EDITORIAL COMMENT

Broadening the Phenotypic Spectrum and the Diagnostic Needs of TTR-Related Cardiac Amyloidosis*

Claudio Rapezzi, MD,a Anna Laura Tinuper, MD,a Massimiliano Lorenzini, MD,a,b

The recent history of transthyretin (TTR)-related amyloidosis has been characterized by a number of paradigm shifts. Initially considered as an essentially neurological, hereditary disease (familial amyloidotic polyneuropathy) (1), it has now become a well-known cause of cardiomyopathy with a hypertrophic/restrictive phenotype. It has also been established that some TTR-related variants and the wild-type form lead to a mainly or exclusively cardiac phenotype (2). With a high number of potentially disease-modifying drugs currently under investigation, the global interest in the disease is increasing rapidly. Furthermore, a number of clinical studies have recently shown that TTR-related cardiomyopathy is a much more frequent condition than expected. Specifically, TTR-related cardiac amyloidosis (CA) has been demonstrated in a significant subgroup of patients with heart failure with a preserved ejection fraction (3), aortic stenosis—particularly those with paradoxical low flow-low gradient (4)—or a hypertrophic cardiomyopathy phenotype initially misdiagnosed as a sarcomeric disease (5). Finally, a number of patients have incidentally been found to have myocardial uptake of 99mTc-DPD on bone scintigraphy carried out for oncological or orthopedic indications and have gone on to receive a diagnosis of ATTR CA (6).

The cardiac magnetic resonance (CMR) study by Martinez-Naharro et al. (7) published in this issue of the Journal illustrates the possibility of further expanding the diagnostic pathways for this condition, for 3 main reasons:

1. It demonstrates a broader morphological spectrum of left ventricular hypertrophy (LVH) than was previously thought.
2. It underlines the great qualitative and quantitative variability of myocardial late gadolinium enhancement (LGE).
3. It focuses on extracellular volume (ECV) evaluated by CMR as a potential marker of the amyloid burden in order to stratify prognosis and evaluate response to treatment during follow-up.

Traditionally, cardiac involvement in TTR-related amyloidosis has been described as a hypertrophic phenotype with symmetric LVH, and this finding has often been considered critical for the differential diagnosis with sarcomeric hypertrophic cardiomyopathy. Surprisingly, data from this study show that asymmetric LVH is present in almost 80% of cases of TTR-related CA (with a reverse septal contour in 30% of these). This finding modifies the aforementioned belief and allows us expand the diagnostic suspicion of CA among patients with hypertrophic phenotype. Another study recently investigated quite a large cohort of patients with wild-type CA by echocardiography and contributed to dispelling the myth of the symmetric LVH in CA (8). The different frequency of asymmetric LVH in the 2 studies is probably related to the greater accuracy of CMR measurements. Among the possible explanations suggested by the authors for the high frequency of

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the aCardiology, Department of Experimental, Diagnostic and Specialty Medicine, Alma Mater Studiorum University of Bologna, Bologna, Italy; and the bUniversity College London Institute for Cardiovascular Science and Barts Heart Centre, St. Bartholomew’s Hospital, London, United Kingdom. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.
asymmetric LVH, specifically when compared with the well-established data for amyloid light-chain (AL) amyloidosis, the most convincing is time related. Indeed, in TTR-related CA, the infiltrative process occurs over a long period, whereas patients with AL-related disease generally die too soon to develop a remarkable increase in wall thickness, probably because of the direct toxic effect of circulating light chains on cardiomyocytes. The second hypothesis, that the different LVH pattern between TTR-related and AL CA could be due to a different total cell mass, regardless of infiltration (higher in TTR than in AL disease), is more speculative and challenging.

Martinez-Naharro et al. (7) found a subendocardial pattern of LGE only in 29% of cases, whereas transmural LGE was present in 71% and almost all cases also showed right ventricular LGE. These observations help us go beyond the initial idea (9) of a preferential subendocardial distribution of LGE in cardiac amyloidosis and are consistent with historical data that shows a broad spectrum of distribution of cardiac infiltration (10).

The data on ECV presented in the study are important from both pathological and clinical perspectives. The authors provide the first demonstration in quite a large cohort of patients that ECV correlates with prognosis, even after adjustment for other prognostic factors. ECV is a reasonable expression of the amyloidotic burden in this disease and, based on this evidence, is a potential endpoint for studies investigating disease-modifying treatments. The need for mortality-surrogate endpoints for clinical and pharmacological research is currently particularly important because TTR-related cardiac amyloidosis is a rare condition, and the number of patients available for prospective trials is limited. The same group of authors has already shown the prognostic value of ECV in AL disease, and ECV reduction following chemotherapy has been shown in a small cohort of patients with AL disease (11), but there is an urgent need of similar studies for TTR CA. It is noteworthy that ECV correlates with cardiac uptake on 99mTc-DPD scintigraphy in terms of semiquantitative score, but whereas ECV measured by CMR provides a quantitative evaluation, attempts to a similar approach with bone tracer scintigraphy have been highly unsatisfactory. The possibility of an early diagnosis of CA by CMR remains little explored, whereas the role of bone tracer scintigraphy for this purpose is well established (12).

Collecting the available data from the present study and other many papers on different imaging techniques in CA (Table 1), one obtains a complex scenario in which no single test emerges over the others, but different techniques are useful at different stages of the diagnostic workup (12).

**TABLE 1 Role Of Different Imaging Techniques and Biomarkers in the Various Phases of Evaluation and Management of TTR-related CA**

<table>
<thead>
<tr>
<th>Phase of Workup</th>
<th>Echo</th>
<th>CMR/NT-proBNP</th>
<th>“Bone Tracers” Scintigraphy</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic suspicion</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>Serum retinol-binding protein 4 (13)</td>
</tr>
<tr>
<td>Definite diagnosis</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Early diagnosis</td>
<td>+</td>
<td>+?</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Functional evaluation</td>
<td>+++</td>
<td>+++</td>
<td>– (+ for MIBG)</td>
<td>++</td>
</tr>
<tr>
<td>Prognostic stratification</td>
<td>+</td>
<td>++</td>
<td>±</td>
<td>(+ (14) Troponin (14)</td>
</tr>
<tr>
<td>Amyloidotic burden</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Response to therapy</td>
<td>+</td>
<td>++?</td>
<td>?</td>
<td>++? 6MWT</td>
</tr>
</tbody>
</table>

*Late gadolinium enhancement extracellular volume and native T1 mapping.

++ very useful, recommended; ++ and + ± useful, to be considered; ± possibly useful; ±/– role uncertain; – not useful; 6MWT = 6-min walk test; ATTR = transthyretin-related amyloidosis; CA = cardiac amyloidosis; CMR = cardiac magnetic resonance; Echo = echocardiography; MIBG = meta iodine-131-meta-iodobenzylguanidine; NT-proBNP = N-terminal pro-B-type natriuretic protein.

---

**REFERENCES**

1. Rapezzi C, Quarta CC, Riva L, et al. Transthyretin-related amyloidoses and the heart: a clinical overview. Nat Rev Cardiol 2010;7:398-408.
4. Longhi S, Lorenzini M, Gagliardi C, et al. Coexistence of degenerative aortic stenosis and wild-type transthyretin-related cardiac

**KEY WORDS** amyloidosis, cardiomyopathies, diastolic, heart failure, magnetic resonance imaging, radionuclide imaging