

CASE REPORT

Hereditary cardiac amyloidosis associated with the transthyretin Ile122 mutation in a white man

J D Gillmore, D R Booth, M B Pepys, P N Hawkins

Abstract

An 83 year old white man with atrial fibrillation was admitted to hospital after a cerebral infarct. Echocardiography was characteristic of cardiac amyloid deposition and subsequent tests confirmed amyloidosis of transthyretin (TTR) type, in association with the Ile122 mutation of the TTR gene; this has only been reported previously in African Americans in whom it occurs with an allele frequency of 2%. Haplotype analysis did not suggest a different founder than for the African Ile122 mutation. Cardiac amyloidosis should be considered among elderly patients presenting with cardiac failure and/or arrhythmia, particularly if they are resistant to conventional treatment; if confirmed, it should be followed by precise characterisation of amyloid fibril type. The prevalence of autosomal dominant cardiac TTR amyloidosis in elderly white people is unknown but early diagnosis and supportive treatment may prevent complications among affected family members.

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Cardiac amyloidosis results from the deposition of insoluble protein fibrils in the cardiac interstitium, along the conduction system, and in the vascular subendothelium; it may lead to restrictive cardiomyopathy, arrhythmias, and occasionally angina.

Amyloid deposits may affect any organ of the body but the factors governing their anatomical distribution are poorly understood.¹ The various amyloid types, now classified according to the precursor protein from which the amyloid fibrils are derived, are associated with particular patterns of organ distribution, but considerable variation exists within amyloid types.² Most often, cardiac amyloid deposits consist of fibrils derived from immunoglobulin light chains (AL amyloidosis), wild-type transthyretin (TTR; senile systemic amyloidosis), or variant TTR (familial amyloid cardiomyopathy).³ Occasionally, the rare hereditary apolipoprotein A-I and fibrinogen α chain amyloidosis syndromes may also affect the heart.

A quarter of hearts from patients over 80 years old, examined after death, contain wild-type TTR amyloid deposits. Almost all of the more than 60 known point mutations of the TTR gene increase the amyloidogenicity of the mature protein and are associated with the clinical syndrome of familial amyloid polyneuropathy, characterised by polyneuropathy and/or cardiomyopathy.⁴ The most common TTR mutation associated with hereditary amyloid cardiomyopathy is the Ile122 mutation, which is found with an allele frequency of 2% in African Americans.³ We report the first white patient discovered to be heterozygous for the TTR Ile122 mutation, after his presentation with a cerebrovascular accident as a complication of TTR amyloid infiltration of the heart.

Case report

An 83 year old white man was admitted in July 1997 with left sided weakness. He was in atrial fibrillation and had a left hemiparesis; computed tomography of the brain confirmed a right cerebral infarct. As well as atrial fibrillation, the electrocardiogram showed left axis deviation and pathological Q waves in leads V1–V4. Echocardiography revealed biventricular hypertrophy and a speckled myocardium characteristic of amyloid infiltration. Chest radiography and routine biochemistry were

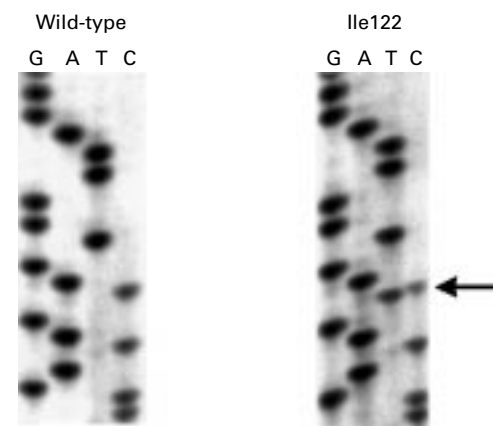


Figure 1 Nucleotide sequence of part of exon 4 of the transthyretin gene from the patient (right) compared with a healthy subject (left). The patient was heterozygous for a single base change, a transition from C to T (arrowed), which alters codon 122 to code for isoleucine instead of valine (antisense strand shown).

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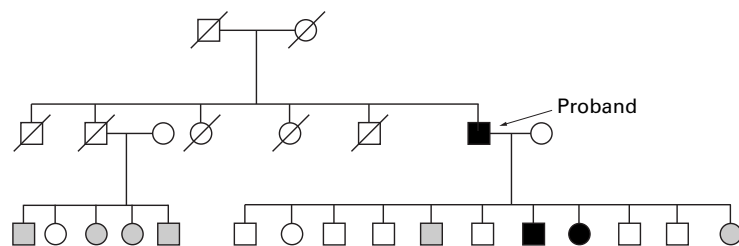


Figure 2 Transthyretin (TTR) genotyping of the present kindred. The arrow indicates the patient. Black symbols, individuals heterozygous for the Ile122 mutation; grey symbols, individuals with wild-type sequence; open symbols, not tested. The two children of the patient who are heterozygous for the TTR Ile122 mutation are currently asymptomatic aged 42 and 40.

normal. The patient was given warfarin and made a good recovery returning to full mobility over the following weeks. Three months later he was well without signs of systemic amyloidosis and complained only of minimal breathlessness on exertion and mild residual left sided weakness. There was no known family history of amyloidosis or African ancestry. There was no evidence of a monoclonal gammopathy and serum amyloid P component scintigraphy did not show significant extracardiac amyloid deposits; a rectal biopsy, stained positively with Congo red, confirmed the diagnosis of amyloidosis.⁵ Immunohistochemical staining of the biopsy tissue with anti-TTR was positive, which confirmed that TTR was the major amyloid fibril constituent. Amplification and sequencing of the patient's TTR gene revealed heterozygosity for the Ile122 mutation (fig 1), which had been described previously only in patients of African descent. Subsequent TTR genotyping of the patient's family is shown in fig 2. The caucasian Ile122 mutation was on haplotype III, as is the African Ile122 mutation.

Discussion

This is the first reported case of familial amyloid cardiomyopathy associated with TTR Ile122 in a white patient. The Ile122 mutation is present in 4% of African Americans and usually results in isolated cardiac amyloidosis from age 60 years onwards, presenting with cardiac failure and/or arrhythmia. Occasionally, there is associated carpal tunnel syndrome, and peripheral polyneuropathy has been reported.³

Amyloid deposits of wild-type TTR are found in 25% of hearts from people over 80 years old, examined after death.⁶ These deposits do not always cause clinical symptoms but the possibility of amyloidosis should be considered when treating elderly patients with heart failure, particularly in cases resistant to conventional treatment with diuretics and ACE inhibitors. The diagnosis of cardiac amyloidosis is suggested by an ECG showing small complexes and/or anterior Q waves in association with concentric left ventricular hypertrophy or restrictive physiology and occasionally a speckled myocardium on the echocardiogram.⁷ However, confirmation of the diagnosis requires biopsy of either the endomyocardium or another affected organ. Once the diagnosis is

confirmed, the use of digoxin, which binds to amyloid fibrils, is contraindicated and overzealous use of diuretics and angiotensin converting enzyme inhibitors should be avoided.⁸

Precise characterisation of amyloid type is important for a number of reasons. Cardiac involvement in AL amyloidosis is associated with a much poorer prognosis than cardiac TTR amyloidosis: the median survival of a patient with significant cardiac AL amyloidosis is 4–6 months; patients with TTR cardiac amyloidosis usually survive for several years after diagnosis.^{9–10} Furthermore, although elderly patients are usually deemed ineligible for liver transplantation or chemotherapy regimens, which are the standard treatments for hereditary TTR and AL amyloidosis respectively, they may be eligible for experimental treatment aimed at reducing circulating TTR levels.

The identification of a mutation of the TTR gene in a patient with TTR cardiac amyloidosis has implications for other family members—for example, in an affected relative, early identification of arrhythmias such as atrial fibrillation may lead to treatment with warfarin and avoidance of digoxin; these measures could prevent complications such as cerebral infarction or sudden death. In addition, at present the age at which cardiac amyloid deposition starts among patients with the Ile122 mutation is unknown.

Finally, the prevalence of the Ile122 mutation in white people is unknown. An estimated 1.2 million African Americans are heterozygous for the mutation, together with an estimated 12 000 homozygotes,³ and although likely to be less prevalent, it may be a significant, as yet unrecognised, cause of heart failure in elderly white people. As the caucasian and African Ile122 mutations are on the same haplotype, the possibility of an ancient common founder cannot be excluded.

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- 1 Pepys MB. Amyloidosis. In: Weatherall DJ, Ledingham JGG, Warrell DA, eds. *Oxford textbook of medicine*, 3rd ed. Oxford: Oxford University Press, 1995:1512–24.
- 2 Husby G. Nomenclature and classification of amyloid and amyloidoses. *J Intern Med* 1992;232:511–12.
- 3 Jacobson D, Pastore R, Yaghoubian R, et al. Variant-sequence transthyretin (Isoleucine 122) in late-onset cardiac amyloidosis in black Americans. *N Engl J Med* 1997;336:466–73.
- 4 Cornwell GG, Murdoch WL, Kyle RA, et al. Frequency and distribution of senile cardiovascular amyloid. A clinicopathologic correlation. *Am J Med* 1983;75:618–23.
- 5 Puchtler H, Sweat F, Levine M. On the binding of Congo red by amyloid. *J Histochem Cytochem* 1962;10:355–64.
- 6 Pitkanen P, Westermark P, Cornwell GG. Senile systemic amyloidosis. *Am J Pathol* 1984;117:391–9.
- 7 Hamer JPM, Janssen S, van Rijswijk MH, et al. Amyloid cardiomyopathy in systemic non-hereditary amyloidosis. Clinical, echocardiographic and electrocardiographic findings in 30 patients with AA and 24 patients with AL amyloidosis. *Eur Heart J* 1992;13:623–7.
- 8 Rubinow A, Skinner M, Cohen AS. Digoxin sensitivity in amyloid cardiomyopathy. *Circulation* 1981;63:1285–8.
- 9 Olsen LJ, Gertz MA, Edwards WD, et al. Senile cardiac amyloidosis with myocardial dysfunction. *N Engl J Med* 1987;317:738–42.
- 10 Skinner M, Anderson J, Simms R, et al. Treatment of 100 patients with primary amyloidosis: a randomized trial of melphalan, prednisolone, and colchicine, versus colchicine only. *Am J Med* 1996;100:290–8.