Neurologic tools to recognize and diagnose hATTR amyloidosis

Family history and multisystem involvement, including neurologic manifestations, should raise clinical suspicion and prompt immediate investigation[1,2]

Neurologic diagnostic workup[3,4]

Several types of tests can help identify signs of hATTR amyloidosis. Diagnosis does not require all of these assessments.

- Sensory-motor assessments
  - EMG
  - NCS
  - QST
- Autonomic assessments
  - Heart rate deep breathing
  - Tilt table
  - SSR
  - QSART
  - ESC measurement

Neurologic findings consistent with hATTR amyloidosis[2,4,5]

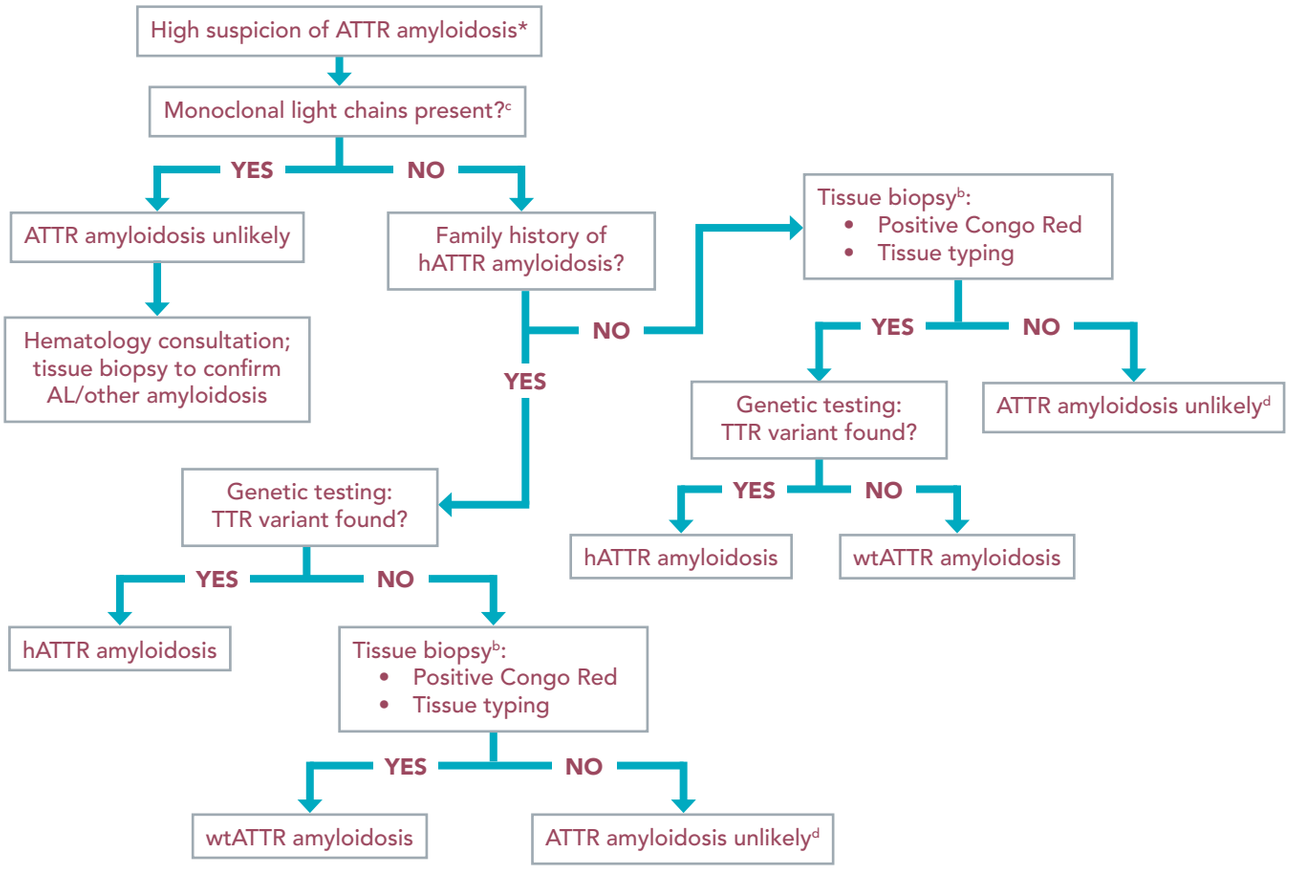
- Axonal length-dependent sensory-motor neuropathy[a]
- Small-fiber sensory neuropathy may progress to large-fiber sensory and motor neuropathy[a]
- Bilateral carpal tunnel syndrome
- Abnormal hemodynamic response and reduced heart rate variability in autonomic testing (e.g., orthostatic hypotension)
- A length-dependent pattern of sweat reduction

Confirmatory assessments[1,6-8]

- Tissue biopsy to determine presence of amyloid[b]
- Genetic testing to confirm a TTR variant

Genetic testing is recommended in cases of suspected hATTR amyloidosis to aid in earlier diagnosis and prompt familial screening.[8,9]

DIAGNOSTIC ALGORITHM FOR ATTR AMYLOIDOSIS[6,7]



*Based on signs, symptoms, and initial findings consistent with hATTR amyloidosis.

Adapted from: Adams et al[6] and Carroll et al[7]

This is not a complete list of all of the available diagnostic tools for hATTR amyloidosis. For more information on cardiac assessments, please see the reverse side.

[a]EMG and NCS may be normal in early stages of the disease.[4]
[b]Possible biopsy sites include labial salivary gland, subcutaneous fatty tissue of abdominal wall, skin, kidney, nerve, and gastrointestinal tract, including submucosa.[1,8]
[c]The 2023 ACC Expert Consensus recommends serum and urine immunofixation electrophoresis and serum free light chain assay to exclude AL amyloidosis in the initial diagnostic workup.[9]
[d]Sensitivity of biopsy can vary by site; negative biopsy may not always rule out ATTR amyloidosis.[8]

AL=amyloid light chain; ATTR=transthyretin-mediated; EMG=electromyography; ESC=electrochemical skin conductance; hATTR=hereditary ATTR; NCS=nerve conduction study; QSART=quantitative sudomotor axon reflex testing; QST=quantitative sensory testing; SSR=sympathetic skin response; TTR=transthyretin; wtATTR=wild-type ATTR.

Cardiac tools to recognize and diagnose hATTR amyloidosis

Family history and multisystem involvement, including cardiovascular manifestations, should raise clinical suspicion and prompt immediate investigation[1,2]

Cardiac diagnostic workup[10,11]

Several types of tests can help identify the signs of hATTR amyloidosis. Diagnosis does not require all of these assessments.

- ECG
- ECHO
- CMRI

Cardiac findings consistent with hATTR amyloidosis[9,11,12,a]

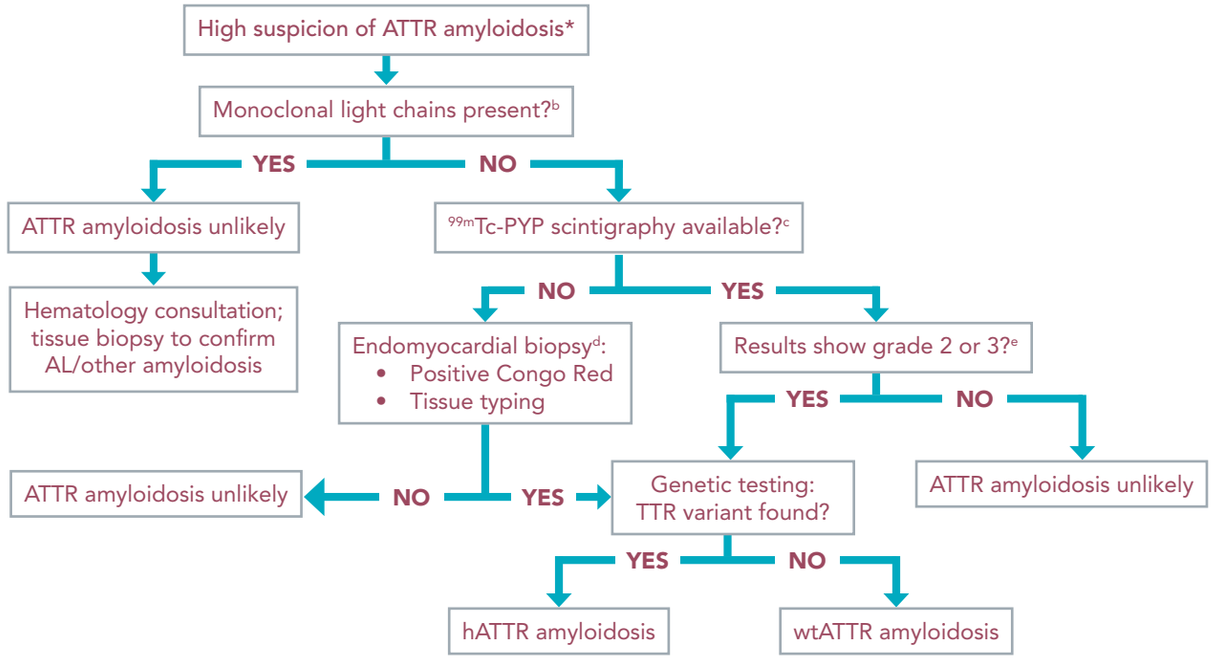
- Left ventricular wall thickening, refractile myocardium (granular sparkling) on echocardiogram
- Reduced longitudinal strain more pronounced at the base than apex (apical sparing pattern)
- Low voltage or progressive reduction in QRS voltage over time or pseudo-infarction pattern and/or atrioventricular block on ECG
- Subendocardial late gadolinium enhancement on CMRI

Confirmatory assessments[1,8,9]

- Nuclear scintigraphy (^{99m}Tc-PYP or ^{99m}Tc-DPD) or endomyocardial biopsy to determine presence of amyloid
- Genetic testing to confirm a TTR variant

Genetic testing is recommended in cases of suspected hATTR amyloidosis to aid in earlier diagnosis and prompt familial screening.[8,9]

DIAGNOSTIC ALGORITHM FOR ATTR AMYLOIDOSIS[9,13]



*Based on signs, symptoms, and initial findings consistent with hATTR amyloidosis.

Adapted from: Kittleson et al[9] and Kittleson et al[13]

This is not a complete list of all of the available diagnostic tools for hATTR amyloidosis. For more information on neurologic assessments, please see the reverse side.

[a]Findings are consistent with those for hATTR amyloidosis and wtATTR amyloidosis.[9]
[b]The 2023 ACC Expert Consensus recommends serum and urine immunofixation electrophoresis and serum free light chain assay to exclude AL amyloidosis in the initial diagnostic workup.[9]
[c]Consider biopsy if scan is negative/equivocal but clinical suspicion is high.[9,13]
[d]Sensitivity of a non-endomyocardial biopsy varies by site; negative fat-pad biopsy is not sufficient to exclude ATTR amyloidosis.[9,13]
[e]Grade 2: cardiac=rib uptake; Grade 3: cardiac>rib uptake with mild/absent rib uptake.[13]

^{99m}Tc-DPD=technetium-99m-diphosphono-1,2-propanodicarboxylic acid; ^{99m}Tc-PYP=technetium-99m-pyrophosphate; CMRI=cardiac magnetic resonance imaging; ECG=electrocardiography; ECHO=echocardiography.

References: 1. Adams D, Koike H, Slama M, et al. *Nat Rev Neurol*. 2019;15(7):387-404. **2.** Conceição I, González-Duarte A, Obici L, et al. *J Peripher Nerv Syst*. 2016;21(1):5-9. **3.** Ando Y, Coelho T, Berk JL, et al. *Orphanet J Rare Dis*. 2013;8:31. **4.** Shin SC, Robinson-Papp J. *Mt Sinai J Med*. 2012;79(6):733-748. **5.** Illigens BMW, Gibbons CH. *Clin Auton Res*. 2009;19:79-87. **6.** Adams D, Ando Y, Beirão JM, et al. *J Neurol*. 2021;268(6):2109-2122. **7.** Carroll A, Dyck PJ, de Carvalho M, et al. *J Neurol Neurosurg Psychiatry*. 2022;93(6):668-678. **8.** Gertz M, Adams D, Ando Y, et al. *BMC Fam Pract*. 2020;21(1):198. **9.** Kittleson MM, Ruberg FL, Ambardekar AV, et al. *J Am Coll Cardiol*. 2023;81(11):1076-1126. **10.** Dharmarajan K, Maurer MS. *J Am Geriatr Soc*. 2012;60(4):765-774. **11.** Maurer MS, Bokhari S, Damy T, et al. *Circ Heart Fail*. 2019;12(9):e006075. **12.** Garcia-Pavia P, Rapezzi C, Adler Y, et al. *Eur Heart J*. 2021;42(16):1554-1568. **13.** Kittleson MM, Maurer MS, Ambardekar AV, et al. *Circulation*. 2020;142(1):e7-e22.

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