CASE REPORT

Severe heart disease in an unusual case of familial amyloid polyneuropathy type I

Miguel Oliveira Santos\textsuperscript{a,\textdagger}, Dulce Brito\textsuperscript{a,\textsection}

\textsuperscript{a} Faculdade de Medicina da Universidade de Lisboa, Centro de Cardiologia da Universidade de Lisboa (CCUL), Lisboa, Portugal
\textsuperscript{b} Serviço de Cardiologia I, Centro Hospitalar de Lisboa Norte, E.P.E., Lisboa, Portugal

Received 1 September 2012; accepted 3 February 2013
Available online 30 August 2013

Abstract  Familial amyloid polyneuropathy type I (FAP type I) is a rare hereditary systemic amyloidosis caused by the Val30Met mutation in the transthyretin (TTR) gene. The clinical onset and spectrum are variable and depend on phenotypic heterogeneity. Cardiac complications (dysrhythmias and conduction disturbances, cardiomyopathy and dysautonomia) indicate a poor prognosis, even after liver transplantation. We report an atypical case of FAP type I, highlighting the severe cardiac involvement and its complications.

Early diagnosis of amyloid heart disease is increasingly important in the context of several clinical trials of promising new and experimental drugs.

© 2012 Sociedade Portuguesa de Cardiologia. Published by Elsevier España, S.L. All rights reserved.

Doença cardíaca grave numa situação invulgar de polineuropatia amiloidótica familiar tipo-I

Resumo  A polineuropatia amiloidótica familiar tipo-I (PAF tipo-I) é um tipo raro de amiloidose hereditária e sistémica causada pela mutação Val30Met no gene da transtirretina (TTR). O início das manifestações e o espectro clínico podem ser variáveis e dependem da heterogeneidade fenotípica. As complicações cardíacas (disritmias e perturbações da condução, miocardiopatia e disautonomia) ditam um prognóstico mais reservado, mesmo após transplante hepático. É descrito um caso clínico atípico de PAF tipo-I com ênfase no grave envolvimento cardíaco e nas suas complicações.

O diagnóstico precoce de cardiopatia amiloidótica tem assumido relevância no âmbito de vários ensaios clínicos com fármacos experimentais promissores.

© 2012 Sociedade Portuguesa de Cardiologia. Publicado por Elsevier España, S.L. Todos os direitos reservados.

\textdagger  Corresponding author.
E-mail address: migueloliveirasantos@hotmail.com (M. Oliveira Santos).

0870-2551/S - see front matter © 2012 Sociedade Portuguesa de Cardiologia. Published by Elsevier España, S.L. All rights reserved.
http://dx.doi.org/10.1016/j.repc.2013.02.011
Case report

A 66-year-old white woman from Lisbon (Portugal) was being followed in the neurology department due to progressive sensorimotor and autonomic polyneuropathy of 12 years' duration. Physical examination showed tetraparesis, thermal hyposthesia and distal muscle atrophy of the lower limbs. Patellar and Achilles tendon reflexes were abolished. Electromyography revealed severe axonal sensorimotor polyneuropathy.

The most common diagnoses of polyneuropathy were excluded. A fat biopsy showed amyloid deposits. Genetic testing was performed and the Val30Met mutation in the transthyretin (TTR) gene was identified in heterozygosity.

The suspicion of amyloid cardiomyopathy had emerged at age 60, when the patient underwent transthoracic echocardiography (echo) during investigation of anginal pain. The echo findings suggestive of amyloid infiltration included an E/A-wave ratio of 0.6 (Doppler mitral inflow), left atrial (LA) dilatation (end-systolic diameter of 50 mm), mitral-aortic valvular thickening and a small pericardial effusion. Left ventricular (LV) dimensions were normal (50 mm in late diastole), with no hypertrophy and preserved systolic function.

One year later, in order to clarify episodes of syncope and dizziness, 24-hour ambulatory electrocardiographic (Holter) monitoring was performed. Supraventricular premature extrasystoles with compensatory pauses of up to 2.5 s were detected. Four months later, sinoatrial block (with some pauses longer than 4 s) was also identified on Holter.

Due to symptomatic bradyarrhythmia a dual-chamber pacing system (DDDR mode) was implanted, and the patient remained asymptomatic for the next five years.

At the age of 66, she was admitted to the cardiology department in heart failure (HF), NYHA class III. Physical examination revealed atrial fibrillation (AF) with a controlled ventricular rate and anasarca (total weight of 100 kg for a calculated ideal dry weight of about 60 kg). The echo examination showed LV wall thickening (15.11 mm), an enlarged LV cavity (58.47 mm at end-diastole), greater LA dilatation (56 mm) and diastolic transmitral flow with an almost restrictive pattern, with an E/A-wave ratio of 2.39 and deceleration time of 147 ms (Figure 1). Mild to moderate mitral regurgitation was also observed. Mild thickening of the aortic and mitral valves persisted as well as the small pericardial effusion, both findings observed six years previously.

The patient’s anasarca (also associated with nephrotic proteinuria and hypalbuminemia) improved slightly with intravenous administration of albumin plus diuretics, but hemodialysis was needed. She lost 40 kg of body fluids and was transferred to the nephrology department.

The patient had mild and well-controlled systemic hypertension. There was no known family history of FAP type I. Both her parents had died of malignant disease at unknown ages. She has a daughter and a son, both healthy adults.

Discussion

The term ”amyloidosis” covers a heterogeneous group of rare diseases (acquired or inherited) characterized by extracellular deposition of abnormal insoluble fibrils resulting from protein misfolding.1-3 Accumulation of amyloid deposits in various tissues impairs their structure and function.4-5

Currently, there are 27 different types of amyloidosis classified according to their precursor protein.1 They may also be classified as systemic or local based on organ involvement.4-5

A definitive diagnosis of amyloidosis is usually made by biopsy specimen, in which Congo red staining reveals a typical red color under microscopy and apple-green birefringence under polarized light.2,3,6 But determination of the amyloid type is only possible by immunohistochemical techniques.6

The heart is usually affected, as part of systemic involvement.7 The most common systemic amyloidoses with myocardial involvement are acquired monoclonal immunoglobulin light-chain amyloidosis and TTR-related forms.5,6 Under the broad designation of amyloidosis, there are several clinically distinct entities that also require different treatment.5 But the severity of cardiac involvement in all forms is an important prognostic factor and early diagnosis remains a challenge.2

FAP type I is a rare autosomal dominant systemic amyloidosis caused by the Val30Met mutation in the TTR gene.8-11 It was first described by Corindo de Andrade, a Portuguese neurologist, in 1952.11 Higher prevalences in endemic areas of Portugal, Japan and Sweden have been reported.9,10 TTR is a plasma protein synthesized mainly in the liver and to a lesser extent in the choroid plexus and ocular tissues.10,12,13 It acts as a carrier for thyroxine and retinol-binding protein.10,13

A wide phenotypic heterogeneity has been found in FAP type I and is influenced by several factors such as

**Figure 1** Echocardiographic findings at age 66. M-mode revealed a dilated left atrium (56 mm) (A), an enlarged left ventricular cavity (58.47 mm) with wall thickening (15.11 mm) and a small pericardial effusion (B). Doppler showed diastolic transmitral flow with an E/A-wave ratio of 2.39 and a deceleration time of 147 ms (C).
Severe heart disease in an unusual case of familial polyneuropathy type I

...so-branched amyloid deposits. In other cases, small clusters of amyloid fibrils are seen. In keeping with the widespread nature of this familial amyloid disease, peripheral nerve biopsies showed perineurial and endoneurial infiltrates of amyloid fibrils. Although the patient had no known family history of amyloidosis, genetic testing confirmed the presence of the Val30Met mutation in the TTR gene. Her parents died without undergoing genetic screening, so three hypotheses may be considered. First, given the condition’s phenotypic variability, her parents may have died prior to the clinical onset of the disease. If this was the case, they may also have had late-onset disease. Second, the parents may also have been asymptomatic owing to gonadal mosaicism. And third, a de novo mutation may have occurred in our patient.

The patient had sinoatrial block and AF, which are frequent complications of cardiac involvement. Stokes–Adams syndrome related to sinoatrial block was treated successfully with pacemaker implantation. Nevertheless...
severity of amyloid cardiomyopathy as denoted by echo findings – including significant LV wall thickening and changes over time in Doppler mitral inflow pattern – is not typical in this type of amyloidosis. The same is true for the clinical severity of HF, which seems to be associated with amyloid cardiomyopathy and significant diastolic dysfunction. The patient’s anasarca may be explained by a maladaptive response to congestive low-output HF as well as by nephrotic syndrome associated with renal amyloid infiltration.

Conclusions

The condition’s phenotypic heterogeneity, as well as the absence of a known family history, should be considered when FAP type I is a diagnostic hypothesis. This helps to avoid late and inaccurate diagnosis and enables counseling of the family with regard to genetic screening.

Symptomatic improvement and prevention of possible SCD can be achieved in patients with bradyarrhythmias by early pacemaker implantation.

Advances in diagnostic techniques that will allow detection of early signs of amyloid heart disease, together with the development of new therapies, are urgently needed to reduce mortality related to cardiac events in FAP type I patients and to offer them a better quality of life.

Due to its multisystemic nature, patients with FAP type I should be referred to specialized centers capable of providing a multidisciplinary approach.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

11. Andrade C. A peculiar form of peripheral neuropathy; familiar atypical generalized amyloidosis with special involvement of the peripheral nerves. Brain. 1952;75:408–27.


