

Editorial

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Transthyretin amyloid cardiomyopathy: the importance of early intervention to improve prognosis.

Montserrat Carrillo Estrada, Axel H. Hernández Pineda

Hospital de Cardiología, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, ciudad de México.

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ABSTRACT

The article "Transthyretin Amyloid Cardiomyopathy: clinical features and staging, indications for treatment and mortality" describes the clinical characteristics of 32 patients diagnosed non-invasively with transthyretin amyloid cardiomyopathy (ATTR-CM). Most patients had wild-type ATTR-CM and presented with New York Heart Association (NYHA) functional class II symptoms, preserved left ventricular ejection fraction, and typical cardiac magnetic resonance findings associated with the disease. Atrial fibrillation was present in 50% of the patients, while 25% had moderate or severe aortic stenosis. The NAC staging system was used in these patients to establish prognosis, with 75% of patients were classified as stage I. Notably, only 25% of patients received the transthyretin stabilizer tafamidis, and most of those who died had not received disease-modifying therapy.

Transthyretin amyloid cardiomyopathy (ATTR-CM) has become extremely important in recent years due to advancements in noninvasive diagnosis and treatment, as well as a higher awareness on the disease. This pathology is characterized by an anomalous folding of transthyretin, a protein synthesized mainly in the liver, leading to the formation of a material called amyloid, depositing in the cardiomyocytes interstitia. This may lead to restrictive cardiomyopathy, which has a somber prognosis if detected in late stages.¹

In the article "Transthyretin amyloid cardiomyopathy: clinical features and staging, indications for treatment and mortality", the authors present the results of a retrospective investigation describing the clinical characteristics, treatment and mortality in a cohort of patients with this diagnosis.² Most of the current information about ATTR-CM is drawn precisely from single-center and observational studies, and registries, allowing to learn about the contemporary behavior of this pathology.

The 32 patients included were diagnosed by a noninvasive modality, with a radioactive tracer bone scan with positive bone uptake (degrees 2 or 3 of Perugini), ruling out a monoclonal component with measurement of serum free light chains, as well as electrophoresis with serum and urine immunofixation. This highlights the current usefulness of bone scans with pyrophosphates for a noninvasive diagnosis of this disease, remembering that in some cases

with non-conclusive results, histological confirmation for cardiac amyloidosis will still be required.³

In this study, in patients in whom the genetic test to detect hereditary ATTR-CM cases was performed, the Val-30Met mutation was found in 6.2% of cases. Half of the patients included in this cohort were in functional class II of the New York Heart Association; and the most frequent extracardiac manifestations were digestive disorders, carpal tunnel syndrome and the presence of peripheral neuropathy. All patients presented abnormal surface ECG. As to the imaging tests, patients presented preserved left ventricular ejection fraction in most cases; with an E/e' median of 16.5 and a global longitudinal strain median of -9.5%, which translates a significant increase in left ventricular filling pressures, as well as deterioration of longitudinal strain in fibers. Cardiac MRI was conducted in 50% of cases, observing typical findings, suggesting a manifest state of the disease. Most patients with reduced ejection fraction died during follow-up.

A very relevant finding is that half of patients included had atrial fibrillation and a fourth presented moderate or severe aortic stenosis. Given the high thromboembolic risk accompanying ATTR-CM, anticoagulation in patients presenting atrial fibrillation is indicated in all patients, regardless of risk estimated by scores such as CHA2DS2-VASc; pharmacological strategies for rhythm or rate control should be used cautiously, due to the low tolerance of nega-

tive chronotropic drugs in this population.⁴ Aortic stenosis that coexists with ATTR-CM is associated with a high rate of adverse cardiovascular events and mortality; in these cases, transcatheter valve implant has proven to be a feasible treatment option, added to disease-modifying therapy.⁵

There are different publications focused on risk stratification in patients with transthyretin amyloid CM; the different available scores include clinical and biochemical characteristics, such as renal function tests and myocardial injury biomarkers measurement (troponins and natriuretic peptides). In this research, the British score of the National Amyloidosis Centre was used, which includes 3 stages and takes NT-proBNP into account (with a cutoff point of 3000 ng/L) and glomerular filtration rate (cutoff point of 45 ml/min).⁶ It was found that three fourths of patients were in stage I. This probably translates the impact of new diagnostic methods enabling a detection of this disease in less advanced stages. Recently, risk estimation has also been proposed with the heart failure classification of the American College of Cardiology/American Heart Association, showing it has a good performance to predict mortality in patients with ATTR-CM.⁷

In the patients included, only a fourth had disease-modifying therapy with tafamidis, a transthyretin tetramer stabilizer, indicated in the treatment for ATTR-CM, both the wild-type and hereditary.³ Recently, the ATTRIBUTE-CM trial has proven the efficacy of acoramidis, another stabilizer with great transthyretin affinity, in terms of mortality, morbidity and functionality compared with placebo.⁸ Also, in the HELIOS-B trial, it was proven that use of vutrisiran, a therapeutic agent of RNA interference, reduced all-cause mortality and cardiovascular events in patients with wild-type and hereditary ATTR-CM, even in those with no treatment with tafamidis.⁹ This makes it a promising therapeutic alternative.

It is important to highlight that in this cohort, most patients that died had no treatment with tafamidis. Ideally, great advancements to achieve an early diagnosis of ATTR-CM should be followed by the onset of disease-modifying treatment. It is particularly important to identify the obstacles there may be in the environment for the administration of a drug that has proven to decrease mortality in patients with ATTR-CM.¹⁰ These real world studies make the gaps between the development of new therapies, scientific validation and their subsequent effective implementation in clinical practice visible.

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