Learning Point for Clinicians

Almost 4% of Afro-Caribbeans possess a mutation associated with the development of cardiac amyloidosis. Around 10% of such patients with heart failure may possess this mutation of transthyretin. Frequently ascribed to race and co-existent hypertension, appearances of left ventricular hypertrophy are often due to hereditary amyloidosis in the Afro-Caribbean population.

Case report

A 68-year-old Afro-Caribbean woman presented with shortness of breath. Past history included bilateral carpal tunnel syndrome. Her father had died in his mid-40s, from heart failure.

The patient was hypertensive (148/103 mmHg) with mild peripheral oedema.

An electrocardiogram showed atrial flutter at 160 beats/min, with low-normal limb lead voltage, and pre-cordial Q-waves (pseudo-infarction pattern). Echocardiography revealed a thickened left ventricular wall (18 mm) and markedly reduced ejection fraction (25%) with moderate diastolic dysfunction. The patient was anticoagulated with warfarin and initially prescribed bisoprolol and digoxin for rate control.

Inflammatory markers and serum amyloid-A levels were normal. Serum and urinary electrophoresis showed no evidence of paraprotein, with normal serum free light chains. Cardiac biomarkers were elevated, with an N-terminal brain natriuretic peptide of 446 pmol/l and a troponin T of 0.04 ng/ml.

Further tests identified heterozygosity for the transthyretin gene mutation V122I (valine substituted for isoleucine at position 122). The bone tracer $^{99}$Tc-dicarboxypropane diphosphonate scan was markedly positive for cardiac based transthyretin amyloid involvement (Figure 1). An $^{123}$I labelled serum amyloid-P component scintigram showed no evidence of visceral amyloid deposition.

Discussion

Afro-Caribbean patients are likely to have ventricular hypertrophy due to racial propensity and a high prevalence of hypertension. Elderly patients may also develop apparent myocardial ‘hypertrophy’ due to senile systemic amyloidosis. Less well appreciated is the fact that almost 4% of Afro-Caribbeans possess a specific mutation of transthyretin, associated with the development of cardiac amyloidosis. Amongst more than 120 recognized mutations of transthyretin, the isoleucine-122 mutation is almost exclusively found in Afro-Caribbeans and is now recognized as the commonest hereditary amyloid cardiomyopathy worldwide.
London clinic reported finding an amyloidogenic mutation in 10% of their Afro-Caribbean patients with heart failure, 89% of whom possessed the isoleucine-122 mutation.3

Until recently, the only available treatment comprised liver transplantation to remove the source of the mutant protein. However, this does not prevent the deposition of wild type transthyretin. The non-steroidal anti-inflammatory diflunisal has been used to stabilize transthyretin in vitro. Tafamadis has recently been licenced to treat transthyretin-related neuropathy in familial amyloid polyneuropathy.4 Human trials of both diflunisal and tafamidis in familial amyloid cardiomyopathy are currently underway. The most recent development has been the use of potent anti-transthyretin small interfering RNA (RNAi therapy); with reductions in transthyretin levels of between 82.3% and 86.8% for both mutant and wild type transthyretin.5

This case is important, highlighting the fact that hereditary cardiac amyloidosis may not be considered in elderly Afro-Caribbean patients. Furthermore, and unlike immunoglobulin light chain amyloidosis, the classic association of a thick heart and a low voltage electrocardiogram is frequently absent. Dungu et al. reported that 44% of their series of 64 patients, with this hereditary transthyretin V122I mutation, had normal or increased voltage and 25% satisfied voltage criteria for left ventricular hypertrophy.6 The recent development in the use of Tc-DPD scintigraphy to identify transthyretin-related cardiac amyloidosis (both mutant and wild types) has proved useful in distinguishing between this and immunoglobulin light chain (Amyloid Light chain [AL]) amyloid deposition. As always, with the amyloid spectrum, an exact diagnosis of amyloid type is essential to determine the correct and very different forms of therapy.

More than 120 mutations of transthyretin have now been reported, of which over 60% are associated with heart involvement. An awareness of this condition, and the emergent therapies, should help a proportion of heart failure patients that have often proved difficult to treat.

Conflict of interest: None declared.

References