Getting to the heart of the matter: cardiac involvement in transthyretin-related amyloidosis

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The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

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This editorial refers to ‘Disease profile and differential diagnosis of hereditary transthyretin-related amyloidosis with exclusively cardiac phenotype: an Italian perspective’, by C. Rapezzi et al., on page 520

Transthyretin-related amyloidosis (ATTR) was originally called familial amyloidotic polyneuropathy (FAP) by Andrade based on the predominant features of a length-dependent axonal neuropathy seen in affected Portuguese patients. With positive identification of transthyretin (TTR) as the precursor protein, and a growing number of new forms of systemic amyloidosis identified, the name was subsequently changed to ATTR. Despite the name change, the disease itself continues to be regarded predominantly as a form of hereditary peripheral neuropathy. The phenotype of cardiac involvement, either as a solitary manifestation of the disease or in association with neuropathy, is probably under-diagnosed due to a lack of awareness of ATTR. As a result, patients who present with cardiac symptoms of ATTR may not gain access to current diagnostic tests or emerging therapies.

Factors that probably contribute to low disease recognition include the overall rarity of ATTR and the regional variation in incidence. For example, most of the data on the typical pattern of disease in ATTR patients who have the most common V30M mutation come from areas in which the disease is endemic, such as Portugal, Japan, and northern Sweden. Symptomatic cardiac amyloidosis in these populations is even less common, further obscuring the importance of heart involvement. A negative family history of cardiac amyloidosis is also not a useful screening method, because the V30M mutation can occur sporadically, even in endemic areas, and is associated with an increased incidence of cardiac amyloidosis in that setting.

As the number of mutations associated with ATTR has increased, it has become clear that the correlation between genotype and phenotype is poorly understood. Affected individuals with different mutations exhibit a wide variation in clinical symptoms, including age of onset, pattern of organ involvement, and severity of disease. Even individuals with the same mutation can manifest vastly different phenotypes depending on factors that are unknown. This heterogeneity makes it extremely difficult to define a classic form of the disease, especially in areas in which the disease is not commonly encountered.

Rapezzi et al. have detailed the clinical spectrum of a large series of ATTR patients seen at a number of referral centres throughout Italy, with an emphasis on cardiac involvement. This effort not only serves to increase the awareness of ATTR in general, but specifically brings into focus the importance of cardiac amyloid in this disease. While a minority were found to have an exclusively cardiac phenotype, by their definition, these 17% who had symptomatic disease only in the heart send a strong message to heighten awareness within the cardiovascular community.

The critical impact of cardiac involvement in systemic amyloidosis is clearly evident in the staging of light chain-associated amyloidosis (AL). While survival in AL patients with cardiac involvement is clearly shorter than in ATTR, the ability to determine prognosis solely on the extent of cardiac disease underscores the vital importance deposition in the myocardium plays in the natural history of systemic amyloidosis. Data from our institution demonstrate that survival in ATTR is linked to cardiac involvement and varies according to the specific mutation present. Thus it is critical not only to recognize cardiac amyloid early in the course of the disease, but also accurately to identify the type of amyloid responsible for the deposits.

Rapezzi et al. document a clinical profile that distinguishes patients with exclusive ATTR cardiac disease from those with hypertrophic cardiomyopathy (HCM), a condition which is commonly confused with amyloid. By highlighting the features that make up this profile: male gender, age > 65 years, heart failure symptoms, symmetric left ventricular (LV) ‘hypertrophy’, and moderately depressed LV function, they have clearly identified a population in which ATTR should be strongly suspected. We propose a diagnostic algorithm that incorporates this information to classify patients into risk groups based on standard initial testing (Figure 1). Patients that meet the high-risk profile criteria should probably undergo additional testing, ideally an endomyocardial
biopsy at a centre experienced in making the diagnosis of amyloidosis, to exclude cardiac amyloid. An endomyocardial biopsy is recommended, as the subcutaneous fat aspirate is positive in only about half of ATTR patients with cardiac involvement (unpublished data). Confirmation of the subtype of amyloid requires availability of specialized testing, such as mass spectroscopy to identify the amyloid precursor accurately. DNA testing is required in cases in which TTR is identified to distinguish between ATTR, in which a mutation in the TTR gene is invariably detected, and senile systemic amyloidosis (SSA), in which no mutation is found. It is worth noting that Rapezzi et al. report a similar clinical profile in ATTR with cardiac involvement and SSA.

An increased awareness of cardiac amyloidosis in general, and ATTR specifically, is a valuable and timely goal. Improved therapies for AL have resulted in better outcomes. Liver transplantation, the only currently available therapy for ATTR, has been called into question as a viable option for patients with cardiac involvement. Novel therapies are currently being developed for ATTR, including small molecule inhibitors such as diflunisal and tafamidis, as well as gene silencing approaches designed to diminish or abolish TTR synthesis. Once the diagnosis of ATTR is confirmed, referral to or consultation with a medical centre with expertise in transplantation and emerging treatments for ATTR is probably indicated.

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**References**


CARDIOVASCULAR FLASHLIGHT

Getting the right diagnosis: ST-elevation myocardial infarction in situs inversus

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A 32-year-old Indian contractor presented to the military hospital in Camp Bastion, Afghanistan, with 2 h of cardiac chest pain. His initial ECG (Panel A) suggested dextrocardia (right-axis deviation, positive complexes in aVR and diminishing R-wave progression). He suffered a VF arrest and received three shocks over the right precordium before return of spontaneous circulation.

He was transferred to the ICU and intubated and invasive monitoring was commenced. He suffered a further three VF arrests requiring DC shocks and his subsequent ECG (Panel B) (with right and left limb leads reversed) showed diagnostic ST-elevation anteriorly. He was thrombolysed with tenectoplase and a transthoracic echocardiogram confirmed dextrocardia with an akinetic anterior wall and an ejection fraction of 15%.

He was commenced on aspirin, clopidogrel, and enoxaparin, and a contrast CT scan confirmed situs inversus totalis (Panel C) and evidence of a LAD thrombus (Panel D). The patient was subsequently evacuated to India to undergo secondary PCI.

Initial dextrocardiac ECG (Panel A) and anterior ST-elevation in reversed leads (Panel B). Non-gated contrast CT demonstrating situs inversus (Panel C) and mid-LAD thrombus (white arrowhead, Panel D). Ao, aorta; RVOT, right ventricular outflow tract; LAD, left anterior descending artery; D1, first diagonal branch of LAD.

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