EDITORIAL COMMENT

Early Identification of Transthyretin-Related Hereditary Cardiac Amyloidosis*

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Amyloidosis is characterized by the extracellular deposition of highly-organized fibrillar aggregates showing a cross-beta super-secondary structure (1). Several proteins are amyloidogenic in humans, resulting in different clinical presentations, either systemic or localized. Transthyretin-related hereditary amyloidosis (ATTR) is a late-onset, dominantly inherited systemic amyloidosis. Heterozygous gain-of-function mutations in the TTR gene confer a high amyloidogenic propensity to transthyretin (TTR), a plasma protein responsible for transporting thyroxine and vitamin A and mostly produced by the liver. Mutations in the TTR gene destabilize the native tetrameric structure of TTR, promoting the dissociation into misfolded monomers, which aggregate and finally form fibrils into target tissues. The disease affects the peripheral and autonomic nerves, leading to severe disability, cachexia, and death; heart involvement often associates with nerve deposition and is responsible for progressive impairment of myocardial function, causing fatal heart failure and dysrhythmias (2). Sporadic, senile systemic amyloidosis is a slowly progressive cardiac amyloidosis that is caused by the deposition of wild-type TTR, usually affects mainly male patients older than 60 years of age, and presents invariably with heart failure.

Diagnosis of ATTR Amyloidosis

The diagnostic workup starts with suspicion of the disease and takes advantage of clinical expertise, noninvasive imaging, and biomarkers (3,4). In non-endemic areas, ATTR amyloidosis remains underdiagnosed, and the diagnosis is delayed by 3 to 4 years because of the absence of a positive family history (sporadic cases), varied presentations, and misdiagnosis (5). In probands, late diagnoses are common because early phenotypic traits are often nonspecific, especially when observed in a fragmented clinical fashion. Diagnosis may be expedited in familial ATTR after the causative mutation of the disease gene is identified in the proband. Cascade family screening identifies early clinical markers and may provide pre-symptomatic diagnosis.

Transthyretin Amyloid Cardiomyopathy

The diagnostic standards for the diagnosis of amyloid cardiomyopathy are those established for light-chain amyloidosis (AL), recently updated (6), a mean left ventricular (LV) wall thickness >12 mm, in the absence of hypertension or other possible causes of LV hypertrophy, and elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) in the absence of renal failure. With the use of 12 mm as the cutoff for LV mural thickness, early cardiac amyloidosis may remain undiagnosed. For instance, in this issue of JACC, Kristen et al. (7) describe endomyocardial biopsy–proven cardiac amyloidosis

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in a patient with 10-mm LV thickness. In this patient, scintigraphy showed heart retention of 2.9%, and cardiac magnetic resonance (CMR) tested negative. Although rare, the endomyocardial biopsy–verified amyloid infiltration when the echocardiographic criteria are not fulfilled suggests that the heart may be affected far before being recognized by imaging. However, establishing the “early cardiac amyloidosis” is a diagnostic process that lacks precise criteria. CMR can either confirm echocardiography-based and/or biomarker-based diagnosis or add information about the severity of the infiltration. The native or noncontrast T1 mapping displays a similar diagnostic performance and disease tracking for both cardiac ATTR amyloid and AL amyloid, but with lower maximal T1 elevation. Native T1 mapping could suggest early cardiac involvement (8) and is negative in healthy mutation carriers. Furthermore, technetium-99m-3-3-diphosphono-1-2-propanodicarboxylic acid (99mTc-DPD) scintigraphy may provide diagnosis earlier than does CMR-based evaluation (9,10).

Although genetic testing identifies mutated relatives (potentially including real “early” patients) of the proband, very few studies have demonstrated higher yield from family screening. In the series presented by Raperzzi et al. (10), 15 of 63 (24%) patients with ATTR were identified by family screening, and 23 of 63 did not fulfill criteria for “amyloid cardiomyopathy.” However, 7 showed some echocardiographic abnormalities, but cardiac amyloid was not detected by the radionuclide imaging. On the other hand, 99mTc-DPD uptake was seen in 4 of 23 patients without amyloid cardiomyopathy with normal LV wall thickness, LV ejection fraction, and transmitral Doppler profile; E/E’ was abnormal in 1 case, and 1 showed nonspecific electrocardiographic T-wave abnormalities (10). These results suggest that there may be cases in which echocardiography is more informative than scintigraphy and vice versa.

In a family-based study including 18 mutated members of 15 families, 6 of 18 patients were defined as healthy carriers. Scintigraphy in 10 of 12 affected patients with ATTR with normal baseline echocardiography was performed at each follow-up occasion together with echocardiography and was stopped when the first signs of heart involvement at echocardiography appeared. In 6 patients, abnormal myocardial radiotracer accumulation was detected 1 to 2 years before morphological echocardiographic abnormalities were detected (11).

**Prognostic Stratification**

In AL amyloidosis, cardiac staging on the basis of cardiac biomarkers troponin and NT-proBNP (12) is widely used in clinical trials and patient care; however, a validated strategy for cardiac workup is still lacking in ATTR amyloidosis. Kristen et al. (7) explored the role of multimodality imaging (echocardiography, CMR, and 99mTc-DPD scintigraphy) and biomarker testing in 60 patients with ATTR cardiac amyloidosis. Scintigraphic findings demonstrated good correlation with echocardiographic morphologic and functional findings, cardiac biomarkers, renal function, and late gadolinium enhancement. At univariable Cox regression, atrial fibrillation, NT-proBNP, cardiac troponin T, estimated glomerular filtration rate, mitral annular plane systolic excursion, LV hypertrophy index, and heart retention were predictors of outcome; however, on multivariable analysis, cardiac troponin T remained the only independent predictor of survival. Contrary to this result, the study by Rapezzi et al. (10) reported that the 99mTc-DPD myocardial uptake is a prognostic determinant of “cardiac” outcome in ATTR, either alone or in combination with LV wall thickness. The question is whether the 2 series are comparable. Kristen et al. (7) investigated 70 patients (New York Heart Association functional class >2: 38.5%), 36 with familial ATTR and 34 with senile systemic amyloidosis, with 10 patients not fulfilling criteria for cardiac involvement. Rapezzi et al. (10) studied 63 patients with genetic ATTR (New York Heart Association functional class >2: 16%), with 23 patients not fulfilling the criteria for cardiac amyloidosis; 14 of the latter were identified by means of family screening. The prevalence of cases with advanced cardiac involvement was higher in the former than in the latter study. Therefore, the results on prognostic stratification remain elusive because of the noncomparable series.

**Is it Time for Staging Cardiac Involvement in ATTR Amyloidosis?**

Staging for cardiac involvement in ATTR amyloidosis could take advantage of family studies in which at least 3 categories of mutated members exist: 1) healthy carriers; 2) affected but asymptomatic mutated family members, in whom imaging (CMR, scintigraphy, or echocardiography) shows abnormal parameters that do not fulfill current criteria for diagnosing cardiac involvement and could be diagnosed with “early cardiac
amyloidosis;” and 3) patients with overt amyloid cardiomyopathy, when current echocardiographic criteria are fulfilled. Three simple stages could provide distinct groups of patients; reverse information from genetics to clinics ([genetic+ → clinics–], [genetic+ → clinics borderline], and [genetics+ → clinics+]) could group patients into comparable series, useful for progressing with stage-specific diagnostic criteria (Fig. 1). The availability of new treatment resources for ATTR amyloidosis, from small molecules such as tafamidis and diflunisal to novel gene-silencing therapies, requires a staging system for patient stratification. International collaboration could gather a wide patient population to define and validate a cardiac staging system.

**Figure 1. Diagnostic Process in ATTR Amyloidosis**

The availability of effective therapies demands early diagnosis to anticipate severe and frequently irreversible end-organ damage (B, massive amyloid infiltration, in green). Early symptoms are frequently overlooked, and the onset of overt congestive heart failure is associated with end-stage cardiac damage, refractory to therapy. The combination of genetic testing, high-sensitivity troponins, and cardiac imaging techniques allows early diagnosis (A, amyloid infiltration of a small intramural vessel), widening the diagnostic windows and, consequently, therapeutic opportunities.

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