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CARDIAC AMYLOIDOSIS WITH A FOCUS ON ATTR-CM.

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ABSTRACT

Cardiac amyloidosis, characterized by the accumulation of abnormal proteins in the heart, is a rare disease that can lead to significant damage and heart failure. The two most common types of cardiac amyloidosis are transthyretin amyloidosis (ATTR) and immunoglobulin light-chain (AL) amyloidosis. Recent advancements in cardiac imaging techniques have helped identify Transthyretin Amyloid Cardiomyopathy (ATTR-CM). Although cardiac magnetic resonance imaging and echocardiography can exhibit distinctive patterns, they are inconclusive in diagnosis when compared to nuclear imaging. The emergence of modern and effective therapies has allowed its early detection and treatment.

KEYWORDS: ATTR, AL, ATTR-CM.

INTRODUCTION

Restrictive cardiomyopathy (RCM) is a diverse group of diseases that exhibit a restrictive left ventricular pathophysiology with a rapid increase in ventricular pressure and minimal increase in volume due to heightened myocardial rigidity.

Persistent restrictive pathophysiology, diastolic dysfunction, non-dilated ventricles, and atrial dilatation characterize RCM. These disorders differ based on pathogenesis, clinical presentation, diagnostic evaluation, treatment, and prognosis. The most common causes of RCM are: Cardiac amyloidosis, cardiac sarcoidosis, and cardiac hemochromatosis.[1,2]

Cardiac amyloidosis occurs primarily by the extracellular deposition of proteins in the myocardium, leading to restrictive cardiomyopathy. Over 30 different proteins can misfold, aggregate, and form amyloid fibrils in vivo and are classified based on the precursor protein. Amyloidosis has two distinct pathophysiologies.[3]

1. Amyloid light-chain (AL) amyloidosis - consists of monoclonal light chains.
2. Amyloid transthyretin (ATTR) amyloidosis - The accumulation of either regular or mutated transthyretin proteins identifies amyloid transthyretin (ATTR) amyloidosis. TTR is a protein produced by the liver (prealbumin) and circulates in the blood, and its primary function is to transport thyroid hormone and vitamin A.[4,5]

These pathophysiologies have fundamentally different disease mechanisms.

Congestive heart failure (CHF) arising due to cardiac amyloidosis may be misdiagnosed as more prevalent conditions like hypertension or diabetes, hence diagnosing the specific type of cardiac amyloidosis, including ATTR, is crucial to practicing cardiologists.

Transthyretin Amyloid Cardiomyopathy (ATTR-CM)

Transthyretin Amyloid Cardiomyopathy (ATTR-CM) is a life-threatening disease often overlooked in older adults. The TTR protein typically circulates in a tetrameric form with four beta-sheet-rich monomers undergoing structural changes; it misfolds, loses its tetrameric form, and aggregates in the myocardium and peripheral nerves.[7] The clinical manifestation of ATTR varies depending on the type and severity of tissue deposition.[8]

ETIOLOGY AND EPIDEMIOLOGY

In a recent cohort of patients with heart failure and increased myocardial wall thickness, 20% of patients had ATTRwt with a prevalence estimated to 1:6000 or 1.1% for the total population.[9] The lack of sensitive diagnostic modalities of ATTR-CM in the past, along with its heterogenous clinical presentation, has resulted in limited data on its prevalence.[10] However, recent developments in nuclear cardiac imaging, such as technetium pyrophosphate scans, have improved diagnostic accuracy and reduced the need for cardiac biopsy. Consequently, more patients are now being screened and diagnosed with ATTR-CM.[11]

The inheritance of ATTR occurs through an autosomal dominant trait, which is caused by pathogenic variations in the TTR gene located on Chromosome 18 that codes for transthyretin. Thus, any mutations in the TTR gene can lead to structural alterations in the TTR protein, resulting in Hereditary transthyretin amyloid (hATTR). Additionally, normal genetic sequencing of TTR can render the TTR tetramer susceptible to misfolding.[9] This form of ATTR is known as wild-type transthyretin amyloid (wATTR).

Wild-type transthyretin amyloid (wATTR).

wATTR-CM also known as senile cardiac amyloidosis is the prevailing type of ATTR-CM, which frequently occurs in older male patients. Studies based on autopsy have revealed a higher incidence of wATTR deposits as age progresses with associated occurrences of atrial fibrillation and myocardial infarction with preserved ejection fraction (HFpEF).[12,13]

The cardioprotective effect of estrogen as well as a smaller heart size, which may not meet the screening threshold for ATTR-CM suggests a lower prevalence of wATTR in females.

Hereditary transthyretin amyloid (hATTR)

The inheritance pattern of hATTR is autosomal dominant, but the theory of disease penetrance is complex. The age of onset for clinical disease in hATTR-CM varies greatly and depends on a specific mutation. Over 100 TTR mutations have been identified, with Val30Met being the most common mutation worldwide.

Hereditary ATTR-CM is more common in Japan, Portugal and Sweden. Val122lle is the most common mutation in the United States, affecting around 3 to 4% of African Americans and 1.5 million carriers.[14] Another mutation that is responsible for hATTR-CM and is the second most common in the US is Thr60Ala (pT80A).

Patients with untreated ATTR-CM have a mean survival rate of approximately 3.5 years from diagnosis, but this can vary depending on the stage of the disease. With the advent of non-invasive diagnostic modalities, survival, and diagnostic rates have improved. The prevalence of cardiac amyloidosis is now believed to be higher than previously estimated. In fact, over 12 years, the prevalence rate has increased from 8 to 17 per 100,000 person-years.[15]

DIAGNOSIS

In recent years, there has been a growing interest in ATTR-CM due to three areas of advancement that were previously considered pitfalls in their diagnosis.

1. Improved imaging techniques have enabled accurate diagnosis of ATTR-CM without invasive procedures like endomyocardial biopsies.
2. Recent studies suggest that a significant number of congestive heart failure patients may have unrecognized ATTR-CM resulting in more thorough examination and diagnosis.
3. Thirdly, with an increased perception of the process of amyloid formation, approved treatment therapies are now available for ATTR-CM.[5]

Correct diagnosis of cardiac amyloidosis is crucial for its proper treatment and management. It is essential to actively inquire about a history of heart failure along with carpal tunnel syndrome[16] and lumbar spinal stenosis.[17] The presence of unexplained peripheral or autonomic neuropathy may indicate the likelihood of hATTR amyloidosis.

Diagnostic modalities

1. Electrocardiogram: Patients diagnosed with TTR amyloidosis commonly exhibit left bundle branch block (LBBB), an advanced degree of atrioventricular (AV) block, and non-specific ST-T segment changes or atrial fibrillation.[18] ATTR-CM may be differentiated from hypertensive or hypertrophic cardiomyopathy by visualizing increased left ventricular wall thickness with a low-voltage ECG pattern. However studies report; 25-40% of patients with ATTR-CM have low voltage criteria with normal limb-lead voltages.[19]

2. Cardiac magnetic resonance imaging (CMR): CMR is an essential diagnostic tool in the identification of cardiac amyloidosis. It aids in distinguishing between amyloidosis, hypertensive heart disease, and sarcoidosis and provides insights into tissue characterization, enabling the early detection of cardiac amyloidosis. Late gadolinium enhancement cardiac magnetic resonance imaging (CMR-LGE) can identify widespread transmural or subendocardial extracellular amyloid deposits with an accuracy rate of 85 to 90%.[20] Amyloidosis results in increased T1 signals, similar to the extracellular volume fraction emerging as a sensitive and quantitative technique to measure amyloid deposition in ATTR-CM. Though it is unable to differentiate between TTR and AL amyloidosis.[21]

3. Echocardiography: Concentric bi-ventricular hypertrophy is due to myocardial infiltration of ATTR; it is more echogenic than ventricular hypertrophy. Though it is not diagnostic but raises clinical suspicion when the septal wall thickness is greater than 12 mm.[22] Bi-atrial enlargement, non-dilated Left ventricle, preserved LV systolic function, and rapid grade of progression in diastolic dysfunction are ubiquitously present. The use of strain echocardiography has become increasingly popular in the early identification of cardiac amyloidosis. It can identify "apical sparing," where there is a decline in the longitudinal strain as the imaging moves from the apical to midventricular and basal segments, which is a characteristic feature of cardiac amyloidosis. This appearance is generally termed - "bulls-eye pattern" or "cherry on top" in strain imaging.[23]

4. Biopsy: The gold standard for diagnosing ATTR-CM is Endomyocardial biopsy, which has a sensitivity and specificity of nearly 100%. The precise identification of the misfolded precursor protein requires immunohistochemistry, mass spectrometry, or laser dissection.[24] When Gastrointestinal and abdominal fat aspirates have been used to diagnose ATTR-CM, their sensitivity varies compared to the gold standard. In wATTR disease, fat aspirate has a sensitivity of only 15%.[25]

5. GENETICS: Identification of genetic variants is crucial in patients with ATTR amyloidosis, as more than 120 variants have been discovered to cause amyloidosis. The most frequent variants are Thr60Ala and Val122lle. Genotyping plays a key role in predicting the patient's prognosis and response to treatment. The distribution of variants varies depending on the patient's ethnicity and geographical location. Authors recommend performing TTR genetic testing in every patient with ATTR-CM, regardless of age, as the results may implicate at-risk family members, wherein genetic counseling may be advised. For offspring of patients with hATTR, the decision to perform testing before a certain age should be taken after careful consideration of individual factors, with guidance from a genetic counselor. There is no established protocol for monitoring disease progression in individuals with a variant genotype, it is recommended to conduct neurologic and cardiac assessments at baseline and over time.[26]

6. Nuclear imaging: A non-invasive method for diagnosing ATTR-CM is nuclear scintigraphy using bone-avid radiotracers is the sole imaging modality capable of accurately providing a diagnosis without an invasive cardiac biopsy. There are three clinically evaluated technetium-labeled radiotracers for identifying ATTR-CM.

a. 99mTc-pyrophosphate (PYP), and
b. Tc99m-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) or
c. Tc99m-hydroxymethylene diphosphonate.

Intravenous injection of TC-PYP administered during the scan selectively binds to the ATTR fibrils and osseous tissue in the circulation. The retention of TC-PYP in the myocardium occurs because of microcalcifications linked with ATTR cardiomyopathy. The myocardial absorption of TC-PYP is assessed and graded, relative to the uptake by the ribs, to obtain a semiquantitative scheme.[27,28]

ADVANTAGES OF TC-PYP

1. It can detect the deposition of ATTR in the myocardium at an earlier stage than the manifestation of structural changes.
2. In the clinical absence of a biopsy or monoclonal proteins detected in urine and serum, TC-PYP assists in diagnosing ATTR-CM with 100% specificity.[11]
3. Additionally, a quantitative analysis of the radiotracer absorption by the heart can aid in differentiating between ATTR and AL cardiac amyloid. An uptake ratio greater than 1.5 in the heart compared to the contralateral chest indicates the presence of ATTR.[29] Certain authors demonstrated that this could precisely be reproduced at multiple sites.[28]
4. It is recommended to perform single photon emission computed tomography (SPECT) and repeat scanning after an hour (or two hours) to confirm that the observed uptake is specific to the cardiac region.

TREATMENT

Supportive treatment of the underlying causes of heart failure is the in-line treatment protocol.

1. Treatment of Heart failure: Dietary sodium restriction and use of diuretics are the mainline treatment in ATTR-CM patients, followed by the administration of renin-angiotensin-aldosterone inhibitors and beta-blockers.

2. Treatment of arrhythmias: Due to its better safety profile in patients with cardiomyopathy and some clinical evidence demonstrating its safety in ATTR-CM, Amiodarone is the preferred antiarrhythmic agent.[30] In cases where chronic right ventricular pacing leads to significant ventricular dys-synchrony, bi-ventricular pacing is often recommended. However, according to the ACC/AHA/HRS guidelines, an implantable cardioverter-defibrillator (ICD) should only be used for secondary prevention.[31]

3. Pharmacological Agents: Certain pharmacological agents such as Patisiran, Inotersen, Tafamidis, Diflusinal, and a combination of Doxycycline and tauroursodeoxycholic acid are currently being reviewed to silence the mutation of the TTR tetramer or block its deposition in the tissues.

CONCLUSION: Contemporary non-invasive imaging techniques have made it possible for healthcare providers to timely diagnose ATTR-CM in determining prognosis. Maintaining a high level of suspicion based on the clinical history and laboratory investigations of the patient can result in an early diagnosis and prompt initiation of therapy. The expertise of an imaging specialist and a personalized approach to determining the appropriate level of multidisciplinary treatment approach would result in an effective management plan for cardiac amyloidosis. Although endomyocardial biopsy remains the gold standard, it is hardly implemented, and cardiac magnetic resonance imaging (CMR) has emerged as a valuable tool in diagnosing cardiac amyloidosis.

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