Review Article

Transthyretin Amyloid Cardiomyopathy - Early Diagnosis is the Key for Better Outcomes

Immaneni Sathyamurthy, M. Indirani[1], Shelley Simon[1]

Departments of Cardiology and [1]Nuclear Medicine, Apollo Main Hospitals, Chennai, Tamil Nadu, India

Abstract

Transthyretin amyloid cardiomyopathy (ATTR-CM) is rare and often diagnosed late. The incidence increases with advancing age, as ATTR tetramers become prone to misfolding and has been categorized as wild type and those due to gene mutations constitute hereditary type. Diagnostic work up should include serum and urinary electrophoresis and immunofixation studies to rule out monoclonal gammapathies. With the introduction of Technitium pyrophosphate scintigraphy, early diagnosis became possible without the need for endomyocardial biopsy. It has a diagnostic sensitivity of 99% and specificity of 86%. Tafamidis, ATTR stabilizer has been approved for the treatment of ATTR-CM which prevents further deposition but does not reverse the process. The benefits are gratifying when therapy is initiated. Functional improvement was observed in 6 months and reduction in mortality in 2 years. This review impresses upon the utility of Technitium pyro phosphate scintigraphy for the early diagnosis and highlights the early initiation of therapy for better outcomes.

Keywords: 99m technetium pyrophosphate scintigraphy, amyloidosis, nuclear scan, tafamidis, transthyretin cardiomyopathy

Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is characterized by the deposition of misfolded transthyretin protein in the extracellular spaces of the myocardium. Abnormal plasma cell proliferation leading to misfolded light chain deposition has been classified as AL-amyloidosis which is more common than ATTR-CM. The deposition of amyloid fibrils in the interstitium can occur in the atria, ventricles, perivascular spaces, valves, and conduction system. The clinical manifestations of heart failure (HF) and arrhythmias sets in, when enough amyloid is deposited to cause left ventricular (LV) wall thickening.

Technetium 99m pyrophosphate (99m Tc-PYP) scintigraphy, a noninvasive nuclear scan, is highly sensitive and specific for diagnosing ATTR.[1-3] This test is devoid of any risk and has changed the diagnostic landscape and made early diagnosis possible without the need for an invasive endomyocardial biopsy (EMB). It enabled screening large number of suspected cases.[4] Early diagnosis and early initiation of specific therapy are the key to improve the outcomes of ATTR-CM.

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jicc

DOI: 10.4103/jicc.jicc_67_24

Pathobiology

Cardiac amyloidosis is often under diagnosed or misdiagnosed as majority of them present in late stages.[5,6] Aging renders ATTR tetramer prone to misfolding and the prevalence has been shown to increase with advancing age[7-10] and these cases were classified as wild type (w-ATTR). Mutations in gene for AATR constitute hereditary type (h-ATTR) but w-ATTR is more common than h-ATTR.[11,12] In the past, definitive diagnosis of ATTR-CM was made by EMB, which when stained with congo red demonstrates apple-green birefringence under polarizing microscope. This being an invasive procedure, carries risk of pericardial tamponade, hematoma and the risk reported being 1%–6%, hence not been widely practiced.[13] Misfolded proteins get deposited in the interstium of myocardium resulting in diastolic dysfunction which can worsen to systolic dysfunction as the disease progresses.[14] Cardiomyopathy has

Address for correspondence: Dr. Immaneni Sathyamurthy, Department of Cardiology, Apollo Main Hospitals, Chennai - 600 006, Tamil Nadu, India.
E-mail: isathya@hotmail.com

How to cite this article: Sathyamurthy I, Indirani M, Simon S. Transthyretin amyloid cardiomyopathy - Early diagnosis is the key for better outcomes. J Indian Coll Cardiol 2025;15:88-93.

Submitted: 06-Sep-2024 **Revised:** 23-May-2025 **Accepted:** 26-May-2025 **Published:** 25-Jul-2025

been reported most commonly with w-ATTR whereas nervous system is affected commonly with h-ATTR.[11,12]

Epidemiology

The data regarding the prevalence of ATTR are limited as it is rare, often diagnosis is missed due to its heterogeneous presentation and lack of sensitive diagnostic tests in the past. Mutations in chromosome 18 have been shown to result in misfolding of ATTR protein (h-ATTR) and an autosomal dominant inheritance with more than 100 different types were reported from various geographical locations.[15] After the introduction of 99m Tc-PYP, about 5000–7000 new cases were identified annually in the US[16] suggesting an increase in detection. In one study, among patients of HF with preserved ejection fraction (HFpEF) associated with increased myocardial thickness (≥14 mm) by echocardiography, a prevalence rate of 20% was reported.[17] In a pooled analysis of 69 studies involving 4669 patients with ATTR-CM, 83% were men.[18] Lower prevalence was observed in women as the diagnosis is often delayed or missed due to small sized hearts and also due to cardio-protective effects of estrogens.[19] True prevalence of w-ATTR in the population is not known, but it was reported to be 20%–25% among octogenarians and 37% in those above 95 years[20,21] confirming that the prevalence increases with age. Recent studies predicted up to 10%–15% of older subjects with HFpEF might have unrecognized w-ATTR.[22] In an autopsy study of 109 patients with antemortem diagnosis of HFpEF, the incidence of w-ATTR was 17%, and in those above the age of 80 years, it was 40%,[8]

Natural History

HFpEF is more common with w-ATTR but EF ≤ 40% has been reported in 30%–50% cases in some studies.[23,24] Data suggest that survival of h-ATTR was worse compared to w-ATTR and the mean survival after the diagnosis reported was 2.5 and 3.5 years, respectively.[25] Mayo clinic classified patients of w-ATTR into three stages for prognostication on the basis of Troponin T and N-terminal pro b-type natriuretic peptide levels, Stage 1 where both below normal range, Stage 2 one of the variable above normal, and stage 3 both parameters elevated and the median survival reported was 66, 42, and 20 months, respectively.[22]

Diagnostic Approach to ATTR-CM

Routine work up should include serum and urinary protein electrophoresis and immuno-fixation studies along with routine electrocardiography, echocardiography, and cardiac magnetic resonance imaging (CMRI). Detailed discussion about these noninvasive tests is beyond the scope of this review. AL-amyloid is more common type of systemic amyloidosis and the diagnosis is confirmed by serum and urinary protein electrophoresis. In AL-amyloidosis the ratio of Lambda versus Kappa free light chains reported was 3:1. Before planning 99mTc-PYP scintigraphy, it is essential to exclude monoclonal gammapathy by serum and urinary electrophoresis and immuno-fixation studies.

Electrocardiogram

The presence of low-voltage electrocardiogram (ECG) disproportionate to left ventricular hypertrophy (LVH) is suggestive of ATTR-CM and this can be used as a screening test. It should be remembered that the absence of low-voltage ECG does not exclude ATTR-CM.

Echocardiography

LVH/biventricular hypertrophy with normal to small sized ventricular cavities, granular and speckling or sparkling appearance of myocardium, restrictive filling pattern, diastolic dysfunction (≥ grade II) and rule of 5 where a', e', s'<5 cm/s are suggestive but not confirmatory of ATTR-CM. Speckle tracking is helpful to detect reduced LV global longitudinal strain (GLS) with apical sparing with progressive worsening of GLS, moving toward basal segments is characteristic of cardiac amyloidosis which gives "Cherry on top"[26] appearance, as shown in Figure 1.

Cardiac magnetic resonance imaging

CMRI for the diagnosis of amyloidosis has been adopted since the 1990s. Typical findings on CMRI include diffuse late gadolinium enhancement, extracellular volume expansion and characteristic T1 relaxation times. In those with diffuse transmural or sub-endocardial deposits, one can diagnose ATTR-CM by CMRI with a sensitivity and specificity of 85%–90%.[27] Parametric imaging was believed to be a more sensitive measure of amyloid burden and hence helpful to assess therapeutic response during the follow-up.[28-30] However, CMRI cannot differentiate between h–ATTR, w-ATTR, or AL-amyloidosis.

Nuclear imaging

99m Tc-PYP scintigraphy

99m Tc-PYP scintigraphy for differentiating AL-amyloidosis from ATTR was developed by Perugini *et al*. by the visual

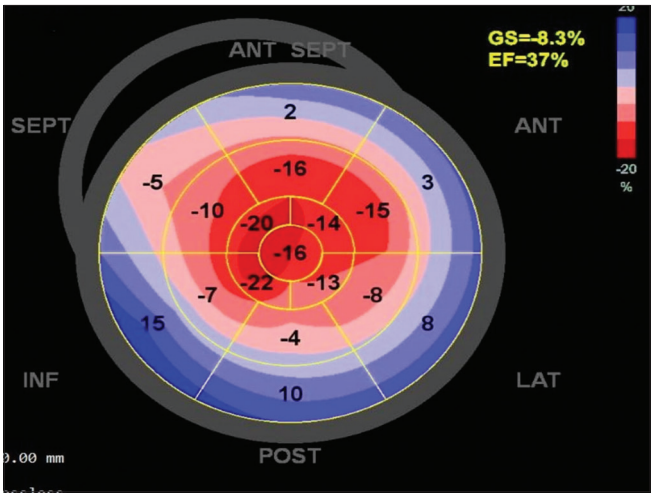

Figure 1: Classical apical sparing of longitudinal strain by strain echocardiography, the apical segments are preserved than the basal segments giving appearance of "Bulls eye pattern" also called "Cherry on top" pattern

comparison of isotope uptake by myocardium to ribs.[31] No specific patient preparation is required for this test. The procedural recommendations of the American Society of Nuclear Cardiology are widely followed.[32]

Radiopharmaceuticals

99m technetium is labeled with PYP in the radiopharmacy laboratory for intravenous administration. Several studies confirmed high sensitivity and specificity of 99mTc-PYP scintigraphy[33,34] for detecting ATTR-CM and recent reports highlighted its value in differentiating from AL-amyloidosis and it was found to be cost effective.[34]

Image acquisition

Both planar (whole body/static) and single-photon emission computed tomographic (SPECT) images are acquired at 1 h and 3 h after administering 15 mCi of 99m Tc-PYP intravenously. At our institution, images are acquired with Siemen's dual-head Gamma camera (SYmbiaT6). Planar imaging aids visual interpretation and quantification of myocardial uptake of the isotope which is compared with uptake by lungs or ribs.

SPECT imaging helps to avoid the overlap of bone uptake and to distinguish blood pool activity from myocardial activity.[34] Whole-body planar imaging assists in identifying the uptake of isotope by the shoulder and hip girdles (a specific sign of systemic amyloidosis).[2]

Image interpretation

Myocardial 99mTc-PYP uptake patterns are categorized into four, either absent, focal, diffuse, or focal and diffuse. There are two approaches for quantifying myocardial isotope uptake.

1. Quantitative approach in which heart (H) to contralateral lung (CL) uptake ratio is measured at 1 h, when myocardial uptake is visually present on SPECT images, H/CL ratios of ≥1.5 it is inferred as ATTR positive while ratios ≤1.5 as ATTR negative[2]
2. Semi-quantitative visual grading is done by the comparison of myocardial uptake to bone (rib) uptake at 3 h and are graded as Grade 0: when no uptake either by myocardium or rib, Grade 1: myocardial uptake less than rib, Grade 2: uptake equal to rib, and Grade 3: when uptake is greater than rib. Visual scores of ≥2 on planar[33,34] or SPECT images can be inferred as ATTR positive and scores <2 as ATTR negative. While grade 2 or 3 or H/CL ≥1.5 uptake is strongly suggestive of ATTR amyloidosis, myocardial uptake can also be observed even in AL amyloidosis, so a complete primary work up is warranted to exclude this diagnosis. Figure 2 illustrates 99mTc-PYP imaging of ATTR-CM.

Specificity of 99m Tc-PYP reduces when monoclonal proteins are present, as 40%–50% of ATTR-CM patients were shown to have co-existing monoclonal gammapathy.[35] Gillmore *et al*. reported a diagnostic sensitivity of 99% and specificity of 86% with 99m Tc-PYP in the absence of monoclonal gammapathies.[4] When the H/CL ratio is ≥1.6, it indicates worst 5-year survival suggesting that this test has prognostic significance.[36] Quantitative imaging is also useful to assess the progression of disease as well as response to therapy.[37]

Endomyocardial biopsy

Patients with grade 2 or 3 cardiac uptake on scintigraphy associated with an abnormal serum or urinary immunofixation, an EMB is indicated for confirmation which has got a sensitivity of 100%. EMB is also indicated in those with positive 99m Tc-PYP scans without clinical or biochemical evidence of cardiac amyloidosis. In rare situations, when the test results are false positive or inconclusive, EMB is essential to confirmation.

With 99m Tc-PYP scintigraphy, in one study involving 173 patients,[37] <10% needed EMB for confirmation. To avoid sampling errors in the setting of patchy myocardial deposition, it was recommended to take biopsy samples from multiple sites (at least 4 sites) to improve the diagnostic yield. Figure 3 illustrates static and sweep images showing isotope uptake only in the right atrium, and in such cases, even EMB from the ventricles may not be confirmatory.

Genetic testing

Once the diagnosis of ATTR-CM is confirmed, genetic testing is indicated to differentiate h-ATTR from w-type.

99m Tc-PYP Scintigraphy for Whom?

To make 99m Tc-PYP scintigraphy a cost-effective screening test, it should be advised for those with severe LVH with or without associated aortic stenosis, those with atrial fibrillation with features of restrictive cardiomyopathy, HFpEF in whom etiology is not clear and in those with unexplained myocardial wall thickness >14 mm by echocardiography.[16,17] Screening for ATTR-CM is also indicated for those with interventricular septal thickness associated with LV sparkling or apical sparing with persistent elevation of troponins in the elderly and those with CMRI evidence of diffuse sub-endocardial LGE pattern coupled with increased extracellular volume.[28] More than half of w-ATTR-CM can present with carpel tunnel syndrome 5–10 years prior to the development of overt HF[38] and 99m Tc-PYP scintigraphy is helpful for the early diagnosis or to rule out ATTR in them. Figure 4 shows flow chart followed at our center for the approach to the diagnosis of ATTR-CM.

Specific Therapy

Therapy includes stabilizers and silencers of the disease process which either slows or halts the progression. Rate-limiting step of ATTR-CM is dissociation of tetramers into monomers with subsequent deposition. Tafamidis has been approved by FDA, which stabilizes transthyretin tetramers and was shown to reduce all-cause mortality, recurrent hospitalizations due to cardiovascular causes, and improvement in the quality of life.[39,40] It slows the progression of disease but does not reverse the preexisting deposition. The benefits are gratifying when the drug is initiated early in the disease process, both for h-ATTR and w-ATTR CM, even though when patients are in

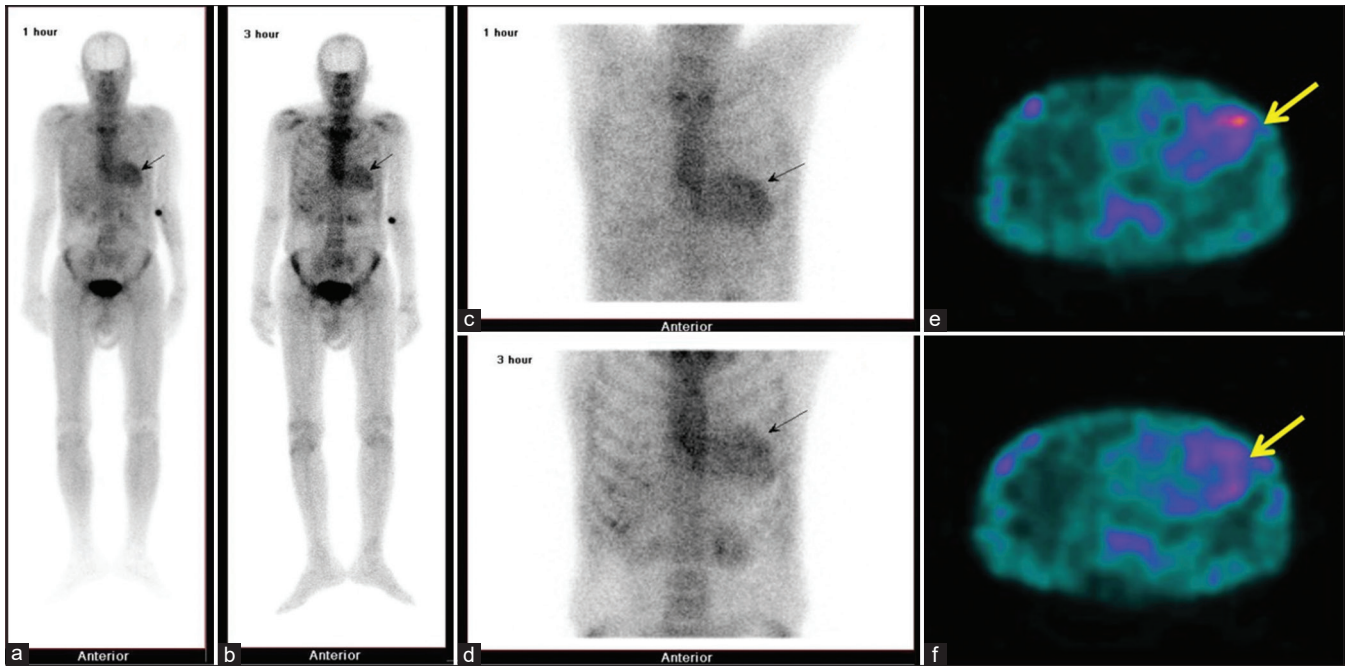

Figure 2: Illustration of a case of ATTR-CM. (a) Sweep images showing 99m technetium Pyrophosphate (99mTc-PYP) uptake by the myocardium at 1 h. (b) Sweep images at 3 h showing visual grading 3 (myocardium uptake more than rib). (c and d) Static images at 1 h and 3 h showing 99m Tc-PYP uptake of the left ventricle. (e and f) single photon emission computed tomographic images at 1 h and 3 h showing Grade 3 uptake (myocardium more than the rib) pointed by yellow arrows

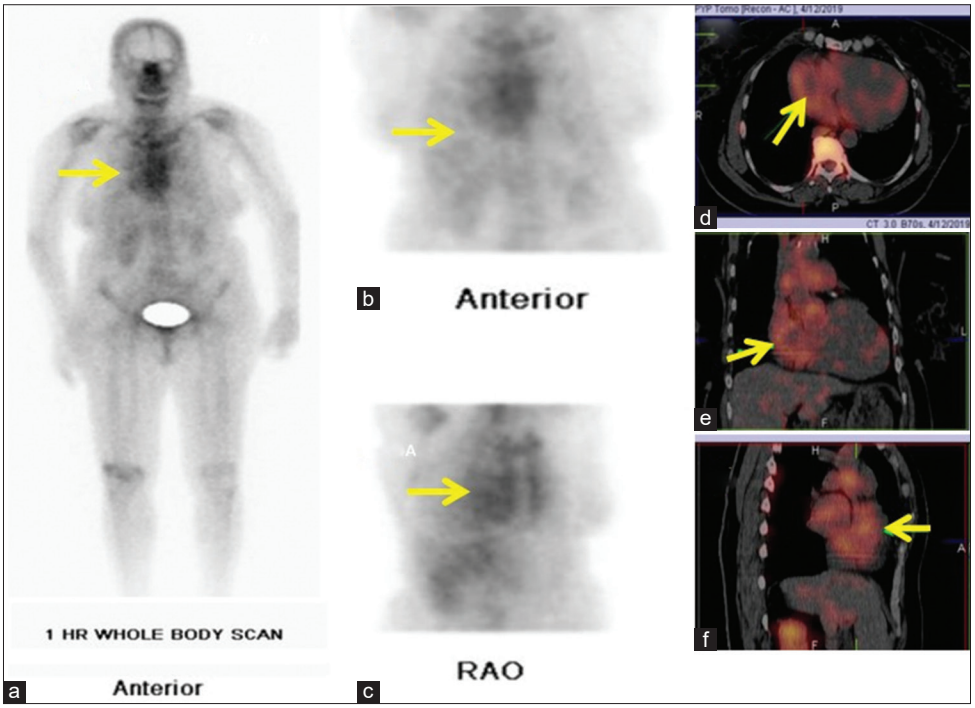

Figure 3: Single-photon emission computed tomographic images showing Technetium 99m pyrophosphate (99m Tc-PYP) uptake by the myocardium shown by yellow arrows. (a) Sweep images at 1 h showing 99m Tc-PYP uptake in the right atrium (yellow arrows). (b) Static image - anterior view. (c) Static image -right anterior oblique view. (d) Axial view, (e) Coronal view, (f) Saggital view

functional class-I or II. Functional improvement was observed in 6 months and reduction in mortality in 2 years.[41-43] The ease of once a day oral administration is an added advantage. Phase 2 clinical trials showed Tafamidis meglumin 20 mg daily stabilized ATTR[43] but found less beneficial in Class III/IV patients. In a phase 2 open label trial involving 31 patients, Tafamidis 20 mg per day stabilized TTR and proved its safety and survival benefit as reported by Maurer *et al*.[43] The dose of

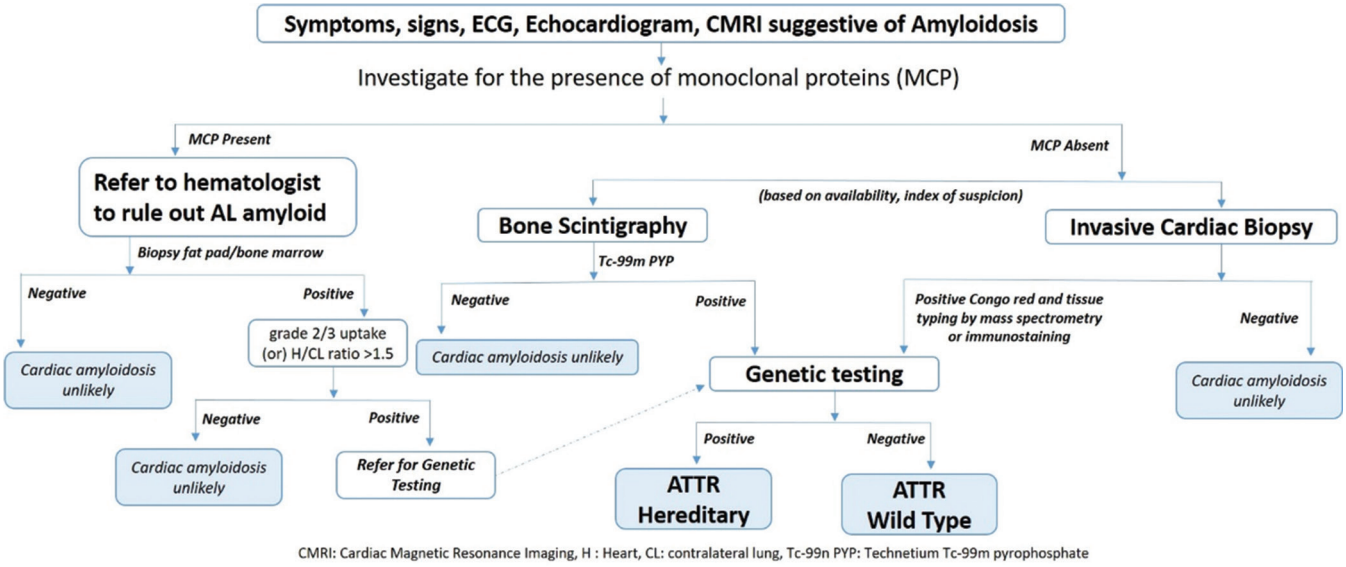

Figure 4: Flowchart showing approach to the diagnosis of cardiac amyloidosis

Tafamidis is 61 mgs and Tafamidis meglumine is 80 mg once a day. The European Society of Cardiology has given class I B recommendation for the use of Tafamidis in ATTR-CM even with NYHA functional class I and II.[42]

In ATTR-ACT (phase 3) trial, Tafamidis meglumine 80 mg, 20 mg or placebo were compared in a ratio of 2:1:2, in 441 patients of ATTR-CM and showed 13.4% absolute reduction in mortality, 32% relative risk reduction in hospitalizations along with improvement in 6-min walk distance and quality of life assessed by Kansas city cardiomyopathy questionnaire[43] and recurrent hospitalizations were observed more often in NYHA class 3 and 4 patients high lighting the need for an early diagnosis and initiation of therapy.[44] The drug that interferes with RNA, Vutrisiran was found to reduce the risk of all cause as well as cardiovascular mortality and repeated hospitilizations and emergency visits due to HF in patient of ATTR-CM in HELIOS-B study, when 25 mg of Vutrisiran was given subcutaneously once in 3 months.[45] This drug can be coprescribed with Tafamedis. Further studies reveal if vutrisiran finds a place in the guidelines for the treatment of ATTR-CM.

Future Directions

Combining stabilizers and silencers are predicted to have complimentary effects on the outcomes and the work is in progress in this direction. Novel therapies aiming at myofibril degeneration with monoclonal antibodies is underway. Gene editing is a novel approach being developed for targeting DNA for silencing the TTR mutations. FDA approved a drug used for Parkinson's disease which also functions as ATTR stabilizer and this may find a place in the therapeutic armamentarium in future. The amyloidosis working group recommended establishing the state of the art multidisciplinary centers of excellence for referral, diagnosis, management, and monitoring the outcomes of these cases.[46]

Conclusions

99m Tc-PYP scintigraphy is diagnostic of ATTR-CM in the absence of monoclonal gammapathies. Introduction of 99m Tc-PYP in the diagnostic armamentarium has certainly helped in screening and early detection of more number of cases. This being a noninvasive test, one can avoid the need for an invasive EMB. Early diagnosis aids in the early initiation of disease specific therapy for the better long-term outcomes.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Papantoniou V, Valsamaki P, Kastritis S, Tsiouris S, Delichas Z, Papantoniou Y, *et al.* Imaging of cardiac amyloidosis by (99m) Tc-PYP scintigraphy. Hell J Nucl Med 2015;18 Suppl 1:42-50.
2. Bokhari S, Castaño A, Pozniakoff T, Deslisle S, Latif F, Maurer MS. (99m) Tc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. Circ Cardiovasc Imaging 2013;6:195-201.
3. Lo Presti S, Horvath SA, Mihos CG, Rajadhyaksha C, McCloskey V, Santana O. Transthyretin cardiac amyloidosis as diagnosed by 99mTc-PYP scanning in patients with acute heart failure and preserved ejection fraction. Crit Pathw Cardiol 2019;18:195-9.
4. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, *et al.* Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation 2016;133:2404-12.
5. Martinez-Naharro A, Hawkins PN, Fontana M. Cardiac amyloidosis. Clin Med (Lond) 2018;18:s30-5.
6. Gertz MA, Benson MD, Dyck PJ, Grogan M, Coelho T, Cruz M, *et al.* Diagnosis, prognosis, and therapy of transthyretin amyloidosis. J Am Coll Cardiol 2015;66:2451-66.
7. Coelho T, Maurer MS, Suhr OB. THAOS – The transthyretin amyloidosis outcomes survey: Initial report on clinical manifestations in patients with hereditary and wild-type transthyretin amyloidosis. Curr Med Res Opin 2013;29:63-76.

8. Mohammed SF, Mirzoyev SA, Edwards WD, Dogan A, Grogan DR, Dunlay SM, *et al.* Left ventricular amyloid deposition in patients with heart failure and preserved ejection fraction. JACC Heart Fail 2014;2:113-22.
9. Castaño A, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, *et al*. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. Eur Heart J 2017;38:2879-87.
10. Witteles RM, Bokhari S, Damy T, Elliott PM, Falk RH, Fine NM, *et al*. Screening for transthyretin amyloid cardiomyopathy in everyday practice. JACC Heart Fail 2019;7:709-16.
11. Pomerance A. Senile cardiac amyloidosis. Br Heart J 1965;27:711-8.
12. Pinney JH, Whelan CJ, Petrie A, Dungu J, Banypersad SM, Sattianayagam P, *et al.* Senile systemic amyloidosis: Clinical features at presentation and outcome. J Am Heart Assoc 2013;2:e000098.
13. Yilmaz A, Kindermann I, Kindermann M, Mahfoud F, Ukena C, Athanasiadis A, *et al.* Comparative evaluation of left and right ventricular endomyocardial biopsy: Differences in complication rate and diagnostic performance. Circulation 2010;122:900-9.
14. Connors LH, Sam F, Skinner M, Salinaro F, Sun F, Ruberg FL, *et al.* Heart failure resulting from age-related cardiac amyloid disease associated with wild-type transthyretin: A prospective, observational cohort study. Circulation 2016;133:282-90.
15. Buxbaum JN, Ruberg FL. Transthyretin V122I (pV142I)* cardiac amyloidosis: An age-dependent autosomal dominant cardiomyopathy too common to be overlooked as a cause of significant heart disease in elderly African Americans. Genet Med 2017;19:733-42.
16. Lindmark K, Pilebro B, Sundström T, Lindqvist P. Prevalence of wild type transtyrethin cardiac amyloidosis in a heart failure clinic. ESC Heart Fail 2021;8:745-9.
17. González-López E, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ, CoboMarcos M, Robles C, *et al*. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. Eur Heart J 2015;36:2585-94.
18. Bruno M, Castaño A, Burton A, Grodin JL. Transthyretin amyloid cardiomyopathy in women: Frequency, characteristics, and diagnostic challenges. Heart Fail Rev 2021;26:35-45.
19. Lane T, Fontana M, Martinez-Naharro A, Quarta CC, Whelan CJ, Petrie A, *et al.* Natural history, quality of life, and outcome in cardiac transthyretin amyloidosis. Circulation 2019;140:16-26.
20. Tanskanen M, Peuralinna T, Polvikoski T, Notkola IL, Sulkava R, Hardy J, *et al.* Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: A population-based autopsy study. Ann Med 2008;40:232-9.
21. Cornwell GG 3rd, Murdoch WL, Kyle RA, Westermark P, Pitkänen P. Frequency and distribution of senile cardiovascular amyloid. A clinicopathologic correlation. Am J Med 1983;75:618-23.
22. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol 2019;73:2872-91.
23. Rapezzi C, Merlini G, Quarta CC, Riva L, Longhi S, Leone O, *et al.* Systemic cardiac amyloidoses: Disease profiles and clinical courses of the 3 main types. Circulation 2009;120:1203-12.
24. Grogan M, Scott CG, Kyle RA, Zeldenrust SR, Gertz MA, Lin G, *et al.* Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. J Am Coll Cardiol 2016;68:1014-20.
25. Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. Circulation 2012;126:1286-300.
26. Zhao L, Tian Z, Fang Q. Diagnostic accuracy of cardiovascular magnetic resonance for patients with suspected cardiac amyloidosis: A systematic review and meta-analysis. BMC Cardiovasc Disord 2016;16:129.
27. Maurer MS, Bokhari S, Damy T, Dorbala S, Drachman BM, Fontana M, *et al.* Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. Circ Heart Fail 2019;12:e006075.
28. Martinez-Naharro A, Treibel TA, Abdel-Gadir A, Bulluck H, Zumbo G, Knight DS, *et al.* Magnetic resonance in transthyretin cardiac amyloidosis. J Am Coll Cardiol 2017;70:466-77.
29. Carvalho FP, Erthal F, Azevedo CF. The role of cardiac MR imaging in the assessment of patients with cardiac amyloidosis. Magn Reson Imaging Clin N Am 2019;27:453-63.
30. Dungu JN, Valencia O, Pinney JH, Gibbs SD, Rowczenio D, Gilbertson JA, *et al.* CMR-based differentiation of AL and ATTR cardiac amyloidosis. JACC Cardiovasc Imaging 2014;7:133-42.
31. Perugini E, Guidalotti PL, Salvi F, Cooke RM, Pettinato C, Riva L, *et al.* Noninvasive etiologic diagnosis of cardiac amyloidosis using 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. J Am Coll Cardiol 2005;46:1076-84.
32. Dorbala S, Ando Y, Bokhari S, Dispenzieri A, Ferrari VA, Fontana M, *et al*. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis part 1 of 2-evidence base and standardized methods of imaging. Circ Cardiovasc Imaging 2021;14:685-725.
33. Gertz MA, Brown ML, Hauser MF, Kyle RA. Utility of technetium Tc 99m pyrophosphate bone scanning in cardiac amyloidosis. Arch Intern Med 1987;147:1039-44.
34. Phull P, Sanchorawala V, Connors LH, Doros G, Ruberg FL, Berk JL, *et al.* Monoclonal gammopathy of undetermined significance in systemic transthyretin amyloidosiss (ATTR). Amyloid 2018;25:62-7.
35. Varga C, Dorbala S, Lousada I, Polydefkis MJ, Wechalekar A, Maurer MS, *et al.* The diagnostic challenges of cardiac amyloidosis: A practical approach to the two main types. Blood Rev 2021;45:100720.
36. Hassan W, Al-Sergani H, Mourad W, Tabbaa R. Amyloid heart disease. New frontiers and insights in pathophysiology, diagnosis, and management. Tex Heart Inst J 2005;32:178-84.
37. Dower J, Dima D, Lalla M, Patel AR, Comenzo RL, Varga C. The use of PYP scan for evaluation of ATTR cardiac amyloidosis at a tertiary medical centre. Br J Cardiol 2022;29:19.
38. Nakagawa M, Sekijima Y, Yazaki M, Tojo K, Yoshinaga T, Doden T, *et al.* Carpal tunnel syndrome: A common initial symptom of systemic wild-type ATTR (ATTRwt) amyloidosis. Amyloid 2016;23:58-63.
39. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, *et al.* Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med 2018;379:1007-16.
40. Lamb YN, Deeks ED. Tafamidis: A review in transthyretin amyloidosis with polyneuropathy. Drugs 2019;79:863-74.
41. Damy T, Garcia-Pavia P, Hanna M, Judge DP, Merlini G, Gundapaneni B, *et al.* Efficacy and safety of tafamidis doses in the tafamidis in transthyretin cardiomyopathy clinical trial (ATTR-ACT) and long-term extension study. Eur J Heart Fail 2021;23:277-85.
42. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599-726.
43. Maurer MS, Elliott P, Merlini G, Shah SJ, Cruz MW, Flynn A, *et al.* Design and rationale of the phase 3 ATTR-ACT clinical trial (tafamidis in transthyretin cardiomyopathy clinical trial). Circ Heart Fail 2017;10:e003815.
44. Keohane D, Schwartz J, Gundapaneni B, Stewart M, Amass L. Tafamidis delays disease progression in patients with early stage transthyretin familial amyloid polyneuropathy: Additional supportive analyses from the pivotal trial. Amyloid 2017;24:30-6.
45. Witteles RM, Garcia-Pavia P, Damy T, Grogan M, Sheikh FH, Morbach C, *et al*. Vutrisiran improves survival and reduces cardiovascular events in ATTR amyloid cardiomyopathy HELIOS-B. JACC 2055;85:1959-70.
46. Cheng R, Kittleson MM, Wechalekar AD, Alvarez-Cardona J, Mitchell JD, Scarlatelli Macedo AV, *et al.* Moving towards establishing centres of excellence in cardiac amyloidosis: An International Cardio-Oncology Society statement. Heart 2024;110:823-30.