'Green Apple' Heart Failure

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ABSTRACT

We report here the clinical case of an Afro-Caribbean patient referred for complete atrioventricular block for whom a diagnosis of hereditary cardiac amyloidosis was eventually confirmed. Hereditary cardiac amyloidosis is an emerging threat in the Caribbean, and the main goal of this report is to raise the awareness of the disease among physicians.

Keywords: Cardiac amyloidosis, complete atrioventricular block, hereditary, transthyretin related amyloidosis

Insuficiencia Cardíaca y 'Manzanas Verdes'

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RESUMEN

Reportamos aquí el caso clínico de un paciente afrocaribeño remitido por bloqueo auriculoventricular completo, a quien eventualmente se le confirmó un diagnóstico de amiloidosis cardiaca hereditaria. La amiloidosis cardiaca hereditaria está surgiendo como una amenaza en el Caribe, y el objetivo principal de este reporte es elevar el nivel de conciencia de los médicos acerca de esta enfermedad.

Palabras claves: Amiloidosis cardíaca, bloqueo auriculoventricular completo, hereditario, amiloidosis relacionada con transtiretina

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CASE REPORT

A 76-year old hypertensive gentleman was referred to the Department of Cardiology for treatment of complete atrioventricular (AV) block. At the initial physical examination, blood pressure was 115/67 mmHg and heart rate was 45 beats per minute (bpm). Mild oedema was noticed in the lower extremities. Chest X-ray showed enlarged cardiac silhouette, with interstitial oedema. At echocardiography, there was marked concentric left ventricular hypertrophy. The initial

Correspondence: Dr J Inamo, Département de Cardiologie Centre Hospitalier Universitaire de Martinique, BP 632, 97200 Fort de France, Martinique. E-mail: jocelyn.inamo@chu-fortdefrance.fr diagnosis was heart failure triggered by AV block, complicating severe hypertensive heart disease. The patient's condition quickly improved with intravenous diuretics and he was discharged after the placement of a sequential AV pacemaker. He was re-hospitalized one month later for a new onset heart failure. A thorough re-evaluation of the clinical data was then performed. A sharp contrast was noticed between the low QRS amplitude in the frontal derivations and the marked left ventricular (LV) wall thickness on the echocardiography (Fig. 1). A sparkling of the LV walls was also noticed, along with a Doppler restriction pattern of the mitral flow and prominent dilation of both atria. Therefore, cardiac amyloidosis was suspected and additional examinations were performed.

Myocardial 99Tc-dicarboxypropane diphosphonate (DCDP) scintigraphy showed marked myocardial uptake of the tracer (Fig. 2). Late global subendocardial enhancement was noticed at magnetic resonance imaging [MRI] (Fig. 3). Eventually, right ventricle endomyocardial biopsy was performed. Routine haematoxylin-eosin staining showed large areas of amorphous substance between the cardiac myocytes, which were predominantly stained by Congo red,

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^{*}Green apple refers to the aspect of Congo red-stained amyloid tissues illuminated by polarized light. A previous case has been presented by Dr Martin (St Lucia) in 2008 at the annual scientific meeting of the Caribbean Cardiac Society.



Fig. 1: Increased wall thickness contrasting with low QRS voltage, a very suggestive pattern of cardiac amyloidosis.



Fig. 2: Enhanced myocardial uptake of 99Tc-dicarboxypropane diphosphonate.

with a characteristic green refringence in polarized light (Fig. 4). DNA sequencing of the transthyretin gene revealed a *Val122Ile* mutation in the fourth exon. All these results allow a definite diagnosis of hereditary transthyretin cardiac amyloidosis for this patient. His medical management included escalation of diuretic therapy and decrease of vasodilators. Eighteen months after his first hospitalization, the patient has required multiple hospitalizations for heart failure and is still on follow-up.



Fig. 3: Late subendocardial enhancement on magnetic resonance imaging.



Fig. 4: Amyloid deposition (*) in haematoxylin-eosin (A) and Congo red (B), with polarization (C), stained endomyocardial biopsy specimens.

DISCUSSION

Hereditary transthyretin related amyloidosis (ATTR) is caused by mutations in the *TTR* gene, which encodes transthyretin (1). Transthyretin is synthesized primarily in the liver and circulates as a homo-tetramer in the plasma where its main function is to transport thyroxine and retinol. Wild-type and mutated transthyretin can both result in amyloid fibril formation, leading, respectively to senile or hereditary amyloidosis. Cardiac and neurologic diseases are the most frequent clinical features of the disease. Excess deposition of amyloid fibrils in the cardiac tissue may increase wall thickness while resulting in severe organ dysfunction. Such deposit occurs also in a wide range of organs, hence the wide spectrum of the disease. The phenotype varies widely, from an almost exclusive neurologic pattern to an isolated cardiac presentation.

Amyloid deposition in the heart occurs in all the tissues. Myocardial infiltration progressively increases ventricular wall thickness, falsely taken as ventricular hypertrophy. Valve leaflets and right and left atria can also be involved in the process. Marked reduction of LV and right ventricle (RV) cavities and altered filling properties result in significant haemodynamic impairment leading to heart failure, even if systolic function seems preserved. Amyloid deposition in the conduction system causes minor to major conduction defects such as complete AV block.

Neurological manifestations include mainly sensory polyneuropathy. Motor dysfunction usually appears in the final course of the disease. Carpal tunnel syndrome is very frequent. Various autonomic nervous system involvement such as dyshidrosis, constipation, orthostatic hypotension, erectile dysfunction, incontinence or urinary retention may also occur.

Nearly 100 mutations of the *TTR* gene have been described, the most frequent being Val30Met and Val122Ile mutations. Val30Met mutation causes a predominantly neurologic hereditary disease which can be found all around the world, notably in Portugal, Japan and Sweden. Val122Ile is found quite exclusively in patients of African ascent, for whom it is probably the most common cause of cardiac amyloidosis (2). This mutation can be found in 4% of African Americans, and is probably similarly prevalent among Caribbean people who share the same African ancestry. The typical presentation is a severe late onset (sixth or seventh decade) restrictive cardiomyopathy with no or little neurologic involvement.

Diagnosis of cardiac amyloidosis usually relies on the confrontation of various elements. Electro- and echocardiography are very suggestive by showing a contrasting combination of low QRS voltage and marked LV wall thickness. Pseudo-infarction patterns and conduction defects are also common electrocardiogram (ECG) findings. Atrial fibrillation and non-sustained ventricular tachycardia are frequent. Besides increased wall thickness, echocardiography often shows small pericardial effusion, and, typically, LV ejection fraction is maintained when mitral annulus motion is severely reduced, with a restrictive pattern of the mitral Doppler flow.

Magnetic resonance imaging has gained interest in the diagnosis, typically showing a diffuse late enhancement pattern due to gadolinium accumulation. Its importance in screening early, sub-clinical stages of the disease has yet to be confirmed.

Myocardial amyloid infiltration can be visualized by 99Tc-dicarboxypropane diphosphonate scintigraphy, which binds avidly to the amyloid deposits.

Hypertension and its complications such as stroke and heart failure are highly prevalent in the Caribbean. Thus, cardiac ATTR should be systematically screened for in any patient with heart failure and increased myocardial thickness on echocardiography, hence the need to increase the This is awareness of the disease among physicians. especially important since the characteristic ECG-echo findings are frequently missed in Afro-Caribbean persons (3). Another challenge to be faced in the Caribbean is the complexity of the diagnostic make-up, which requires expensive diagnostic tools such as MRI, which may not be readily available in the region. Alternative pathways must be evaluated, and, accordingly, it has been postulated that a combination of a genetic mutation, easy to detect, with suggestive echo imaging, might equate to a positive diagnosis.

In conclusion, cardiac ATTR may be an emerging heart disease in the Caribbean region. While it is a diagnostic challenge to date, effective tools to cure or prevent the disease are sure to emerge in the future.

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