Unveiling ATTR-CM Among Patients with Common Cardiac Conditions

Keyur Shah, MD

Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) has become an increasingly recognized cause of heart failure (HF) in older adults.[1] ATTR-CM is a progressive disease in which the tetrameric transthyretin (TTR) protein is destabilized into monomers that aggregate into amyloid fibrils and deposit in the myocardium.[2,3] Amyloid deposition reduces cardiac chamber compliance, causing a restrictive ("stiff heart") physiology and increases wall thickness, thus presenting as a phenocopy of hypertrophic cardiomyopathy.[4,5]

There are two forms of ATTR-CM.[6] Wild-type ATTR-CM is an acquired form that affects people usually after the sixth decade of life.[2,7] While the prevalence and risk factors for developing wild-type ATTR-CM are not well defined, it is the most frequently diagnosed form of ATTR-CM in clinical practice.[2,6,7] The variant or hereditary form of ATTR-CM can arise from destabilizing mutations in the *TTR* gene and has a varying age of onset depending on the mutation.[1,2] While there are over 100 disease-causing mutations, the most frequently diagnosed mutation in North America predominantly affects elderly Black individuals.[1,7]

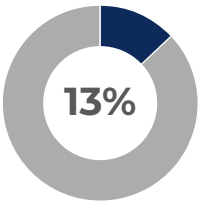
People with ATTR-CM experience progressive HF and are often misdiagnosed as having hypertensive heart disease or "garden variety" HF with preserved ejection fraction (HFpEF).[8,9] However, traditional HF treatments not only have little proven efficacy for ATTR-CM but also can have deleterious effects.[5] With the emergence of FDA-approved disease-modifying treatments for ATTR-CM, timely diagnosis and intervention are critical to improve patient quality of life and prevent premature death.[10] Cardiac and extracardiac manifestations of ATTR-CM can provide clues for earlier diagnosis.

Masked Cardiac Presentation

The clinical manifestations of ATTR-CM masquerade as otherwise common cardiac conditions.[11,12] Individuals with ATTR-CM are seen by a variety of cardiac providers, and the disease will often "hide in plain sight."[12]

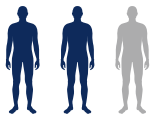
ATTR-CM commonly presents as...

Aortic stenosis

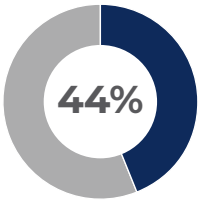


of people **referred for TAVR** to treat **severe aortic stenosis** were found to have ATTR-CM[13]

Atrial fibrillation and conduction disease

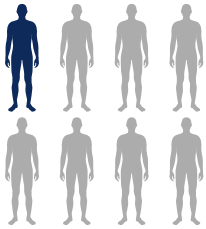


2 in 3 people with wild-type ATTR-CM have **atrial fibrillation**[14]



of people with wild-type ATTR-CM will **receive a pacemaker**[15]

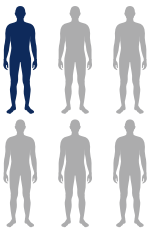
HFpEF



1 in 8 people admitted with **HFpEF, aged ≥60 years, and with LV hypertrophy** were diagnosed with ATTR-CM[15]

1 in 20 people with HFpEF have **moderate or severe amyloid deposition** in their hearts on postmortem evaluation[16]

Hypertrophic cardiomyopathy



1 in 6 people aged ≥50 years initially diagnosed with **hypertrophic cardiomyopathy** are later **confirmed** to have ATTR-CM[17]

ATTR-CM, transthyretin amyloid cardiomyopathy; HFpEF, heart failure with preserved ejection fraction; LV, left ventricle; TAVR, transcatheter-based aortic valve replacement.

Dr Shah received compensation from BridgeBio Inc. for consulting services. BridgeBio provided medical writing support for this article.

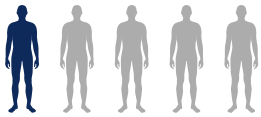
bridgebio

Orthopedic and Neuropathic Findings

The clinical presentation of ATTR-CM is heterogeneous and includes a range of extracardiac symptoms.[6,11,12] These symptoms often predate HF symptoms and can serve as early warning signs of ATTR-CM.[6] Recognizing extracardiac manifestations can raise the index of suspicion for ATTR-CM.

Orthopedic manifestations

Carpal tunnel syndrome

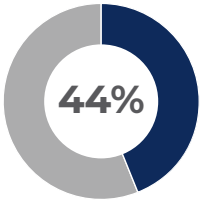


1 in 5 people with ATTR-CM have a history of **CTS**[18]

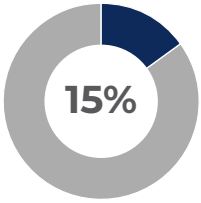
CTS often occurs **5-9 years prior** to ATTR-CM diagnosis and is more prevalent in males[18]

1 in 20
people who **have bilateral CTS** will go on to have ATTR-CM[19]

Spontaneous tendon rupture



of people with ATTR-CM have a history of **biceps tendon rupture**[20]

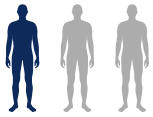


of people with ATTR-CM have had **bilateral biceps tendon rupture**[20]

Arthropathy

People with ATTR-CM are **5–6 times** more likely to have a history of **major joint replacements** than the general population[22]

Nearly **1 in 4** people with ATTR-CM have a **history of total knee or hip replacement** about **7 years prior** to diagnosis of ATTR-CM[21]



Nearly **1 in 3** people with ATTR-CM have had a **diagnosis of a significant shoulder pathology**, with rotator cuff tear as the predominant diagnosis[22]

ATTR-CM, transthyretin amyloid cardiomyopathy; CTS, carpal tunnel syndrome.

Dr Shah received compensation from BridgeBio Inc. for consulting services. BridgeBio provided medical writing support for this article.

Clinical clues of ATTR-CM

Cardiac

Imaging[11,23]

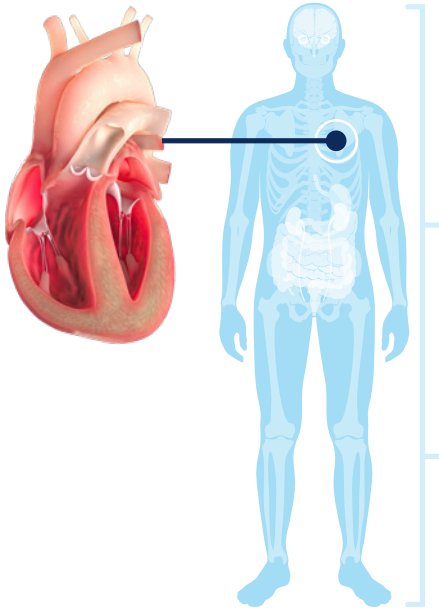
- Echocardiography: Left ventricular wall thickness >12 mm, apical sparing pattern on GLS, restrictive LV filling, and diastolic dysfunction

Electrical[11]

- Electrocardiogram: Discrepancy between LV wall thickness and QRS voltage, conduction abnormalities, atrial fibrillation, pseudo-infarction pattern

Laboratory[12,24]

- Low serum TTR (prealbumin)
- Elevated NT-proBNP
- Detectable troponin



Orthopedic[11]

- Bilateral carpal tunnel syndrome
- Spinal stenosis
- Spontaneous tendon rupture
- Arthropathy

Neuropathic[11]

- Polyneuropathy and/or dysautonomia

If any present, consider evaluating for ATTR-CM

Conclusion

Recognizing the manifestations of ATTR-CM is key to preventing misdiagnosis and facilitating early intervention.[8–10] If an individual presents with the cardiac and extracardiac clues discussed above, referring the patient to a cardiac specialist for further evaluation could improve their prognosis and quality of life.[10]

References

1. Lane T, et al. *Circulation*. 2019;140(1):16–26.
2. Rintell D, et al. *Orphanet J Rare Dis.* 2021;16(1):70.
3. Nativi-Nicolau J, et al. *ESC Heart Fail.* 2021;8(5):3875–3884.
4. Ruberg FL and Berk JL. *Circulation.* 2012;126(10):1286–1300.
5. Mankad AK, Shah KB. *Curr Cardiol Rep.* 2017;19(10):97.
6. Rozenbaum MH, et al. *Cardiol Ther.* 2021;10(1):141–159.
7. Ruberg FL, et al. *J Am Coll Cardiol.* 2019;73(22):2872–2891.
8. Nativi-Nicolau JN, et al. *Heart Fail Rev.* 2022;27(3):785–793.
9. Gillmore JD, et al. *Circulation.* 2016;133(24):2404–12.
10. Tomasoni D, et al. *Front Cardiovasc Med.* 2023;10:1154594.
11. Kittleson MM, et al. *Circulation.* 2020;142(1):e7–e22.
12. Gertz M, et al. *BMC Fam Pract.* 2020;21(1):198.
13. Nitsche C, et al. *J Am Coll Cardiol.* 2021;77(2):128–139.
14. Grogan M, et al. *J Am Coll Cardiol*. 2016;68(10):1014–20.
15. González-López E, et al. *Eur Heart J*. 2015;36(38):2585–94.
16. Mohammed SF, et al. *JACC Heart Fail*. 2014;2(2):113–22.
17. Garcia-Pavia P, et al. *Eur. Heart J.* 2023;44(Suppl. 2).
18. Milandri A, et al. *Eur J Heart Fail.* 2020;22(3):507–515.
19. Westin O, et al. *Am Coll Cardiol.* 2022;80(10):967–977.
20. Cappelli F, et al. *J Intern Med.* 2021;289(6):831–839.
21. Rubin J, et al. *Amyloid.* 2017;24(4):226–230.
22. Basdavanos A, et al. *Am J Cardiol.* 2023;190:67–74.
23. Cuddy SAM, et al. *JASE*. 2022;35:A31–A40.
24. Greve AM, et al. *JAMA Cardiol*. 2021;6(3):258–266.

Dr Shah received compensation from BridgeBio Inc. for consulting services. BridgeBio provided medical writing support for this article.