Dr KK Aggarwal
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TRANSTHYRETIN CARDIAC AMYLOIDOSIS: MYTHS, CHALLENGES AND SOLUTIONS

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- There are two major types of amyloidosis: light chain amyloidosis and transthyretin amyloidosis (ATTR).
- Transthyretin is a tetrameric protein and appears like a four-leaf clover. Genetic mutations lead to tetramers changing to dimers, which are unstable and result in the formation of amyloid fibrils, which are resistant to proteolysis. They are deposited in the heart and various systems of the body.
- Amyloidosis is a systemic disease similar to diabetes.
- The prevalence of senile systemic amyloidosis, also called the wild type amyloidosis, is reportedly 25% in patients ≥85 years of age. Wild type ATTR is more often seen in elderly men. The variant amyloidosis is population specific. V122I is seen in the US, Caribbean, Africa; V30M is seen in Portugal, Sweden, Japan; while T60A is seen the UK and Ireland.
- In early onset disease, neurological complications are more likely, while in late onset disease, cardiac manifestations are more likely.
- There is a diverse clinical presentation, such as carpal tunnel syndrome, lumbar stenosis, gait disturbances, peripheral neuropathy, autonomic neuropathy, gastrointestinal (GI) disturbances, orthostatic hypotension, syncope, valvular heart disease, heart blocks, arrhythmias.
- Patients carrying the V142I mutation have worse heart failure (HF) outcomes (Atherosclerosis Risk in Communities [ARIC] study).
- The type of mutation also decides the disease penetrance.
- Patients with Leu111Met mutation have an early onset of disease, whereas in ATTRwt gene mutation, the disease presents late.

- Till about a decade back, the prevalence of amyloidosis was at the threshold for rare disease. This was possibly an underestimation as the sample included only hospitalized patients.
- AL amyloidosis is a rare disease; there are ~2,500 cases in the US and only 50% have cardiac involvement. Hereditary forms of amyloidosis are seen in 4% of African American (carriers). There are several thousand cases. There are about 1 million cases of the wild type amyloidosis.
- Disease starts with carpal tunnel syndrome; patients develop peripheral neuropathy and it takes several years before the disease is diagnosed.
- In patients who have cardiac amyloidosis, the conventional HF therapy is poorly tolerated. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) can worsen orthostatic hypotension. Digoxin binds to amyloid fibrils resulting in increased toxicity.
- Just because a patient has hypertension and aortic stenosis (AS) does not mean that the patient cannot have amyloidosis. TTR amyloidosis is a disease of the elderly, who often have hypertension. Left ventricular hypertrophy (LVH) and AS are common.
- Studies have shown that a large number of patients with cardiac amyloidosis have comorbid conditions such as hypertension, coronary artery disease (CAD), diabetes mellitus (DM), atrial fibrillation and chronic kidney disease (CKD).
- Presence of low ejection fraction does not rule out cardiac amyloidosis.
- Most of these patients do not present with HF; heart blocks are present in a minority of patients. Low-voltage electrocardiogram (ECG) is supposed to be the hallmark, but it is present in only about 27% of cases.
- Another challenge is the complicated diagnostic evaluation of suspected cardiac amyloidosis. Tissue biopsy is the gold standard.
- Red flags must be identified. If the patients have HF, thick ventricles along with the presence of certain features like carpal tunnel syndrome, low-voltage EKG, cherry on top Echo pattern.
- Imaging of hypertrophy, amyloid fibrils, extracellular volume in the heart can now be done.
- Echocardiography is usually the first step showing LVH, right ventricular hypertrophy (RVH) and hypertrophy of the interatrial septum. Restrictive physiology is classically seen in patients with amyloidosis.
- Strain imaging improves diagnostic accuracy.
- Echo is a very sensitive test, but is not very specific.
- Cardiac magnetic resonance imaging (MRI) has high accuracy for cardiac amyloidosis with sensitivity of 85% and specificity of 92%. Although it is very specific, it does not differentiate between the types of amyloidosis. MRI is very useful to follow the treatment response.
- There were sporadic case reports on cardiac uptake on bone scans in elderly men who underwent bone scans for prostate cancer. These are the patients who have wild type amyloidosis. Bone scintigraphy is now being used to diagnose cardiac amyloidosis. It is widely available, easy to perform and has very high accuracy for transthyretin amyloidosis (ATTR). If AL amyloidosis has been ruled out by monoclonal antibodies, the specificity is as high as 100%.
- The focus is based on imaging-based diagnosis.
- Now targeted therapies are available: TTR suppressors/silencers (inotersen, patisiran), which cleave the mRNA that makes the protein within the cells. The other class of drugs is TTR stabilizers and fibril disrupters (tafamidis/diflunisal or Doxy/taurodesoxycholic acid [TUDCA]). Only preclinical studies with Doxy/TUDCA.
- *In vivo* gene editing for transthyretin amyloidosis using CRISPR-Cas9 is a new exciting therapeutic approach to treat ATTR amyloidosis (*NEJM. Aug. 5, 2021*).
- T119M is benevolent rescue mutation, which is present in some patients that causes stabilization of this protein. Acoramidis (AG 10) acts in a similar manner to T119M and is being studied in phase III clinical trials.
- Treatment not only involves targeted therapy towards the disease but also nontargeted symptomatic management helps the patient to feel better in the short-term – reduction/discontinuation of β-blockers, ACEI/ARBs, avoid digoxin, treatment of orthostatic hypotension, prokinetic agents for gastroparesis, management of arrhythmias (Afib) and pacemakers for heart blocks. Diuretic therapy with loop diuretics is the mainstay. Treatment of HF in patients with amyloid must be less aggressive.

- One of the myths about transthyretin amyloidosis is that it is a rare disease. It is not so. In Chicago, there is V142I mutation; about 60k patients in Chicago are carriers of this mutation. V30M mutation is found in UK and Japan. The Thr60Ala mutation is found in Ireland.
- Amyloidosis is not a death sentence; palliation and supportive care are not the only options. The elderly patients are being treated with transcatheter valves and clips.
- Heart failure with preserved ejection fraction (HFpEF) is not the classic presentation; many patients have reduced ejection fraction.
- Aggressive treatment of HF may be detrimental in these patients.
- The challenges in TTR cardiac amyloidosis include long delay in diagnosis, overlapping clinical features, lack of awareness on prevalence, diagnosis and therapy, diagnostic challenges and coexistence with other cardiac conditions, hesitation in reducing or stopping conventional therapy.
- The solutions include understanding disease prevalence and distribution in communities; it's a disease without any barriers especially the wild type amyloidosis.
- Diagnosis is important not only for the patient, but also for the family members as it runs in families.
- Targeted therapy is now available; nontargeted therapy is also a therapy. Reduction or removal of medications also forms part of the treatment.
- Wild type amyloidosis has been noted to be more prevalent in men. The male-to-female ratio is 50:1.
- For hereditary amyloidosis the prevalence is more equal – 1:1 or 2:1 for men and women. In US, the prevalent mutation is V142I and the ration is 1:1 or 2:1 between men and women. The age of onset is late, around 65 years.
- The V30M mutation occurs in younger people in their 40s.
- It is a generational disease and knowledge about parents carrying the mutation is important as it is an autosomal heterozygous dominant mutation.
- Amyloidosis is a debilitating disease. It starts with neuropathy; patients lose their fine and gross motor skills.
- Many patients have diabetes and hypertension, both of which can mimic symptoms of amyloid. Carpal tunnel syndrome is not a neuropathy. Diabetes does not give bilateral carpal tunnel syndrome.
- The disease has a relation with age. Certain mutations express the disease at a certain age. The type of mutation also decides the types of symptoms. If detected early, there is no cardiomyopathy. Once cardiomyopathy develops, the life span is limited. With the wild type, the life span is longer; but with mutation type, the life span is shorter.
- Patients of amyloidosis must be vaccinated against COVID-19.

Participants – Member National Medical Associations: Dr Yeh Woei Chong, Singapore, Chair-CMAAO; Dr Alvin Yee-Shing Chan, Hong Kong, Treasurer, CMAAO; Dr Heidi Stensmyren, President-World Medical Association; Dr Ravi Naidu, Malaysia, Past President-CMAAO; Dr Wasiq Qazi, Pakistan, President-elect, CMAAO; Dr Angelique Coetzee, South Africa; Dr Akhtar Hussain, South Africa; Dr Md Jamaluddin Chowdhury, Bangladesh; Dr Debora Cavalcanti, Brazil; Dr Qaiser Sajjad, Pakistan

Invitees: Dr Saurabh Malhotra, USA; Dr Veena Aggarwal, India; Dr Patricia La Brooyi; Dr Yeo Khoonhui; Dr EC Ng; Prof Arun Jamkar; Dr S Sharma, Editor-IJCP Group

Moderator: Mr Saurabh Aggarwal

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