Recognizing Cardiac Manifestations of Transthyretin Amyloidosis (ATTR)[1]

CLINICAL

- Shortness of breath[2]
- Edema[2]
- Palpitations and arrhythmias[2]
- Fatigue
- Heart failure symptoms
- Family history of heart failure
- Orthostatic hypotension[2]

IMAGING

- Increased left ventricular wall thickness
- Grade 2 or worse diastolic function
- Abnormal longitudinal strain with apical sparing
- Diffuse subendocardial or transmural LGE on CMR imaging with increased extracellular volume fraction

ELECTRICAL

- Conduction system disease/pacemaker
- Atrial fibrillation
- Pseudoinfarct pattern
- Discordant QRS voltage for degree of increased left ventricular wall thickness on imaging

LABORATORY

- Persistent low-level troponin elevation
- Elevated B-type natriuretic peptide or N-terminal pro–B-type natriuretic peptide

ACC 2023 Diagnostic Algorithm for ATTR[1]

Clues from patient history, ECG, echocardiogram, CMR

Monoclonal protein?

- Serum kappa/lambda free light chain (abnormal if ratio is <0.26 or >1.65)
- Serum and urine IFE (abnormal if monoclonal protein detected)

YES

Consultation with hematologist
Biopsy (affected organ/surrogate site)

- Positive Congo red
- Tissue typing by mass spectrometry

AL-CM

NO

^{99m}Tc-PYP

- Grade 2/3 uptake

NO

Cardiac amyloidosis unlikely

Consider endomyocardial biopsy despite negative or equivocal ^{99m}Tc-PYP imaging if there is a high clinical suspicion for cardiac amyloidosis or if scintigraphy is unavailable.

YES

ATTR-CM

Genetic testing

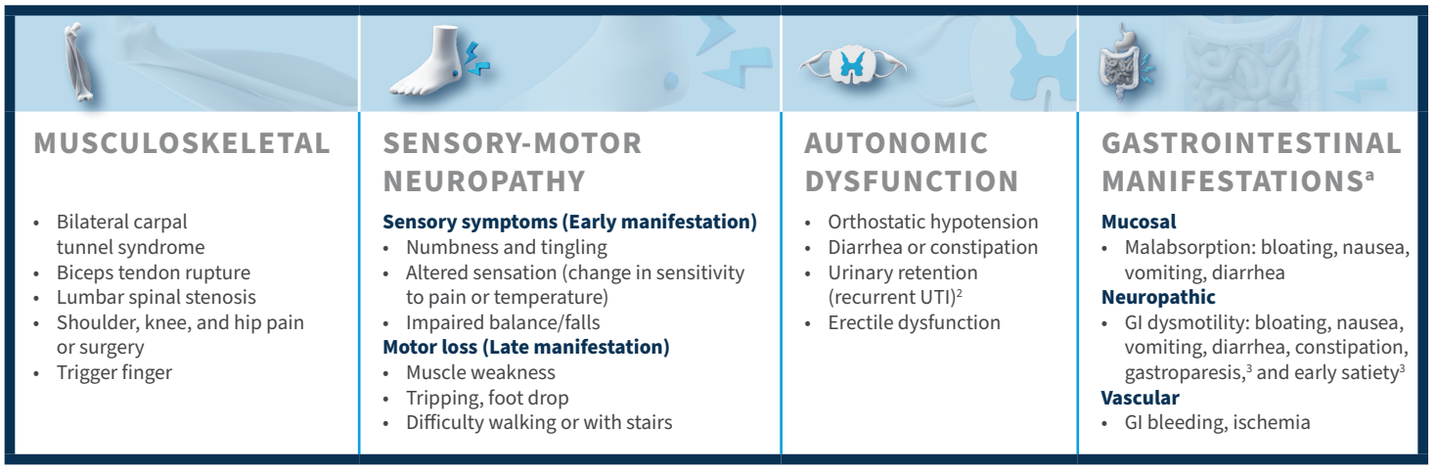
hATTR

wtATTR

^{99m}Tc-PYP, technetium-99m pyrophosphate; **ACC**, American College of Cardiology; **AL-CM**, monoclonal immunoglobulin light-chain amyloidosis with cardiomyopathy; **ATTR**, transthyretin amyloidosis; **ATTR-CM**, transthyretin amyloidosis with cardiomyopathy; **CMR**, cardiac magnetic resonance; **ECG**, electrocardiogram; **hATTR**, hereditary transthyretin amyloidosis; **IFE**, immunofixation electrophoresis; **LGE**, late gadolinium enhancement; **PYP**, pyrophosphate; **wtATTR**, wild-type transthyretin amyloidosis.

1. Kittleson MM, et al. *J Am Coll Cardiol*. 2023;81(11):1076-1126; **2.** Adams D, et al. *Orphanet J Rare Dis*. 2021;16:411.

Recognize Extracardiac Manifestations of ATTR Due to Toxic Fibril Deposition[1]



MUSCULOSKELETAL

- Bilateral carpal tunnel syndrome
- Biceps tendon rupture
- Lumbar spinal stenosis
- Shoulder, knee, and hip pain or surgery
- Trigger finger

SENSORY-MOTOR NEUROPATHY

Sensory symptoms (Early manifestation)
- Numbness and tingling
- Altered sensation (change in sensitivity to pain or temperature)
- Impaired balance/falls

Motor loss (Late manifestation)
- Muscle weakness
- Tripping, foot drop
- Difficulty walking or with stairs

AUTONOMIC DYSFUNCTION

- Orthostatic hypotension
- Diarrhea or constipation
- Urinary retention (recurrent UTI)[2]
- Erectile dysfunction

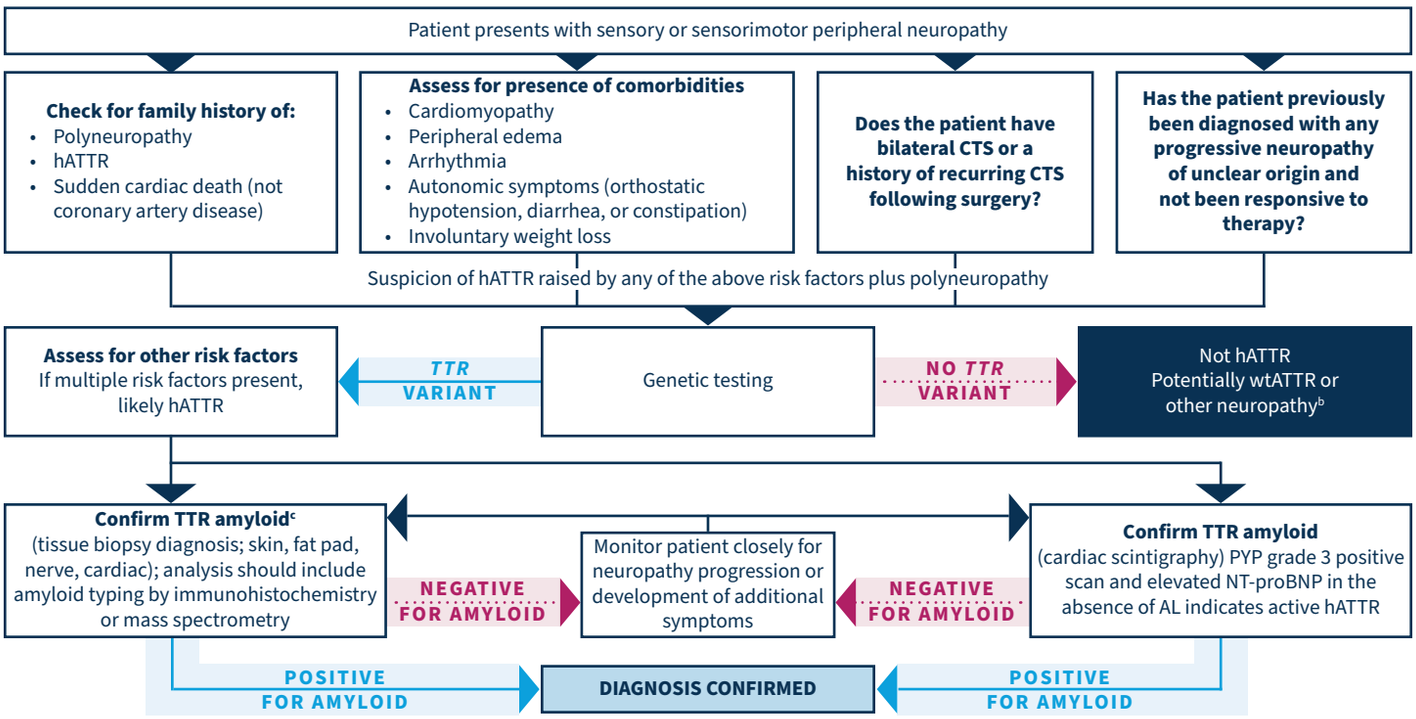
GASTROINTESTINAL MANIFESTATIONS[a]

Mucosal
- Malabsorption: bloating, nausea, vomiting, diarrhea

Neuropathic
- GI dysmotility: bloating, nausea, vomiting, diarrhea, constipation, gastroparesis,[3] and early satiety[3]

Vascular
- GI bleeding, ischemia

Diagnosing Suspected hATTR with Polyneuropathy[4]



Adapted from Karam C, et al. 2024[4]

[a]GI symptoms may be difficult to attribute to GI amyloid deposition as cardiac involvement and medication side effects may also cause abdominal pain, nausea, diarrhea, or constipation.

[b]Patients may be assessed for genetic conditions including Charcot–Marie–Tooth disease and hereditary neuropathy with liability to pressure palsies, or screened for vitamin B12 deficiency, diabetes (hemoglobin A1C assessment), thyroid dysfunction, monoclonal gammopathy (immunofixation electrophoresis), or AL amyloidosis (immunoglobulin free light chain assessment).

[c]Importance of tissue diagnosis is greater when concurrent possible causes of peripheral neuropathy (ie, B12 deficiency, diabetes mellitus, paraproteinemia, etc) are present. In certain cases where there is no alternative cause for a progressive neuropathy, especially when multisystem features are present, a biopsy may not be necessary. A negative tissue biopsy in a patient with a high suspicion of hATTR does not exclude a diagnosis, and further investigation (ie, scintigraphy) or close follow-up is warranted.

AL, amyloid light chain; **ATTR**, transthyretin amyloidosis; **CTS**, carpal tunnel syndrome; **GI**, gastrointestinal; **hATTR**, hereditary transthyretin amyloidosis; **NT-proBNP**, N-terminal pro-brain natriuretic peptide; **PYP**, pyrophosphate; **TTR**, transthyretin; **UTI**, urinary tract infection; **wtATTR**, wild-type transthyretin amyloidosis.

1. Kittleson MM, et al. *J Am Coll Cardiol*. 2023;81(11):1076-1126; **2.** Bentellis I, et al. *Clin Auton Res*. 2019; 29(Suppl 1):S65-S74; **3.** Adams D, et al. *Orphanet J Rare Dis*. 2021;16:411; **4.** Karam C, et al. *Muscle Nerve*. 2024;69(3):273-287.