Algorithms for Cardiac Amyloidosis Diagnosis: How to apply them in practice?

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Cardiac amyloidosis has long been an entity neglected by most doctors, being considered a rare disease with limited treatment options. Recent diagnostic and therapeutic advances have brought a renewed vision in the evaluation strategies of the different forms of amyloidosis that potentially affect the heart.^{1,2} In this article we carry out a critical reflection on the importance of early diagnostic suspicion and use of contemporary algorithms to instrumentalize the cardiologist for clinical practice.

Diagnostic suspicion

The main obstacle to rapid and proper diagnosis of cardiac amyloidosis is the absence of early suspicion in patients who have clinical hints (red flags) that could – or should – trigger an investigation. This phenomenon becomes even more clear when it is documented that before the definitive diagnosis of amyloidosis or cardiac involvement due to amyloid deposition, investigation may take several months or years, usually involving many doctors from different specialties. In a study by the University of Toulouse, the average delay between the onset of symptoms and the diagnosis of amyloidosis was 8, 10 and 18 months, respectively,

for light chain amyloidosis (AL), wild-type transthyretin amyloidosis and hereditary transthyretin amyloidosis.³ Similarly, the number of health professionals that each patient needs to consult on their “journey” for the correct diagnosis may vary substantially. In interviews with family members and patients with amyloidosis, predominantly due to deposition

of light chains, the diagnosis was not established during the first year after symptom onset in more than 1/3 of cases and the diagnosis was made only after consulting with 5 different doctors in 32%.⁴

It is critical to emphasize that for a disease characterized by continued myocardial deposition, but at a heterogeneous

rate, the delay in diagnosis can have significant implications from a therapeutic and prognostic point of view. The cardiologist must continuously look for clues that should increase clinical suspicion.⁵⁻⁸ In practice, these are warning signs that suggest amyloid deposition in the bone-tendon-muscular system (carpal tunnel syndrome, particularly bilateral; lumbar canal stenosis or biceps tendon rupture) and peripheral neuropathic involvement (sensory and motor), particularly if associated with autonomic dysfunction (postural hypotension, gastroparesis and changes in bowel habits). The resting electrocardiogram – a simple, inexpensive, but fundamental test – can provide relevant clues if it identifies the presence of conduction system disturbances, the appearance of pseudo Q waves or low voltage in a patient with signs of increased wall thickness in other imaging exams. The scenario of heart failure with preserved ejection fraction, particularly in males, in patients with advanced age and with manifestations of biventricular involvement, should increase the suspicion index for cardiac amyloidosis. Finally, proteinuria on the common urine test, loss of renal function, macroglossia, and the diagnosis of “low-flow and low-gradient” aortic stenosis – particularly of the paradoxical type – may also be suggestive of cardiac amyloidosis.

Initial Cardiac Imaging Exams

Cardiac imaging as an initial assessment is mandatory, but which exam should be requested is not consensual, and transthoracic echocardiography and/or cardiac magnetic resonance with evaluation of delayed enhancement are often recommended. Suggestive echocardiographic signs are thickening of the walls of both ventricles, which are usually not dilated, valve thickening, and pericardial effusion. An important warning sign on cardiac magnetic resonance, in addition to the respective findings identified on echocardiography, is the presence of diffuse subendocardial delayed enhancement. The assessment of left ventricular global longitudinal strain on the echocardiogram and the identification of relative preservation of the apical deformation (apical sparing) is a suggestive finding of cardiac amyloidosis, but not pathognomonic. Likewise, the multiparametric evaluation on cardiac resonance identifying an increase in native T1 time and extracellular volume may be strongly suggestive of cardiac amyloidosis.⁹

Diagnostic Algorithms and Flowcharts

Once the clinical suspicion of cardiac amyloidosis is established, the cardiologist – or responsible physician

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– must launch a rational investigation strategy. Several algorithms and diagnostic flowcharts have been proposed with this objective. None of the proposed regimens will be perfect for all patients, since there is a wide variety of initial clinical presentations, depending on the type of amyloidosis in question (due to light chain, mutant or wild-type transthyretin deposition). Many algorithms (Figures 1 and 2) suggest that all suspected patients should be initially screened only for plasma dyscrasias (presence of monoclonal proteins). The European Society of Cardiology (Figure 3) proposes that concomitant myocardial scintigraphy with a bone radiotracer (99mTc-DPP/PYP/HMDP) should be requested and the diagnostic definitions be based on the combination of results. The recent position statement on the diagnosis and treatment of cardiac amyloidosis (Figure 4) clearly separates the hematological route and the cardiology route of investigation, emphasizing that the suspicion of light chain amyloidosis (LA) should be considered a medical emergency, and that the cardiologist should act together with the hematologist for accelerated referral of diagnostic and therapeutic procedures. Our position statement also recommends performing an endomyocardial biopsy in doubtful cases and, according to finding of cardiac amyloid deposition (positive congo red staining), indicates protein typing by mass spectroscopy or immunohistochemistry.

Regardless of the recommended or chosen algorithm, some facts, and scenarios in the investigation of cardiac amyloidosis are central, deserve attention and appear in almost all flowcharts. These can be summarized into 10 cardinal rules described below:

1. Evaluation of monoclonal proteins. We should simultaneously order three tests to increase the accuracy in identifying monoclonal proteins: (1) serum kappa and lambda free chain ratio, (2) serum protein immunofixation, and (3) urinary protein immunofixation.

2. Hematological route. The presence of abnormal monoclonal proteins in hematological screening in individuals suspected of having cardiac deposition suggests the presence of light chain amyloidosis (LA) and the patient should quickly proceed with the investigation with tissue biopsies aimed at clinical presentation, which may include collection of bone marrow, renal and myocardial tissue. The hematologist must be involved in the investigation process early on.

3. Abdominal fat biopsy. Abdominal fat biopsy, a test frequently used for the diagnosis of systemic amyloidosis, has an inadequate negative predictive value to rule out the diagnosis.

4. Diagnosis of amyloidosis without the need for biopsy. The diagnosis of cardiac amyloidosis due to transthyretin deposition, without the need for tissue biopsy, can be achieved

Figure 1 – International Expert Panel diagnostic algorithm (2019)⁵

Viewpoint

Figure 2 – Canadian societies diagnostic algorithm (2020)⁶

Figure 3 – Diagnostic algorithm of the European Society of Cardiology Working Group (2021)⁷

Figure 4 – Diagnostic algorithm of the Heart Failure Department of the Brazilian Society of Cardiology (2021)⁸ ATTR: transthyretin amyloidosis; CMR: cardiac magnetic resonance; ECG: electrocardiogram; TTR: transthyretin.

with the use of myocardial scintigraphy with a bone radiotracer (the marker available in Brazil is ^{99m}Tc pyrophosphate). For this purpose, marker uptake must be moderately or markedly positive (grade 2 or 3 and/or cardiac versus contralateral uptake > 1.5) and the 3 hematological screening tests must demonstrate the absence of monoclonal proteins.

5. Transthyretin gene mutations. Genetic tests for evaluation of mutations related to specific phenotypes (neurological, cardiac, or mixed) are indicated for patients diagnosed with cardiac amyloidosis due to transthyretin deposition. The results of this assessment have implications for family counseling and genetic counseling.

6. Altered scintigraphy & presence of monoclonal proteins. A small but not negligible percentage of patients with amyloidosis due to light chain deposition may simultaneously have positive bone radiotracer uptake in myocardial scintigraphy with hematological tests that identify the presence of monoclonal proteins.

7. Monoclonal gammopathy of uncertain significance. On the other hand, the identification of a monoclonal protein is not diagnostic of light chain amyloidosis (AL). In addition, monoclonal gammopathy of undetermined significance may also coexist with wild-type transthyretin deposition amyloidosis, especially in elderly patients.

8. Endomyocardial biopsy. Direct analysis of myocardial tissue may be essential in scenarios where clinical suspicion is high and other tests are inconsistent, or when myocardial scintigraphy with a bone radiotracer is not available.

9. Mass spectroscopy and/or immunohistochemistry. Tissue analysis by mass spectrometry and/or immunohistochemistry are not readily available for most patients but should be used in doubtful scenarios or with conflicting findings during the investigation, as they allow a definitive diagnosis and can differentiate the type of amyloid deposits.

10. Clinical suspicion, the cornerstone. Diagnostic clues can appear separated from other signs/symptoms and at different time frames in the natural history of the disease, affecting apparently unrelated bodily systems. The cardiologist should place amyloidosis within the scope of their differential diagnoses, because without an initial clinical suspicion no flowchart or algorithm will work.

Conclusion

Amyloidosis, an underdiagnosed, life-threatening entity, has long been considered untreatable. However, the recent availability of disease course-modifying therapies has renewed efforts to raise awareness about the initial symptoms of the disease and the assessments that are available to confirm its diagnosis.¹⁰ Clinical clues (red flags) must be remembered and involve manifestations of cardiac, renal, tendon or neurological involvement. The use of diagnostic flowcharts is recommended to assist the physician in investigating suspected cases in a systematic, rational, and orderly manner. These algorithms, however, are not infallible, since the disease has a very large spectrum of clinical presentations, which can vary substantially according to the phase and system in which amyloid deposition occurs.

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Conception and design of the research; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Rohde LE.

Potential Conflict of Interest

Luis E. Rohde participated in consulting activities, advisory boards or lectures with Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Novartis and Pfizer.

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