A white man with a very African form of hereditary amyloid cardiomyopathy

Introduction

Hereditary amyloidosis is most frequently caused by mutations of the protein transthyretin, with more than 120 already described. The mutation of transthyretin which encodes an isoleucine for valine substitution at position 122 (Val122Iso) usually presents with isolated cardiac disease, occurs in 3–4% of African-Americans and was initially thought unique to this racial population. This article describes this mutation causing severe cardiomyopathy in a white man with a brief discussion of the prevalence and treatment options.

Discussion

The mutation of transthyretin which results in substitution of isoleucine for valine at position 122 (Val122Iso) usually presents with isolated cardiac disease, occurs in 3–4% of African-Americans (Jacobson et al, 1997) and was initially thought unique to this racial population (Jacobson et al, 1997). The Val122Iso mutation is now recognized as the most common transthyretin mutation worldwide. Interestingly, the Vervet monkey is the only other primate known to carry this same mutation, and like man originated in Africa (Ueda et al, 2012). Up to 10% of Afro-Caribbeans with heart failure carry an amyloidogenic mutation, most commonly that encoding the Val122Iso transthyretin variant (Dungu et al, 2012).

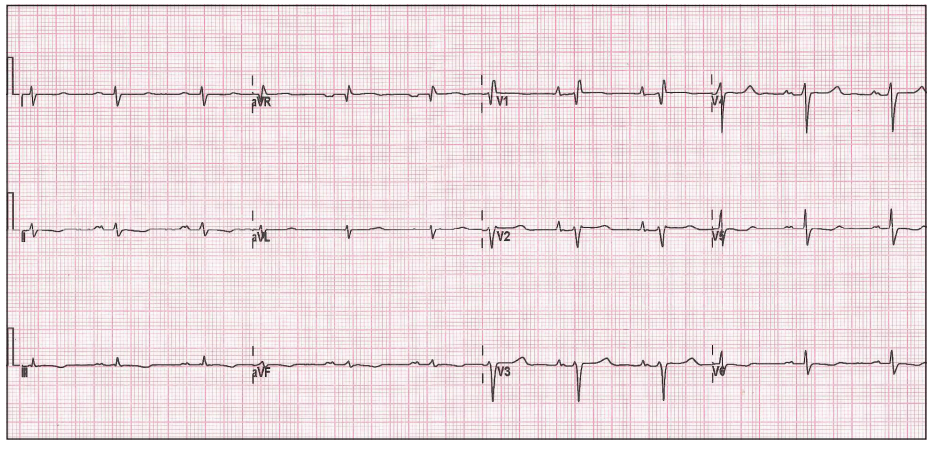
Gillmore et al (1999) described the first white man with this mutation 15 years ago. Isolated cases have since been reported (Hamidi Asl et al, 2001), with one undergoing cardiac transplantation (Ammirati et al, 2012). The UK National Amyloidosis Centre have now seen 129 patients with this mutation, of whom five (3.9%) had no evidence of African ancestry.

Isolated cardiac involvement combined with cardiac uptake on a diphosphonate technetium-99 radioisotope scan and absence of a plasma cell dyscrasia in the current patient made transthyretin-type amyloid highly likely, although senile systemic amyloid, caused by deposition of wild-type transthyretin, needed consideration. Both senile systemic amyloid and familial amyloid cardiomyopathy resulting from transthyretin mutations, such as the one presented here, typically result in cardiac amyloidosis which can be clinically indistinguishable from cardiac AL amyloidosis (previously termed 'primary'). Importantly, the treatment and prognosis

Dr Simon W Dubrey *is Consultant Cardiologist and* **Dr Sarah Ghonim** *is ST3 in Cardiology in the Department of Cardiology, Hillingdon Hospital, Uxbridge, Middlesex UB8 3NN and* **Dr Julian D Gillmore** *is Senior Lecturer in the National Amyloid Centre, Division of Medicine, Royal Free Hospital, London*

Correspondence to: Dr SW Dubrey (simon.dubrey@thh.nhs.uk)

Figure 1. 12-lead electrocardiogram demonstrating low limb voltage (<0.5 mV).



Case Report

A 66-year-old Caucasian man presented with shortness of breath of 12 months' duration and more recent numbness and paraesthesiae in both hands on waking. Electrocardiography confirmed an atrial tachycardia, successfully treated by ablation therapy. An echocardiogram and cardiac magnetic resonance imaging scan were reported as suspicious for amyloid, the latter showing diffuse late endocardial enhancement with gadolinium.

There was no significant past medical or family history of amyloidosis. The patient was still able to ski and exercise regularly.

Warfarin, diuretics and low dose candesartan were prescribed. No other features of cardiac compromise or amyloid 'stigmata' were evident, aside from features of carpal tunnel syndrome.

An electrocardiogram showed low voltage in both limb and precordial leads (*Figure 1*). Repeat echocardiography (*Figure 2*) showed bi-atrial dilatation, concentric biventricular wall thickening with normal cavity size and preserved systolic function (ejection fraction 54%). Features supporting diastolic dysfunction included an E:E' ratio of 13, reduced long axis function and atrial enlargement. A diphosphonate technetium radionucleotide (99mTc-DPD) scan demonstrated myocardial uptake, indicative of transthyretin amyloid. Serum amyloid P scintigraphy showed no additional visceral organ involvement. No serum paraprotein, Bence Jones protein, serum free light chain abnormality or albuminuria were detected. Renal and liver function were normal, while both NT-proBNP and troponin-T were marginally elevated. An abdominal fat biopsy did not reveal amyloid but subsequent sequencing of the transthyretin gene confirmed heterozygosity for the mutation encoding the amyloidogenic Val122Iso variant of transthyretin.

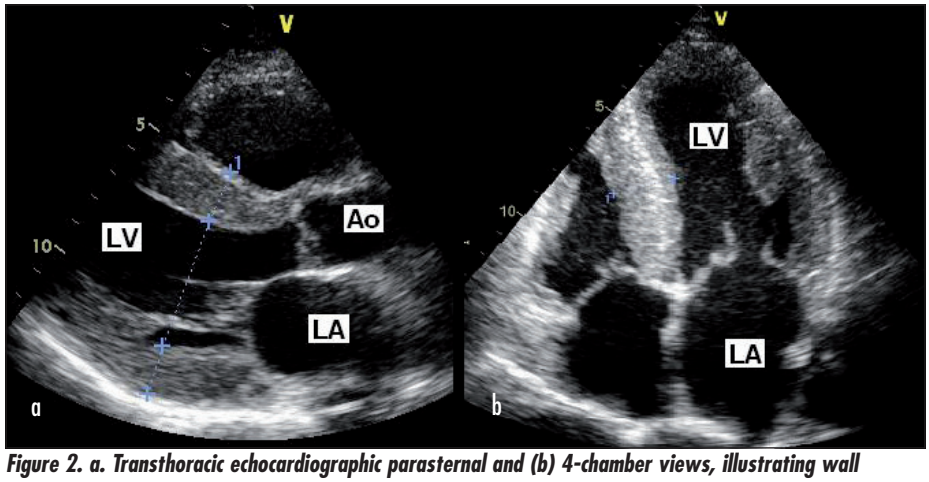


Figure 2. a. Transthoracic echocardiographic parasternal and (b) 4-chamber views, illustrating wall thickening (interventricular septum 2.1 cm) and characteristic features of amyloid cardiomyopathy. Ao = aorta; LA = left atrium; LV = left ventricle.

differ widely between these types of amyloid cardiomyopathy.

This patient will be considered for one of several trials of novel therapeutic agents which are the only means of obtaining disease-modifying treatment. Recent developments involve transthyretin stabilizing molecules, including the non-steroidal anti-inflammatory drug diflunisal (Berk et al, 2013). Trials of tafamadis meglumine, a transthyretin stabilizer that occupies its thyroxine binding site, are already underway for familial amyloid cardiomyopathy (Coelho et al, 2012). Most recently, developments have focused on reducing transthyretin levels in the plasma using small interfering RNA (also called silencing RNA) and anti-sense oligonucleotide technology; agents of this nature are currently undergoing human trials to reduce mutant and wild type transthyretin levels (Ackermann et al, 2012; Coelho et al, 2013).

Conclusions

Historically, cardiac 'hypertrophy' in Afro-Caribbean patients was often ascribed as being the result of a racial feature and/or the effect of hypertensive heart disease. Increasingly, such appearances are now being identified as being a consequence of hereditary amyloidosis, with cardiac involvement, caused by this particular Val122Iso genetic variant. The authors suggest that this specific type of amyloidosis be considered in any patient presenting with a thick-walled restrictive cardiomyopathy, regardless of race. **BJHM**

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LEARNING POINTS

- Patients with no obvious African racial origin are now being identified with this hereditary form of amyloid cardiomyopathy, originally considered exclusive to Afro-Caribbeans.
- In Afro-Caribbean patients with a thick-walled heart consideration should always be given to likelihood of amyloid cardiomyopathy as the aetiology.
- The combination of a thick-walled heart and a low voltage electrocardiogram should always prompt suspicion for amyloid heart disease.
- Diphosphonate technetium-99 scanning has proved useful in the identification of transthyretin amyloid cardiomyopathies