What's New in Cardiac Amyloidosis?

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Abstract

Amyloidosis is characterized by the localized or systemic deposition of proteins with unstable tertiary structure, which aggregate and form amyloid fibrils. Cardiac amyloidosis is a frequently underdiagnosed condition and it is an important cause of heart failure. There are more than 30 known types of amyloid proteins, but only five often infiltrate the heart, causing cardiac amyloidosis. These are: light chain immunoglobulin, heavy chain immunoglobulin, transthyretin, serum amyloid A and apolipoprotein AI, mostly in light chain immunoglobulin or transthyretin forms. According to the type of fibrillar protein deposited, cardiac amyloidosis has different clinical courses, prognosis and different forms of treatment. In this review, we address new techniques that allow the diagnosis of this entity, especially in situations of heart failure with preserved ejection fraction and restrictive heart diseases. Early diagnosis is fundamental in defining the best therapeutic approach and in the prognosis of these patients.

Introduction

Amyloidosis is characterized by the localized or systemic deposition of proteins with unstable tertiary structure, which aggregate and form amyloid fibrils. These fibrils are insoluble and remarkably resistant to proteolysis and are capable of depositing in the heart, kidneys, liver, gastrointestinal tract, lungs and soft tissues. These fibrillar protein deposits result in dysfunction of the affected organ or tissue.[1]

Cardiac amyloidosis (CA) is a frequently underdiagnosed heart disease and a major cause of heart failure. There are more than 30 types of known amyloid proteins, but only five often infiltrate the heart, causing heart disease. They are the following: Light chain immunoglobulin (AL), heavy chain immunoglobulin, transthyretin (TTR), serum amyloid A and apolipoprotein AI. The AL and TTR forms are the most common ones and have different clinical courses, prognosis and different forms of treatment.[1] In the AL form, the fibrils are composed of light chain immunoglobulins produced by a population of plasma cell clones located in the bone marrow. Their treatment is based on chemotherapeutics that target the plasma cell. In the TTR form, the deposits are formed by anomalous monomers or dimers of the TTR hepatic tetrameric protein, whose origin may be related to genetic mutations of familial origin (TTRmutated or TTRm) or the wild/senile form (TTRs). More than one hundred known mutations are associated with TTRm, related to the autosomal dominant inheritance, which can affect individuals of any age, predominantly older men.[2]

Keywords

Amyloidosis/physiopathology; Heart Failure; Amyloid; Echocardiography, Doppler; Immunoglobulin Light-Chain Amyloidosis; Drug Therapy.

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AL cardiac amyloidosis

CA related to AL deposits accounts for about 70% of the cases.[3] It is caused by clones of plasma cells that infiltrate the bone marrow in less than 10% of the total cellularity, which differentiate multiple myeloma. Despite their small size, clones can initiate devastating damage to multiple organs by depositing light chain proteins. All organs can be affected, except for the central nervous system.[3]

The observation that patients undergoing chemotherapy had a significant clinical recovery despite the absence of reduced amyloid deposits suggests that myocardial damage is not directly and exclusively related to the deposition of fibrillar proteins per se, but probably to exposure to circulating light chain proteins.[4]

Cardiac amyloidosis in TTR form

The TTR protein is composed of 127 amino acids produced by the liver and circulates in the form of a homotetramer, acting as a transporter for thyroxine and as a retinol binding protein. However, destabilization of the TTR protein promotes dissociation into monomers, which acquire the fibrillar form and get deposited in the tissues.[4]

TTR CA can be acquired or associated with TTRs (previously known as "senile systemic amyloidosis"), or hereditary, associated with variants in the TTR gene, called mutant TTR. TTRm is related to more than one hundred gene mutations. The most common allele in the United States, caused by a replacement of valine by isoleucine at position 122 (Val122Ile), is found in 3.4% of African Americans.[5-8] The frequency of Val122Ile in populations with heart failure remains largely unknown. In the Blocker Evaluation of Survival Trial (BEST), where CA was an exclusion criterion, the prevalence of Val122Ile was as high as 10% among African Americans older than 60 years of age with heart failure class III-IV and ejection fraction (EF) of 35% or less. In another case-control study with asymptomatic Val122Ile patients, this allele appears to cause significant risk for the development of heart failure. Once symptomatic, Val122Ile patients with heart failure have a worse prognosis, with a median survival of just over 2 years. Together, among African Americans who have heart failure and preserved EF, the T12 Val122Ile mutation may be an underdiagnosed cause.[5]

A retrospective study identified the most frequent mutations in patients with amyloid polyneuropathy related to TTRm. Of the 448 patients tested, of which 128 were of Brazilian origin, 90.6% had the TTRVal30Met mutation,[9] more frequent in Portuguese descendants, and 4.7% had Aps38Tyr mutations; TTR Ile107 Val; TTR Val71Ala and TTR Val122Ile.[10]

Epidemiology

AL amyloidosis is a rare condition with an estimated prevalence of 8 to 12 per million, with about 3,000 new cases diagnosed per year in the United States, 30 to 50% of which are associated with myocardial involvement, and 10 to 15% are associated with multiple myeloma. [11-15] The prevalence of TTR CA is uncertain. These cases are underdiagnosed, since conditions previously attributed to normal aging are probably due to cardiac amyloid deposition, leading to heart failure with preserved EF, aortic stenosis and atrial fibrillation of the elderly.[5] Among heart failure patients with preserved EF, autopsy data reveal amyloid deposits in 32% when the age exceeds 75 years and only in 8% in the younger ones.[15,16]

Clinical manifestations

The main clinical manifestations are related to the infiltrated organs. CA is the prototype of infiltrative cardiomyopathy. About 80% of the patients have the cardiac manifestation represented by heart failure with preserved EF. Some clinical manifestations are the red flags for amyloidosis research: presence of heart failure associated with increased myocardial thickness, especially when there is no left cavity dilatation and/or EF decrease; pericardial effusion, atrioventricular block, increased interventricular and/or valvular septal thickness, strain disorders with apical preservation on echocardiogram; history of bilateral carpal tunnel syndrome (especially in men), atraumatic biceps tendon rupture, unexplained neuropathic pain, orthostatic hypotension and diagnosis of unexplained ventricular hypertrophy.[1]

Diagnosis

Electrocardiogram usually presents low-voltage QRS complexes. However, this change presents a prevalence ranging from 60% in the AL form to 20% in TTR.[17,18] The "hallmark" of CA is the disproportion between ventricular hypertrophy and QRS voltage.[18]

Doppler echocardiography is an important diagnostic tool. The most frequent findings by the conventional technique are symmetrical increase of ventricular thickness, preserved-dimensioned cavities, left atrial enlargement with preserved EF, and increased pulmonary pressures. EF is preserved until the final stages of the disease. Pericardial effusion may be present in up to 50% of the cases, and about 80% show signs of diastolic dysfunction when Doppler is used. The speckle racking technique adds sensitivity to the diagnosis, since both longitudinal strain (LS) and radial strain (RS) are abnormal in CA. Quarta et al.[19] demonstrated an inverse correlation between global LS and left ventricular ejection fraction (LVEF), with $r = -0.55$ and $p < 0.001$; positive correlation between global LS and mean LV wall thickness ($r = 0.34$; $p < 0.001$); and weak inverse correlation between global LS deceleration time and E wave ($r = -0.39$; $p < 0.001$). TTRm CA showed the strongest correlation between global LS and LVEF ($r = -0.61$; $p < 0.001$) and mean LV wall thickness ($r = 0.56$; $p < 0.001$), while TTR CA was more associated with the correlation between LS and E wave — deceleration time ($r = -0.43$; $p = 0.009$). Among patients with AL amyloidosis, we found a weak direct correlation between lambda light chain and E/A ratio (early ventricular/late filling velocity rate, Spearman $p = 0.44$; $p = 0.002$). No correlation was found between light chain (kappa or lambda) and wall thickness, LVEF or SR/LS values. Interestingly, apical LS does not change in CA. [19,20]

Magnetic resonance imaging using the late gadolinium enhancement technique is able to locate the foci of involvement and quantify the extracellular volume that may reflect the amyloid deposits. Diffuse subendocardial or transmural late enhancement may characterize CA and predict mortality.[22] The involvement may not be restricted to LV, with extension to the right ventricle and atria. Dungu et al.[23] created a late enhancement score in CA capable of differentiating the AL and TTR forms: the QUALE SCORE. The TTR CA form has a more prominent late enhancement, predominantly of the transmural form and with extension to the right ventricle compared to the LA form, being associated with a higher ventricular mass index, higher volumes and lower LVEF. An increased gradient between the base and the apex, which is common in the TTR form, correlated with the echocardiographic findings of reduced strain in the basal portion, both in its longitudinal and radial forms, associated with apical sparing.[20]

Several studies have demonstrated the ability of scintigraphy with Tc99m 2,3-Dicarboxipropane-1,1-Diphosphonate (DPD-Tc-99m), Tc99m Methylenediphosphonate (MDP-Tc99m) and Tc99m Pyrophosphate (PYP-Tc99m) to discriminate the amyloid subtype, differentiating AL forms from TTR forms. However, the pathophysiological mechanism related to the affinity of bone markers of scintigraphy to amyloid fibrils is not known.[23,24] Between the 1970s and 1980s, the observation that the concentration of these makers in the cardiac area was related to CA, later proved by endomyocardial biopsy, brought to the scene of this rare pathology another noninvasive diagnostic tool.[23,24] One of the hypotheses for the binding of these bone markers to amyloid fibrils would be the greater amount of calcium present in the TTR protein than in AL.[2] Of the three markers, the two with the best performance are DPD-Tc99m and PYP-Tc99m. As the DPD-Tc99m is not available in Brazil, the PYP-Tc99m will be the focus of this discussion.

The testing technique is relatively simple, inexpensive and with no specific preparation. The bone marker is injected into the peripheral vein. Chest images are acquired within 1 hour after. In this image, two regions of interest (ROIs) are drawn, one of them on the cardiac area and the other, mirrored, located in the contralateral hemithorax, in the pulmonary field. The counts (i.e., amount of radioactive material concentrated in these areas) are measured in the two ROIs, and a ratio between uptake in the left hemithorax and the right hemithorax is calculated. Ratios greater than 1.5 have sensitivity of 84.6% and specificity of 94.5% for the diagnosis of CA in the TTR form.[2] Three hours after injection, full-length images are acquired in the anterior and posterior projections

associated with the acquisition of single-photon emission tomography (SPECT) images of the thorax. SPECT images are useful for better locating which cardiac cavities are infiltrated by amyloid protein. The intensity of PYP-Tc99m concentration in the cardiac area correlates with the subtype of amyloid. The degree of concentration is compared to the bony uptake of the rib cage, being grade 3 of greater intensity than the costal arches; grade 2 of equal concentration intensity as the arches; grade 1 with a lower concentration than the arches; and zero degree, without significant cardiac concentration of the marker. Intense concentrations (grades 2 to 3, Figure 1) are strongly associated with TTR-type CA, such that some authors suggest the rejection of cardiac biopsy in these situations, since 90% sensitivity and 97% specificity values were found for the diagnosis of CA in the TTR form.[26] Less intense concentrations (grade 1, Figure 2) or no concentration suggest the AL form when there is clinical suspicion. In both situations, it is recommended to complement with the following detailed laboratory research, to rule out and/or confirm the presence of light chain antibodies related to AL CA.

Laboratory and pathological diagnosis

The laboratory diagnosis of AL form includes the search for light chain antibodies by electrophoresis of proteins in serum and urine, since a percentage of the amyloidosis AL is associated with multiple myeloma. Immunofixation of urine and blood, and quantification of the antibody light chain freelite complement laboratory investigation of the AL form. Abnormal values of serum freelite do not close the diagnosis of AL, since 5% of the population older than 65 may have monoclonal gammopathy of undetermined significance. The κ/λ ratio may change in patients with renal failure, since they are filtered by the glomerulus, so some authors suggest a different normal value for chronic renal patients, which makes the diagnosis more challenging in this population.[1]

The dosage of the N-terminal portion of B-type natriuretic peptide pro-hormone (NT-proBNP) is an excellent marker of CA dysfunction. The circulating light chain particularly exerts a toxic effect on protein kinase that promotes the expression of NT-proBNP, so that its values are higher in the AL form compared to TTRm and TTRs.[1]

Considering these laboratory data, the ideal diagnostic sequence, according to Maurer et al.,[1] would be the algorithm described in Figure 3.

Endomyocardial biopsy is the gold standard for CA diagnosis. Considering the limitation of samples taken from the interventricular septum in the right ventricle using the central venipuncture technique (in a surgical center or hemodynamic room) and the complexity of an LV biopsy, associated to the risks inherent to the procedure, such as ventricular perforation with cardiac tamponade, tricuspid valve leaflet lesion, ventricular arrhythmias and/or hematoma at the puncture site, this diagnostic option should be carefully selected and sometimes even disregarded.[25] The positivity of the sample in Congo Red closes the diagnosis of amyloid infiltration, but does not differentiate its subtypes. Mass spectrometry has high sensitivity and specificity to differentiate the subtypes of amyloid fibrils, but it is still a poorly available technique. The importance of noninvasive diagnostic methods gains even more value.

Family screening is essential, as is the diagnosis of the index case. In hereditary cases, genetic advice is necessary.

Treatment

Until recently, the TTR amyloidosis form presented no other therapeutic option than heart/liver transplantation, a procedure of high complexity and morbidity and mortality. Recently, through the perception of the stabilization of CA in patients with familial amyloid neuropathy associated with TTRm, a series of studies was initiated to investigate the action of TTR

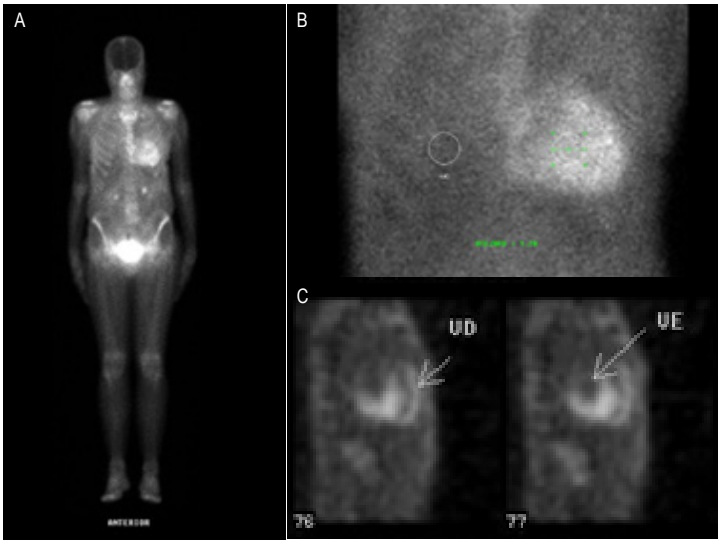

Figure 1 – *Example of scintigraphy with PYP-Tc99m to investigate cardiac amyloidosis, which was strongly positive (grade 3), suggesting the transthyretin form (ratio of pyrophosphate-Tc99m uptake degree between left and right hemithorax was equal to 1.78). (A) Full body scan with intense cardiac uptake of the radiopharmaceutical drug. (B) Regions of interest, with circles designed to measure the uptake degree. (C) Tomographic images (SPECT) detailing the marker concentration not only in the left ventricle, but also with right ventricular involvement, later confirmed by the presence of mutation in the genetic analysis. Source: author's archives.*

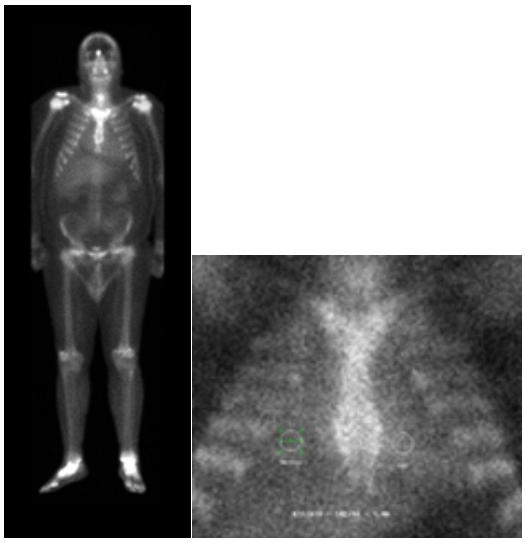

Figure 2 – *Example of scintigraphy with PYP-Tc99m to investigate cardiac amyloidosis, which was weakly positive (grade 1), indicating probable subtype of light chain amyloidosis (ratio of pyrophosphate-Tc99m uptake degree between left/right hemithorax = 1.06), later confirmed by laboratory findings. Source: author's archives.*

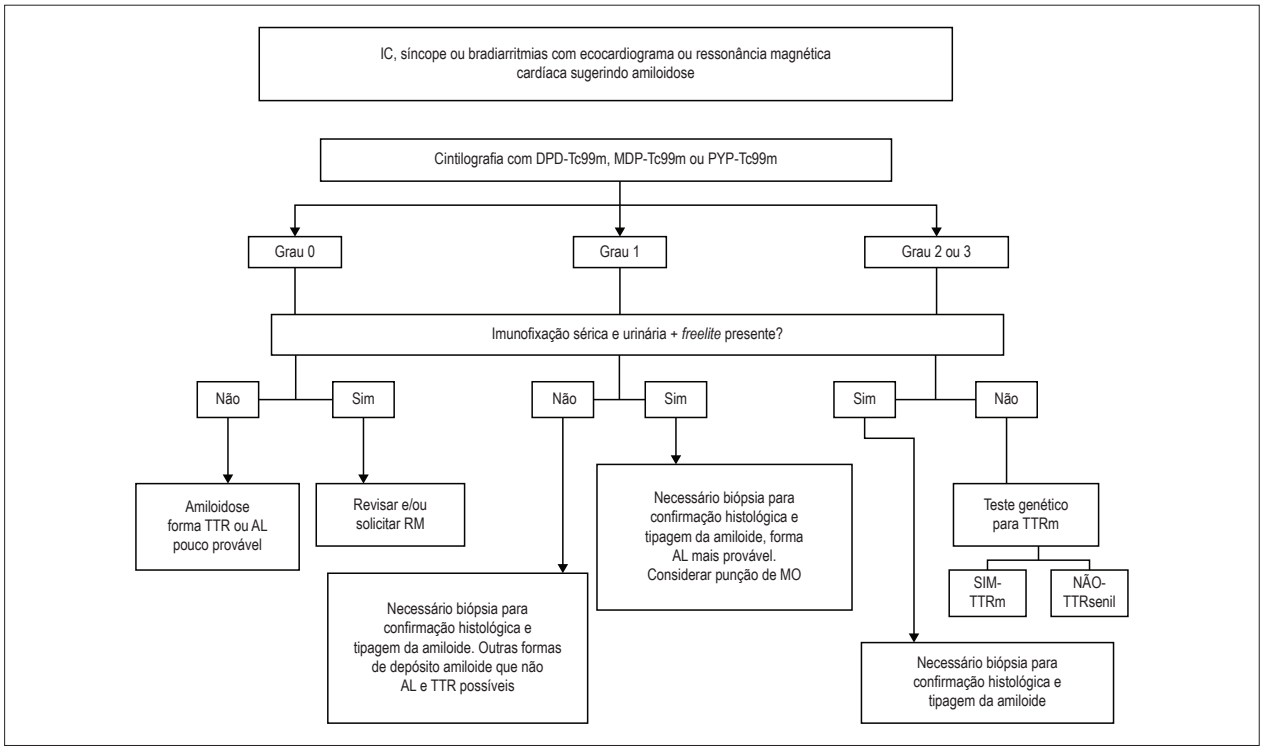

Figure 3 – *HF: heart failure; DPD-Tc-99m: Tc99m 2,3-dicarboxypropane-1,1-diphosphonate; MDP-Tc99m: Tc99m methylenediphosphonate; PYP-Tc99m: Tc99m pyrophosphate; TTR: transthyretin; AL: light chain immunoglobulin; MRI: magnetic resonance imaging; BM: bone marrow.*

stabilizers on myocardial involvement. Some preliminary data already show an independent association of TTR stabilizing drugs such as tafamidis and diflunisal, in patients with TTR CA with composite result of survival and orthotopic cardiac transplantation.[26] A prospective multicenter study (ATTRACT)[27] testing the efficacy of tafamidis in the TTR CA form is in the process of being published and should bring new prospects to this group of patients.

The AL form already has an established chemotherapy and the decision of the therapeutic scheme depends on clinical and genetic factors associated. The t (11;14) translocation is observed in 50% of patients and is associated with a worse

response to bortezomib and immunomodulators, even after the addition of cyclophosphamide. In these cases, the choice of oral melphalan or autologous transplantation should be considered. The gain of 1q21 is less frequent in LA than in multiple myeloma, but it can be found in up to 20% of the cases. This mutation is associated with poorer results with oral therapy with melphalan and dexamethasone without the addition of bortezomib.[3] At least three Vλ genes contribute to the coding of most λ light chains: IGLV2-14, IGVL6-57 and IGLV3-1. The LV1-44 gene is associated with myocardial involvement, the main determinant of survival.[4] Generally, the AL form has a hematologist-oriented treatment.

Conclusion

Cardiac amyloidosis should be investigated by the cardiologist, whenever restriction findings, increased ventricular thickness and/or heart failure with preserved ejection fraction are present. The existence of less invasive diagnostic methods corroborates early diagnosis and improvement of the prognosis of these patients.

Authors' contributions

Manuscript writing: Quagliato PC; Critical revision of the manuscript as for important intellectual content: Quagliato PC.

Potential Conflicts of Interest

There are no relevant conflicts of interest.

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