Unfolding the Intricate Details of an Unspoken Threat - Transthyretin Amyloid Cardiomyopathy

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Abstract: A steady and catastrophic cardiac condition known as transthyretin amyloid cardiomyopathy (ATTR-CM) - A type of Cardiac Amyloidosis. The definition, epidemiology, afflicted population, pathogenesis, symptoms, subtypes, diagnosis and pharmaceutical therapeutic techniques are all covered in this article's thorough discussion of ATTR-CM. This article addresses the molecular processes which lead to transthyretin amyloid fibrils accumulating and depositing, as well as the damage that amyloid does to the structure and function of the heart. The underlying mutations, familial inheritance patterns, and the necessity of identifying and screening individuals who may be susceptible to this disease are all covered in the article. The diagnostic possibilities to determine ATTR-CM are outlined in the diagnosis section. To provide an in-depth review of therapeutic methods of management are put forward. This comprehensive review is an informative tool for medical practitioners, researchers, and for those who want to learn about the management of ATTR-CM.

DEFINITION

Transthyretin amyloid cardiomyopathy is a relatively rare but severe variant of restrictive cardiomyopathy that results in transthyretin fibril deposits in the chambers of the heart. It may appear as new or worsening heart failure, in addition to a new conduction system illness. This disease was frequently disregarded in clinical settings due to a lack of awareness as well as successful diagnostic methods. Early diagnosis and treatment are now feasible, thanks to developments in cardiac imaging technology and excellent therapy alternatives. (1)

SUB-TYPES

Transthyretin, or prealbumin, is a protein made in the liver and functions to transport substances, such as thyroid hormone and vitamin A, throughout the body. ATTR amyloid occurs when this protein does not form correctly, causing it to accumulate in tissues such as the heart, nerves, and other organs. There are 2 types of ATTR cardiomyopathy. The most common type happens spontaneously in a person and is not passed down in a family through genes. The other type is inherited and caused by a change in the TTR gene. It is important to note that not everyone who inherits the genetic change or variant that causes ATTR will develop the disease. (2)

There are two forms of ATTR amyloidosis, wild-type ATTR amyloidosis (ATTRwt) and hereditary ATTR amyloidosis (hATTR), also known as ATTRv (v for ‘variant’). (3)

WILD TYPE ATTR

ATTR can be triggered by an autosomal dominant hereditary transmission of mutant TTR genes (ATTRm) or by a wild-type variant of this disease (ATTRwt), which was previously referred to as senile cardiac amyloidosis (SCA). As the world’s population demographics, ATTRwt will become the most common kind of cardiac amyloidosis recognised by clinicians. Diagnosis of systemic amyloidosis is frequently delayed, either due to an erroneous assumption that it is a rare condition or due to misdiagnosis due to overlap with other disorders. (4)

Conventional 2D echocardiography can demonstrate several of the previously recognised characteristic features of ATTRwt-CA. The cornerstone of clinical treatment is diuresis, although ACE inhibitors and nitrates enhance the risk of symptomatic hypotension. Due to the fixed stroke volume and requirement of a rapid heart rate to sustain cardiac output, high-dose beta-blocker can frequently be poorly tolerated. (5)

Increased wall thickness is another basic echocardiography characteristic associated with ATTRwt-CA. When wall thickness rises in the absence of a stimulus such as hypertension, predisposing hemodynamic parameters (e.g., aortic stenosis), or inheritable conditions (e.g., hypertrophic cardiomyopathy, Fabry's disease), diagnostic suspicion should be heightened. (6)

ATTRwt is not a life-threatening condition. The median life expectancy of ATTRwt patients after diagnosis was 43 months, by a prospective cohort study, with a decline in the 6-minute walk test and ejection fraction (EF) over the first 18 months. (7) Fortunately, potential ATTRwt therapies are in late-stage clinical research. TTR stabilising agents such as tafamidis and diflunisal, which were discovered to be useful for FAP, are instances of pharmacologic treatments. (8)

Hereditary type
Hereditary transthyretin amyloidosis with polyneuropathy (formerly known as Familial Amyloid Polyneuropathy) is a rare disease that results from mutations in the gene encoding transthyretin (TTR) and is marked by multisystem extracellular amyloid deposition, leading to organ and tissue dysfunction. (9)

Given the increasing understanding of the disease among medical professionals and the current broad availability of genetic testing, the incidence of hATTR amyloidosis is bound to rise, particularly in non-endemic countries. hATTR has now been reported in at least 29 different countries around the world on an ongoing basis. The disease is transmitted through generations as an autosomal dominant feature. Patients having homozygous damaging mutations, as well as compound heterozygous patients, have been recognised.

In endemic spots, where a positive family history is common, hATTR is relatively easy to diagnose and is often made within a year of the disease's initial stages. Once a mutation has been discovered within a family, genetic counselling for asymptomatic carriers is essential in these domains. Carriers need to be evaluated on an ongoing basis for the purpose to detect early symptoms or warning signs of the disease and commence anti-amyloid drugs as quickly as possible. Diagnosis is considerably harder in non-endemic segments, where diagnosis could have been delayed by 4-5 years because of an array of parameters, particularly a common negative family history. (10)

Early-onset hATTR-Val30Met amyloidosis leads to "discomfort" (numbness and neuropathic pain) in the feet, which begins to spread proximally, in addition to impaired pain and/or temperature sensation attributed to the involvement of unmyelinated and small myelinated fibres; impairment of light touch and deep sensibility, as effectively as motor fibres, usually occur later in the disease's course. (11)

PATHOPHYSIOLOGY

TTR protein that has been misfolded develops insoluble filaments. They reside in interstitial deficiencies in the myocardium, stiffening and rigidifying it. TTR deposition accelerates myocardial fibrosis and eventually hinders mechanical function. On cardiac imaging, the myocardium gazes more substantial and hypertrophied due to TTR deposition. Diastolic dysfunction develops first by a compromise in ventricular compliance. Myocardial dysfunction can cause global systolic dysfunction in later stages. (12)

Diastolic dysfunction elevates the left ventricular end-diastolic pressure and overall left atrial pressure. In such people, persistently elevated left atrial pressures and dilatation increased the risk of developing atrial arrhythmias. Myocardial infiltration frequently has an impact on the electrical conduction system as well. (13)

Misfolded TTR protein deposition is frequent outside of cardiac tissue in the autonomic and peripheral neural systems. The nervous system is more typically impacted by hATTR, whereas cardiomyopathy is more commonly found with wATTR-CM. (14)

ATTR-CM is characterized by primary infiltration of the atrial walls with progressive loss of atrial function and increased stiffness. LA stiffness is a strong independent predictor of mortality after adjusting for known predictors. Atrial electro-mechanical dissociation emerged as a distinctive functional phenotype identifying patients in SR with worse prognosis. (15)

Left ventricular (LV) hypertrophy might grow slowly over time as a result of pathologic TTR amyloid deposits in the heart, with relatively late recognition due to the sluggish evolution of the condition. The presence of additional comorbid conditions, such as diabetes, hypertension, chronic kidney disease, and atrial fibrillation, might hinder ventricular relaxation and promote a pro-oxidative state, which may speed up the deposition of TTR in the myocardium. This second concept may help to explain why many mutant TTR carriers are asymptomatic and show no symptoms of cardiac involvement until later on in life when concurrent diseases like diabetes and hypertension have taken a toll on the heart. (16)

AFFECTED POPULATIONS

More than 90% of patients in most of the cohorts and registries examined are men and Caucasian, even though whether this represents a true disease preference in this cohort or a referral bias is unknown. Apart from universal heart involvement, soft tissue involvement increases the risk of bilateral carpal tunnel syndrome, spinal stenosis, or spontaneous biceps tendon rupture (17)

1.) OLDER POPULATION

The most common form of ATTR-CM is undoubtedly wild-type ATTR-CM, nonetheless, the actual population prevalence of ATTR-CM is unknown. Several postmortem investigations found that the prevalence of wtATTR myocardial deposits increased with age, ranging as high as 20% to 25% in octogenarians and 37% in those over 95 years old (18)

In an autopsy examination of 109 patients with an antemortem diagnosis of HFpEF, 17% demonstrated wtATTR myocardial deposits, with 5% having moderate to severe interstitial deposition that supported an underlying aetiology. Furthermore, among patients aged >80 years (n = 35), the incidence of wtATTR deposits increased substantially to 40%, with an obvious preference in male patients. (19)

2.) AORTIC STENOSIS

ATTR-CM and aortic stenosis patients exhibit equivalent demographics. ATTR-CM occurs in 6% to 12% of patients with severe aortic stenosis 43, 44 complying with surgical valve replacement by retrospective investigations. (20)

The phenomena of low-flow, low-gradient severe aortic stenosis in older adults may be explained in part by the presence of ATTR-CM and restrictive physiology. (21)

3.) CARPAL TUNNEL SYNDROME
ATTR amyloidosis may trigger deposits in the soft tissues, leading to nerve entrapment problems that include carpal tunnel syndrome. Deposits in the flexor retinaculum and tenosynovial tissue within the carpal tunnel were more frequently seen in ATTR than in AL and tend to be accompanied by bilateral symptoms. (22)

SYMPTOMS
ATTR-CM should be considered in elderly patients with recurrent HF exacerbations, despite their ejection fraction status. They frequently show exhaustion, poor exercise tolerance, and shortness of breath, and are categorised into functional categories II to IV, respectively, of the New York Heart Association (NYHA). Additionally, they have substantial proper ventricular involvement, which results in peripheral symptomatic conditions such as high jugular venous pressure, lower-body oedema, hepatic congestion, and ascites. Cardiorenal syndrome frequently develops in the latter stages. unexpectedly these individuals often acquire resistance to beta-blockers, angiotensin convertase enzyme inhibitors (ACEi), or angiotensin receptor blockers (ARB) that they previously approved.(23)

DIAGNOSIS
The heterogeneity of symptoms upon presentation leads diagnosis to being delayed. An expert team gathered virtually across India to design a guidance tool for ATTR-CM diagnosis. The panel suggested a younger age (40 years) for suspecting ATTR-CM, with a thick-walled non-dilated hypokinetic ventricle as one of the main alerting flags. Electrocardiogram (ECG) and echocardiogram (ECHO) results were advised as the main tests to raise the suspicion, while nuclear scintigraphy and haematological testing were recommended to confirm the diagnosis and rule out amyloid light-chain (AL) amyloidosis. In the presence of red flags, cardiac magnetic resonance (CMR) and biopsy were advised. Considering the dearth of medical advice in the Indian environment, a standardised diagnostic algorithm was also developed.(24)

ECG
Due to its low cost, ease of use, and absence of radiation, echocardiography remains an effective screening technique for ATTR cardiomyopathy. When cardiac amyloidosis is suspected, this is the initial test that needs to be used. (25). A nondilated left ventricle with concentrically thickened myocardial characterised by improved echogenicity, thickening of the right ventricular free wall, as well as dilated atria and interatrial septum are common early findings on echocardiography. (26)

SEROLOGY
Unlike AL amyloidosis, which has circulating biomarkers (light chains), ATTR-CM has insufficient biomarkers for which to test. There are novel serologic assays for the endogenous TTR ligand retinol-binding protein 4, which may eventually serve as a tested biomarker. (27)

IMAGING
Imaging is certainly a centre of a noninvasive ATTR-CM diagnosis. Transthoracic echocardiography, cardiovascular magnetic resonance (CMR), and cardiac scintigraphy are the three modalities that have been proven to be beneficial and, at times, diagnostic for ATTR-CM. (28)

TRANSTHORACIC ECHOCARDIOGRAPHY
Despite its drawbacks, transthoracic echocardiography may identify an array of abnormalities that should alert the doctor about the possibility of cardiac amyloid. Notably, there is a symmetrical rise in left ventricular (LV) thickness, that is sometimes mislabeled as LV hypertrophy. LV hypertrophy is triggered by myocyte hypertrophy, as opposed to cardiac amyloidosis, which is caused by increased extracellular amyloid protein deposition in normal myocytes. Due to the thick and dense myocardium the trademark sparking or "speckled appearance" word is frequently used when referring to the myocardium. Pleural and pericardial effusions were common, however, they are often overlooked because they are insignificant in terms of hemodynamic importance. Diastolic measures indicated an intricate filling pattern with substantial bi-atrial dilatation. However, these diastolic modifications frequently appear in later phases of the disease process. (29)

ENDOMYOCARDIAL BIOPSY
Endomyocardial biopsy has generally been considered the gold standard for ATTR-CM diagnosis as it gives particularly high sensitivity and specificity, especially when multiple places on the myocardium are biopsied and histopathologically investigated for amyloid using Congo Red staining. (30)

TREATMENT
TAFAIMDIS
In the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT), Tafamidis has been proven successful treatment for transthyretin amyloid cardiomyopathy (ATTR-CM). (31) Tafamidis meglumine (20 mg) was authorised by the European Medicines Agency (EMA) in 2011 for stage, I ATTRv polyneuropathy based on the findings of an 18-month phase III clinical trial (NCT00409175) in which it was able to prevent disease progression in 60% of those treated compared to 38% in the placebo group.(32)
Tafamidis reduces disease progression in both cardiomyopathy and peripheral neuropathy by inhibiting the rate-limiting component of amyloid manufacturing, dissociation into monomers.

**ADMINISTRATION**

Tafamidis is used orally and is now available in two strengths as soft capsules:
- Tafamidis meglumine capsules, 20 mg (which is equal to 12.2 mg tafamidis free acid).
- Tafamidis 61 mg free acid pills

Dosage in ATTR cardiomyopathy (authorised by the FDA): Tafamidis meglumine 80 mg (four 20 mg capsules) or tafamidis 61 mg (single capsule) orally once a day is the suggested dose. (33)

**DIFLUNISAL**

Diflunisal, a non-steroidal anti-inflammatory medicine, is capable of stabilising the TTR tetramer in vitro and may prevent amyloid deposits in the heart from misfolding monomers and dimers. It is one of two small substances that have been studied in animal studies as well as human clinical trials for TTR polyneuropathy. Diflunisal's intake has been contentious due to its suppression of cyclooxygenase enzymes and corresponding gastrointestinal bleeding and renal impairment. Between June 2009 and December 2011, 77 patients were treated with diflunisal (250 mg twice a day) when combined with either a histamine receptor antagonist or a proton pump inhibitor in a phase 2 small open-label study being conducted at Columbia University. Diflunisal, treated individuals had no hospitalisations for worsening heart failure, no significant changes in cardiac function, and a modest rise in brain natriuretic peptide and troponin I after a three-month follow-up.

**ADMINISTRATION**

Diflunisal was well tolerated in ATTR cardiac amyloid patients at a dose of 250 mg orally twice daily. (34)

**AG10**

AG10 is an excellent TTR selective kinetic stabiliser. AG10 inhibited the dissociation of both wild-type TTR and V122I mutation-related TTR in vitro testing. (35). Another pharmacological investigation discovered that AG10 had more hydrogen bonding interactions than tafamidis, indicating a stronger bonding connection with the tetramer receptors and likely higher TTR stability. (36)

**DISCUSSION**

ATTR-CM is a type of Cardiac Amyloidosis caused by a proliferation of erroneous transthyretin protein deposits in the heart. The definition, epidemiology, disease pathophysiology, affected population, symptoms, subtypes, diagnosis, and therapeutic approaches were all addressed within this article. The study additionally addressed the molecular pathways that contribute to the accumulation and deposition of transthyretin fibrils of amyloid, in addition to the adverse effects that amyloid triggers on the structure and function of the heart. Imaging methods, ECG, Serology, and Transthoracic echocardiography, were all discussed as diagnostic tools for ATTR-CM. The primary drugs used to mitigate disease progression, reduce symptoms, and improve overall patient outcomes have been included in the treatment methods for therapy.

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