- Summary
  - Carpal tunnel and spinal stenosis around time of presentation
  - Severe LV thickening out of proportion to hypertension
  - Low voltage on ECG
  - African American
- The diagnosis of ATTR amyloidosis was not considered in this patient
- Endomyocardial biopsy showed ATTR amyloid deposits
- TTR genetic testing reveals V122I (p.V142I) variant
Remember, Not All ATTR-CM Is Secondary to V122I in African Americans

104 African-American patients with ATTR-CM who underwent TTR genetic testing

Echocardiogram in ATTR-CM

Independent prognostic parameters in ATTR Cardiomyopathy

- TTR Cardiomyopathy n=1240
- Wild Type n=766
- Hereditary n=474

- Stroke volume index
- E/e'
- Right atrial area index
- Longitudinal strain
- Severe aortic stenosis

Chacko et al., European Heart Journal 2020
Opportunities to Diagnose Along the Disease Continuum

Normal heart

Septum → 11 mm
Asymptomatic

Septum → 13 mm
Mild conduction dz

Wall thickness → 14 mm
Mild DOE
Paroxysmal Afib
Minimally ↑ PR interval

Wall thickness 16 mm
LA wall ↑ thickness
Mild LE edema
QRS widening
NT-proBNP > 1000

“Full blown” ATTR-CM

Time in Years

Courtesy of M. Hanna, MD, Cleveland Clinic

Afib, atrial fibrillation; ATTR-CM, transthyretin amyloidosis cardiomyopathy; DOE, dyspnea on exertion; dz, disease; LA, left atrium; LE, left extremity; NT-proBNP, N-terminal pro B-type natriuretic peptide.
Hereditary Transthyretin Amyloidosis
Take Home Points

• High index of suspicion

• Carpal tunnel syndrome, spinal stenosis, biceps tendon rupture?

• Unexplained neuropathy, peripheral and/or autonomic?

• Unexplained LVH or heart block, consider this diagnosis?

• Ethnicity & Race Important
  • Irish descent? (p.T80A)
  • African American or Afro-Caribbean? (p.V142I)
  • Portuguese/Japanese/Swedish? (p.V50M)

• Use appropriate diagnostic algorithm

• Make the diagnosis
Thank You.