Hereditary Transthyretin Amyloidosis
Identification and Diagnosis

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Disclosures

- Consulting: Pfizer, Inc.
- Advisory Board: Alnylam Pharmaceuticals, Inc.; Eidos Therapeutics, Inc.
- Speakers Bureau: Alnylam Pharmaceuticals, Inc.

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Outline

• Overview and Prevalence of Hereditary ATTR
• Clinical Features
• Clinical Presentations
• Diagnosing Hereditary ATTR
• Future Directions
Overview and Prevalence of Hereditary ATTR
Amyloid comes in a variety of “flavors”

- Amyloidosis is a disorder of protein folding
- Misfolded proteins deposit in organs resulting in organ dysfunction
- AL & ATTR most common (~95%) cardiac involvement

<table>
<thead>
<tr>
<th>Amyloid protein</th>
<th>Precursor</th>
<th>Main features</th>
<th>Myocardial involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL</td>
<td>Immunoglobulin light chain</td>
<td>Primary myeloma associated</td>
<td>Frequent</td>
</tr>
<tr>
<td>ATTR</td>
<td>Transthyretin</td>
<td>Familial</td>
<td>Variable according to genotype</td>
</tr>
<tr>
<td>ATTR</td>
<td>Transthyretin</td>
<td>Wild type</td>
<td>Constant</td>
</tr>
<tr>
<td>Aβapo Al</td>
<td>Apolipoprotein Al</td>
<td>Familial</td>
<td>Occasional but severe</td>
</tr>
<tr>
<td>Aβapo AβII</td>
<td>Apolipoprotein AβII</td>
<td>Familial</td>
<td>Exceptional</td>
</tr>
<tr>
<td>Aββ</td>
<td>Fibrinogen β chain</td>
<td>Familial</td>
<td>Exceptional</td>
</tr>
<tr>
<td>ALys</td>
<td>Lysozyme</td>
<td>Familial</td>
<td>Exceptional</td>
</tr>
<tr>
<td>AA</td>
<td>Serum AA</td>
<td>Secondary, reactive</td>
<td>Exceptional</td>
</tr>
<tr>
<td>A β2 M</td>
<td>β2 microglobulin</td>
<td>Hemodynamically associated</td>
<td>Exceptional</td>
</tr>
<tr>
<td>IAA</td>
<td>Atrial natriuretic factor</td>
<td>Atrial fibrillation</td>
<td>Atrial tissue</td>
</tr>
</tbody>
</table>

**TTR: Structure & Physiologic Binding**

- Transthyretin (Prealbumin) transports thyroxine ($T_4$) and retinol (Vit A) in plasma and CSF
  - Homotetramer – 4 identical 127 amino acid monomers
- Variant forms of TTR protein are encoded by amyloidogenic TTR mutations
  - TTR gene located on long arm of chromosome 18
  - >120 TTR variants described: single amino acid substitutions → mutant subunits
  - Tetramers with ≥ 1 mutant subunits are kinetically or thermodynamically unstable
  - Dissociate under physiologic conditions to release monomers prone to misfolding

Adapted from Buxbaum NEJM 2018
TTR Amyloidosis: Amyloidogenic Cascade

Functional TTR structure → Pathologic TTR structures

- Mutations
- Aging

Adapted from Canadian Journal of Cardiology 2020 36322-334DOI: (10.1016/j.cjca.2019.12.034)
Clinical Manifestations

- Loss of sensation
- Muscle weakness
- Impaired ambulation

- Orthostatic hypotension
- Syncope/falls
- Constipation/diarrhea
- Urinary retention/UTIs

- Heart failure
- Arrhythmias/syncope
- Impaired exercise capacity

TTR Amyloid Polyneuropathy (ATTR-PN or FAP)

TTR Amyloid Cardiomyopathy (ATTR-CM or FAC)
hATTR: Genotype-Phenotype Correlation

Mutations Causing Disease

Inheritance: Autosomal dominant

Penetrance: Incomplete; multi-factorial determinants incompletely understood

Symptom onset: Presenting age varies by mutation, environmental factors

Disease progression

Asymptomatic

Symptomatic

1. Production of mutant TTR
2. Initiation of non-fibrillar TTR deposition
3. Initiation of amyloid deposition


ATTR: Worldwide Distribution & Characteristics

Transthyretin Amyloid Outcomes Survey (THAOS)


### Disease Distribution

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mutation</th>
<th>Population &amp; Age of Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>wtATTR-CM</td>
<td>None (Wild Type)</td>
<td>Accumulations in &gt;20% of &gt;80yo Male predominant (9:1) +70 years</td>
</tr>
<tr>
<td>hATTR-CM (FAC)</td>
<td>V122I (V141I)</td>
<td>3-4% African Americans (West African Descent) Male predominant (3:1; Gene+ 1:1) &gt;60 years</td>
</tr>
<tr>
<td>hATTR-CM and/or -PN (or mixed FAC-FAP)</td>
<td>T60A (T80A)</td>
<td>Northern Ireland descent Male predominant (2:1) &gt;45 years</td>
</tr>
</tbody>
</table>
ATTR: Distribution in Europe (THAOS)

**Figure 1** THAOS Enrollment According to Country

- **Total Subjects**: N=390
- **15.4% of Total**

hATTR Amyloidosis in the United States

Prominence of TTR V122I (p.V142I) mutation

Prevalence of p.Val142Ile Variant
- Among African Descent: 3.0% - 3.5%
- General Population*: 0.3% - 1.6%
*Proportionate to percentage of population that is of African descent
- Among vATTR-CM: 66% - 79%

Demographics of p.Val142Ile vATTR-CM
- African descent: 75% - 100%
- Male predominance: 73% - 96%
- Age of symptom onset: 63 years
- Age of diagnosis: 67 - 71 years
- Atrial fibrillation: 25% - 38%
Increasing Recognition of ATTR-CM

- Increased awareness (with emergence of therapies)
- Validated non-invasive diagnostic techniques
- Increased access to genetic testing / screening

Adapted from Lane, et al. Circulation 2019
Clinical Features
hATTR: Systemic Manifestations

Clinical history / Physical exam

- **CNS manifestations**
  - Progressive dementia
  - Headache
  - Ataxia
  - Seizures
  - Spastic paraparesis
  - Stroke-like episodes

- **Renopathy**
  - Proteinuria
  - Nephrotic

- **Carpal tunnel syndrome**

- **Autonomic neuropathy**
  - Orthostatic hypotension
  - Repeated urinary tract infections (due to urinary retention)
  - Sexual dysfunction
  - Sweating abnormalities

- **Ocular manifestations**
  - Vision abnormalities
  - Glaucoma
  - Abnormal conjunctival vessels
  - Papillary abnormalities

- **Cardiovascular manifestations**
  - Conduction block
  - Cardiomyopathy
  - Arrhythmias
  - Mitral valve prolapse

- **GI manifestations**
  - Nausea & vomiting
  - Early satiety
  - Diarrhea
  - Severe constipation
  - Malabsorption
  - Unintentional weight loss

- **Peripheral sensory-motor neuropathy**
  - Typical: axonal fiber length-dependent, symmetric, and relentlessly progressive in distal to proximal direction


Adapted from Nativi-Nicolau, et al. HF Reviews, 2021

Adapted from Nativi-Nicolau, et al. HF Reviews, 2021
ATTR-CM: Infiltrative & Restrictive

Restrictive CMP
- Increased mass (LVH & RVH) without dilatation
- Stiff, poorly compliant
- Progressive diastolic filling abnormalities
- Atrial infiltration impairs atrial contraction

Amyloid Deposits
- Deposition into the extracellular space
  - Stiffened extracellular space
  - Myocyte compression
  - Microvascular ischemia
  - Direct myocyte damage
- Dysfunction – myocardial, conduction, valvular
Mixed Phenotypic Presentations

Adapted from Wixner, et al. Orphanet J Rare Dis 2014

TTR V142I+ Carriers (Mt. Sinai BioMe)

- Cardiac
- Autonomic neuropathy
- Peripheral neuropathy
- Any phenotype

hATTR: Mixed Phenotypic Presentations

Distribution by Gender

**FIGURE 1** Association Between Sex and Phenotypes in Patients With ATTRv Amyloidosis

- **A** Overall, Males, Females
  - Predominantly cardiac: 60.2%, 57.4%, 64.6%
  - Predominantly neurologic: 23.7%, 24.6%, 22.4%
  - Mixed: 16.1%, 18.0%, 13.0%

- **B** Predominantly Cardiac, Mixed, Predominantly Neurologic
  - Predominantly Cardiac: 31.3%, 36.5%, 41.6%
  - Mixed: 68.7%, 63.5%, Male, Female
  - Predominantly Neurologic: 58.4%

Clinical Presentations
ATTR-CM: Underrecognized cause of HFrEF

Hospital Admission (Imaging)

Distribution of ejection fraction in subjects hospitalized with heart failure

<table>
<thead>
<tr>
<th>Ejection Fraction (%)</th>
<th>HFrEF</th>
<th>HFrEF</th>
<th>HFrEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>5</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>10-20</td>
<td>10</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>20-30</td>
<td>15</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>30-40</td>
<td>20</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>40-50</td>
<td>25</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>50-60</td>
<td>30</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>60-70</td>
<td>35</td>
<td>40</td>
<td>45</td>
</tr>
<tr>
<td>70-80</td>
<td>40</td>
<td>45</td>
<td>50</td>
</tr>
<tr>
<td>&gt;80</td>
<td>45</td>
<td>50</td>
<td>55</td>
</tr>
</tbody>
</table>

Technetium 99m bone tracers (DPD, PYP, HDP) have ~90% sensitivity/specificity for identifying ATTR cardiac amyloid

Caution: must exclude AL amyloid, focal uptake occurs in the setting of previous MI, unclear role in early detection

~15% of HFpEF have ATTR cardiac amyloid

**ATTR-CM: Other associated conditions**

### Atrial Fibrillation

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>AL amylodosis (%)</th>
<th>ATTRm (%)</th>
<th>ATTRwt (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rappezi et al.</td>
<td>233</td>
<td>12</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>Longhi et al.</td>
<td>262</td>
<td>9</td>
<td>11</td>
<td>40</td>
</tr>
<tr>
<td>Pinney et al.</td>
<td>138</td>
<td>16</td>
<td>NA</td>
<td>43</td>
</tr>
<tr>
<td>Kristen et al.</td>
<td>216</td>
<td>16</td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td>Grogan et al.</td>
<td>360</td>
<td>NA</td>
<td>NA</td>
<td>62</td>
</tr>
</tbody>
</table>

Adapted from van den Berg, et al. Eur Heart J 2019

### Aortic Stenosis (16%) - Columbia Univ. TAVR Experience

**Increased LV wall thickness (5-10%)**

Adapted from Cardano, et al. Eur Heart J 2017

**Carpal Tunnel Syndrome (10%)**

Adapted from Spyers et al. JACC 2016
Diagnostic delays are common and diagnosis in ATTR-CM and diagnosis is often made at a more advanced stage

- Median diagnostic delay: 39 months
- 42% of patients had diagnostic delay >4 years
- 23% of patients waited 6 months to 4 years for diagnosis

Hereditary ATTR

‘Red flag’ presenting features and diagnostic testing for Cardiologist

<table>
<thead>
<tr>
<th>Clinical signs / symptoms</th>
<th>Diagnostic testing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
</tr>
<tr>
<td>• Biventricular HF presentation (dyspnea, orthopnea, edema)</td>
<td>• Elevated natriuretic peptides</td>
</tr>
<tr>
<td>• Intolerance to HF GDMT</td>
<td>• Chronic mild troponin elevation</td>
</tr>
<tr>
<td>• Low-normal BP; prior HTN</td>
<td>• Negative monoclonal proteins (i.e., sIFE, uIFE, sFLC)</td>
</tr>
<tr>
<td>• Late-onset LVH w/o HTN</td>
<td></td>
</tr>
<tr>
<td>• Atrial fibrillation / flutter</td>
<td>Basic Labs</td>
</tr>
<tr>
<td>• SSS / AV block</td>
<td></td>
</tr>
<tr>
<td>• Aortic stenosis</td>
<td></td>
</tr>
<tr>
<td><strong>Nerves</strong></td>
<td></td>
</tr>
<tr>
<td>• Carpal tunnel syndrome</td>
<td>• Discordant LVH on imaging vs. relative low voltage on ECG</td>
</tr>
<tr>
<td>• Lumbar spinal stenosis</td>
<td>ECG</td>
</tr>
<tr>
<td>• Peripheral neuropathy</td>
<td></td>
</tr>
<tr>
<td>• Orthostatic hypotension</td>
<td></td>
</tr>
<tr>
<td><strong>Kidney</strong></td>
<td></td>
</tr>
<tr>
<td>• Renal impairment</td>
<td>• Concentric LV hypertrophy</td>
</tr>
<tr>
<td>• Diffuse subendocardial LGE</td>
<td>• Biventricular hypertrophy</td>
</tr>
<tr>
<td>• Prolonged T1 relaxation times</td>
<td>• Longitudinal strain (globally impaired, relative apical sparing)</td>
</tr>
<tr>
<td>• Increased ECV</td>
<td>TTE</td>
</tr>
<tr>
<td><strong>GI</strong></td>
<td></td>
</tr>
<tr>
<td>• Weight loss</td>
<td></td>
</tr>
<tr>
<td>• Nausea, early satiety</td>
<td></td>
</tr>
<tr>
<td>• Diarrhea/constipation</td>
<td></td>
</tr>
</tbody>
</table>

‘Red flags’ facilitate identification of hATTR-CM

DISCOVERY Study

Akinboboye, et al. Amyloid 2020
Diagnosing hATTR Amyloidosis
Common Misconception
Low voltage ECG = sensitive for cardiac amyloidosis

Adapted from Cyrilie, et al. Am J Cardiol 2014
Echo for Cardiac Amyloidosis

2D TTE

Infiltrative Features

Longitudinal Strain

‘Relative’ Apical Sparing
Apical
-------------- > 1.0
Basal + Mid

Narotsky, et al. Canadian J Cardiol 2016

Adapted from Maurer, et al. Circulation 2017
CMR for Cardiac Amyloidosis

Cardiac Amyloidosis
LVH
LGE
Tc99m-PYP Scanning for ATTR-CM

Diagnostic scoring

Clinical Suspicion
- Heart failure, syncope, or bradyarrhythmia with ECG suggesting/indicating cardiac amyloid
- Rule out plasma cell dyscrasia by serum and urine IFE & serum free light chains

Bone Scintigraphy
with 99mTc-DPD/HMDP/PYP

Grade 0
Absent cardiac uptake

Grade 1
Mild uptake less than bone

Grade 2 to 3
Moderate to higher uptake than bone

Uptake in the heart (arrow)

Diagnosis*

In a subgroup of 374 patients with EMB:

- Absence of a monoclonal protein by sFLC measurement

- Grade 2 or 3 cardiac uptake on radionuclide scan

100% specific for presence of cardiac ATTR amyloid

Adapted from Gillmore, et al. Circulation 2016
Tc99m-PYP Scanning for ATTR-CM

Diagnostic scoring

A. Tc99m scan of patient with ATTR cardiac amyloidosis

B. Tc99m scan of patient without ATTR cardiac amyloidosis

C. Calculations

Visual score
0 = Myocardial uptake absent
1 = Myocardial uptake < rib
2 = Myocardial uptake = rib
3 = Myocardial uptake > rib

H/CL ratio = (heart ROI mean counts/pixel) / (contralateral ROI mean counts/pixel)

Positive Tc99m scan for ATTR

Qualitative: Visual score ≥ 2 (88% sens, 88% spec)
Quantitative: H/CL ratio ≥ 1.5 (92% sens, 97% spec)

Adapted from Castano, et al. JAMA Cardiol 2016
Tc99m-PYP Scanning for ATTR-CM

Importance of SPECT Imaging

Multi-modality Imaging for CA

CENTRAL ILLUSTRATION Imaging in Cardiac Amyloidosis

## Diagnostic Tests for Cardiac Amyloidosis

### Imaging / Blood Biomarkers

<table>
<thead>
<tr>
<th>Diagnostic and Management Goals</th>
<th>2D TTE</th>
<th>Speckle tracking strain</th>
<th>Cardiac MRI</th>
<th>Tc99m-PYP</th>
<th>PET</th>
<th>Natriuretic peptides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raise Suspicion</td>
<td>Green</td>
<td>Yellow</td>
<td>Green</td>
<td>Green</td>
<td>Yellow</td>
<td>Green</td>
</tr>
<tr>
<td>Early Diagnosis</td>
<td>Red</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Red</td>
<td>Yellow</td>
<td>Red</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Red</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Red</td>
<td>Yellow</td>
<td>Red</td>
</tr>
<tr>
<td>Subtyping</td>
<td>Green</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Red</td>
<td>Yellow</td>
<td>Red</td>
</tr>
<tr>
<td>Ventricular Assessment</td>
<td>Green</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Red</td>
<td>Yellow</td>
<td>Red</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Green</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Red</td>
<td>Yellow</td>
<td>Red</td>
</tr>
<tr>
<td>Amyloid Burden</td>
<td>Green</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Red</td>
<td>Yellow</td>
<td>Red</td>
</tr>
<tr>
<td>Response to Therapy</td>
<td>Green</td>
<td>Yellow</td>
<td>Yellow</td>
<td>Red</td>
<td>Yellow</td>
<td>Red</td>
</tr>
</tbody>
</table>

### Key

- **Established Utility**: Multicenter experiences and/or multiple publications and/or international expert consensus
- **Potential Utility**: Single-center experiences
- **Low Utility**: Case reports and cases series

Adapted from Castano, et al. Curr Cardiovasc Risk Rep 2017
Diagnosing Cardiac Amyloidosis

Tissue biopsy

Identifying Amyloid

• Extra-cardiac biopsy
  • Bone marrow, abdominal fat pad, labial salivary gland
  • Yield: AL (>70%), ATTRm (50-70%) ATTRwt (20-25%)

Typing Amyloid

• Endomyocardial biopsy (EMB)
  • ~100% sensitive / specific

• Congo red stain to identify amyloid
  • Apple green birefringence (polarized light)

• Typing of amyloid
  • Immunohistochemistry (IHC)
    • Less accurate; problematic high background
  • Laser dissection mass spectrometry (mass spec)
    • Gold standard; Mayo Clinic Lab send out

• Genetic test to establish TTR genotype
  • Blood test – PCR

Adapted from Connors LH, et al. Circulation 2016

Siddiqi, et al. EHJ 2017

Tissue biopsy
Cardiac Amyloidosis - Duke Diagnostic Algorithm

**Clinical Features**
- Heart failure
- Autonomic dysfunction
- Bilateral carpal tunnel syndrome
- Macroglossia
- Periarticular ecchymoses

**Presentation**
- Electrocardiography
  - Low voltage
  - Infracted pattern without history of coronary artery disease
  - Conduction disease
  - Atrial fibrillation
- Echocardiography
  - \( \uparrow \) wall thickness
  - Diastolic dysfunction
  - Impaired global longitudinal strain (GLS)
  - Apical sparing on GLS
- Cardiac Magnetic Resonance
  - Diffuse late gadolinium enhancement

**Suspicion for cardiac amyloidosis: evaluate for both AL and TTR amyloidosis**

**Evaluation for AL amyloidosis**
- Serum immunofixation electrophoresis (IFE)
- Urine IFE
- Serum free light chains

**Evaluation for TTR amyloidosis**
- Metyrapone test
- Pyrophosphate nuclear scintigraphy

**Synthesize data to determine diagnosis**
- Presence of monoclonal protein on gen test
  - Suggests AL
  - Does not suggest AL
  - Lack of monoclonal protein on all 3 tests
  - Does not suggest TTR

- Strong uptake (Grade 2 or 3) or H/C ratio 2.5
  - Suggests TTR

- Attempts:
  - Perform BMB, fat aspirate/tip pad biopsy, or EMB to confirm amyloid deposits
  - Mass spectrometry to confirm AL cardiac amyloidosis

- Unlikely cardiac amyloidosis, or is rare amyloid (Ap=A, MA)
  - TTR gene sequencing
  - Mass spectrometry to determine type of amyloid (if any)

- Likely cardiac amyloidosis or hereditary TTR cardiac amyloidosis
  - Wild-type TTR cardiac amyloidosis
Hereditary ATTR with Neuropathy Diagnostic Algorithm Continued

Clinical suspicion of amyloid neuropathy (refer to Figure 2)

Confirmation of ATTRv amyloidosis

DNA sequencing
Analysis of the amyloidogenic TTR variant

Amyloid typing
Immunohistochemistry or mass spectrometry

Biopsy of amyloid deposition
Possible biopsy sites: Labal salivary gland; subcutaneous fatty tissue of abdominal wall; skin; kidney; nerve; gastrointestinal tract including submucosa

Congo red staining with characteristic green birefringence under polarized light

Patient follow-up after diagnosis

Clinical examination every 6 months (every 3 months for stages II/III) unless responding well to treatment

Neurology
• New or progressed symptoms
• Functional scores (eg, walking ability, polyneuropathy disability, neurological impairment score)
• Autonomic (eg, bladder/urinary tract infection, orthostatic hypotension, erectile dysfunction, and gastrointestinal disturbances including diarrhea and early satiety)

Cardiology
• Electrocardiography
• Echocardiography and NT-proBNP

Ophthalmology
• Modified body mass index, weight

• Genetic testing availability:
  - Clinically directed testing
  - Health-system associated cohort projects
  - Direct-to-consumer genetic testing companies
• Professional genetics expertise and counseling is a necessity in the clinical setting
• Cascade clinical screening and genetic testing for first-degree family members should be offered, along with genetic counseling
Future Directions
Challenges

- Symptomatic disease attributable to TTR variants repeatedly underdiagnosed clinically
- Use of genetic analysis for identifying TTR variants in the diagnostic or pre-symptomatic setting remains uncommon
- Clinical penetrance is variable and incompletely understood; no clear genetic predictors of who will get symptomatic ATTR
- Pre-symptomatic testing for TTR variants (e.g., V122I) will need to be linked to clinical tests that reliably determine subclinical disease and response to therapy
Conclusions
**Hereditary ATTR Take Home Points**

- Hereditary ATTR presentations vary by genotype
  - Mixed neuro-cardiac presentations are common
- >120 pathogenic TTR mutations
  - TTR V122I variant = most prominent in US and worldwide
    - Affects 1 out of 25 people of African descent
- ATTR-CM is not an uncommon disease
  - There are many undiagnosed cases in HF, Afib, AS, etc.
- Increased awareness is needed to find patients
  - Be attentive to multi-systemic ‘red flags’
- Cardiac imaging techniques can increase diagnostic yield
  - Biopsy no longer a necessity in hATTR-CM
- Genomic medicine may change natural history of hATTR
Thank You.