Cardiac amyloidosis: non-invasive diagnosis and current treatment strategies

Introduction

The systemic amyloidoses are a group of disorders characterized by the deposition of misfolded protein in one or more tissues of the body. The proteins come from a number of origins, but all form fibrillar beta sheet structures that disrupt the structure and function of the tissue.

Cardiac involvement is a key feature of hereditary amyloidosis, a rare, but underdiagnosed, autosomal dominant condition (Lachmann et al, 2002). It results from a mutation in one of several genes, most commonly the transthyretin gene. This encodes a homogenic tetramer produced by the liver which is responsible for transport of thyroid hormones around the body (Kelly, 1998).

This article illustrates a patient with a known mutation whose diagnosis was confirmed using cardiac magnetic resonance imaging, and gives an overview of diagnosis and management of this condition.

Discussion

Infiltration of the myocardium with amyloid fibrils causes a restrictive cardiomyopathy resulting in impairment of filling and later frank systolic dysfunction. The resultant heart is thickened with deposited protein. The ventricular wall may give the appearance of ventricular hypertrophy, but rather than being enlarged the myocytes are restricted by the laying down of amyloid fibrils. Several investigations may elucidate the diagnosis:

Electrocardiogram

Amyloidosis should be considered as a differential in the presence of low voltage complexes and signs of chronic heart failure. Atrial fibrillation is a common finding, as deposition of protein in the atria disrupts electrical conduction; this can also occur within the ventricular conducting system, causing atrioventricular block, although bundle–branch block is unusual (Rahman and Helou, 2004).

Echocardiogram

The ventricular walls typically show a 'granular sparkling' appearance and are thickened with a widened intra-atrial septum, which is highly suggestive of cardiac amyloidosis. Ventricular function is typically preserved late into disease with a normal ejection fraction; this contrasts with light chain (AL) amyloidosis (Dubrey et al, 1997), where

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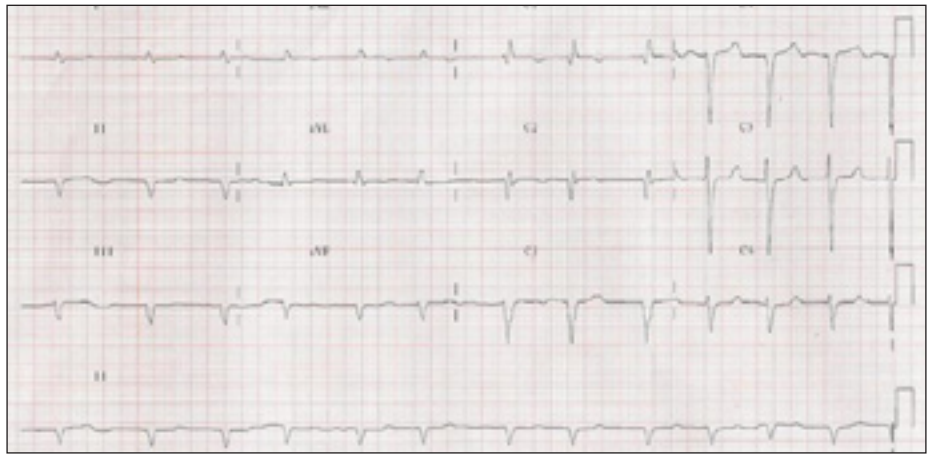
Figure 1. Electrocardiogram showing atrial fibrillation with low voltage complexes and right bundle–branch block.



Case Report

A 70-year-old Irish man presented with several months of breathlessness and lethargy, which had become acutely worse over the preceding week. Exercise tolerance had decreased to around 40 yards, having previously been unlimited. Other symptoms included episodes of dizziness on standing and an occasional cough productive of small amounts of white sputum. There was no previous history of cardiac disease or any regular medication.

Examination revealed pitting oedema up to the mid-thigh and a grade 4 pansystolic murmur consistent with mitral regurgitation. There was decreased air entry and dullness of both lung bases. The abdomen was mildly distended with ascites and there was non-tender, smooth hepatomegaly extending to 4 cm below the costal margin that had been documented 2 years previously.

A 12-lead electrocardiogram (*Figure 1*) demonstrated atrial fibrillation with right bundle–branch block and complexes of less than 0.5 mV in amplitude in the limb leads. Echocardiography showed a left ventricular wall thickness of 16 mm (normal range 7–12 mm), but with preserved left ventricular function. There was mild mitral and aortic regurgitation. Myocardial perfusion imaging demonstrated normal resting left ventricular function with no evidence of inducible ischaemia and an ejection fraction of 60%. A thickened myocardium was noted, as well as mild irregular areas with reduced uptake throughout the myocardium in a non-coronary distribution, that was presumed to be artefact.

Subsequent to these investigations, it was found that echocardiography had been conducted in 2000 after two siblings had been diagnosed with hereditary amyloidosis caused by a mutation in the transthyretin gene. The patient was positive for the mutation, but had no evidence of amyloid disease at this time. The family was part of a large West Irish pedigree with an autosomal dominant alanine substitution in the gene at position 60. The diagnosis was subsequently confirmed using cardiac magnetic resonance scanning (*Figure 2*).

immunoglobulin light chains are themselves toxic to cardiac myocytes and lead to rapid reduction in ventricular function.

Cardiac biopsy

Biopsy may be necessary to confirm the diagnosis in certain subtypes of amyloidosis when superficial biopsy samples do not contain amyloid protein. This is an invasive investigation undertaken only if there is clinically strong suspicion of cardiac amyloid involvement and diagnosis cannot be obtained in any other manner.

Serum amyloid P scanning

This involves the injection of a radioiodine tracer that is specific for the serum amyloid P protein that associates with amyloid fibrils. It allows quantification of amyloid load and mapping of tissue distribution, but is ineffective in scanning hollow organs such as the heart and gastrointestinal tract.

Cardiac magnetic resonance imaging

As described by Maceira and Joshi (2005), cardiac magnetic resonance is increasingly used for detailed non-invasive assessment of cardiac amyloid involvement. Although it is not currently readily available, tertiary centres around the UK are progressively offering it to suitable patients. Typical findings are shown in *Figure 2*.

As the liver is the main source of abnormal protein in hereditary amyloidosis, the mainstay of treatment has traditionally been liver transplantation. However, the disease may continue to progress after transplant if amyloid deposits are present in tissues (Dubrey and Davidoff, 1997). Researchers including Tojo and Sekijima (2006) are investigating drugs such as diflusinal that bind the precursor proteins or their supporting molecules, stabilizing their structure and preventing conformational change, although none of these has proceeded past the development stage as yet.

In established disease, supportive medical therapy is the key to improving quality of life, controlling arrhythmias and reducing symptoms of heart failure. Agents used are typically the same as those for other causes of heart failure and arrhythmias. Digoxin must be used with caution, as reported by Rubinow et al (1981), as it binds irreversibly to amyloid fibrils, resulting in hypersensitivity.

Conclusions

Cardiac magnetic resonance scanning can provide an excellent tool for diagnosis of cardiac amyloidosis in conjunction with other non-invasive investigations, such as electrocardiography and echocardiography. Cardiac amyloidosis should be considered as a diagnosis in patients with evidence of restrictive cardiomyopathy.

Curative options in hereditary amyloidosis are scarce once the disease is well established, so early genetic testing and intervention are necessary in the presence of a strong family history. Referral to a tertiary centre is essential if the diagnosis is suspected. **BJHM**

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Figure 2. a. Four chamber gradient echo cine image of the heart. There is concentric left ventricular (LV) hypertrophy and biatrial enlargement. A large right-sided pleural effusion (PE) is also noted. b. The same plane following the administration of gadolinium contrast agent. There is a classic pattern of near-circumferential subendocardial late enhancement (arrows) of both the left and right ventricle (RV) giving rise to a 'zebra-type' pattern with a relatively dark blood pool. IVS = intra-ventricular septum; LA = left atrium; MV = mitral valve; RA = right atrium; TV = tricuspid valve.