My Approach to Evaluation of Cardiac Amyloidosis

Avaliação da Amiloidose Cardíaca: Como eu Faço

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Recent advances have been made in the diagnosis and treatment of cardiac amyloidosis (CA).[1,4]

Types of CA

The different types of CA[1-4] include primary amyloidosis (AL) and transthyretin (TTR) hereditary (TTR_m mutant, familial) or wild type (TTR_{wt}, wild type) amyloidosis.

AL amyloidosis occurs as a result of plasma cell dyscrasias, such as in multiple myeloma. This is a systemic disease in which plasmocytes produce fragments of gamma globulin light chains that aggregate as amyloid and is deposited in the heart and other organs. It is a rapidly progressive disease, with a poor prognosis when heart failure (HF) remains untreated (survival of less than 6 months).

Fragments of the liver protein TTR or pre-albumin aggregate as TTR amyloid and are deposited in several organs. TTR_{wt} causes senile amyloidosis, with worse evolution than AL amyloidosis (mean survival of 4 years), which is presumably underdiagnosed. It often causes HF with preserved ejection fraction (EF) in elderly adults.[13]

Familial amyloidosis (TTR_m) can be manifested in various forms depending on the mutation, including polyneuropathy or cardiomyopathy; its prognosis depends on the mutation. It is an autosomal dominant disease, which affects the TTR-encoding gene, with more than one hundred different mutations described so far. Considering its possible late penetration, differential diagnosis of senile amyloidosis (TTR_{wt}) is mandatory.

Pathophysiology

Amyloid substance is deposited in the interstitial space of the ventricles (diastolic dysfunction (DD), restrictive physiology, and systolic dysfunction) and atria (sinus node disease and atrial fibrillation (AF)), in the conduction tissue (conduction disorders), small intramural arteries (cardiac microvascular ischemia), valves (mild-to-moderate regurgitation), and pericardium (small pericardial effusion).

Although deposition is diffuse, it may, at an early stage, spare the apex (apical sparing) and primarily affect the interventricular septum, which can be confused with hypertrophic cardiomyopathy.[5]

Diagnosis

CA is diagnosed by combining clinical data with electrocardiogram (ECG), echocardiogram, and/ or cardiac magnetic resonance imaging findings (Figures 1 to 3).

The type of amyloidosis (AL or TTR) is diagnosed based on scintigraphy with 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD; or hydroxyl-methylene-diphosphonate (HMDP)) (Figure 4), genetic analysis, and laboratory screening tests for monoclonal gammopathies.

Clinical data

The prominent symptoms of AL include plasmacytic dyscrasia and nephrotic syndrome; macroglossia and periorbital purpura are rare but pathognomonic signs.

In senile amyloidosis, bilateral carpal tunnel syndrome, spinal cord stenosis, and spontaneous biceps rupture may occur years before myocardiopathy.

Senile amyloidosis should also be suspected in hypertensive elderly adults with spontaneous improvement in their arterial hypertension or in patients with left ventricular hypertrophy (LVH) and diastolic dysfunction more severe than the expected for the time and severity of hypertension; or in the presence of non- regression of LVH, function and symptoms after surgical or percutaneous intervention on aortic valve stenosis; or in the presence of AF with controlled /slow ventricular rate.

In familial amyloidosis, the clinical findings depend on the causal mutation (predominant polyneuropathy, predominant cardiomyopathy, and mixed conditions).

From a cardiological standpoint, the clinical findings consist of heart failure with preserved ejection fraction (HF-EFp), predominantly left or right, associated with AF and/or changes in auriculoventricular conduction (A-V).

Complementary examinations

In the diagnosis of AL, a narrow gamma globulin spike in protein electrophoresis may raise suspicion; immunofixation of serum gamma globulins and light chains in the blood and urine and quantitative assessment and calculation of the ratio between light chain levels must be performed.

In imaging, CA is a good example of the complementary role of different imaging methods.

Keywords

Cardiac Amyloidosis; Echocardiography; Diagnosis.

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Editorial

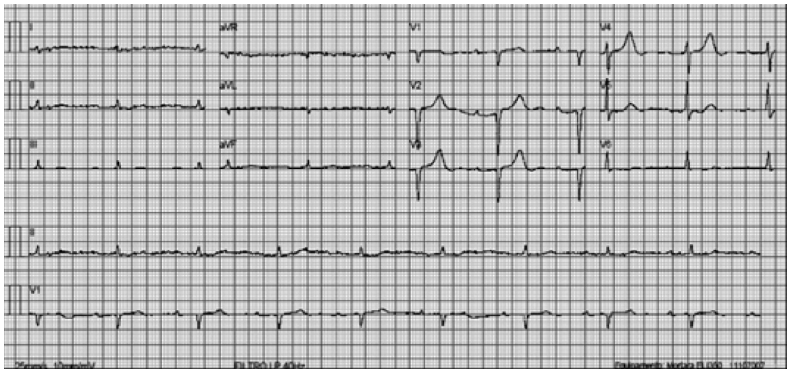

Figure 1 – *Electrocardiogram for cardiac amyloidosis. Low-voltage QRS and QS patterns in the right precordial leads and first-degree atrioventricular block.*

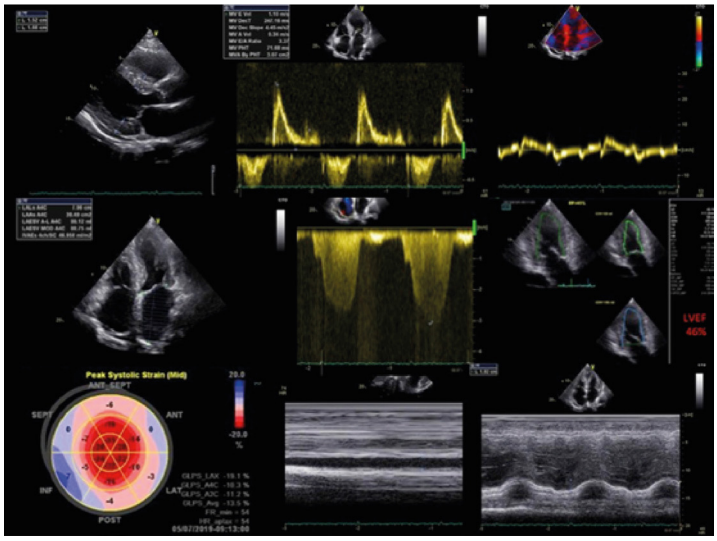

Figure 2 – *Echocardiogram for cardiac amyloidosis. Moderate concentric left ventricular hypertrophy, biatrial dilation, sparkling, interatrial septal hypertrophy, and small pericardial effusion were observed. Slightly decreased left ventricular ejection fraction (46%), abnormal longitudinal global strain (-13.5%), apical sparing. Diastolic dysfunction with increased filling pressures: low myocardial (systolic and diastolic) velocities, E/e' > 15, 3.1 m/s maximum tricuspid regurgitation velocity. Borderline longitudinal systolic function of the right ventricle (18 mm systolic excursion of the tricuspid ring), elevated right atrial pressure (a slightly dilated inferior vena cava with highly decreased respiratory kinetics).*

Discrepancies between the ECG (low absolute or relative voltage) and the echocardiogram (LVH) suggest CA. In addition, the ECG often reveals pathological Q in right precordial leads (Figure 1).

Cardiac imaging

The echocardiogram is the first-line imaging examination, indicated for all patients showing moderate LVH, usually concentric, biatrial dilation, sparkling, valve thickening, RV and interatrial septum hypertrophy, and pericardial efflux.

Regional and global DD are early findings, often with increased filling pressures (DD grade II or III). Tissue doppler reveals low systolic and diastolic velocities, and two-dimensional speckle tracking echocardiography shows apical sparing. The left ventricular ejection fraction is usually only slightly decreased, and the global longitudinal strain is abnormal (Figure 2).

Cardiac magnetic resonance imaging also provides useful data and is indicated when the echocardiogram is suboptimal, showing a highly specific pattern of global or segmental subendocardial late enhancement, with similar myocardial and blood-pool gadolinium kinetics (similar T1). Native T1 mapping and quantification of the extracellular volume (increased in CA) are useful, especially in patients with renal failure, in whom the use of gadolinium is contraindicated (Figure 3).

Technetium-99m (Tc-99m) scintigraphy with DPD (or other bone-avid radiotracers) is a non-invasive, inexpensive, and accessible complementary examination for assessing active

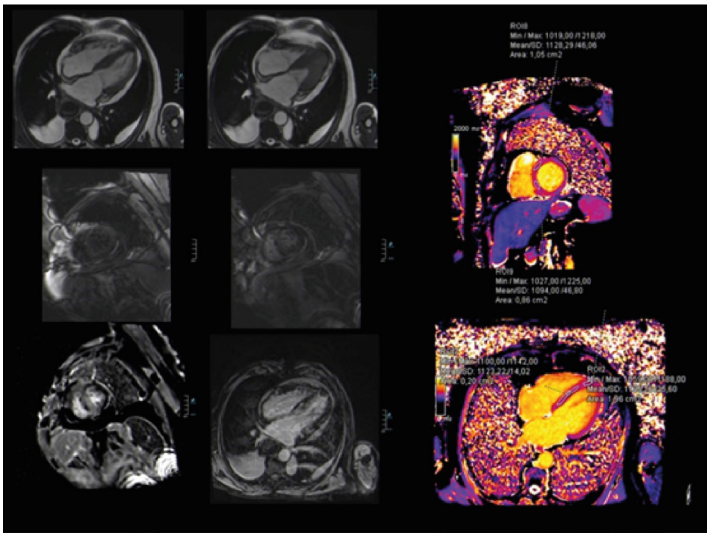

Figure 3 – *Cardiac magnetic resonance imaging for cardiac amyloidosis. Adequate morphofunctional characterization in cases of suboptimal or dubious echocardiogram. Highly specific, circumferential subendocardial late enhancement pattern. Highly increased native T1.*

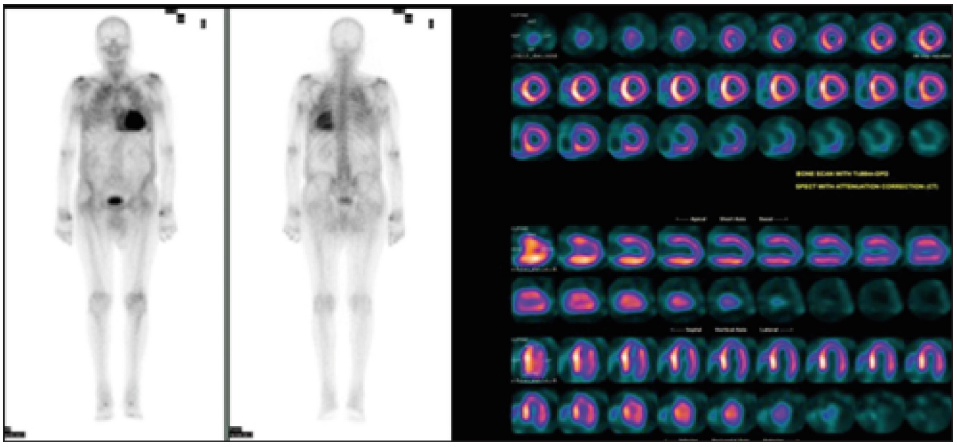

Figure 4 – *Technetium-99m scintigraphy. 2,3-dicarboxipropane-1,1-diphosphonate in cardiac amyloidosis. Increased cardiac uptake compared with the contralateral rib uptake (grade 3), with septal and basal predominance.*

bone formation, comparing its cardiac uptake (identification of microcalcifications in amyloid tissue) with the contralateral rib uptake (Figure 4). Scintigraphy data can be quantitative or semi-quantitative (grades 1 to 3; in the absence of AL amyloidosis, a grade 2 or 3 result has 100% sensivity and positive predictive value for TTR amyloidosis, excluding the necessity of cardiac biopsy; however, a genetic test for the differential diagnosis between TTR_m and TTR_{wt} amyloidosis is additionally required).

Lastly, in the 14% cases of AL amyloidosis, Tc-99m scintigraphy with DPD was also positive. Laboratory exclusion of monoclonal gammopathy is always mandatory.

Cardiac biopsy shows 100% sensitivity, in contrast to abdominal fat biopsy, with sensitivity ranging from 60% to 80% in AL and familial amyloidosis (TTR_m), but of only 14% in senile amyloidosis (TTR_{wt}).

Genetic analysis is indicated for TTR amyloidosis to confirm the diagnosis of familial amyloidosis. There are mutations with predominant polyneuropathy (V30M, familial amyloid polyneuropathy) and mutations with predominant cardiomyopathy; of these, the most commonly found

mutations are Val122 Ile (common in Africans or African descendants and often labeled as hypertensive heart disease), Leu111Met, Thr60Ala, and Ile68Leu,[6] as well as mutations with mixed symptoms of neuropathy and cardiomyopathy.

Conflict of interest

The authors have declared that they have no conflict of interest.

References

1. Donnelly J, Hanna M. Cardiac amyloidosis: an update on diagnosis and treatment. Cleve Clin J Med. 2017;84(12 Suppl 3):12-26.
2. Ruberg F, Grogan M, Hanna M, Kelly J, Maurer M, Transthyretin Amyloid Cardiomyopathy. J Am Coll Cardiol. 2019;73(22):2872-91.
3. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A,, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation. 2016;133(24):2404-12.
4. Maurer MS, Bokhari S, Damy T, Dorbala S, Drachman BM, Fontana M, et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. Circ Heart Fail. 2019;12(9):e006075.
5. Cardim N, Brito D, Rocha Lopes L, Freitas A, Araújo C, Belo A, et al. The Portuguese Registry of Hypertrophic Cardiomyopathy: Overall results. Rev Port Cardiol. 2018;37(1):1-10
6. Damy T, Kristen A, Suhr O, Maurer M, Planté-Bordeneuve V, Yu C, et al. Transthyretin cardiac amyloidosis in continental Western Europe: an insight through the Transthyretin Amyloidosis Outcomes Survey (THAOS). Eur Heart J. 2019 Apr 1. pii: ehz173.