

Clinical, Electrocardiographic and Echocardiographic Findings in Significant Cardiac Amyloidosis Detected Only at Necropsy: Comparison with Cases Diagnosed in Life

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Summary

Background: Currently, many cases of heart amyloidosis still fail to be diagnosed.

Objective: To disclose factors related to the difficulty in attaining the diagnosis of cardiac amyloidosis.

Methods: We compared the clinical, electrocardiographic and echocardiographic data of 17 patients in whom amyloidosis was diagnosed only at the necropsy (group I) with data from 9 patients in whom the disease was diagnosed in life (group II). The quantitative variables were compared by t-test and qualitative ones by Fisher's exact test. Significance was set at $p \leq 0.05$.

Results: The two groups showed differences regarding age (group I: 75.29 ± 11.61 , group II: 58.67 ± 11.07 years), association with other cardiac disease (group I: 52.94%, group II: 0%), low voltage at the ECG (group I: 17.65%, group II: 66.67%), and diastolic dysfunction at the echocardiogram (group I: 7.69%, group II: 62.50%). Some degree of left ventricular thickening was found in 75% of necropsy cases and 100% of controls ($p=0.23$), but wall thickness was lower in group I (free left ventricular wall: 1.20 ± 0.28 cm versus 1.53 ± 0.18 cm in group II, $p=0.01$). Systolic dysfunction was present in 57.89% of the cases, without significant difference between the groups.

Conclusion: Amyloidosis is diagnosed when the clinical, ECG, and echocardiogram patterns are "typical", but most of the cases fail to be diagnosed, especially in elderly people, due to the association with other cardiac diseases, lack of diastolic dysfunction at the echocardiogram and only a slightly thickened ventricular wall. (Arq Bras Cardiol 2008; 90(3):191-196)

Key words: Amyloidosis / diagnosis; myocardium / pathology; electrocardiography; echocardiography.

Introduction

Amyloidosis is a well-recognized disease characterized by the extracellular deposition of different types of insoluble beta-fibrillar proteins. Cardiac involvement may occur in distinct forms of the disease, such as senile or light chain-associated amyloidosis¹. The amyloid myocardium becomes firm and noncompliant². The amyloid deposit may be restricted to the atrial septum, as relatively common in elderly people, or more diffuse, involving the ventricles. In the latter situation, it can cause heart failure with a poor prognosis, which is not well characterized by classic determinants^{1,3}. Cardiac amyloidosis is usually demonstrated in patients with this syndromic diagnosis and a relatively small cardiac area, as well as alterations such as low voltage at the electrocardiogram and a restrictive-infiltrative pattern at the echocardiogram, especially if there is known systemic amyloidosis or other heart diseases have been ruled out.

Despite advances in adjuvant methods, the diagnosis of cardiac amyloidosis is still poor. In our hospital it has been observed that, unless the deposition is linked to an underlying disease or has a familial pattern, many cases are still detected only at necropsy, a fact also mentioned by others⁴⁻⁶. This difficulty can also be recognized by the fact that in a large series of endomyocardial biopsies, which were performed to establish the causes of cardiomyopathies, cardiac amyloidosis was found in 18% of the cases, without previous clinical identification of the disease⁷.

The objective of the present study was to compare clinical, electrocardiographic and echocardiographic findings in patients with amyloidosis diagnosed at necropsy with others, in whom the diagnosis was attained in life.

Patients and methods

We searched the files of the Laboratory of Pathological Anatomy of Instituto do Coração (The Heart Institute- InCor), University of São Paulo School of Medicine for cases seen from 1977 to 2004, in which amyloidosis of myocardium was considered the main cause of death or a significant contributor to it, in the presence of another main heart disease. The cases

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in which the deposit was an incidental finding, e.g., in the atrial septa of elderly patients, or even in the ventricles, if restricted to scarce patchy foci, were not included. The percent area of the myocardium occupied by amyloid in the cases with another associated cardiac disease was similar to that present in the cases with isolated amyloidosis.

None of our patients had any underlying disease, such as those that cause antibody light chain deposition.

The clinical files and necropsy results were reviewed. The following data were recorded: age; gender; systolic and diastolic arterial blood pressure and heart rate at entrance; presence of any associated heart disease; presence of heart failure or shock; syncope; *digitalis* intoxication. Concerning the electrocardiogram (ECG), the following findings were recorded as suggestive of amyloid deposition: inactive area, conduction disturbances, premature ventricular beats or atrial fibrillation, low voltage and alterations in the ventricular repolarization.

In most cases, two-dimensional echocardiogram complemented by M-mode and color-Doppler recordings, obtained according to the recommendations of the American Society of Echocardiography^{8,9}, were available. The measures of left ventricular (LV) septum and posterior wall thickness in diastole, LV internal end-diastolic dimension (LVDd), and left atrium size were registered. Ejection fraction (EF) was calculated by the Teichholz et al¹⁰ method; cases with EF <55% were considered as having systolic dysfunction. The transmitral flow velocity was used to analyze LV diastolic function. The sample volume was placed at the tip of the mitral valve leaflets in the four-chamber apical view. Peak early diastolic velocity (E-wave), peak late diastolic velocity (A-wave), E/A ratio and early filling deceleration time were measured. Diastolic dysfunction was considered if the patient had any of the following patterns: abnormal relaxation, pseudonormal flow pattern, or restrictive pattern (E-wave much greater than A-wave).

The following echocardiographic patterns were considered: general diagnosis of systolic or diastolic dysfunction; left ventricular wall thickening (commonly called "hypertrophy", but which, in fact, does not correspond to real cardiomyocyte hypertrophy, but rather to thickening due to the extracellular deposit in amyloidosis), considering the cases in which the measure was above 12mm or if a subjective evaluation had been written in the reports; granular sparkling pattern of the wall; thickening of atrial septum; valvular thickening; valvular incompetence.

For comparison of results, we also searched the hospital

records for the same data in the clinical files of the patients in whom the diagnosis of cardiac amyloidosis was established in life, through the clinical/echocardiographic pattern. The search was conducted at the Medical-Hospital Information Unit of InCor. Among these, only cases with a pathological confirmation of the deposition were included.

Quantitative variables were compared by *t*-test and the qualitative ones by Fisher's exact test; results were considered significant if $p \leq 0.05$.

Results

Twenty-two cases of amyloidosis were identified among 8,917 necropsy cases (0.41%). In one of them the diagnosis had been made prior to death. This disease was also found in the clinical files of another 15 patients (who, therefore, were diagnosed in life and were used as controls); the presence of the disease was confirmed either by biopsy (8 cases) or by necropsy (one case). Four cases and one control were excluded because the complete files were not found. Eight of the controls had the diagnosis confirmed by biopsy (all cardiac biopsies). The cases were divided in two groups: group I - 17 cases with diagnosis established only at the necropsy; group II - 9 cases with diagnosis established in life.

The patients' clinical data are shown in Table 1. Eleven patients (64.71%) from group I and 4 (44.44%) from group II were female; the difference in gender distribution was not significant ($p=0.42$). As expected, heart failure was observed in most patients and the difference between the two groups was not significant. The same occurred regarding systolic and diastolic systemic blood pressures, heart rate and the presence of *digitalis* intoxication. Of the 26 patients that were enrolled in the study, 9 (34.62%) had another associated cardiac disease (all from group I) and the difference between the two groups was significant ($p=0.01$). The associated diseases were: 5 cases of isolated ischemic heart disease, 2 cases of isolated systemic arterial hypertension, 1 case with both prior conditions and 1 case with the association between systemic arterial hypertension and rheumatic mitral valve disease.

Mean and median ages for group I were 75.29 and 74 years; for group II, they were 58.67 and 60 years, respectively (*t* test, $p < 0.01$). It is noteworthy that even when the cases with another associated cardiac disease were excluded, the difference in age remained significant (group I - 71.00, group II - 58.67; $p=0.04$).

Table 1 - Clinical data from patients in group I (amyloidosis detected only at necropsy, n=17 unless noted differently) and group II (amyloidosis diagnosed in life, n=9 unless differently noted). Mean values and standard deviations of the continuous variables and percentage of cases with the present characteristic in the qualitative variables.

Group	Age (years)	Gender	Systolic BP	Diastolic BP	Heart rate	HF/Shock	Syncope	AD	DI
I	75.29 ± 11.61	F 64.71%	107.31 ± 23.68 (n=14)	68.46 ± 12.14 (n=14)	92.62 ± 15.54 (n=14)	88.24%	11.76%	52.94%	5.88%
II	58.67 ± 11.07	F 44.44%	101.67 ± 24.01 (n=6)	68.33 ± 6.83 (n=6)	78.00 ± 14.07 (n=6)	100%	0.00%	0.00%	0.00%
p	< 0.01	0.42	0.64	0.97	0.07	0.53	0.53	0.01	0.53

BP - blood pressure; HF - heart failure; AD - association with another heart disease; DI - digitalis intoxication; F - female.

As shown in Table 2, low voltage at ECG was found in 66.67% of cases in group II and in only 17.65% in group I ($p=0.03$); the remaining ECG features (inactive areas, conduction disturbances, alterations in ventricular repolarization, and atrial fibrillation) had no significant difference between the two groups.

Table 3 shows the most important echocardiographic findings. Although no difference was found regarding the presence or not of any left ventricular thickening (75% of cases and 100% of controls, $p=0.23$), left ventricular wall thickness or ventricular septum thickness was significantly lower in group I when compared to group II (1.20 x 1.53cm, $p<0.01$, and 1.26 x 1.51cm, $p=0.04$, respectively). The differences in systolic dysfunction (66.67% of cases in group I versus 37.5% in group II, $p=0.38$) and ejection fraction (0.49 ± 0.13 in group I versus 0.52 ± 0.09 in group II, $p=0.65$) were not significant. On the other hand, most patients in group II (62.5%) had diastolic dysfunction, found in only 7.69% of cases in group I ($p=0.02$). No significant difference was detected regarding granular sparkling echogenicity and atrial septum thickness (both absent in group I and present in 12.5 and 25% of cases in group II, respectively; $p=1.00$ and 0.47), as well as regarding valvular incompetence and thickening, found in 75.00% and 25.00%, respectively, of cases in group I and in 71.43 and 28.57 of cases in group II (both $p> 0.05$, data not shown in any Table).

Figure 1 exemplifies one case of association between amyloidosis and another cardiac disease in an elderly patient. A graph summarizing all significant differences between patients with and without diagnosis during life is shown in Graphic 1.

Discussion

Although the detection of many cardiovascular diseases has improved in our hospital in the past decades, due to the experience of cardiologists and the improvement in the quality of diagnostic tools, mainly imaging resources, cardiac amyloidosis is still frequently detected only at the necropsy. As discussed in the following paragraphs, the concepts about the clinical aspects and the complementary tests that can actually be applied to just some of the cases seem to play a role in this problem.

The diagnosis of amyloidosis is mostly taken into consideration when the patient with heart failure is known to have the systemic form of the deposit disease⁵ or when other cardiac diseases are ruled out. Nevertheless, in our group of patients in whom no case of systemic amyloidosis was present, 34.62% of patients had another associated heart disease. None of the cases had the diagnosis of amyloidosis attained in life. Therefore, in the presence of heart failure at a degree not expected for the cardiac disease presented by the patient, one should suspect of the association with amyloidosis. Ischemic heart disease was the most common association in our cases. It is worth mentioning that amyloid deposition can contribute to coronary artery obstruction⁶, which indeed occurred in some of the patients enrolled in this study.

The association with another cardiac disease could be the reason why, in spite of the fact that the incidence of amyloidosis increases with age¹¹, in our study the patients with diagnosis attained in life were significantly younger than those without a diagnosis. Nevertheless, even by excluding cases with another cardiac disease, the difference in age between the two

Table 2 - Electrocardiographic findings from patients in group I (amyloidosis detected only at necropsy, n=17) and group II (amyloidosis diagnosed in life, n=19). Percentage of cases with the present characteristic in each group.

Group	Inactive area	Blockage	Ventricular premature beats	Low voltage	Alterations in ventricular repolarization
I	47.06%	41.18%	35.29%	17.65%	17.65%
II	55.56%	33.33%	11.11%	66.67%	22.22%
p	1.00	1.00	0.36	0.03	1.00

Table 3 - Echocardiographic findings from patients in group I (amyloidosis detected only at necropsy) and group II (amyloidosis diagnosed in life). Mean values and standard deviations of the continuous variables and percentage of cases with the present characteristic in the qualitative variables.

Group	S	P	LVDd	LA	EF	H	SD	DD	GS	AST
I	1.26 ± 0.27 (n=11)	1.20 ± 0.28 (n=12)	4.88 ± 0.81 (n=12)	4.27 ± 0.63 (n=9)	0.49 ± 0.13 (n=11)	75% (n=12)	66.7% (n=12)	7.69% (n=13)	0% (n=7)	0% (n=7)
II	1.51 ± 0.20 (n=8)	1.53 ± 0.18 (n=8)	4.27 ± 0.42 (n=7)	4.26 ± 0.54 (n=7)	0.52 ± 0.09 (n=6)	100% (n=9)	37.5% (n=8)	62.5% (n=8)	12.5% (n=8)	25% (n=8)
p	0.04	0.01	0.15	0.98	0.65	0.23	0.38	0.01	1.00	0.47

S - septum thickness (cm); P - posterior wall thickness (cm); LVDd - left ventricular diastolic diameter(cm); LA - left atrium (cm); EF - ejection fraction; H - thickening ("hypertrophy") of the left ventricular wall (either measured or only described); SD - systolic dysfunction; DD - diastolic dysfunction; GS - granular sparkling pattern of echogenicity; AST - increase in atrial septum thickness.

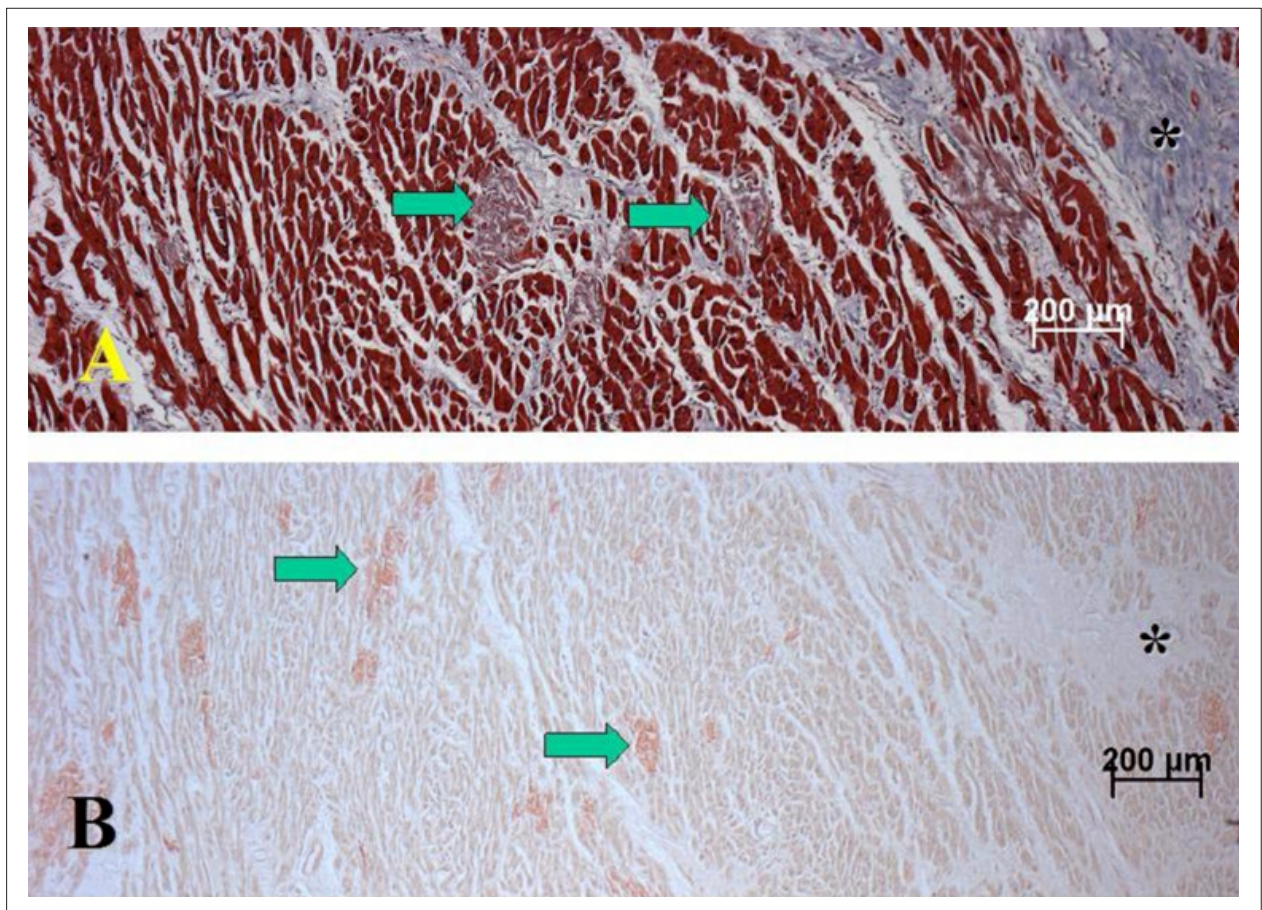
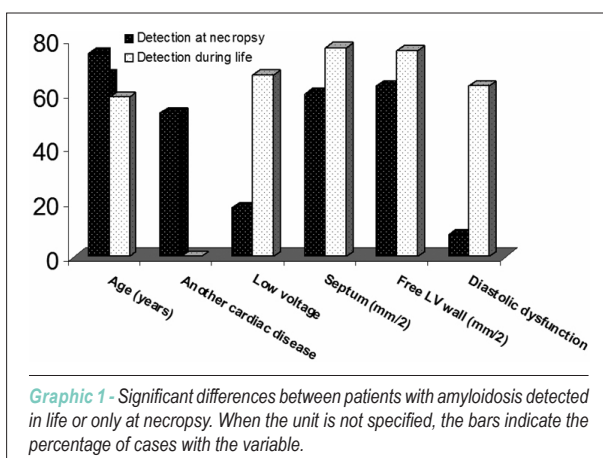


Fig. 1 - A - Histological section of the myocardium showing a fibrotic area (healed myocardial infarction), indicated by the asterisk and the presence of several deposits of extracellular amorphous material, some of which pointed out by arrows. B - Congo-red staining confirming the characterization of this material as amyloid. (Objective magnification: 5x).



Graphic 1 - Significant differences between patients with amyloidosis detected in life or only at necropsy. When the unit is not specified, the bars indicate the percentage of cases with the variable.

groups remains significant. This possibly occurs because senile amyloidosis is frequently restricted to the atrial septum, causing no heart dysfunction; however, it should be kept in mind that the overall incidence of the disease, including symptomatic cases, increases with age¹¹.

The involvement of the cardiovascular system by amyloidosis is polymorphic: cardiac failure in the restrictive pattern, atrial fibrillation, intraventricular conduction delays, ventricular tachycardia, syncope, pulmonary embolism and sudden death due to ventricular fibrillation have been described¹². The criteria for amyloid heart disease diagnosis are defined as thickening of the left ventricular (LV) wall > 12 mm without history of systemic high blood pressure and at least one of the following features: atrial dilation with small-sized ventricles, pericardial effusion and restrictive pattern of heart failure¹².

Although *digitalis* intoxication is known to be common in amyloidosis, it was not found in our patients diagnosed in life. It was present in two cases of group I (one with and one without another cardiac disease), but this fact did not help to detect the deposit. Regarding the other clinical variables, the absence of differences between the two groups was expected.

The electrocardiogram is a non-invasive method that can help to attain the diagnosis of amyloidosis. Low voltage in the limb leads or poor R wave progression in the precordial leads are the hallmark of ECG findings in amyloidosis. As pointed

by Dubrey et al¹³, the suspicion of cardiac amyloidosis should be raised if the ECG showed the characteristic feature of low QRS voltage, together with the finding of increased ventricular wall thickness, since left ventricular thickening due to other causes shows high QRS voltages. On the other hand, Murtagh et al¹⁴ found low voltage in only 46% of patients. We also showed that a considerable number of patients (8/26, or 8/17 if patients with associated diseases are not taken into account) do not present this ECG feature, leading to a significant difference between the groups. Thus, low voltage can be considered a good diagnostic clue, but of which absence should not be overestimated when ruling out amyloidosis. Other ECG findings, such as infarct patterns, can be found in the presence or absence of obstructive atherosclerotic coronary disease, due to amyloid deposition in the microcirculation and the smaller intramyocardial arteries. Atrial fibrillation and conduction abnormalities are also common¹², but these alterations were present in both groups of our patients, with no differences between them.

It is well known that amyloidosis increases the thickness of the ventricular wall¹³, which is commonly called "hypertrophy". However, it is noteworthy that this increase is frequently less exuberant than the expected, with a mean of 1.37 cm (septum) and 1.33 cm (left ventricular free wall). This is the reason why the diagnosis is difficult to achieve ($p < 0.05$ for both measures).

Another idea concerning cardiac amyloidosis that hinders its diagnosis is that usually there is diastolic dysfunction, whereas systolic dysfunction was present in 57.89% of our cases and diastolic in only 28.57% of them. This was due in part to the association with other diseases, but even considering only the cases in whom amyloidosis was the main finding, a slight predominance of systolic (6 patients of 11; 54.55%) was found over diastolic (6 of 12; 50%) dysfunction.

The other "typical" signs of amyloidosis, namely granular sparkling echogenicity and atrial septum thickness, appeared at relatively low proportions, even in cases in which the diagnosis was attained in life.

Rahman et al.¹⁵ proposed a combination of noninvasive criteria as a useful diagnostic tool for patients with a diagnosis hypothesis of cardiac amyloidosis; however, there are many cases in which the disease is not even suspected. An overall analysis of our data indicates that the difference between the two groups in our series is how typical the clinical presentation is. Only cases that were clinically very characteristic were diagnosed in life. It is noteworthy that the patients in group I of our series had a particularly severe clinical picture, having received medical care at a high complexity hospital and died due to the disease. Nevertheless, exuberant features were absent; at the early stages, the disease detection must be even more difficult. The factors associated to the nonaccomplishment of the diagnosis of cardiac amyloidosis were: older age, association with another cardiac disease, systolic instead of diastolic dysfunction, and a wall thickness that is slightly, but not severely, increased. This diagnosis should be taken into account not only in the presence of known systemic disease, but also when considering causes of heart failure, even in patients without the classic clinical, electrocardiographic, and echocardiographic findings, including those with another heart disease.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any graduation program.

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