ATTR-CM: The Disease

• ATTR-CM is a rare condition that is life-threatening, underrecognized, and underdiagnosed\(^1-^6\)

Suspect the Signs of ATTR-CM

• The diagnosis of ATTR-CM is often delayed or missed\(^1-^3\)

Detect ATTR-CM Utilizing Nuclear Scintigraphy

• Tools used to diagnose ATTR-CM include nuclear scintigraphy (eg, PYP cardiac imaging), endomyocardial biopsy (EMB), and genetic testing\(^4,^7-^10\)

\(^{99m}\text{Tc}\)-pyrophosphate.
AMYLOIDOSIS

Amyloidosis is a group of diseases in which amyloid fibrils deposit into the extracellular space of the heart. The amyloid fibrils are formed by an aggregation of misfolded proteins. The most common amyloid fibril proteins that can infiltrate the heart and lead to cardiac amyloidosis are immunoglobulin light chain (AL), a hematological emergency, and transthyretin (ATTR). As for ATTR-CM specifically, it is found mostly in older patients, in whom misfolded transthyretin proteins deposit in the heart. This rare condition is life-threatening, underrecognized, and underdiagnosed.

MOST COMMON TYPES OF CARDIAC AMYLOIDOSIS

- Transamyloidosis (ATTR)
- Immunoglobulin light chain amyloidosis (AL)
- Wild-type ATTR (wtATTR)
- Hereditary ATTR (hATTR)

IT IS CRITICAL TO CLINICALLY DIFFERENTIATE BETWEEN ATTR AND AL, AS AL REQUIRES IMMEDIATE TREATMENT AND HAS A DIFFERENT CLINICAL COURSE.

COMMON SIGNS AND SYMPTOMS IN wtATTR AND hATTR

- Cardiac
  - Fatigue
  - Shortness of breath
  - Edema
  - Arrhythmias
  - HFpEF
  - Aortic stenosis
- Soft Tissue
  - Lumbar stenosis
  - Biceps tendon rupture
- GI
  - Diarrhea
  - Constipation
  - Nausea
  - Early satiety
- Neurologic
  - Carpal Tunnel Syndrome
  - Peripheral neuropathy
  - Orthostasis
  - Weakness

IT IS CRITICAL TO CLINICALLY DIFFERENTIATE BETWEEN ATTR AND AL, AS AL REQUIRES IMMEDIATE TREATMENT AND HAS A DIFFERENT CLINICAL COURSE.
**HIDDEN IN Plain Sight**

**SUSPECT ATTR-CM**

ATTR-CM is an underdiagnosed cause of heart failure, particularly heart failure with preserved ejection fraction (HFpEF) in older adults.\(^1\)

**CONSIDER THE FOLLOWING CLINICAL CLUES, ESPECIALLY IN COMBINATION, TO RAISE SUSPICION FOR ATTR-CM AND THE NEED FOR FURTHER TESTING**

- **HFpEF:** heart failure with preserved ejection fraction in patients typically over 60 years old\(^1,12,23,24\)
- **INTOLERANCE** to standard HF therapies, ie, ACEi/ARBs and beta blockers\(^7,13,25\)
- **DISCORDANCE** between QRS voltage and LV wall thickness\(^7,15,28\)
- **DIAGNOSIS** of carpal tunnel syndrome or lumbar spinal stenosis\(^1,13,16,29,30\)
- **NERVOUS SYSTEM**—autonomic nervous system dysfunction, including gastrointestinal complaints or unexplained weight loss\(^1,12,16,33\)

**CLUES THAT MAY RAISE SUSPICION OF CARDIAC AMYLOIDOSIS**

- **HFpEF:** heart failure with preserved ejection fraction in patients typically over 60
  - In ATTR-CM, diastolic function is impaired due to amyloid fibril deposition in the myocardium resulting in thicker and inelastic ventricles thereby decreasing the stroke volume. It is not until the later stages of ATTR-CM disease that ejection fraction drops\(^34,35\)
  - Imaging clues, such as reduced longitudinal strain with apical sparing, may help increase suspicion\(^7,39\)
- **INTOLERANCE** to standard HF therapies, ie, ACEi/ARBs and beta blockers
  - Patients can develop a decrease in stroke volume, which can lead to low blood pressure. As a result, they can develop an intolerance to blood pressure–lowering therapies\(^13,25\)
- **DISCORDANCE** between QRS voltage and LV wall thickness
  - The classic ECG feature of ATTR-CM is a discordance between QRS voltage to LV mass ratio\(^7,15,28\)
- **DIAGNOSIS** of carpal tunnel syndrome or lumbar spinal stenosis
  - Carpal tunnel syndrome and lumbar spinal stenosis are often seen in ATTR-CM due to amyloid deposition in these areas\(^1,13,16,29,30,37\)
  - Carpal tunnel syndrome in ATTR-CM often precedes cardiac manifestations by several years\(^2,16,38\)
- **ECHO**cardiography showing increased LV wall thickness
  - Increased wall thickness without a clear explanation (eg, hypertension) should raise suspicion for cardiac amyloidosis\(^7,12\)
  - Extracellular amyloid deposition results in an increased LV wall thickness that tends to be greater in ATTR-CM than in AL cardiac amyloidosis, with reported thicknesses for ATTR-CM often being over 15 mm\(^12,26,28,32\)
- **NERVOUS SYSTEM**—autonomic nervous system dysfunction, including gastrointestinal complaints or unexplained weight loss
  - Gastrointestinal complaints due to autonomic dysfunction include diarrhea and constipation\(^11\)
  - Orthostatic hypotension due to autonomic dysfunction is another symptom that may occur with ATTR-CM\(^11,12\)

ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

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**Suspect The Signs Of ATTR-CM**

ACC, American College of Cardiology; AL, ATTR amyloidosis; CAN, cardiac amyloidosis; FAB, familial amyloidosis; FAP, familial amyloidosis polyneuropathy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrdEF, heart failure with reduced ejection fraction and atrial fibrillation; NNE, Novartis; NNE, Novartis; NRE, Novartis; P, percutaneous; PCI, percutaneous coronary intervention; RAAS, renin-angiotensin-aldosterone system; RCT, randomized controlled trial; TAP, taurine derivative amyloidosis; TAI, taurine acidification; TKI, tyrosine kinase inhibitor; TVR, transformylase activatable vasculropathy-related.
IF YOU SUSPECT ATTR-CM

TOOLS FOR DIAGNOSIS

ADVANCED IMAGING TECHNIQUES TO HELP RAISE SUSPICION

ALTHOUGH THESE TECHNIQUES CANNOT DIAGNOSE ATTR-CM, ABNORMAL FINDINGS SHOULD PROMPT FURTHER TESTING TO ESTABLISH A DIAGNOSIS OF ATTR-CM. NONINVASIVE IMAGING TECHNIQUES INCLUDE:

- Advanced echocardiography with speckle tracking strain imaging
  - Relative apical sparing of global longitudinal strain
  - “Ice cream cone with a cherry on top” sign

- CMR, with late gadolinium enhancement, and distinct T1 mapping
  - Increased extracellular volume, ECV

- CMR, cardiac magnetic resonance imaging; ECV, extracellular volume; LGE, late gadolinium enhancement.

DETECT TRANSTHYRETIN AMYLOID CARDIOMYOPATHY (ATTR-CM)

PYP CARDIAC IMAGING (NUCLEAR SCINTIGRAPHY)

- A noninvasive, widely available diagnostic tool with high sensitivity and specificity for ATTR-CM
- Both Planar and SPECT imaging should be reviewed and interpreted using visual and quantitative approaches
  - SPECT imaging is necessary for studies that show planar myocardial uptake because they can help differentiate myocardial uptake from blood pool or overlying bone uptake
- Uses 99mTc-Pyrophosphate (99mTc-PYP), a radioactive tracer utilized as an adjunct in the diagnosis of ATTR-CM, though not FDA approved for that use
- A multicenter international study of scintigraphy at amyloid centers of excellence demonstrated 100% specificity for ATTR-CM using visual grade 2 or 3 with concurrent testing to rule out AL
- American Society of Nuclear Cardiology (ASNC) Practice Points highlight the importance of PYP cardiac imaging in diagnosing ATTR-CM noninvasively and thereby guide patient management
- If clinical suspicion remains high for cardiac amyloidosis in spite of a negative or inconclusive 99mTc-PYP scan, biopsy should be considered

ENDOMYOCARDIAL BIOPSY (EMB)

- Requires histology with Congo red staining with apple-green birefringence to diagnose cardiac amyloidosis
- To determine amyloid type, immunohistochemistry testing and/or mass spectrometry should be performed
- Patients may experience diagnostic delay for a number of reasons, including risk of complications and the need for specialized centers and expertise

GENETIC TESTING IS USED TO DETERMINE IF THE DISEASE IS HEREDITARY DUE TO A MUTATION IN THE TTR GENE. GENETIC COUNSELING AND GENE SEQUENCING ARE RECOMMENDED FOLLOWING THE CONFIRMATION OF ATTR-CM.

PYP, pyrophosphate.
*Please consult individual labeling for risks.
IF YOU SUSPECT ATTR-CM
TOOLS FOR DIAGNOSIS

NUCLEAR SCINTIGRAPHY

USING NUCLEAR SCINTIGRAPHY TO HELP SUPPORT DIAGNOSIS OF ATTR-CM

- A landmark study suggests that a reliable diagnosis of ATTR-CM can be made with nuclear scintigraphy in the absence of histology when all of the following criteria are met:
  - The patient has heart failure with evidence of cardiac amyloidosis via echocardiography or cardiac magnetic resonance
  - Nuclear scintigraphy results fall within the parameters of the grading system (i.e., grade 2 or 3)
  - Immunoglobulin light chain amyloidosis (AL) cardiac amyloidosis has been ruled out via blood and urine tests
- Histological confirmation and typing via biopsy should be pursued in cases of suspected cardiac amyloidosis when these criteria are not satisfied
- If a patient is positive for ATTR-CM with nuclear scintigraphy, genotyping is recommended to determine if it’s wtATTR or hATTR

QUANTIFYING MYOCARDIAL PYP UPTAKE

In clinical practice, both a semi-quantitative visual scoring and quantitative approach are applied:

1. Semi-quantitative: visual comparison to bone uptake at 3 hours
   - Cardiac uptake of 99mTc-PYP evaluated using a visual scoring method in relation to bone uptake (applies a grading system)
2. Quantitative: myocardial to contralateral lung ratio of uptake at 1 hour

Both planar and single-photon emission computed tomography (SPECT) imaging should be reviewed and interpreted using visual and quantitative approaches. SPECT imaging is necessary for studies that show planar myocardial uptake because it can help differentiate myocardial uptake from blood pool or overlying bone uptake.

*Also known as variant ATTR.

hATTR, hereditary ATTR; wtATTR, wild-type ATTR, previously known as senile cardiac amyloidosis, senile systemic amyloidosis, or age-related amyloidosis.

GRADING SYSTEM

SEMI-QUANTITATIVE VISUAL GRADING OF MYOCARDIAL 99mTc-PYP UPTAKE BY COMPARISON TO BONE (RIB) UPTAKE

<table>
<thead>
<tr>
<th>GRADE</th>
<th>MYOCARDIAL 99mTc-PYP UPTAKE</th>
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<tbody>
<tr>
<td>Grade 0</td>
<td>No uptake and normal rib uptake</td>
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<tr>
<td>Grade 1</td>
<td>Uptake less than rib uptake</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Uptake equal to rib uptake</td>
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<tr>
<td>Grade 3</td>
<td>Uptake greater than rib uptake with mild/absent rib uptake</td>
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*American Society of Nuclear Cardiology (ASNC), ASNC Practice Points: 99mTc-sodium pyrophosphate imaging for transthyretin cardiac amyloidosis. Available at: https://www.asnc.org/files/1%2F1%2F%20ASNC%20Amyloid%20Prac%20Point%20%20WEB.pdf.
### IF YOU SUSPECT ATTR-CM

**TOOLS FOR DIAGNOSIS**

#### STUDY DESIGN

Gillmore, et al (2016) conducted a study to determine the diagnostic value of bone scintigraphy in ATTR-CM patients. A total of 1217 patients were evaluated of whom 857 patients with histologically proven amyloid (374 with endomyocardial biopsies and 360 patients subsequently confirmed to have nonamyloid cardiomyopathies) myocardial radiotracer uptake on bone scintigraphy was >99% sensitive and 86% specific for cardiac ATTR amyloid. False positives were almost exclusively found from uptake in patients with cardiac AL amyloidosis. The authors concluded that bone scintigraphy enables the diagnosis of cardiac ATTR amyloidosis to be made without the need for tissue biopsy in patients who do not have a monoclonal gammapathy. Repeat information: within the study, several analyses were conducted and included identification of ATTR-CM with 100% specificity with scintigraphy visual grade 2 or 3 and concurrent rule out of AL.  

#### A DIAGNOSTIC ALGORITHM FOR PATIENTS SUSPECTED WITH ATTR-CM

**A POTENTIAL PATHWAY TO DIAGNOSIS**

<table>
<thead>
<tr>
<th>Highened Clinical Suspicion for Cardiac Amyloidosis</th>
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<td>Patient centered counseling on diagnostic process</td>
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**Testing for AL Cardiac Amyloidosis**

**Presence of monoclonal protein by free light chain assay and serum/urine immunofixation?**

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<tr>
<th>Biopsy</th>
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<td>Congo Red Positive</td>
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<td>Congo Red Negative</td>
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<th>Tissue Typing</th>
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<td>Immunohistochemistry</td>
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<td>Mass Spectrometry (AL vs TTR vs Other)</td>
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<th>unlikely AL Cardiac Amyloidosis</th>
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<td>Unlikely ATTR Cardiac Amyloidosis</td>
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<th>ATTR Cardiac Amyloidosis</th>
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<td>TTR Genotyping</td>
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<td>wtATTR</td>
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*Rule out AL: testing for presence of monoclonal protein via serum and urine immunofixation.

†Serum Free light chain assay.


AL, immunoglobulin light chain amyloidosis; ATTR, transthyretin amyloidosis; ALTR, hereditary ATTR; wtTTR, wild-type TTR, previously known as senile cardiac amyloidosis, senile systemic amyloidosis, or age-related amyloidosis.

Data from Gillmore, et al (2016) conducted a study to determine the diagnostic value of bone scintigraphy in ATTR-CM patients. A total of 1217 patients were evaluated of whom 857 patients with histologically proven amyloid (374 with endomyocardial biopsies and 360 patients subsequently confirmed to have nonamyloid cardiomyopathies) myocardial radiotracer uptake on bone scintigraphy was >99% sensitive and 86% specific for cardiac ATTR amyloid. False positives were almost exclusively found from uptake in patients with cardiac AL amyloidosis. The authors concluded that bone scintigraphy enables the diagnosis of cardiac ATTR amyloidosis to be made without the need for tissue biopsy in patients who do not have a monoclonal gammapathy. Repeat information: within the study, several analyses were conducted and included identification of ATTR-CM with 100% specificity with scintigraphy visual grade 2 or 3 and concurrent rule out of AL.

†Diagnostic algorithm devised by Brunjes DL, et al.  

‡Both planar and single-photon emission computed tomography (SPECT) imaging should be reviewed and interpreted using visual and quantitative approaches. SPECT imaging is necessary for studies that show planar myocardial uptake because it can help differentiate myocardial uptake from blood pool or overlying bone uptake.

§If clinical suspicion remains high for cardiac amyloidosis in spite of a negative 99mTc-PYP scan, biopsy may be considered to evaluate for other types of infiltrative cardiomyopathy (eg, AL).

*Also known as variant ATTR.*