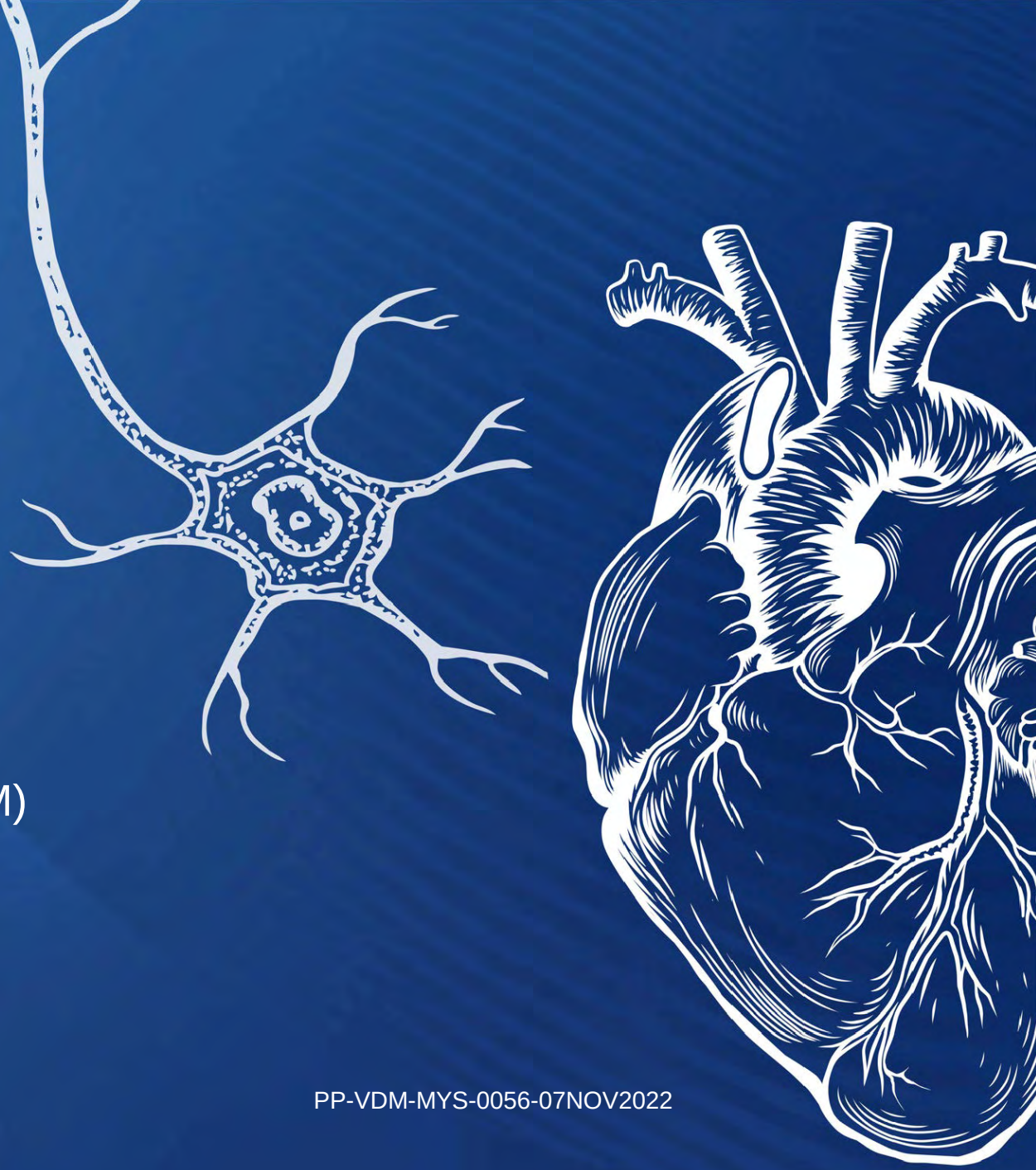
Ruling out Light-Chain (AL) amyloidosis in ATTR-CM

Transthyretin amyloid cardiomyopathy (ATTR-CM)



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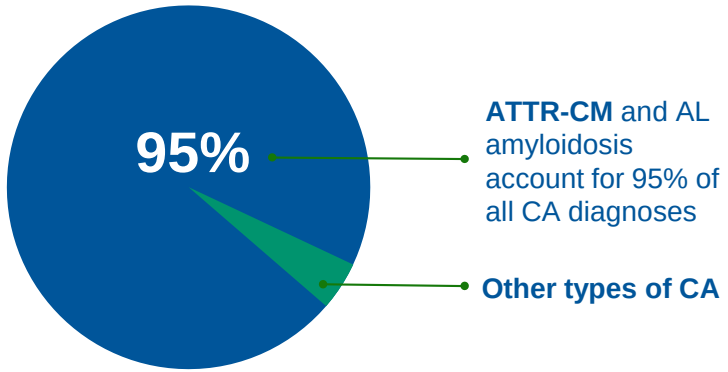
ATTR-CM and Light Chain (AL) amyloidosis have similar symptom presentation which may make diagnosis challenging

It is important to **clinically differentiate between cardiac manifestations of ATTR and AL amyloidosis,** as they have different clinical courses and treatment options, and **AL amyloidosis is considered a hematologic urgency**[1,2]

Causes of Cardiac Amyloidosis (CA)[3]



ATTR-CM is under recognized, may present with symptoms similar to AL and may be misdiagnosed due to incomplete testing[4,5]

Symptoms that may present in both ATTR-CM and AL amyloidosis

Cardiovascular[3,6-8]
- Heart failure with potential intolerance to standard therapy
- Cardiac arrhythmia
- Aortic stenosis
- Low voltage relative to left ventricular (LV) mass
- Echocardiography showing increased LV wall thickness

Nervous System[4,8-10]
- Automatic neuropathy
- Orthostatic hypotension
- Peripheral sensory motor dysfunction
- Peripheral neuropathy
- Unexplained weight loss
- Sexual impotence

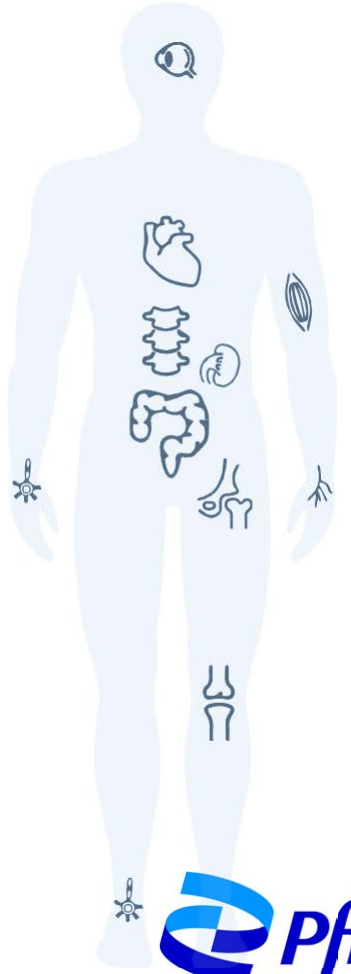
Ocular[4,11,12]
- Vitreous opacity
- Glaucoma
- Periorbital purpura*

Musculoskeletal/Orthopedic[4]
- Carpal tunnel syndrome

Renal[10,13,14]
- Renal impairment
- Nephrotic syndrome*
- Cardiorenal symptoms

Other [4,10,15]
- Gastrointestinal complaints
- Macroglossia (large tongue)*
- Nail dystrophy*

*More commonly seen in AL



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Ruling out light chain amyloidosis (AL) is a key step in achieving a definitive ATTR-CM diagnosis[16]

SERUM AND URINE TESTS FOR RULING OUT AL AMYLOIDOSIS*

	Serum protein electrophoresis (SPEP) with immunofixation†	Urine protein electrophoresis (UPEP) with immunofixation†	Serum free light chain assay
What does it detect?	Clonal immunoglobulin and/or clonal light chain	Clonal immunoglobulin and/or clonal light chain	Free kappa chain Free lambda chain kappa: lambda ratio
Most sensitive test for:	Confirming clonal immunoglobulin production	Confirming clonal light chain production	Detecting low-level clonal light chain production; clonality assumed if ratio is far from 1:1
Normal range	No M-spike present	No M-spike present No proteinura[4]	Kappa:lambda ratio=0.26-1.65‡

- AL amyloidosis is a hematological urgency and **requires immediate treatment**
- Survival of untreated patients with AL amyloidosis with cardiac involvement may be **<6 months**
- Cardiac localization of radiotracer by bone scintigraphy can occur in **approximately 30% of patients with AL amyloidosis**
- **Specific disease-modifying therapies for AL amyloidosis are** available

*If any of these tests are abnormal, bone scintigraphy should not be used to make the diagnosis of transthyretin amyloidosis, and a biopsy is recommended. Adapted from Witteles et al., 2019 Table 1, which uses SPIE (serum protein electrophoresis with immunofixation) and UPIE (urine protein electrophoresis with immunofixation) acronyms.

†SPEP and UPEP are more sensitive than protein electrophoresis without immunofixation and should be ordered as preferred test.

‡In patients with kidney disease, mild elevations in the kappa:lambda ratio are frequently encountered. In the setting of a normal SPEP/UPEP, a kappa:lambda ratio up to 2.5 can typically be considered normal.

AL=light chain; ATTR-CM=transthyretin amyloid cardiomyopathy.

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AL rule out is an important step in the diagnostic pathway. All three tests should be sent to evaluate for AL in order to maximize sensitivity and specificity[17]

Order Studies to Test for Abnormal Monoclonal Protein*

Serum Kappa/Lambda Free Light Chain Ratio	Serum Protein Immunofixation	Urine Protein Immunofixation
Abnormal result: Ratio <0.26 or >1.65	**Abnormal result:** Monoclonal protein is detected	**Abnormal result:** Monoclonal protein is detected

Key Considerations:

- It is recommended that all three tests be sent to evaluate for AL amyloidosis. However, monoclonal protein presence does not rule out the possibility of ATTR-CM
- Amyloid subtyping is the only way to effectively differentiate between ATTR-CM and AL Amyloidosis

Adapted and reprinted with permission from Maurer MS, et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. *Circ Heart Fail*. 2019;12:e006075. doi:10.1161/CIRCHEARTFAILURE.119.006075 © 2019 American Heart Association, Inc. All rights reserved.

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Immunofixation of the serum and urine is a much more sensitive test and usually demonstrates a monoclonal band. Thus, immunofixation and serum-free light chains should always be measured when amyloidosis is suspected.[17] Urine protein electrophoresis with immunofixation can be performed on spot or 24-h urine collection.

If you **suspect ATTR-CM at any point** in the patient evaluation, refer patients to a cardiologist

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