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Editorial

Transthyretin Cardiac Amyloidosis: From Rare Monogenic Disease to Common Pathway in Heart Failure?

Amiloidosis cardiaca por transtiretina: antes una enfermedad monogénica minoritaria, ¿ahora una vía común en la insuficiencia cardiaca?

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Cardiology has seen major advances in the care of many diseases. The disease of our time as cardiologists is heart failure (HF), and specifically, HF in the elderly.[1] While substantial progress has been made in the care of HF with reduced ejection fraction, the development of new drugs is becoming increasingly hard and progress has, with a few exceptions, stalled.[2] Perhaps half of patients have HF with preserved or substantially preserved ejection fraction, which is more common in the elderly,[3] but there has been no progress with no approved therapies available for reducing mortality or hospitalization.[4] This lack of progress is in part due to our approach to HF—we broadly treat it as a single entity in both clinical trials and clinical care based on criteria such as ejection fraction or the presence/absence of hypertrophy, and our therapies focus on broad pathways activated in all HF patients rather than patient-specific processes. We need to select the fundamental underlying processes in a targeted way.

One candidate process that has been substantially overlooked is transthyretin (TTR) amyloid infiltration of the myocardium. Amyloidosis is caused by the deposition of misfolded protein in various tissues and organs. Around 30 proteins are amyloidogenic, but ventricular myocardium is simpler—it is mainly affected by just 2 proteins: primary light chain (AL) amyloid and TTR amyloid. Transthyretin amlyoid occurs in 2 forms: wild-type and hereditary. The hereditary form is often considered clinically by the primary organs they affect, either neurological (familial amyloid polyneuropathy [FAP]) or cardiac (familial amyloid cardiomyopathy [FAC]).[5]

Cardiac TTR amyloid is considered rare but there is increasing evidence that it is commoner than previously thought, particularly in the elderly. We have known for decades that around 25% of octogenarians have evidence of TTR deposits at autopsy. In the last few years, there is increasing recognition of TTR occurring as a dual pathology in other diseases, with several recent studies identifying TTR in up to 5% of hypertrophic cardiomyopathy patients, 13% of HF patients with preserved ejection fraction,[6,7] and (data currently in unpublished abstract form only) between 6% and 15% of patients with aortic stenosis, the latter being in the older patients undergoing percutaneous valve replacement.

Why this increasing recognition? Technology drives our understanding. Here it is imaging advances, and there are 2 major advances in cardiovascular magnetic resonance (CMR) and nuclear scintigraphy.[8,9] It has been noted that bone tracers localize to the heart. These tracers (m99Tc dicarboxypropane diphosphonate [DPD], m99Tc pyrophosphate [PYP], or m99Tc hydroxymethylene diphosphonate [HMDP], depending on the country) are extremely sensitive to amyloid, particularly TTR amyloid. As a simple test, this has tremendous promise. The second technology is CMR. Cardiac magnetic resonance has advantages in imaging cardiac structure and function, but it is tissue characterization that adds value to echocardiography. Amyloid infiltration of the myocardium is a continuum from no amyloidosis to overt amyloidosis. In amyloidosis, typical patterns of late gadolinium enhancement (LGE) are seen: subendocardial in the earlier phase, later transmural, but prior to the use of the phase-sensitive inversion recovery technique, this could be difficult to detect at times.[10] Even with the phase-sensitive inversion recovery technique, the pre-LGE phase of modest infiltration was completely missed. A new technique, T_1 mapping, helps. T_1 is a fundamental magnetic property of myocardium. It can be measured without the addition of an exogenous contrast agent (native T_1) or pre- and postcontrast to derive the extracellular volume (ECV). This value reflects the free water between cells in the myocardium. Water becomes elevated if something is keeping it there—edema, fibrosis, or amyloid. Both the T_1 and ECV elevate before LGE is present.[11,12]

In their article published in *Revista Española de Cardiología*, Gallego-Delgado et al.[13] explored persons with mutations in TTR known to cause the polyneuropathy, FAP, mainly from the mutation val30Met—a mutation that has founder effects and is endemic in some regions (14 patients from Huelva, 7 from Mallorca). They looked for cardiac involvement using CMR with T_1 mapping and ECV quantification, which has not been done before. In 31 patients, 5 had elevation of the ECV, all of which had positive bone tracer scintigraphy (here with DPD). This ECV elevation was substantial. The normal ECV is around 25% (itself high—myocardium has a lot of extracellular fluid in capillaries and between cells related to collagen—skeletal muscle is much lower, perhaps 10%), but the positive patients had an ECV of 49%. Although ECV

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elevation is nonspecific, as the water could be related to fibrosis, amyloid or edema, at these sorts of levels, the ECV becomes more specific as fibrosis cannot get much above 40% to 45% in life.

Here an ECV of > 35.7% was diagnostic of cardiac involvement. The ECV elevation tracked key cardiac imaging parameters such as LV mass and atrial size but was also strongly related to N-terminal pro-B-type natriuretic peptide. They also correlated with markers of neurological involvement. There were some limitations: the ECG was not documented (discordance between wall thickness and the ECG is a good sign) and the study sample was small (not surprising given the relative rarity of FAP).

Why is this important? First, it highlights the technical progress in imaging for cardiac amyloid, both using CMR and bone tracers. Here the CMR was at 3T and Philips manufacture. Traditionally, cardiac amyloidosis has required histological proof. Pending guidelines will suggest that this is no longer needed.[14] Second, it reminds us that TTR is a multisystem disease and categories (FAP, FAC), although clinically useful, are not absolute. Third, it has lessons for clinical care—red flags exist. For example, HF in clinical practice with carpal tunnel syndrome, especially bilateral, certain ethnicities (African American, Portuguese, certain areas of Spain, Ireland, Sweden), LGE, and discordant wall thickness to ECG voltage.

However, the most important point is that it highlights amyloid as a cardiac disease, and that diagnosis can be established earlier. Transthyretin amyloid is not untreatable. Although traditionally liver transplantation has been used in familial disease with high penetrance (TTR is synthesized mainly in the liver), there are other therapeutic options both current and under development, such as TTR stabilizers (tafamidis, diflunisal) and drugs that reduce production (RNA silencing or interference). On the horizon are therapeutic approaches to remove established amyloidosis.[15] These therapies need to be developed further. The rare monogenic forms of amyloid such as FAP can provide the platform for this with likely translation of approaches to wild-type TTR, both in isolation but also potentially where it occurs as a dual pathology in HF, aortic stenosis, or nonamyloid cardiomyopathy.

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CONFLICTS OF INTEREST

None declared.

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