ORIGINAL ARTICLE

Mid-term Outcome of Patients with Diagnosis of Transthyretin Cardiac Amyloidosis

Evolución a mediano plazo de pacientes con diagnóstico de cardiopatía amiloidótica por transtiretina

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ABSTRACT

Background: Cardiac involvement is the main cause of morbidity and mortality in amyloidosis, regardless of the underlying pathogenesis of amyloid production, and transthyretin (TTR) amyloidosis is one of the most frequent variants.
Objective: The aim of this study was thus to assess the characteristics of a cohort of patients with diagnosis of TTR cardiac amyloidosis (ATTR-CM).
Methods: Baseline data and diagnostic and follow-up methodology were collected from 49 patients treated at the cardiomyopathy clinic of our institution.
Results: Median follow-up was 1,258 days (410-2004). Mean age was 79±9 years, and 57% of patients were in functional class (FC) I, 26% in FC II and 16% in FC III-IV at follow-up onset. Diagnosis was made with diphosphonate scintigraphy in 92% of patients and 24% required a biopsy. Overall mortality was 19%, with 15% of cardiovascular death. The rate of hospitalization for heart failure was 29% and 63% of patients worsened their FC.
Conclusions: Follow-up of patients with ATTR-CM expresses the changes undergone by the diagnostic process, with a reduction of invasive studies and time to characterization. The diagnosis of patients at "early stages of the disease" seems to have an impact on mid-term outcomes.

Key words: Amyloid Neuropathies, Familial - Cardiomyopathies - Heart Failure

RESUMEN

Introducción: El compromiso cardíaco es la principal causa de morbimortalidad en la amiloidosis, independientemente de la patogenia productora del amiloide subyacente. La amiloidosis por transtiretina (TTR) es una de las variantes más frecuentes, por lo cual el objetivo de este trabajo fue evaluar las características de una cohorte de pacientes con diagnóstico de cardiopatía amiloidótica por TTR (CA-TTR)
Material y métodos: Se recabaron datos de los estudios basales, de la metodología diagnóstica y de la evolución de 49 pacientes en seguimiento en la Clínica de Miocardiopatías de nuestra institución.
Resultados: La mediana del tiempo de seguimiento fue de 1258 días (410-2004) y la edad promedio de 79 ± 9 años. Al inicio del seguimiento, el 57% de los pacientes estaban en clase funcional I, el 26%, en II y el 16%, en III-IV. El diagnóstico se basó en centellograma con difosfonatos en el 92%; en el 24% requirió biopsia. La mortalidad global fue del 19%, con 15% de muerte cardiovascular. La tasa de internación por insuficiencia cardíaca fue 29%; el 63% de los pacientes empeoró su clase funcional.
Conclusiones: El seguimiento de nuestros pacientes con CA-TTR expresa los cambios que ha sufrido el proceso diagnóstico, con una reducción de estudios invasivos y tiempo para la caracterización. El diagnóstico de pacientes en etapas "tempranas" de la enfermedad parece impactar en los resultados a mediano plazo.

Palabras clave: Neuropatías amiloides familiares - Miocardiopatías - Insuficiencia cardíaca

INTRODUCTION

Amyloidosis is a group of diseases characterized by abnormal deposits of "amyloid" proteins. Chronic build-up of these proteins in the interstitial space of different tissues alters their organic function. (1-3)
Cardiac involvement is the main cause of morbidity and mortality in systemic amyloidosis, regardless of the pathogenesis of underlying amyloid production. Cardiac amyloidosis is a disease characterized by extracellular amyloid infiltration which deposits in the myocardium and other cardiac structures, resulting in infiltrative cardiomyopathy.
Various types of amyloid-related diseases have been described, but only two of them are responsible for

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more than 95% of cardiac amyloidosis: light chain amyloidosis and transthyretin amyloidosis. (4, 5)
Transthyretin (TTR) is a protein mainly synthesized in the liver (less than 5% is synthesized in the choroid plexus and retinal pigment epithelium) whose function is to transport thyroxin and retinol. The pathologic formation of TTR fibrils occurs when the tetrameric structure is dissociated into intermediaries which disaggregate into oligomeric species, protofilaments and fibrils of insoluble amyloid. The formation of TTR-mediated amyloid can be directly attributed to a mutation of the transthyretin gene (called hereditary variant or hATTR) or it can also be observed in patients without genetic mutations (called wild-type variant or wATTR, previously known as senile amyloidosis). (6)
In this study we aimed to report the outcome of a cohort of patients with amyloidosis TTR cardiomayopathy (ATTR-CM) describing the diagnostic tools, form of clinical and imaging presentation and treatment received.

METHODS

The study analyzed patients with ATTR-CM diagnosis followed-up at the Cardiomyopathy Clinic of Instituto Cardiovascular de Buenos Aires.

Clinical data, complementary studies and evolution were recorded. A cardiologist established the functional class (FC) according to the New York Heart Association (NYHA) classification.

ATTR-CM diagnosis was performed following international guideline recommendations, after ruling out other forms of amyloidosis.

An echocardiogram and free light-chain assay was done in all patients. Follow-up was conducted through the electronic clinical history system and, whenever necessary, by telephone contact or personal interview.

Statistical analysis

Discrete variables were expressed as percentage and continuous variables as mean or median, with their corresponding standard deviation or interquartile range (IQR) according to their distribution. Sample normal distribution was defined with the Kolmogorov Smirnov method. In case of multiple comparisons, the Wilcoxon signed-rank test was used for paired samples. Kaplan Meier curves were performed to assess the time of event occurrence. A two-tailed p value <0.05 was considered statistically significant. All data were analyzed using SPSS 21 IBM software package.

Ethical considerations

An informed consent was requested for study participation. The institutional Ethics and Teaching Committee approved the performance of the study which was conducted following the principles of the Declaration of Helsinki.

RESULTS

A total of 49 patients were evaluated between January 2015 and January 2020, with median follow-up of 1,258 days (420-2004) for all adverse events (minimum 106 and maximum 5,006 days).

Mean age was 79±9 years, 88% were men, 84% had hypertension and 48% diabetes (Table 1).

Fifty-seven percent of patients were in FC I, 26% in FC II and 16% in FC III-IV. The main symptom reported was dyspnea in 63% of patients, followed by palpitations (20%), angina (18%) and dizziness or syncope (8%).

Time elapsed between follow-up by a cardiologist (not necessarily from the cardiomyopathy team) and diagnosis was 353 days (IQR 78-813). Only 14% of patients had received cardiac amyloidosis as primary diagnosis; 26% had been diagnosed as hypertensive heart disease and 16% as ischemic heart disease.

The electrocardiographic assessment showed that 62% of cases presented with predominantly sinus rhythm (30 patients), generally with preserved PR time [150 ms (IQR 130-320)] and only 16% of cases (8 patients) fulfilled strict low voltage criteria (Table 2).

The echocardiogram revealed median septal thickness of 16 mm (IQR 14-18), atrial area of 28 mm2 (IQR (26-32) and mostly preserved systolic function

Table 1. Baseline characteristics of the population

Variable	Value
Age (years)*	79.2 ± 9.23 (56-96)
Male gender	42/49 (87.7)
Hypertension	41 (83.6)
Dyslipidemia	23 (47.9)
Diabetes	8 (16.3)
Current smoker/ex-smoker	16 (32.6)
Previous infarction	2 (4.1)
Prior PCI	6 (12.2)
Prior CABG	2 (4.1)
Prior VRS	4 (8.2)
Carpal tunnel syndrome	15 (30.6)
Atrial fibrillation	21 (42.8)
Pacemaker	6 (12.2)
ICD	1 (2.05)
Initial diagnosis	
Hypertensive heart disease	13 (26.5)
Hypertrophic cardiomyopathy	4 (8.2)
Amyloidosis	7 (14.3)
Valvular heart disease	6 (12.2)
Ischemic heart disease	8 (16.3)
Other	10 (20.4)
Functional class at follow-up onset	
I	28 (57.1)
II	13 (26.5)
III-IV	8 (16.3)
Scintigraphy	45 (91.8)
MRI	13 (26.5)
Tissue biopsy	12 (24.5)
Genetic test	30 (61.2)

*indicates mean±SD (IQR); the rest of the variables are expressed as n (%). PCI: Percutaneous coronary intervention. CABG: Coronary artery bypass grafting. VRS: Valve repair surgery. ICD: Implantable cardioverter defibrillator. MRI: Magnetic resonance imaging.

with ejection fraction of 52% (IQR 43-58) (Table 3).

Imaging studies were done using diphosphonate scintigraphy in 92% of patients and magnetic resonance imaging in 26%. Only 24% of patients had a tissue biopsy study.

All patients had negative light chain assay and 30 (61%) underwent a genetic study, which was negative in 29 cases.

Two patients lost to follow-up were removed from the denominator to calculate the rate of events. Overall mortality was 19% and cardiovascular mortality 15%. Twenty-nine percent of patients were hospitalized for heart failure and the same percentage presented atrial fibrillation (excluding those who already had it at study onset) (Figures 1 and 2)

In 96% of cases, patients were treated with diuretics, 23 patients had access to tafamidis and 20 received combinations of doxycycline/tauroursodeoxycholic acid and green tea.

DISCUSSION

This work shows various aspects of the follow-up of a cohort of patients with ATTR-CM. We would be interested in emphasizing 5 relevant points of this investigation:

First, we have thought for many years that patients with cardiac amyloidosis are those with severe restrictive physiology, with great biatrial enlargement and systolic dysfunction. However, in this cohort we see that baseline characteristics of ATTR-CM patients show some not so "typical" features. In half of the patients, the atrium is <28 cm2, median EF is 52% and 32% have mitral pattern III or less. Understanding that the disease is produced by unbalanced amyloid deposit and "clearance", it seems reasonable to assume continuous progression of effects, escalating from mild to severe forms. With the advent of effective therapies for TTR amyloidosis, there is a growing need of recognizing the first signs of the disease and identifying the populations at risk for screening. (7, 8)

The electrocardiogram is still a key element to detect suspected amyloidosis. However, it seems that we should abandon thinking only of cardiac amyloidosis when we find low voltages, since in our experience this only occurred in 16% of patients. Absence of signs of hypertrophy in the electrocardiogram in accordance

Table 2. Electrocardiographic parameters at follow-up onset

Variable	Value
Rhythm	
Sinus	30 (62)
AF	15 (30)
Atrial flutter	1 (2)
Pacemaker	3 (6)
PR interval (ms)*	150 (130-230)
AV block	10/49 (20%)
QRS duration (ms)*	100 (90-130)
QRS morphology	
CRBBB	13 (26%)
CLBBB	4 (8%)
Unspecific conduction disorders	2 (4%)
Pacemaker	3 (6%)
LAFB	4 (8%)
Low voltage	6 (16%)
Pseudoinfarction	10 (20%)

*indicates mean/median (IQR); the rest of the variables are expressed as n (%). AF: atrial fibrillation. AV: atrioventricular. CRBBB: Complete right bundle branch block. CLBBB: Complete left bundle branch block. LAFB: Left anterior fascicular block.

Table 3. Echocardiographic variables at the onset and end of follow-up

Variable	Value*
Ejection fraction at study onset	52.0 (43-58)
Mitral flow pattern	
Normal	1/43 (2.3)
Prolonged relaxation	5/43 (11.6)
Pseudonormal	8/43 (18.6)
Restrictive	5 (11.6)
Monophasic	24 (55.8)
Left atrial area (cm2)	28 (26-32)
Maximum septal thickness (mm)	16.5 (14-18)
Pulmonary systolic pressure (mmHg)	38 (27.5-50)
TAPSE (mm)	15 (13.7-19.2)
TDI RV S wave (cm/s)	8 (6-10)
E/e´ ratio	15.5 (12-20)
Ejection fraction at the end of follow-up (%)	44.5 (38.2-55.7)

*indicates mean/median (IQR), except for mitral flow pattern, where n/N is shown (%). TAPSE: Tricuspid annular plane systolic excursion. TDI: Tissue Doppler imaging. RV: Right ventricular

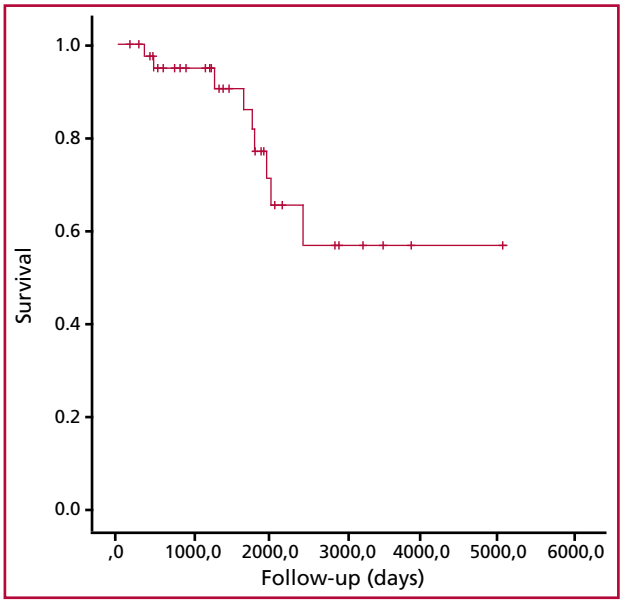

Fig. 1. Follow-up overall mortality

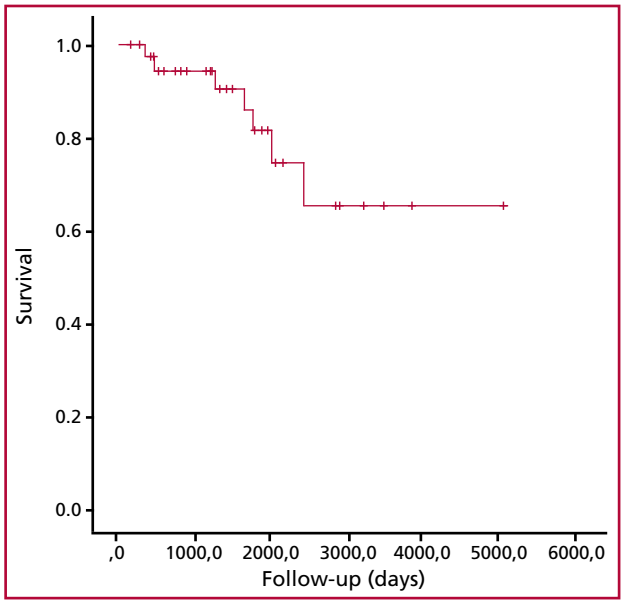

Fig. 2. Follow-up cardiovascular mortality

Table 4. Clinical variables at the end of follow-up

Variable	Value
Functional class at the end of follow-up	
I	11 (57.1)
II	16 (26.5)
III-IV	21 (16.3)
Overall mortality	9 (19.1)
Cardiovascular mortality	7 (14.8)
Atrial fibrillation	8/28 (10.7)
Pacemaker implantation	8/43 (18.6)
Hospitalization for heart failure	14/49 (28.6)
ICD implantation	2/46 (4.3)
Total follow-up (days)*	1,258 (410-2004) (106-5,066) min: 106; max: 5,066
Symptom onset to diagnosis (days)*	352 (78-813)
Follow-up initiation to diagnosis (days)*	514 (105-1688)
Diagnosis to CV death (days)*	330 (123-548)
Diagnosis to overall death (days)*	350 (135-590)

*indicates mean/median (IQR); the rest of the variables are expressed as n (%) or n/N (%)
ICD: Implantable cardioverter defibrillator. CV: Cardiovascular.

with the patient's myocardial thicknesses should be a warning signal. (7-10)

Second, our experience highlights the changes generated by the development of new protocols for the diagnosis of this disease. The biopsy, which up to a few years ago was the "gold standard" to classify a patient has become much less frequent. The combination of diphosphonate scintigraphy with light chain assay in blood and urine allows typification with great certainty in more than 90% of patients. (11-14) An anatomopathological study is relegated to cases where previous studies are not conclusive. In our cohort, the first patients had cardiac magnetic resonance imaging and endomyocardial biopsy studies as diagnostic tests and the last scintigraphy and light chain assay. A critical error, which we have learnt to avoid, is to assume that because the scintigraphy is negative the patient does not suffer from a form of TTR amyloidosis. Conversely, a positive scintigraphy does not certify a TTR amyloidosis diagnosis if it is not associated with a negative free light chain assay. (15)

Third, we wish to emphasize the importance of genetic tests. We believe that TTR genotype should be requested to every patient assessed for suspected TTR amyloidosis. Distinguishing between wATTR and ATTR amyloidosis has important implications for patient management. The two TTR amyloidosis subtypes have different presentation and prognosis. Wild-type TTR amyloidosis has a late onset which generally mainly affects the heart. (16-20) Conversely, hATTR amyloidosis is a dominant autosomal disease of incomplete penetrance, with earlier onset of symptoms and variable presentation depending on the specific TTR mutation, among other causes, and cardiac, neurological or mixed phenotypes. In case of hereditary ATTR-CM, a genetic study and first-degree family clinical screening should be considered. Finally, the differentiation between wATTR and hATTR amyloidosis may affect treatment selection, taking into account that so far there is only strong evidence for the use of tafamidis in the former variant, while for the latter patisiran and inotersen are added. (21, 22) Therefore, in the next few months we aim that this genetic test is done to all our patients.

Fourth, follow-up shows a relatively good evolution of patients with lower than expected mortality. We understand that this could be associated to three aspects. The first is the low number of patients, with high data weakness. The second could be due to the high proportion of patients with "early" stages of the disease, with preserved EF and adequate FC, and lastly, to the important number of patients who has access to medication of proven efficacy in the reduction of disease progression, such as tafamidis. (20, 23, 24)

Fifth and last, we would like to stress that we are living a time of great changes in the management of this disease. Regarding treatment, the future seems to be associated to the potential benefit of combined therapies of TTR production inhibition with those that stabilize the tetrameric chains that can move to the blood pool, with the aim of reducing to a minimum the concentration of monomers capable of tissue deposition. This, added to the early identification of the affected population would reduce the morbidity and mortality of this disease. If we could think ahead, the development of therapies that could break down the already deposited amyloid without affecting the healthy myocytes would be ideal for the more advanced forms. (4, 9, 18, 24–26)

Limitations

It is important to point out that what we have shown represents the evolution of a group of patients with close follow-up in a cardiovascular center, where a significant percentage of patients had access to drugs with proven benefit in TTR amyloidosis outcome. For different reasons, at the time of publishing this article, only 61.2% of patients had undergone a genetic test. Even though the demographic characteristics would indicate that most of them would be wild-type, this cannot be confirmed until the test has been performed to all patients.

CONCLUSIONS

Follow-up of patients with ATTR-CM expresses the changes undergone by the diagnostic process, with a reduction of invasive studies and time to characterization. The diagnosis of "early stages of the disease" that are far away from traditionally considered characteristics might impact on mid-term outcomes.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material)

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