Review article

Amyloidosis. Also a Heart Disease

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A B S T R A C T

The term cardiac amyloidosis refers to the involvement of the heart as a result of amyloid deposition in heart tissue either in the context of a systemic disease or as a localized form. Several amyloid proteins can produce amyloid deposits in the heart. Each of these amyloidoses has characteristic clinical (cardiac and extracardiac) features, its own course, and a specific diagnosis and treatment. Since cardiac involvement may be the first-manifestation of amyloidosis, the cardiologist may be the first healthcare professional to see the patient and must always consider this diagnosis. In this review, we consider the amyloidosis characteristics that may present with cardiac involvement, from the cardiologist’s viewpoint and in light of our experience. We review in detail when and how to establish the diagnosis and how to treat these patients' cardiac involvement and the underlying amyloid disease.

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Amiloidosis. También una enfermedad del corazón

R E S U M E N

El término amiloidosis cardíaca hace referencia a la afección del corazón como consecuencia del depósito de amiloide en el tejido cardíaco, ya sea en el contexto de una afección sistémica o de una forma localizada. Diversas proteínas proamiloidóticas pueden dar lugar a depósitos amiloide en el corazón. Cada una de las amiloidosis producidas por estas proteínas presenta evolución, diagnóstico y tratamiento específicos, de forma que se presentan de manera clínica (cardíaca y extracardíaca) más característica. Dado que la primera manifestación de los pacientes con amiloidosis puede deberse a la afectación cardíaca, el cirujano cardíaco puede ser el primer profesional que atienda a estos pacientes y debe plantearse este diagnóstico siempre. En esta revisión presentamos, desde el punto de vista del cirujano cardíaco y a la luz de nuestra experiencia, las características de las diferentes amiloidosis que pueden cursar con afectación cardíaca revisando detalladamente cuándo y cómo establecer su diagnóstico. Además, repasamos el manejo terapéutico en estos pacientes tanto en lo referente a la afección cardíaca como a la enfermedad de base productora de la proteína amiloidótica.

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Abbreviations

BMT: bone marrow transplant
HF: heart failure
HTx: heart transplant
LTx: liver transplant
TTR: transthyretin

INTRODUCTION

Amyloidosis is a generic term used to refer to the extracellular deposition of abnormal insoluble fibrils made up of different low-molecular weight subunits (from 5 to 25kDa). These deposits are derived from soluble proteins which, after undergoing changes in the way they are configured, adopt a structure that consists predominantly of anti-parallel folded beta sheets.1

Anatomopathologically, amyloid deposits appear as hyaline material which is stained by Congo red (green refraction under polarized light), thioflavín T (producing an intense yellow-green fluorescent stain), and Alcian blue (green stain), as shown in Figure 1.2

Over 20 proteins are known to be capable of producing amyloid deposits in different body tissues and they lead to a variety of pathologies, such as Alzheimer or prion diseases (Table 1).

Depending on the organs which are affected, amiloidoses can be classified as systemic or localized.3 In systemic forms of amyloidosis, deposits are produced in several organs, vascular walls, and connective tissue and they elicit clinical signs of multi-organ involvement. In localized forms the deposits are confined to a single organ or tissue and as a result their clinical manifestations are limited to the system to which the affected organ or tissue belongs.

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The term cardiac amyloidosis refers to heart involvement as a result of amyloid deposition in heart tissue, either as a systemic amyloidosis (which is most often the case) or a localized form of the condition.

Not all amyloid precursors affect the heart, and their varied nature means that the recognition and treatment of cardiac amyloidosis is by no means a simple task (Table 2).

Given that clinical cardiac symptoms may be the first manifestation of these complex and interesting diseases, the cardiologist is likely to be the first professional to identify these patients and early initiation of treatment depends on his/her skill in identifying the disease and confirming the diagnosis.

Amyloidosis is a complex disease with a family pattern in some cases, and cardiovascular and extracardiac clinical symptoms. In this review we will go over the clinical features of cardiac amyloidosis and the diagnostic strategy to employ in order to recognize and treat it depending on its subtype, from the point of view of the cardiologist.

**AMYLOIDOSIS AS A HEART DISEASE**

Although various types of amyloid can infiltrate the heart, only the senile, secondary (AA), and primary (AL) variants of the disease and some hereditary forms (ATTR, AApO-A, and FibA amyloidosis), can produce significant cardiovascular symptoms.

The cardiac infiltration pattern is similar in all of them and it can affect both contractile function and vascular flow or electrical conduction.

The deposits are distributed as nodular aggregates with ramifications that envelop and isolate myocytes. In the initial phases the deposits cause mild diastolic dysfunction but, as the disease progresses, a thickening of the walls occurs and the relaxation and elasticity of the ventricles is impaired. The increase in pressure which occurs in the more advanced phases leads to a restrictive physiology and considerable dilation of the atria. As the disease progresses, necrosis of the myocytes ensues (partly as a direct toxic effect of amyloid) and interstitial fibrosis develops. As a result of all these phenomena, in the advanced stages of the disease there may be impairment of systolic function.

Ischemia as a result of amyloid infiltration of the microvascular system also contributes to this process. The diffuse infiltration of the microvascular vessels generates several endomyocardial sites of ischemia and microinfarctions. Surprisingly, epicardial arteries are not usually significantly affected.

Deposits in conduction tissue are uncommon, although perivascular fibrosis secondary to ischemia does usually affect the sinus node and the His bundle.

**AMYLOIDOSIS AS A GENETIC DISEASE**

The importance of inheritance in the expression of amyloid diseases has been known for years.8 Some amyloidoses are exclusively due to genetic defects but, in addition, other genetically determined factors probably have an influence in the development of some acquired forms of amyloidosis.

Three types of genetic abnormalities have been identified in relation to amyloid proteins: polymorphisms,9 mutations,10 and genetically determined post-translational modifications.11

Considerable differences have been found in the presentation and clinical course of amyloidosis amongst subjects with the same genetic defect.12 This therefore indicates that environmental factors and disease-modifying genes have an important role in the expression of this disease.

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**Figure 1.** Cardiac biopsies of a patient with hereditary transthyretin cardiac amyloidosis. A, hematoxylin-eosin staining (×200): the amyloid deposits (*) are visible as amorphous material between the myocytes. B, immunohistochemical staining to detect transthyretin (×400) reveals reddish brown deposits surrounding the myocytes. C, thioflavin T staining (×200): yellow-green deposits around the myocytes correspond to deposits of amyloid material. Modified from a paper by García-Pavía et al.,2 courtesy of Dr. C. Salas from the Hospital Universitario Puerta de Hierro, Madrid, Spain.
Table 1
Human Amyloid Proteins

<table>
<thead>
<tr>
<th>Amyloid</th>
<th>Precursor</th>
<th>S/L</th>
<th>Clinical type</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL</td>
<td>Immunoglobulin light chain</td>
<td>S, L</td>
<td>Primary amyloidosis</td>
</tr>
<tr>
<td>AH</td>
<td>Immunoglobulin heavy chain</td>
<td>S, L</td>
<td>Primary amyloidosis</td>
</tr>
<tr>
<td>ATTR</td>
<td>Transthyretin</td>
<td>S, L</td>
<td>Familial senile</td>
</tr>
<tr>
<td>Aβ2M</td>
<td>β2 microglobulin</td>
<td>S</td>
<td>Dialysis-related</td>
</tr>
<tr>
<td>AA</td>
<td>Serum Amyloid A</td>
<td>S</td>
<td>Related to chronic infection and inflammation</td>
</tr>
<tr>
<td>AApoAI</td>
<td>Apolipoprotein A-I</td>
<td>S</td>
<td>Familial, nephropathy, Senile deposit in aortic intima</td>
</tr>
<tr>
<td>AApoAII</td>
<td>Apolipoprotein A-II</td>
<td>S</td>
<td>Familial, nephropathy</td>
</tr>
<tr>
<td>AGel</td>
<td>Gelsolin</td>
<td>S</td>
<td>Familial, nephropathy (Meretoja syndrome)</td>
</tr>
<tr>
<td>Alys</td>
<td>Lysozyme</td>
<td>S</td>
<td>Familial, nephropathy</td>
</tr>
<tr>
<td>AFib</td>
<td>Fibrinogen α</td>
<td>S</td>
<td>Familial, nephropathy</td>
</tr>
<tr>
<td>ACys</td>
<td>Cystatin C</td>
<td>S</td>
<td>Familial, brain haemorrhage (Icelandic)</td>
</tr>
<tr>
<td>AβRI/ADan</td>
<td>AβRI protein precursor (AβRI)</td>
<td>S</td>
<td>Familial, dementia (British and Danish)</td>
</tr>
<tr>
<td>Aβ</td>
<td>Amyloid protein precursor (APP)</td>
<td>L</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>APnP</td>
<td>Prion (PRP)</td>
<td>L</td>
<td>Spongiform encephalopathy</td>
</tr>
<tr>
<td>ACal</td>
<td>Procalcitonin</td>
<td>L</td>
<td>Thyroid C cell tumours</td>
</tr>
<tr>
<td>AAPP</td>
<td>Inlet amyloid polypeptide</td>
<td>L</td>
<td>Insulinomas, DM2 and age</td>
</tr>
<tr>
<td>AANF</td>
<td>Atrial natriuretic peptide (ANP)</td>
<td>L</td>
<td>Age-related atrial amyloidosis</td>
</tr>
<tr>
<td>APro</td>
<td>Prolactin</td>
<td>L</td>
<td>Prolactinomas, age</td>
</tr>
<tr>
<td>AIns</td>
<td>Insulin</td>
<td>L</td>
<td>Local deposits related to insulin pumps</td>
</tr>
<tr>
<td>AMed</td>
<td>Lactadherin</td>
<td>L</td>
<td>Senile deposit in aortic media</td>
</tr>
<tr>
<td>Aker</td>
<td>Keratoepithelin</td>
<td>L</td>
<td>Familial, corneal dystrophy</td>
</tr>
<tr>
<td>ALac</td>
<td>Lactoferrin</td>
<td>L</td>
<td>Corneal amyloidosis</td>
</tr>
<tr>
<td>AβMI</td>
<td>Semenogelin</td>
<td>L</td>
<td>Senile deposits in seminal vesicles</td>
</tr>
</tbody>
</table>

DM2, diabetes mellitus type 2; L, localised; S, systemic.
' Yet to be assigned nomenclature.

Table 2
Amyloidosis Subtypes That Significantly Affect the Heart

<table>
<thead>
<tr>
<th>Amyloidosis type</th>
<th>Protein</th>
<th>Extent affected the heart</th>
<th>Median survival (months)</th>
<th>Usual extracardiac symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary (AL)</td>
<td>Immunoglobulin light chain</td>
<td>50%</td>
<td>13 (4 if HF at diagnosis and if not treated)</td>
<td>Nephropathy, proteinuria, autonomic dysfunction, CTS, neuropathy, macroglossia, purpura</td>
<td>Chemotherapy + BMT</td>
</tr>
<tr>
<td>Secondary (AA)</td>
<td>Serum amyloid A</td>
<td>5%</td>
<td>24.5</td>
<td>Nephropathy, proteinuria, hepatomegaly</td>
<td>Treatment for underlying inflammatory/infectious process</td>
</tr>
<tr>
<td>Hereditary TTR (ATTR)</td>
<td>Transthyretin</td>
<td>Depending on the mutation</td>
<td>70</td>
<td>Neuropathy, autonomic dysfunction</td>
<td>Liver transplant</td>
</tr>
<tr>
<td>Hereditary Apo-II (AApoAI)</td>
<td>Apolipoprotein A-I</td>
<td>Depending on the mutation</td>
<td>No data</td>
<td>Nephropathy</td>
<td>Liver transplant</td>
</tr>
<tr>
<td>Hereditary fibrinogen A (AFib)</td>
<td>Fibrinogen</td>
<td>Rare</td>
<td>No data</td>
<td>Nephropathy</td>
<td>Liver transplant</td>
</tr>
<tr>
<td>Senile (ATTR)</td>
<td>Transthyretin</td>
<td>100%</td>
<td>75</td>
<td>CTS</td>
<td>Support</td>
</tr>
</tbody>
</table>

BMT, bone marrow transplant; CTS, carpal tunnel syndrome; HF, heart failure.

The identification of patients whose amyloidosis is due to a genetic defect is of great importance, as it modifies the treatment and has considerable implications for their relatives.2 Given that the presence of monoclonal bands (monoclonal gammopathy of undetermined significance) is common in the general population, the hereditary causes of amyloidosis must always be taken into consideration and appropriately excluded. In an English reference center, up to nearly 10% of patients with no family history compatible with hereditary amyloidosis and who were diagnosed with the AL form of the disease presented mutations in some of the genes linked to hereditary amyloidosis (primarily genes coding for fibrinogen and transthyretin [TTR]).13

**TYPES OF AMYLOIDOSIS WHICH CAUSE HEART INVOLVEMENT**

As mentioned above, only certain amyloid proteins affect the heart (Table 2). The variable presentation and clinical course of the different variants of amyloidosis mean that they are independent entities.14 The cardiologist must be familiar with
all of them, as, when faced with a patient with amyloidosis, the differential diagnosis will be limited to one of them.

**AL Amyloidosis**

The most common form in developed countries, AL amyloidosis is produced by the deposition of the variable domain, or part of it, derived from a monoclonal form of an immunoglobulin light chain. Practically any dyscrasia that affects B lymphocytes (myeloma, lymphoma, macroglobulinemia, etc.) can produce this monoclonal protein and trigger amyloidosis.

The disease normally appears over the age of 50 years, but it can develop before. Its distribution is similar for both sexes, with a slight predominance in males, depending on the series.\textsuperscript{15,16} Multi-organ involvement is the norm, although in 5% of cases the heart is the only organ clinically affected.\textsuperscript{15}

In 90% of cases there are deposits in the heart, but only 50% of patients have symptoms or signs of cardiac involvement when they are diagnosed.

Cardiac involvement decides the prognosis. The average total survival rate is 13 months and falls to 4 months without treatment if there are already signs of heart failure (HF) when the diagnosis is confirmed.\textsuperscript{17} Even when another organ or system is predominantly affected, cardiac involvement is the worst prognostic factor.\textsuperscript{17}

As the prognosis for AL amyloidosis is substantially worse than for other types of cardiac amyloidosis,\textsuperscript{18} it has been pointed out that circulating light chains might have a direct toxic effect.\textsuperscript{3}

**AA Amyloidosis**

AA amyloidosis involves the deposition of serum amyloid A protein (SAA), an acute-phase reactant, raised levels of which are persistently found in chronic infectious and inflammatory processes.

In Spain it is usually associated with rheumatoid arthritis, familial Mediterranean fever, chronic infections, and inflammatory bowel disease.

Renal involvement is the main symptom and proteinuria and kidney failure are nearly always a feature. The suppression of SAA production can lead to a decrease in amyloid deposits and improved renal function.\textsuperscript{18} Cardiac involvement is rare (5%) and, if it does occur, it is usually mild.\textsuperscript{19} Median survival is slightly over 24 months.\textsuperscript{4}

**Hereditary Amyloidoses**

There are autosomal dominant conditions in which the amyloid aggregates are the result of the deposition of mutant proteins. In the different hereditary forms of amyloidosis, only apolipoprotein A-I, fibrinogen A, and much more frequently TTR can be deposited in the heart.

**Apolipoprotein A-I**

The apolipoprotein A-I (APOA1) gene is located on chromosome 1 and, so far, 16 mutations have been described.\textsuperscript{20} When this gene is involved the clinical manifestations of the disease vary, depending on the type and location of the mutation within the gene.\textsuperscript{20} As well as affecting the heart, the manifestations described include: nephropathy, neuropathy, skin deposits, liver involvement, and laryngeal dysfunction.

**Fibrinogen A**

The fibrinogen alpha chain (FGA) gene is located on chromosome 4 and all the amyloid mutations described to date (10) are found on exon 5. All patients with this mutation present almost exclusively renal involvement. It is rare for cardiac involvement to be significant, although it can be severe.\textsuperscript{21} The way the disease is expressed is highly variable and there may be no family history, which makes diagnosis difficult.

**Transthyretin**

TTR or prealbumin, like apolipoprotein A-I and fibrinogen A, is a protein predominantly synthesized in the liver. The gene which codes for TTR is located on chromosome 18 and over 100 mutations have been described. Its different mutations give rise to different phenotypes.\textsuperscript{22} Neuropathic, cardiac, renal, and ocular (caused by intraventricular deposits) forms have been reported. Cardiac involvement usually occurs over the age of 50 years and seems to be more common in men, which has led to the proposal that being female has a possible protective role against developing this disease.\textsuperscript{16} One of the commonest mutations is Val30Met. This mutation is endemic in regions of Portugal, Sweden, and Japan and its prevalence in these areas can reach 1:600. Although the predominant clinical symptoms are neuropathic, the heart may also be affected.\textsuperscript{22} Other mutations, such as Thr59Lys or Glu89Lys, are involved in predominantly cardiac amyloidosis with severe and limiting symptoms.\textsuperscript{22} From 3% to 4% of black individuals in the United States are carriers of the Val122Ile mutation, which is linked to the development of cardiac amyloidosis in people over 60 years old.\textsuperscript{22} In an extensive autopsy study of senile amyloidosis patients, 23% of the black subjects had this mutation, while it was not present in white individuals.\textsuperscript{23} Although the prevalence of amyloidosis caused by this mutation is unknown, it is probably underdiagnosed due to cardiac hypertrophy in these patients being attributed to hypertensive cardiomyopathy.

**Senile Amyloidosis**

In autopsies performed on elderly patients, amyloid deposits are often found in the atria (formed by the accumulation of atrial natriuretic peptide) and the ventricles (where, in contrast, they are derived from the nonmutant form of TTR). In the vast majority of cases, these deposits are not clinically significant. However, in some subjects there are massive ventricular deposits and they lead to a condition known as senile amyloidosis, which is characterized by enlargement of the heart and HF.

Senile amyloidosis is rare under the age of 60 but can reach a prevalence of up to 25% to 36% in people over the age of 80.\textsuperscript{24} It almost exclusively affects males\textsuperscript{24} and, unlike in other types of amyloidosis, it does not usually affect organs (except for the presence of carpal tunnel syndrome).

Despite the advanced age of the patients and the extensive cardiac infiltration, the HF it causes is easier to control and average survival is 75 months, which is much higher than for other types of amyloidosis.\textsuperscript{14} In any case, the death of these patients is usually related to the progression of HF and the appearance of arrhythmias.

**CARDIOVASCULAR SYMPTOMS**

**Heart Failure**

Although the extracardiac symptoms of amyloidosis are very varied, the most common clinical manifestation is diastolic HF
with congestive signs. Although the pressure in the left ventricle is high, lung edema is uncommon.

**Angina**

Some patients suffer from angina, which is linked to vascular amyloid infiltration. Sometimes the angina is accompanied by jaw claudication.25 As we mentioned above, the affected vessels are normally intramyocardial and the epicardial arteries usually fail to show lesions.

**Syncope or Presyncope**

The presence of syncope or presyncope is common in cardiac amyloidosis and results from the combination of autonomic dysfunction (which is common in these patients) and/or arrhythmias in a heart with little functional reserve. The deposits alter adrenergic regulation of heart rate, as well as baseline regulation and cardiac response to neurohormonal stimulation.26 High blood pressure (HBP) often disappears if the patient was previously hypertensive and postural hypotension secondary to excessive diuresis or autonomic neuropathy develops.15

The appearance of effort syncope has a bad prognosis, as it is a marker of severe restrictive cardiomyopathy and is associated with high mortality in the 3 months following its occurrence, generally as a result of sudden death.27

**Arrhythmias**

Atrial fibrillation is common, owing to the progressive dilation of the atria and restrictive physiology.28 When atrial fibrillation is present, it is associated with a high incidence of thromboembolism.

Although ventricular arrhythmias are common, they do not often cause syncope and they are not usually the presenting symptom of the disease.29

Despite what people tend to think, high-grade atrioventricular blocks and symptomatic sinus node dysfunction are rare.30 Although the sinus node can be affected by deposits, conduction disorders are more typical of the His-Purkinje system and the function of the atrioventricular node is generally preserved.

Although sudden death is common in these patients,29 it is more frequently due to electromechanical dissociation than to the development of ventricular arrhythmias.

**Other Symptoms**

Rarer forms of presentation include cardiac tamponade, as a result of amyloid deposition in the pericardium,31 or the excessive accumulation of amyloid in the interventricular septum, which resembles hypertrophic cardiomyopathy.32 Although dynamic obstruction of the outflow tract of the left ventricle can occur,33 it is rare. It has been pointed out that asymmetrical septal hypertrophy is more typical of patients with hereditary forms than those with AL amyloidosis.32

Lastly, it is of note that a stroke may be the first manifestation in a significant number of cases.34 Most of the time the cause of the stroke is cardioembolic and is caused by the formation of clots in the heart.

**EXTRACARDIAC SYMPTOMS**

Although it depends on the type of amyloidosis, our experience is that another organ is nearly always affected to a greater or lesser extent. The presence of extracardiac symptoms is an important factor when considering the diagnosis of this disease and, as a result, they must be specifically considered.

Many dermatological signs have been associated to cardiac amyloidosis but we might single out cutaneous amyloid deposits, the almost pathognomonic periorbital purpura and capillary fragility (which, together with the deficit of coagulation factors, is responsible for causing cutaneous bruising).25

The presence of macroglossia (in 10% to 20% of AL amyloidosis patients) can cause taste impairment or dysphonia. The combination of macroglossia and periorbital purpura is not a very sensitive indicator (10%-20%), but it is highly specific for establishing the diagnosis.36

Sometimes patients report that their nails break easily and grow slowly, which is also an indication of the systemic nature of the disease.

The neurological symptoms include a history (even a family history) of carpal tunnel syndrome, and sensitive and autonomic polynuropathy.

Discomfort in the right hypochondrium may be due to congestion or amyloid infiltration of the liver.37

Lastly, renal involvement is the norm in certain types of amyloidosis (AA, Afib) and it is common in others (AL). Proteinuria is frequent even in the nephrotic range (>3 g/24 h) and can be confirmed by a simple test. This may be the first factor that leads us to suspect this diagnosis.

**DIAGNOSIS**

**Suspected Amyloidosis**

The cardiologist must consider a diagnosis (Fig. 2) of cardiac amyloidosis when facing any patient with diastolic HF, restrictive cardiomyopathy or ventricular wall thickening in the absence of valvular abnormalities or HBP (or HBP which remits spontaneously).

The presence of extracardiac symptoms and/or a classic family history (neuropathy, carpal tunnel syndrome, HF around the age of 50, etc.) should also orient the diagnosis.

**Cardiac Assessment**

**Echocardiogram**

Using echocardiography, various signs of amyloidosis can be found, although the classic signs (Fig. 3) are only characteristic of advanced phases of the disease.38 The earliest finding is thickening of the left ventricle wall (particularly in the absence of HBP), associated with evidence of diastolic dysfunction.38,39,40 The presence of thickened walls is obviously not very specific, since it is found in other cardiac diseases such as hypertensive cardiopathy, hypertrophic cardiomyopathy, and other infiltrative heart diseases (hemochromatosis, sarcoidosis, Fabry disease, etc.). A “granular” pattern in the myocardium has been proposed as a typical sign of this disease entity39,40, however, its usefulness is limited, as it also appears when there are other causes of hypertrophy.39 It is sensitivity is low,41 and it can only be evaluated in the absence of second harmonic generation. On the other hand, diastolic dysfunction is the echocardiographic finding of this
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degree. Amyloid deposits affect the flexibility of the ventricle, which translates as a decrease in the velocity of blood flow through the mitral valve in the initial phases of diastole (reduction in the E wave) and an increase in the late phase (an increase in the A wave), owing to greater dependence on atrial contraction when the ventricle is filled. A reduction in the E:A ratio is an early sign of the disease. However, as the ventricles become less flexible, there is an increase in the pressure in the atria and the initial filling velocity increases, resulting in a pseudonormalization of the E:A ratio. Finally, in advanced stages, it is normal to find a restrictive filling pattern, with a reduced E-wave deceleration time and low A-wave velocity, together with abnormalities in pulmonary vein blood flow.41

The use of tissue Doppler and strain rate imaging may be of special interest in this disease. With tissue Doppler imaging, we detect a reduction in diastolic speeds in both early and late phases of the disease, which can lead to its identification even when there is practically no ventricular hypertrophy.42 Strain rate imaging allows us to document cardiac disease in its early stages, as it detects impairment of longitudinal contractile function.43 Furthermore, its findings have even been associated with the subsequent development of HF and the possibility of distinguishing different types of amyloidosis.44

Figure 2. Diagnostic procedure for cardiac amyloidosis. APOA1, apolipoprotein A-I; BMB, bone marrow biopsy; BNP, brain natriuretic peptide; ECG, electrocardiogram; FGA, fibrinogen A; HBP, high blood pressure; HF, heart failure; LVH, left ventricular hypertrophy; SAP, serum amyloid P component; TTR, transthyretin. If chronic inflammatory/infectious processes which could produce amyloidosis A have been ruled out.
Other echocardiographic findings include the presence of thickened valves, mild pericardial effusion, biventricular dilation and thickening of the interatrial septum. Although all these signs are described in 40% to 60% of patients (with the exception of thickening of the interatrial septum, which is less common), we are talking about very selected series of patients in advanced phases of the disease. Systolic dysfunction also does not appear until advanced phases.

**Electrocardiogram**

The largest series described to date of electrocardiography (ECG) in patients with biopsy-confirmed amyloidosis showed that only 46% of the patients presented the classic finding of low voltages (QRS amplitude \( \leq 0.5 \) mV in all the limb leads or \( \leq 1 \) mV in all the precordial ones). In fact, electrocardiographic signs of ventricular hypertrophy (defined by Cornell or Sokolow criteria) were found in 16% of the patients. Other findings included the usual presence of a pseudoinfarction pattern (without signs of infarction on the echocardiogram) in 47% of the patients; 76% of the patients showed no conduction disorders, only 3% presented second or third degree atrioventricular blocks (21% were first degree blocks), and 14.5% presented bundle-branch block (in 9% right bundle-branch block and in 5.5% left bundle-branch block). Atrial fibrillation or flutter was only found in 10% of the patients. None of the electrocardiographic variables had prognostic implications in this study. The possibility of combining ECG and echocardiogram findings was evaluated and it was found that the combination of low voltages and ventricular thickening was more sensitive in diagnosing amyloidosis than both tests, conducted separately. In the light of our experience, the prevalence of low voltages is significantly lower in TTR amyloidosis patients than in AL amyloidosis patients (30% vs 50%). This observation underlines the importance of exploring the diagnosis in depth when dealing with any suspected case of amyloidosis, even when typical findings are lacking.

**Magnetic Resonance Imaging**

Magnetic resonance imaging (MRI) allows excellent morphological assessment (it is especially useful when there are technical limitations in echocardiographic images). It offers high reproducibility and the added advantage of enabling us to perform scans using the late gadolinium enhancement technique (Fig. 4). Amyloid deposition specifically affects the kinetics of gadolinium distribution between the blood and the myocardium. Thus, after the administration of gadolinium there is a greater shortening of the subendocardial T1 and of the difference between the T1 signal of the subendocardium and the blood. This smaller difference between the subendocardium and the blood is believed to reflect the rapid uptake of gadolinium by the amyloid deposits in the myocardium and its rapid blood clearance. The pattern of gadolinium uptake in patients with cardiac amyloidosis was initially described as subendocardial and general (without being confined to one coronary region, as occurs in ischemic cardiopathy). It has subsequently been demonstrated that the pattern of gadolinium uptake can also be patchy, localized, or transmural and that there are even patients, who, despite having cardiac amyloid deposits, show no gadolinium uptake. It is also worthy of mention that the selection of the T1 inversion time may be particularly difficult in certain cases and that, despite employing multiple T1 sequences, the myocardial signal cannot be properly eliminated, which prevents the determination of myocardial gadolinium uptake pattern. Some studies have associated the general and subendocardial uptake patterns with more advanced phases of the disease. In fact, although the diagnostic role of MRI has not been entirely established, the coexistence of this “typical” uptake pattern together with the demonstration of amyloid in another organ can now be interpreted as synonymous with cardiac amyloidosis and, therefore, cardiac biopsy can be avoided. Unfortunately, we still do not know the role that MRI may have in diagnosis during the early phases of the disease. As for the prognostic role of MRI, it does not seem that the presence and extension of gadolinium deposits influence the course of the disease in these patients but larger studies are needed, as it has been indicated that other techniques, such as T1 mapping, might be able to better characterize the amount of interstitial amyloid and offer important prognostic information.

**Confirmation of the Diagnosis of Cardiac Amyloidosis**

The confirmation of the diagnosis of cardiac amyloidosis requires the demonstration of amyloid deposits in a biopsy, although the latter need not necessarily be a cardiac biopsy. If there are typical echocardiographic signs and amyloid deposition is demonstrated in other tissues, the diagnosis of cardiac amyloidosis can be regarded as valid.

Other tissues, which are more accessible than cardiac tissue and are routinely used, include rectal mucosa (sensitivity 75%-85%) and abdominal fat tissue aspirate, which is even more sensitive (84%-88%) without risk of bleeding or perforation.
Like other centers, we have sometimes used a salivary gland biopsy with excellent results, even in patients with a negative abdominal fat biopsy.

If the biopsy of other tissues is negative and the suspicion of cardiac amyloidosis persists, a cardiac biopsy is necessary. Four endomyocardial samples ensure 100% sensitivity for the detection of the disease.

**Diagnosing the Type of Amyloidosis**

Given that the prognosis and, in particular, the treatment of this disease depend on the type of amyloidosis, once the diagnosis of cardiac amyloidosis has been confirmed, it is essential to know what type of amyloidosis we are going to treat.

There are different immunohistochemical and immunofluorescence techniques to enable us to distinguish the type of amyloid material that we are dealing with, although they are not available in all centers and, when they are, they do not usually include unusual subtypes of hereditary amyloidosis. Neither can they distinguish the two types of amyloidosis as a result of TTR deposition (senile and hereditary TTR amyloidosis), for which we will need to resort to genetic analysis to rule out certain mutations.

If it has not been possible to determine subtype in the biopsy, AL amyloidosis must be ruled out by excluding the existence of a dyscrasia that produces light chains. To do this we recommend serum or urine immunofixation rather than electrophoresis, given that the amount of paraprotein is likely to be small and immunofixation is more sensitive. Kits for detecting light chains in plasma are even more sensitive (10 times more than immunofixation). These kits provide a quantitative test, which measures concentrations of kappa and lambda free light chains (normal value: 3.3–19.4 and 5.7–26.3 mg/dl, respectively) and the kappa/lambda ratio (normal value: 0.26–1.65). As light chains are excreted through the kidneys, levels of both will be raised if the kidneys are affected, but it is the kappa/lambda ratio value that will tell us if there is monoclonal production of one of them. A kappa/lambda ratio of <0.26 indicates the existence of a clonal lambda-chain-producing population (which is most commonly found) and a >1.65 ratio indicates a kappa-producing population. It has been demonstrated that the combination of an abnormal kappa/lambda ratio and a positive immunofixation reaction has a sensitivity of 99% for diagnosing AL amyloidosis.

In these cases, a bone marrow biopsy will give us the final answer as to which blood dyscrasia is producing the paraprotein.

It is important to remember that up to 10% of subjects over 70 years of age may have a monoclonal band in an immunofixation assay (monoclonal gammopathy of undetermined significance). The kit for detecting plasma light chains will deliver a normal result in these cases and other tests will have to be performed to exclude other forms of amyloidosis (including DNA analysis to distinguish hereditary and senile forms).

Nuclear tests merit one final comment. Traditionally, scintigraphy has been employed in specialized centers to detect the serum amyloid P component (SAP), in order to evaluate the systemic extension of amyloid deposits and even to monitor response to treatment. Given that labelled SAP is not commercially available, that this technique is not very sensitive in patients with TTR amyloidosis and that it does not enable us to describe
significant renal involvement with a decrease in the concentration of albumin as a result of the nephrotic syndrome, very high doses of diuretic drugs may be necessary. Weight control and daily regulation of water balance (adjustment of diuretic drugs depending on variations) is very important in these patients so that hospital admissions can be prevented.

There is no data on the use of betablockers, but, given that these patients may have autonomic neuropathy, they may cause low blood pressure and bradycardia.

Angiotensin-converting enzyme inhibitors and angiotensin II-receptor blockers are usually poorly tolerated (except in senile amyloidosis) and must be used with care, since they can cause severe hypotension even at low doses (also found in relation to autonomic neuropathy).

Digoxin and some calcium antagonists bind to amyloid deposits, so their administration is complicated because it is very difficult to control their concentrations. As a result of digoxin binding to amyloid deposits, digitalis intoxication may occur even at normal serum concentrations.

Anticoagulant therapy must be initiated if the echocardiogram shows blood clots in the heart, atrial fibrillation, or a lack of atrial contraction. Some authors recommend anticoagulant therapy systematically if the transmitral A wave velocity is $<20$ cm/s.

Amiodarone is usually well tolerated if a decision is taken to use it to try to maintain sinus rhythm.

Although sudden death is common, it appears to be more associated with electromechanical dissociation than with ventricular arrhythmias, so it is not clear whether defibrillators are useful in this population. In the largest published series (19 defibrillator recipients) only 2 subjects received appropriate electric shocks, while there were 6 cases of sudden death as a result of electromechanical dissociation (one in a patient who had previously received a suitable electric shock.)

When a pacemaker is indicated, the general recommendations must be followed. However, given that in these patients other coexisting factors exacerbate episodes of low cardiac output (autonomic neuropathy and hypoalbuminemia), the threshold for implanting these devices is usually very low.

Figure 5. $^{99m}$Tc-DPD scintigraphy in a patient with transthyretin amyloidosis. There is intense radiotracer uptake by the heart and attenuated bone uptake.

deposits in dynamic structures like the heart, its usefulness in cardiac amyloidosis is limited.

$^{99m}$Tc-DPD scintigraphy has been proposed as an interesting technique for distinguishing between cardiac deposits of TTR amyloid and those found in AL amyloidosis. The hearts of TTR amyloidosis patients (albeit hereditary or senile) would take up $^{99m}$Tc-DPD, while those of AL amyloidosis patients would not (Fig. 5). After several years applying this technique, we have found that when the uptake is abundant or absent it does enable us to distinguish the two etiologies, but up to a third of AL amyloidosis patients show a modest cardiac uptake.

TREATMENT

The treatment of cardiac amyloidosis has two facets: on the one hand, the treatment of cardiac symptoms and, on the other hand, the treatment of the underlying disease which produces the amyloid protein.

Cardiac Treatment

The basis of cardiac treatment is the administration of diuretic drugs to control congestive symptoms. If the patient shows

Treatment of the Underlying Disease

AL Amyloidosis

Definitive treatment of AL amyloidosis involves the administration of chemotherapy designed to eliminate or control the dyscrasia that produces the amyloid paraprotein. Chemotherapy can stop the formation of amyloid and lead to the reduction of deposits in many patients. Various regimes are used in AL amyloidosis patients, including treatments that imply the use of new drugs like rituximab or bortezomib. Intensive therapy with high doses of melphalan and a bone marrow transplant (BMT) is the treatment of choice in AL amyloidosis, although it is associated with a high mortality rate (10%-25%). Cardiac amyloidosis is one of the major factors that determines whether response to this treatment is satisfactory, so we believe that patients with decompensated HF, an ejection fraction $<40$% or systolic blood pressure $<90$ mmHg should not be subjected to a BMT. Furthermore, patients with significant involvement of two or more organs have high morbidity and mortality rates and, consequently, they do not seem to be good candidates for this procedure. In our opinion, given the complexity of these patients, to achieve optimal management it is essential that they are treated in centers with plenty of experience, where there is close collaboration amongst different specialists.
Hereditary Amyloidoses

In these diseases the only effective procedure for treating the source of amyloid protein production is liver transplantation (LTx). Since the first LTx was performed on a patient with hereditary TTR amyloidosis in 1991, more than 700 of these transplants have been performed. The result is usually good and the liver of these patients can be employed for LTx to suboptimal recipients (domino transplantation). Unfortunately, it has been confirmed that a domino transplant can lead to the development of amyloidosis in the recipient. In families with various members who have suffered from cardiac amyloidosis and in which other members are carriers of the mutation, we have encountered problems in establishing the optimal time for performing LTx to prevent irreversible cardiac involvement. The opinion of more experienced centers is that LTx should not be performed until there is significant clinical involvement of an organ or system.

AA Amyloidosis

The treatment of the underlying inflammatory/infectious disease in AA amyloidosis reduces plasma concentrations of SAA and spectacularly improves prognosis. The new biological drugs (tumor necrosis factor and interleukin 1 inhibitors) suppress the acute response in patients with autoimmune diseases and prevent the development of AA amyloidosis. Colchicine treatment in patients with familial Mediterranean fever also prevents the disease from developing.

Heart Transplantation

When cardiac involvement is very severe, a heart transplant (HTx) and ventricular support devices are the only options that can significantly prolong the survival of these patients. However, ventricular support devices have rarely been used in this clinical situation and HTx has been performed sporadically, given the possibility of the disease progressing to other organs and the recurrence of amyloidosis in the graft.

Although many of the transplant centers in the world reject these patients, this is a feasible option if it is confirmed that significant amyloidosis only affects the heart.

In patients with AL amyloidosis and confinement of the disease to the heart (who would not be able to undergo a BMT), HTx followed by high-dose post-transplant chemotherapy and BMT has been performed successfully. Although 1-year survival in some series is nearly 80%, given the difficult management of immunosuppression during the BMT and other complications, we think that this therapy should be performed only in experienced centers.

In the case of familial amyloidosis, if HTx is considered it should be combined with LTx, which could be performed at the same time or after the HTx. However, although it has been pointed out that mutant cardiac amyloid deposits could act as native protein “binders,” we believe that there is insufficient evidence for supporting simultaneous liver and heart transplantation, as it adds significant risk and almost the only benefit that it affords is logistical.

In 2009 a report was published on the Spanish experience of HTx in amyloidosis patients from 1984 to 2008. During this period, 25 patients (0.4% of the total number of HTx) underwent a transplant for amyloidosis. Thirteen of them had AL amyloidosis, 10 hereditary TTR amyloidoses, and 2 AA amyloidosis. Five of the 10 ATTR patients underwent LTx, 3 died before the operation and 2 did not undergo any transplant procedure. The acute mortality (first month post-HTx) in the amyloidosis patients was no different from that of the general group, but chronic survival was substantially lower (36% vs 64% at 5 years). With respect to subgroups, ATTR patients showed the best prognosis, although this was probably influenced by the fact that only 3 patients with AL amyloidosis underwent a BMT.

New Therapies

Various molecules which affect amyloid deposits have been presented in recent years as potential treatments for these patients. Some of them exert their effects by eliminating the SAP component of amyloid deposits, with the aim of reducing amyloid aggregates and facilitating their elimination. Studies to evaluate the dose and tolerability of some of these molecules are currently underway.

Another promising approach is the stabilization of the TTR molecule to avoid its abnormal folding and its deposition by administering diflunisal or flufenamic acid (anti-inflammatory drugs which stabilize the tetrameric form of TTR) or new molecules (Fx-1006A). An international trial on diflunisal (http://clinicaltrials.gov/show/NCT00294671) has now been launched for patients with familial TTR amyloidosis, but only patients with neuropathic but no significant cardiac involvement can be included. Recently, several trials evaluating the effectiveness of Fx-1006A in patients with neuropathic or cardiac disease (only patients with Val122Ile mutation or senile form) have been completed. The results have not been published yet.

CONCLUSIONS

Cardiac amyloidosis is a condition which includes a range of diseases, depending on the amyloid precursor subtype. It may be confined to a particular organ or system but more often affects other organs and systems. Given that the cardiologist is likely to be the first professional to confront this disease, he or she must be familiar with the different subtypes of amyloidosis which can affect the heart and should consider the diagnosis of this entity in all patients with symptoms compatible with the disease.

Although no noninvasive test is 100% diagnostic, the combination of a family or clinical (cardiac and/or extracardiac) history and compatible echocardiographic findings and ECG abnormalities make this diagnosis highly probable.

Early diagnosis is essential in some forms of amyloidosis (AL and AA), as treatment can arrest and even reverse the development of the disease. The correct identification of hereditary forms of amyloidosis is also crucial to planning adequate treatment and proper assessment of family members.

Currently, new therapies designed to stabilize amyloid precursors and eliminate deposits are being investigated.

CONFLICTS OF INTEREST

None declared.

REFERENCES


