TRANSTHYRETIN AMYLOID CARDIOMYOPATHY (ATTR-CM)

ATTR-CM: The Disease
• ATTR-CM is a rare condition that is life-threatening, underrecognised, and underdiagnosed\(^1\)-\(^7\)

Suspect the Signs of ATTR-CM
• The diagnosis of ATTR-CM is often delayed or missed\(^2\),\(^5\),\(^7\)

Detect ATTR-CM Utilizing Nuclear Scintigraphy
• Tools used to diagnose ATTR-CM include nuclear scintigraphy (eg, \([^{99m}\text{Tc}]\text{-PYP/}\) \([^{99m}\text{Tc}]\text{-DPD/}^{99m}\text{Tc-HMDP}\) cardiac imaging), endomyocardial biopsy (EMB), and genetic testing\(^2,\(^8\)

\(^{99m}\text{Tc-DPD, }^{99m}\text{technetium-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid; }^{99m}\text{Tc-HMDP, }^{99m}\text{technetium-labeled hydroxymethylene diphosphonate; }^{99m}\text{Tc-PYP, }^{99m}\text{technetium-labeled pyrophosphate.}\)
UNDERSTANDING TRANSTHYRETIN AMYLOID CARDIOMYOPATHY (ATTR-CM)

Amyloidosis is a group of diseases in which amyloid fibrils deposit into the extracellular spaces of different organs, which ultimately leads to progressive organ dysfunction. 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 amyloid fibril protein (AL) and transthyretin amyloid fibril protein (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, underrecognised, and underdiagnosed.

Most Common Types of Cardiac Amyloidosis

- Transthyretin amyloidosis (ATTR)
- Immunoglobulin light chain amyloidosis (AL)
- Wild-type ATTR (ATTRwt)
- Hereditary ATTR (hATTR)

It is important to clinically differentiate between ATTR and AL, as they have different clinical courses.

WILD-TYPE VS HEREDITARY ATTR-CM

WILD-TYPE ATTR-CM

Wild-type ATTR-CM (ATTRwt) is idiopathic and is not considered to be a hereditary disease. It is thought to account for the majority of all ATTR-CM cases.

SOME PATIENT CONSIDERATIONS

- Ethnicity: predominantly white
- Mostly men
- Symptom onset typically over the age of 60 years
- Heart failure
- Cardiac arrhythmias, particularly atrial fibrillation
- History of bilateral carpal tunnel syndrome

PROGNOSIS

- Median survival: ~3.5 years

HEREDITARY ATTR-CM

Hereditary ATTR-CM (hATTR) is due to a mutation in the TTR gene. Inherited mutations in TTR are common in patients of African (Val122Ile), Irish (Thr60Ala), Italian (Ile68Leu), and Danish (Leu11Met) descent.

SOME PATIENT CONSIDERATIONS

- Men and women
- Symptom onset may occur as early as 50-60 years of age
- Heart failure
- Neurological symptoms (peripheral and autonomic)
- Gastrointestinal symptoms
- History of bilateral carpal tunnel syndrome

PROGNOSIS

- Median survival: ~2 to 3 years

COMMON SIGNS AND SYMPTOMS IN ATTRwt AND hATTR

- Cardiac
  - Fatigue
  - Shortness of breath
  - Edema
  - Arrhythmias
  - HFpEF
  - Aortic stenosis

- Soft Tissue
  - Lumbar stenosis
  - Ruptured distal biceps tendon

- GI
  - Diarrhea
  - Constipation
  - Nausea
  - Early satiety

- Neurologic
  - CTS
  - Peripheral neuropathy
  - Orthostasis
  - Weakness

*Also known as variant hATTR.

CTS, carpal tunnel syndrome; GI, gastrointestinal; HFpEF, heart failure with preserved ejection fraction.
H.I.D.D.E.N. IN PLAIN SIGHT

SUSPECT TRANSTHYRETIN CARDIAC AMYLOIDOSIS (ATTR-CM)

ATTR-CM is an underdiagnosed cause of heart failure, particularly heart failure with preserved ejection fraction (HFpEF) in older adults.5–7

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 old5–7

• 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.33–35

• Imaging clues, such as reduced longitudinal strain with apical sparing, may help increase suspicion.9,33

INTOLERANCE to standard HF therapies, ie, ACEi/ARBs and beta blockers9,22,23

• 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 therapies22,23

DISCORDANCE between QRS voltage and LV wall thickness24–26

• The classic ECG feature of ATTR-CM is a discordance between QRS voltage to LV mass ratio.9,12,25

DIAGNOSIS of carpal tunnel syndrome or lumbar spinal stenosis3,11,13,20–22,27–29

• Carpal tunnel syndrome and lumbar spinal stenosis are often seen in ATTR-CM due to amyloid deposition in these areas3,11,13,20,22,27–29

• Carpal tunnel syndrome in ATTR-CM often precedes cardiac manifestations by several years4,13,36

ECHOCARDIOGRAPHY showing increased LV wall thickness6,11,26,30,31

• Increased wall thickness without a clear explanation (eg, hypertension) should raise suspicion for cardiac amyloidosis6–7

• 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 more than 15 mm11,26,31

NERVOUS SYSTEM—autonomic nervous system dysfunction, including gastrointestinal complaints or unexplained weight loss6,11,17,32

• Gastrointestinal complaints due to autonomic dysfunction include diarrhea and constipation14

• Orthostatic hypotension due to autonomic dysfunction is another symptom that may occur with ATTR-CM6,11,32

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ECG, electrocardiography.
IF YOU SUSPECT TRANSTHYRETIN AMYLOIDOSIS CARDIOMYOPATHY (ATTR-CM)

TOOLS FOR DIAGNOSIS

NONINVASIVE TESTING CAN DIAGNOSE ATTR-CM

**NONINVASIVE**

- **NUCLEAR SCINTIGRAPHY**
  - Uses a radioactive bone tracer, \(^{99m}\text{Tc-PYP}, ^{99m}\text{Tc-PYROPHOSPHATE; \(^{99m}\text{Tc-DPD,} \quad ^{99m}\text{Tc-3,3-DIPHOSPHONO-1,2-PROPANODICARBOXYLIC ACID; \(^{99m}\text{Tc-HMDP,} \quad ^{99m}\text{Tc-HYDROXYMETHYLENE DIPHOSPHONATE})^8**

- **BLOOD AND URINE TESTING TO RULE OUT AL**

**INVASIVE**

- **ENDOMYOCARDIAL BIOPSY (EMB) + AMYLOID TYPING**

**GENETIC TESTING**

NUCLEAR SCINTIGRAPHY IN COMBINATION WITH TESTING TO RULE OUT LIGHT CHAIN CAN DIAGNOSE ATTR-CM

DISCOVER THE TOOLS TO DIAGNOSE ATTR-CM

**NUCLEAR SCINTIGRAPHY**

- A noninvasive, readily available diagnostic tool with high sensitivity and specificity for ATTR-CM
- Uses a radioactive bone tracer, \(^{99m}\text{Tc-PYP}, ^{99m}\text{Tc-PYROPHOSPHATE; \(^{99m}\text{Tc-DPD,} \quad ^{99m}\text{Tc-3,3-DIPHOSPHONO-1,2-PROPANODICARBOXYLIC ACID; \(^{99m}\text{Tc-HMDP,} \quad ^{99m}\text{Tc-HYDROXYMETHYLENE DIPHOSPHONATE})^8**

- A multicentre international study demonstrated 99% sensitivity for ATTR-CM (visual grade 1-3). A separate analysis within the study demonstrated 100% specificity for visual grade 2,3 with concurrent testing to rule out AL**†

†Multicentre study conducted to determine the diagnostic value of bone scintigraphy in patients with ATTR-CM. Of 1217 evaluable patients, 374 underwent endomyocardial biopsy, and 843 were diagnosed with presence and type or absence of amyloid on basis of extracardiac histology combined with echocardiography with or without cardiac magnetic resonance imaging (CMR).

**ENDOMYOCARDIAL BIOPSY (EMB)**

- Diagnosis of cardiac amyloidosis requires the histology to show Congo red staining with apple-green birefringence\(^8\)
- Additional tests to determine amyloid type are recommended following diagnosis of cardiac amyloidosis\(^8\)
- Risk of complications and the need for specialised centres and expertise may contribute to a diagnostic delay\(^8\)

**GENETIC TESTING**

- Used to determine if the disease is hereditary due to a mutation in the TTR gene\(^7\)
- Genetic counseling and gene sequencing are recommended following confirmation of ATTR-CM\(^7\)

\(^7\)Also known as variant ATTR.\(^1\)

\(^8\)Rule out AL: testing for presence of monoclonal protein via serum and urine immunofixation + serum free light chain assay.