Cardiac Amyloidosis: Heterogenous Pathogenic Backgrounds

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Abstract

Cardiac amyloidosis is a fatal disorder which develops on the basis of the different pathologic conditions in systemic amyloidosis: the most common underlying disease is immunoglobulin light chain-derived primary amyloidosis and the next is transthyretin-related hereditary amyloidosis; the latter disorder, typically represented by familial amyloid polyneuropathy, was long regarded as an endemic disease. However, this disorder has now been shown to involve a highly variable clinical picture due to a large number of transthyretin gene mutations, and many patients with diverse ancestors suffer from severe cardiac amyloidosis. Additionally, senile systemic amyloidosis is now noted as a cause of cardiac dysfunction in elderly individuals. Echocardiogram and myocardial technetium-99m-pyrophosphate scintigraphy can provide characteristic findings. Immunohistochemistry on tissue amyloid, biochemical analysis of serum and urine proteins, and DNA sequencing are usually employed to determine the disease-related amyloid fibril protein. Although systemic amyloidosis has become treatable, the prognosis of each patient who received up-to-date and effective, but nevertheless stressful, therapy depends on the severity of cardiac involvement by amyloid deposition. (Internal Medicine 43: 1107–1114, 2004)

Key words: cardiac amyloidosis, amyloid, cardiomyopathy, secondary myocardial disease

Introduction

Cardiac involvement by marked amyloid deposition is referred to by the term “cardiac amyloidosis” or “amyloid heart disease”. This disorder is hemodynamically classified as restrictive cardiomyopathy (1), and clinically intractable heart failure with or without serious types of conduction block appears. Cardiac amyloidosis commonly occurs in the different forms of amyloidosis, the vast majority of which involve systemic organs (2). It is well known that cardiac amyloidosis is the most serious complication in the amyloidosis patients, even though the clinical manifestations of systemic amyloidosis vary considerably on the basis of diverse phenotypes. Amyloidosis was long considered to be an incurable disease, but during the past 10 years new therapeutic approaches have succeeded in halting the progression of the disease in a few forms of systemic amyloidosis (3, 4), and some patients showed apparent clinical improvement. When we consider the indications for these promising therapies for amyloidosis patients, the severity of cardiac amyloidosis has become a critical determinant.

Here, I review the current knowledge on cardiac amyloidosis, focusing on the heterogenous pathogenic backgrounds.

Classification of Amyloidosis

Amyloidosis is now classified into many different forms on the basis of the chemical nature of its amyloid precursor protein (5). Representative systemic amyloidoses consist of immunoglobulin light-chain (AL)-derived primary amyloidosis, reactive (secondary) AA amyloidosis, transthyretin (ATTR)-related hereditary amyloidosis and β2-microglobulin (Aβ2M)-derived dialysis-related amyloidosis (Table 1). Among these four the most frequent underlying disorder that produces cardiac amyloidosis is primary AL amyloidosis and the next is ATTR type hereditary amyloidosis, while the remaining two forms rarely produce this cardiac complication (2). Recently, senile systemic amyloidosis, which was previously called senile cardiac amyloidosis, has been noted to cause cardiac amyloidosis in elderly individuals (6).

To make a correct diagnosis, proven amyloid deposition in biopsy specimens is an initial step and immunohistochemical staining with antibodies to diverse amyloid fibril proteins is necessary for the classification of the different forms of amyloidosis (7). Additionally, gene analysis of amyloid precursor proteins is required in hereditary amyloidosis (8) (Fig. 1).
**Table 1. Characteristics of the Four Major Types of Systemic Amyloidoses**

<table>
<thead>
<tr>
<th>Type</th>
<th>Fibril composition</th>
<th>Precursor protein</th>
<th>Underlying disorders</th>
<th>Clinical features</th>
<th>Laboratory findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL (primary)</td>
<td>Monoclonal immunoglobulin light chain</td>
<td>(\lambda) or (\kappa) light chain (ratio of (\lambda) or (\kappa), 3:1)</td>
<td>Plasma cell dyscrasia</td>
<td>Cardiomyopathy nephropathy hepatomegaly shoulder-pad sign carpal tunnel syndrome</td>
<td>M-proteinemia, Bence Jones protein in urine</td>
</tr>
<tr>
<td>ATTR (familial)</td>
<td>Transthyretin</td>
<td>Variant forms of transthyretin</td>
<td>Inheritance</td>
<td>Peripheral and autonomic neuropathy, cardiomyopathy, vitreous opacities</td>
<td>Gene mutations of transthyretin</td>
</tr>
<tr>
<td>AA (reactive)</td>
<td>Amyloid A protein</td>
<td>Serum amyloid A protein (SAA)</td>
<td>Chronic inflammatory disorders</td>
<td>Nepropathy, hepatomegaly gastroenteropathy</td>
<td>Elevated levels of SAA, CRP in serum</td>
</tr>
<tr>
<td>A(\beta)M</td>
<td>(\beta)2 microglobulin</td>
<td>(\beta)2 microglobulin</td>
<td>Long-term hemodialysis</td>
<td>Osteoarticular disorders bone cysts, carpal tunnel syndrome</td>
<td>Elevated levels of (\beta)2 microglobulin in serum</td>
</tr>
</tbody>
</table>

**Diagnosis of Cardiac Amyloidosis**

Cardiac amyloidosis causes intractable arrhythmia, conduction blocks and congestive heart failure, and the patients with this disorder show characteristic electrocardiogram (ECG) and echocardiographic findings: the abnormal ECG consists of low voltage in the standard limb leads and QS pattern in the right precordial leads (a healed antero-septal myocardial infarction pattern) with or without conduction blocks. On echocardiogram marked symmetrical thickening of ventricular walls and ventricular septum, normal or decreased left ventricular internal dimensions and reduced left ventricular diastolic function are seen, usually accompanied by hyperrefractile myocardial echoes (the so called granular sparkling appearance) (9, 10) (Fig. 2A and B). Myocardic technetium-99m pyrophosphate (Tc-99m-PYP) scintigraphy is also valuable (11, 12) (Fig. 2C): this isotope may bind to amyloid fibril-associated calcium molecules, producing a positive shadow in amyloid heart. Demonstration of amyloid deposition on biopsied tissues is clinically definitive: endomyocardial biopsy is not always required, alternatively biopsy of gastric and rectal mucosa, skin, and aspirated abdominal fat tissue is recommended. At autopsy the cardiac weight is considerably increased (mean weight \(\geq 500\) g), showing symmetrical thickening of the ventricular septum and left ventricular free wall with rubbbery consistency and a waxy appearance (13).

**AL Systemic Amyloidosis**

AL systemic amyloidosis is caused by deposition of amyloid fibrils, the precursor of which is the N-terminal portion of immunoglobulin light chain. This abnormal protein (M-protein) is produced by plasma cells with a monoclonal proliferative process (14). AL amyloidosis in association with multiple myeloma can be distinguished from primary AL amyloidosis by a combination of the following three criteria: i) the percentage of plasma cells (>20%) and their immature appearances on bone-marrow biopsy; ii) the amount of monoclonal serum gammopathy; and iii) the presence of lytic skeletal bone lesions (15).

The organs most commonly involved are the heart and the kidney, either individually or together. The clinical features of this disorder were reported on the basis of two large US series (15, 16). Median age at presentation in Boston University’s series was 59 years and that in Mayo Clinic’s was 64 years. Both sexes were almost equally affected. At the time of definitive diagnosis 15 to 20\% of the patients suffered from cardiac amyloidosis with congestive heart failure, and an abnormal echocardiogram indicating cardiac involvement was seen in almost two-thirds of these. Certain clinical manifestations frequently coexist: nephrotic-range proteinuria (\(\geq 3.0\) g/day) occurred in more than 40\% of the patients, and carpal tunnel syndrome, which often preceded a diagnosis of amyloidosis by several years, was seen in about 28\% of them. Low blood pressure and postural hypotension were commonly present. The median duration of survival from diagnosis was 1.08 (0.83–1.25) years, but that in patients with congestive heart failure was 0.75 (0.59–1.00) years, which was significantly shorter when compared to patients without severe cardiac involvement (2.34: 1.58–2.92 years) (15). Echocardiographic or Doppler flow parameters, such as shortened deceleration time and increased early diastolic filling velocity to atrial filling ratio, were shown to be predictors of cardiac death in patients with this disease (17, 18). It has been also proposed that integrated backscatter (19) and tissue Doppler (20) ultrasonic images obtained from amyloid-involved myocardium can provide useful prognostic information. Recently, serum levels of brain natriuretic peptide (BNP) (21), N-terminal pro-BNP (22) and cardiac
Troponins (23) were reported to be very sensitive biomarkers in predicting the survival of AL amyloidosis patients with cardiac amyloidosis.

The previous treatments for AL amyloidosis, including the oral administration of colchicine or melphalan alone, and a regimen with combined prednisolone and colchicines, did not have any significant effects on the survival of patients (24). However, during the past 10 years high-dose intravenous melphalan therapy with stem-cell transplant rescue has been employed in US and European institutes, producing an apparent improvement in patients' conditions (25–28): in the Boston Medical Center 312 patients underwent this transplant, resulting in an overall treatment-related mortality of 13% and a complete hematologic response rate of 40%. With a median follow-up of 4 years 54% of the treated patients remain alive (29). However, the patients with severe cardiac amyloidosis are not tolerant for this effective treatment because of cardiac toxicity by chemotherapy and corticosteroid-induced over-hydration. In Japan we started high-dose melphalan with auto-peripheral blood stem cell trans-
plantation in 2001 (30, 31) and more than 10 patients have been treated as such (32). To reduce treatment-related death, our Japanese criteria (32) for the selection of patients pay special attention to cardiac function evaluated by echocardiography (Table 2). A few US patients underwent cardiac transplantation for severe cardiac amyloidosis, but their postoperative courses were unsatisfactory (33).

**Hereditary Amyloidosis**

Most patients with hereditary amyloidosis are characterized by the presence of peripheral somatic and autonomic neuropathy and thus, familial amyloid polyneuropathy (FAP) has been idiomatic used for this disorder. FAP used to be considered a disease peculiar to endemic areas and there are four well-known endemic foci of this disease in the world: Oporto in Portugal (34), the northern part of Sweden (35), and Arao (36) and Ogawa (37, 38) in Japan. However, during the past 20 years a number of FAP families have been found in non-endemic areas (39), and it is now recognized that FAP exists in many nations worldwide.

An amyloid precursor in FAP is a variant form of transthyretin (TTR) and in nomenclature the term “ATTR type FAP” has been recently employed (5). All TTR variants which lead to the formation of amyloid fibrils are accompanied by one amino acid substitution. To date, more than 100 mutations have been identified as a causative gene abnormality in ATTR type FAP (40). The clinical phenotype of this...
The disease seems to vary considerably on the basis of these many TTR mutations, but the most common one, involving the substitution of methionine for valine at position 30 (Val30Met), causes the classic phenotype of FAP, showing polyneuropathy that starts in the legs and severe autonomic dysfunctions. The clinical concept of ATTR type FAP is conventionally divided into two groups (39): Val30Met ATTR and non-Val30Met ATTR types and, in what follows cardiac involvement in FAP is therefore described according to this classification.

In the Val30Met ATTR type it was previously thought that, although the patients in endemic areas showed a high incidence of various ECG abnormalities with conduction disturbances, which frequently required the implantation of a pacemaker, they rarely suffered from cardiac amyloidosis with congestive heart failure (41–43). Postmortem examinations reported that amyloid deposition on the myocardium was localized to the subendocardial area including the conduction system (38). However, it has been recently noted that some FAP patients with Val30Met ATTR who developed the disease at a later age also suffered severe cardiac amyloidosis with congestive heart failure, and most of them originated from nonendemic areas (44–46): there were more than 50 kindreds with Val30Met ATTR previously reported from nonendemic areas in Japan (47). It is well known that in this disease the age of onset differs greatly between patients in endemic foci and those in nonendemic areas (39, 47): the age of onset in the vast majority of the former patients is the late twenties to early forties, and the early fifties to late sixties in the latter. It has been strongly suggested that aging is an important factor in causing severe deposition of amyloid on the myocardium in patients with ATTR type FAP (46) and it is, therefore, understandable that the patients in nonendemic areas are more prone to develop severe cardiac amyloidosis.

Non-Val30Met TTR-type FAP is being increasingly recognized and a total of 22 non-Val30Met ATTRs have been found among Japanese that relate to the development of FAP (39). Several previous reports (48–51) indicated that FAP patients with this type frequently had serious cardiac symptoms including intractable heart failure, especially in patients whose initial symptom was a carpal tunnel syndrome (52–54). This tendency was confirmed by our recent study (46), based on the significant number of patients: at the time of admission 75% of the patients in this group had clinically apparent cardiac amyloidosis in addition to peripheral somatic and/or autonomic neuropathy, while the cardiac disorder was present in only 18% of the patients with Val30Met ATTR. Moreover, it has been shown that many ATTRs produce hereditary amyloidosis with a predominant clinical manifestation of cardiac amyloidosis (Fig. 2) (Table 3) (40). Most patients with non-Val30Met ATTRs had a later age of onset and usually lacked an apparent family history. Thus, they frequently seemed to be sporadic and the common initial misdiagnosis for them was primary systemic amyloidosis (55).

FAP was long considered to be incurable, but liver transplantation is now a very promising therapy, because the liver produces most of the TTR in serum (56). Since the first success in Sweden in 1990 (57) more than 700 patients had undergone liver transplantation by the end of 2003 (58). In Japan, partial liver transplantation from living donors has been mainly carried out (59, 60). A better 5-year patient survival was reported in the Val30Met ATTR type patients.
compared to those with non-Val30Met ATTRs (80% vs. 59%, respectively, p<0.001) (58). The cause of this difference mainly depends on the diverse frequency of cardiac complications between the two groups. In addition, it has been recently noted that after transplantation rapid deterioration of cardiac function with further thickened ventricular wall occurred in some FAP patients, although polyneuropathy and autonomic failure were stabilized or slightly improved. These findings were originally obtained from the patients with non-Val30Met ATTRs who possibly had substantial amyloid deposition in the myocardium before operation (61–63). However, a similar finding has been observed in typical FAP patients with Val30Met ATTR (64) and in the pathogenesis of this form of cardiac amyloidosis, wild-type TTR is regarded as playing a central role (65). It is, therefore, critical to clarify the severity of cardiac amyloid deposition when considering liver transplantation in FAP patients.

Senile Systemic Amyloidosis

Senile systemic amyloidosis (SSA) is a disorder affecting the elderly (6). Amyloid in this disease is composed of wild-type (unmutated) TTR (66), which can be distinguished from hereditary TTR-related amyloidosis with deposition of mutated TTR molecules. This disease is associated with aging and is a relatively frequent finding at autopsy: the prevalence of SSA in the elderly (>80) was found to be 22–25% based on examination of autopsy-derived cardiac specimens in the US (67) and European countries (68), but in Japan it might be much lower.

On pathological examination the heart was the most frequently and heavily involved, while the second pronounced site of amyloid deposition was in the lungs. Renal medulla which included the papilla was occasionally affected and patchy or segmental deposits of amyloid were consistently seen in small arteries in many tissues (6). These amyloid deposits were found by chance at autopsy and usually were insufficient to produce clinical symptoms. SSA is typically manifested by cardiac disorders with congestive heart failure, arrhythmia and/or conduction blocks. Recently, carpal tunnel syndrome due to deposits of wild type TTR-derived amyloid has been noted (69), which in some cases might precede the cardiac manifestations of SSA (70, 71). There has been no effective treatment for this disease.

In summary, cardiac amyloidosis develops in different molecular backgrounds and it is emphasized that it more occurs frequently in hereditary amyloidosis patients than previously recognized.

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References

Current Progress in Cardiac Amyloidosis


