Saudi Journal of Medical and Pharmaceutical Sciences **ISSN 2413-4929 (Print)**
Scholars Middle East Publishers **ISSN 2413-4910 (Online)**
Dubai, United Arab Emirates
Website: https://saudijournals.com/ DOI: 10.36348/sjmps.2016.v02i05.003

Review Article

Contemporary Review of Cardiac Amyloidosis

***Mohammed Ahmed Zahrani MD*[1, 2]**
[1]*Section of Internal Medicine, Section of Cardiology, Department of Internal Medicine, College of Medicine, Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada*
[2]*Section of Internal Medicine, King Abdulaziz University, Jeddah, Saudi Arabia*

***Corresponding Author:**
Mohammed Ahmed Zahrani
Email: zahrani_mohd@yahoo.com

Abstract: Cardiac amyloidosis is underdiagnosed. Prevalence is increasing with age. Diagnosis can be elusive and challenging. High index of suspicion is required for recognition and prompt diagnosis. Cardiac amyloid diagnosis carries important therapeutic and prognostic implication. We outline the prevalence, types, clinical presentation, diagnosis, prognosis and treatment of cardiac amyloidosis.
Keywords: Cardiac amyloidosis, Prevalence, treatment

INTRODUCTION

Amyloidosis is a rare systemic disease, with estimated incidence of 1 to 5 cases per 100,000 people [1]. It is characterized by deposition of amyloid fibrils that derive from the aggregation of misfolded protein such as abnormal light chains and transthyretin.

The type of amyloidosis defined by the type of protein deposits. Cardiac involvement varies based on amyloidosis subtype. The most common subtype of cardiac amyloidosis is light chains amyloidosis (AL amyloidosis) with 50% of cases will have cardiac involvement. Other types include Wild type transthyretin (senile amyloidosis), mutant amyloidosis (familial ATTR) and localized atrial amyloidosis.

CLINICAL PRESENTATION

Age of onset between 5thand 6thdecade for AL amyloidosis while Wide type transthyretin patients tend to be older with disease onset in 7th decade. Amyloidosis is more common in men and those of Caucasian descents [2].

AL amyloidosis patients present with rapidly progressive biventricular heart failure. In some cases right side heart failure more predominant with peripheral edema and ascites. 25% of patients develop ischemic chest pain as a result of deposition of amyloid fibril in small branches of coronary artery. It is commonly associated with other system involvement such as renal, gastrointestinal tracts and soft tissues.

Wilde type transthyretin's patients present with progressive biventricular heart failure. It is only involved the heart with no other system involvements. Chronic illness such as hypertension (HTN), diabetes (DM), chronic kidney disease (CKD) and atrial fibrillation are more prevalent in this group of patients than patients with AL amyloidosis.

Mutant TTR (familial ATTR) is autosomal dominant disease, with age of onset in second decade and onward. Affected patients at young age tend to have cardiac involvement and neuropathy. While if age of onset in 5th decade or after, it tend to have predominantly cardiac involvement [2].

Isolated atrial amyloid presents as increase prevalence of atrial arrhythmia. It is diagnosed on surgical specimen of excised atrial appendage. As the name imply is limited to the atria with no ventricular involvement and as such no targeted therapy toward amyloid is required.

DIAGNOSIS

Diagnosis of amyloidosis can be challenging and high index of suspicion required. As often amyloid presentation with cardiac involvement tend to have similar symptoms and signs to other causes of heart failure and can be easily missed. Prompt recognition and diagnosis is required as it carries therapeutic and prognostic implications.

Endomyocardial biopsy demonstrates amyloidosis is considered the gold standard to diagnose cardiac amyloidosis. Alternatively, echocardiographic evidence of amyloidosis in a patient with a positive result of noncardiac biopsy is sufficient for diagnosis. Left ventricle (LV) wall thickness >12 mm, in the absence of other cardiac causes such as HTN or valvular heart disease is used to define cardiac involvement [3].

There are certain clues should raise the suspicion for amyloid including rapidly progressive heart failure despite medical treatment, presence of other systems involvement beside the heart such as renal, gastrointestinal, liver, lung, soft tissues and neuropathy, family history of amyloidosis, Low voltages on electrocardiogram and echocardiographic changes suggestive of amyloid.

ANCILLARY TESTS IN CARDIAC AMYLOIDOSIS

Electrocardiogram (ECG) frequently shows low limb leads voltage in 70% of patients with AL amyloidosis and 50% of patients with wild type ATTR. Conduction abnormalities are common ranging from first degree AV block to complete heart block. Left bundle branch block is rare in AL amyloidosis and more common in wild type ATTR. Atrial fibrillation presents in up to 34% of AL amyloidosis' patients and between 55% and 67% in wild type ATTR. Other ECG's changes include right axis, q wave in V1-V3 and nonspecific ST or T wave changes [2].

Transthoracic echocardiography (TTE) features of amyloid include concentric LV wall thickness > 12 mm, in the absence of hypertension and valuvlar heart disease, Normal to small LV cavity size, increase right ventricle (RV) wall thickness and granular appearance of the myocardium resulting from extracellular amyloid deposition. Bi-atrial enlargement is common and often seen without LV dilation. It is not uncommon to see valve thickening of mitral and tricuspid valve and to less extent aortic valve without significant valve dysfunction. Small pericardial effusion can be seen in advance cases and seldom lead to cardiac tamponade. Left ventricular function (LVEF) is usually preserved with often impaired LV longitudinal function. Diastolic dysfunction presents and range from grade 1 to grade 3 in advance disease with elevated LV filling pressure

Cardiac MRI is emerging tools for diagnosis of amyloidosis when finding on TTE is equivocal or to help to differentiae types of infiltrative cardiomyopathy or as complementary to echocardiogram. Cardiac MRI with intravenous gadolinium is contraindicated in patients with low glomerular filtration rate (GFR) less than 30 ml/min/BSA, which are not uncommonly seen in amyloidosis, as renal involvement is common. It is also contraindicated in patients with devices non compatible with MRI, and as many as 30% of patients with amyloidosis will have pacemaker or Implantable Cardioverter Defibrillators (ICD). Features of cardiac amyloidosis on MRI include LV and RV concentric thickening with normal cavity size, thickening of intra atrial septum, Delayed gadolinium enhancement typically shows diffuse and irregular enhancement of the myocardium. The enhancement pattern is quite variable and it can be patchy or diffuse and it can be circumferential or subendocardial in distribution. Myocardial nulling is seen on cardiac MRI and it can be a useful feature to differentia between amyloidosis and hypertrophic cardiomyopathy. The sensitivity of cardiac MRI for diagnosing cardiac amyloidosis was 80% and specificity of 94%. The positive predictive value was 92% and negative predictive value of 85% [4].

PROGNOSIS OF CARDIAC AMYLOIDOSIS

Prognosis varies based on subtype of cardiac amyloidosis. AL cardiac amyloidosis carries the worst prognosis. In a retrospective study by Sperry et al, they studied 360 patients with cardiac amyloidosis (191 patients with AL amyloidosis and 169 with ATTR amyloidosis). The 1year mortality was 59% in AL amyloidosis and 20% in ATTR amyloidosis. The 3 years mortality was 72% in AL subtype and 38% in ATTR subtype [5].

In a prospective observational study by Connors et al of 121 patients with wild type ATTR amyloidosis, the median survival measured from biopsy diagnosis was 46.69 months and 5-year survival was 35.7%. The cause of death was cardiac in 78% of cases [6].

Predictor of worse prognosis and mortality are AL subtype, elevated serum brain natriuretic peptide, decreased left ventricular ejection fraction, and increased relative wall thickness, age, NYHA class ≥3, severe tricuspid regurgitation, and global longitudinal strain, low voltage by either limb or precordial criteria or Troponin T [5, 6].

TREATMENT

Treatment of amyloidosis requires a multidisciplinary approach with involvement of cardiologist, hematologist and health-allied personals.

Management of cardiac amyloidosis requires a twofold approach: one is directed toward management of heart failure and second directed at suppressing amyloid production.

Therapy should be tailored based on patient age, comorbidities, patient's wish, risk score and biomarker which include NT-proBNP, cardiac troponin T level and difference of involved and uninvolved light chain.

In AL subtype treatment is directed to stop plasma cell clone from producing misfloded free light chains. Bortezomib based regimens are preferred first line due to better response rate and better outcome [7]. In a study by Venner *et al*, [8] 43 patients with AL amyloidosis, 74% of them had cardiac involvement. They received cyclophosphamide, bortezomib, and dexamethasone upfront or at relapse. Patients treated upfront had higher rates of complete hematological response 65.0% and the estimated 2-year progression-free survival was 66.5% for patients treated upfront.

High dose melphalan (HDM) and autologous stem cell transplantation (ASCT) is the preferred first line treatment for selected patients with modified mayo stage I & II. HDM-ASCT is not generally recommended as first line therapy for patients with any of the following: Cardiac amyloidosis with NT-proBNP>590 pmol/l and/or troponin-T >0.06 ng/ml, severe autonomic neuropathy, significant gastrointestinal (GI) bleeding due to amyloid, advanced renal failure, age over 70 years, symptomatic recurrent amyloid related pleural effusions or poor Eastern Cooperative Oncology Group performance status >2 [7].

Thalidomide, lenalidomide and pomalidomide have emerged as important agents. However, it is poorly tolerated with reported side effect in 65% of patient [9].

High dose melphalan combined with steroid used to be the first line but falling out of favor and now being used where bortezomib is contraindicated or as second line agent in relapse.

Cardiac response defined as: 30% decrease in NT-proBNP level and 300 ng/L decrease if baseline NT-proBNP 650 ng/L and/or NYHA class response if 2 class decrease if baseline NYHA 3 or 4.Cardiac progression define as: NT-proBNP level increase by 30% and 300 ng/L or 33% increase in cardiac troponin or ejection fraction decrease by 10% [10].

Liver transplant to remove the amyloidgenic precursor is preferred first line therapy in familial ATTR. After liver transplant, there are subset of patients will progress to develop cardiac amyloidosis and neuropathy as result of deposition of wild type ATTR. Patients with advance cardiac amyloidosis will require combined heart and liver transplant. The 20-year survival after liver transplant was 55.3% [11].

Patients with wild type TTR do not require liver transplant, and often are not candidate for heart transplant because of age and multiple comorbidities. Tafamidis blocks a rate limiting step in the TTR amyloid cascade. It been shown to maintain TTR stabilization with no significant change in biochemical or echocardiography at 12 months in patients with wild type ATTR, however, 15 out 31 patients had clinical progression in the same study [12].

The second fold is directed toward treating heart failure. Diuretics are the mainstay therapy in heart failure. It reduced edema and filling pressure, however, often results in hypotension. It poorly tolerated because of hypotension, autonomic dysfunction, low cardiac output and impaired kidney function. An angiotensin converting enzyme inhibitors and angiotensin II receptor blockers are poorly tolerated for above mention reasons and even small doses may result in worsening hypotension. B blockers are poorly tolerated as well, but small doses maybe required for rate in control in atrial fibrillation. Digoxin binds to amyloid fibril and lead high level in the myocardium; as such it may be used with caution as may lead to arrhythmia and toxicity [13].

Calcium channel blocker use is contraindicated as often exacerbate heart failure [14]. The role of ICD in primary prevention is not well established, although cardiac amyloidosis patients at increased risk of sudden death, it appears the majority of sudden cardiac death is secondary to elecromechanical dissociation. In as study by Kristen et al, 2008, 19 patients with biopsy proven cardiac amyloidosis and a history of syncope and/or ventricular extra beats received an ICD. 2 patients with sustained ventricular tachyarrhythmias were successfully treated by the ICD and 7 patients died due to electromechanical dissociation [15].

Lin *et al*, [16], studied 53 patients with cardiac amyloidosis who underwent ICD implantation. ICD implantation was for primary prevention of sudden cardiac arrest in 41 (77%) patients and secondary prevention in 12 (23%) patients. The rate of appropriate ICD shocks was 32% in the first year. However, appropriate ICD therapy did not translate into overall survival benefit.

More studies are needed to determine criteria and develop risk score for patients that may drive most benefit from ICD. At this point ICD may be useful in patients with aborted sudden death or syncope secondary to ventricular arrhythmia, after carful assessment of life expectancy, patient's wishes, risk and benefit. Pacemaker is indicated in patients with advance heart block or symptomatic bradycardia.

CONCLUSION

Cardiac amyloidosisis under diagnosed. It should be suspected in patients with HFpEF with no clear etiology of heart failure, rapidly progressive heart failure and when other systems involved such as renal, neuropathy and soft tissues. Treatment is twofold, to relieve symptoms of congestion and to stop amyloid production. The mortality rate is high with over all poor prognosis despite treatment.

ABBREVIATIONS

Light chains amyloidosis (AL amyloidosis), hypertension (HTN), diabetes (DM), chronic kidney disease (CKD), familial ATTR (familial or hereditary transthyretin related amyloidosis), Left ventricle (LV), Electrocardiogram (ECG), Transthoracic echocardiography(TTE), right ventricle (RV), Left ventricular function (LVEF), glomerular filtration rate(GFR), Implantable Cardioverter Defibrillators (ICD), MRI (magnetic resonance imaging), NYHA (new york heart association classification), NT-proBNP (N terminal- pro brain type natriuretic peptide), High dose melphalan (HDM), autologous stem cell transplantation(ASCT),

REFERENCES

1. George, A., & Mcclements, B. (2015). Cardiac amyloidosis presenting as recurrent acute coronary syndrome with unobstructed coronary arteries: Case report, *Indian Heart Journal, 67*(6), 570-573.
2. Mann, D. L., & Braunwald, E. (2015). *Braunwald's heart disease: A textbook of cardiovascular medicine*. Philadelphia, PA: Elsevier, Saunders.
3. Gertz, M. A., Comenzo, R., Falk, R. H., Fermand, J. P., Hazenberg, B. P., Hawkins, P. N., Merlini, G., Moreau, P., Ronco, P., Sanchorawala, V., Sezer, O., Solomon, A. & Grateau, G. (2005), Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): A consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis. *Am. J. Hematol., 79*, 319–328.
4. Vogelsberg, H., Mahrholdt, H., Deluigi, C. C., Yilmaz, A., Kispert, E. M., Greulich, S., . . .& Sechtem, U. (2008). Cardiovascular Magnetic Resonance in Clinically Suspected Cardiac Amyloidosis. *Journal of the American College of Cardiology, 51*(10), 1022-1030.
5. Sperry, B. W., Vranian, M. N., Hachamovitch, R., Joshi, H., Ikram, A., Phelan, D., & Hanna, M. (2016). Subtype-Specific Interactions and Prognosis in Cardiac Amyloidosis. *J Am Heart Assoc., 5*, e002877.
6. Connors, L. H., Sam, F., Skinner, M., Salinaro, F., Sun, F., Ruberg, F. L., . . .& Seldin, D. C. (2015). Heart Failure Due to Age-Related Cardiac Amyloid Disease Associated With Wild-Type Transthyretin: A Prospective, Observational Cohort Study. *Circulation*, *101*(9), 1847-1854.
7. Wechalekar, A. D., Gillmore, J. D., Bird, J., Cavenagh, J., Hawkins, S., Kazmi, M., . . .& Pratt, G. (2014). Guidelines on the management of AL amyloidosis. *British Journal of Haematology Br J Haematol, 168*(2), 186-206.
8. Venner, C. P., Lane, T., Foard, D., Rannigan, L., Gibbs, S. D., Pinney, J. H., . . .& Wechalekar, A. D. (2012). Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival. *Blood, 119*(19), 4387-4390.
9. Palladini, G. (2005). The combination of thalidomide and intermediate-dose dexamethasone is an effective but toxic treatment for patients with primary amyloidosis (AL). *Blood, 105*(7), 2949-2951.
10. Palladini, G., Dispenzieri, A., Gertz, M. A., Kumar, S., Wechalekar, A., Hawkins P. N., Schönland, S., Hegenbart, U., Comenzo, R., Kastritis, E., Dimopoulos, M. A., Jaccard, A., Klersy, C., & Merlini, G. (2012). New Criteria for Response to Treatment in Immunoglobulin Light Chain Amyloidosis Based on Free Light Chain Measurement and Cardiac Biomarkers: Impact on Survival Outcomes. *JCO*, 4541-4549.
11. Ericzon, B., Wilczek, H. E., Larsson, M., Wijayatunga, P., Stangou, A., Pena, J. R., . . .& Suhr, O. (2015). Liver Transplantation for Hereditary Transthyretin Amyloidosis. *Transplantation, 99*(9), 1847-1854.
12. Maurer, M. S., Grogan, D. R., Judge, D. P., Mundayat, R., Packman, J., Lombardo, I., . . .& Falk, R. H. (2015). Tafamidis in Transthyretin Amyloid Cardiomyopathy: Effects on Transthyretin Stabilization and Clinical Outcomes. *Circulation: Heart Failure, 8*(3), 519-526.
13. Rubinow, A., Skinner, M., & Cohen, A. S. (1981). Digoxin sensitivity in amyloid cardiomyopathy. *Circulation, 63*(6), 1285-1288.
14. Gertz, M. A., Falk, R. H., Skinner, M., Cohen, A. S., & Kyle, R. A. (1985). Worsening of congestive heart failure in amyloid heart disease treated by calcium channel-blocking agents. *The American Journal of Cardiology, 55*(13), 1645.
15. Kristen, A. V., Dengler, T. J., Hegenbart, U., Schonland, S. O., Goldschmidt, H., Sack, F., . . .& Bauer, A. (2008). Prophylactic implantation of cardioverter-defibrillator in patients with severe cardiac amyloidosis and high risk for sudden cardiac death. *Heart Rhythm,5*(2), 235-240.
16. Lin, G., Dispenzieri, A., Kyle, R., Grogan, M., & Brady, P. A. (2013). Implantable Cardioverter Defibrillators in Patients with Cardiac Amyloidosis. *J Cardiovasc Electrophysiol Journal of Cardiovascular Electrophysiology, 24*(7), 793-798.