Pathophysiology and treatment of cardiac amyloidosis

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Abstract | Amyloid cardiomyopathy should be suspected in any patient who presents with heart failure and preserved ejection fraction. In patients with echocardiographic evidence of ventricular thickening and without a clear history of hypertension, infiltrative cardiomyopathy should be considered. If imaging suggests the presence of amyloid deposits, confirmation by biopsy is required, although endomyocardial biopsy is generally not necessary. Assessment of aspirated subcutaneous fat and bone-marrow biopsy samples verifies the diagnosis in 40–80% of patients, dependent on the type of amyloidosis. Mass spectroscopy can be used to determine the protein subunit and classify the disease as immunoglobulin light-chain amyloidosis or transthyretin-related amyloidosis associated with mutant or wild-type *TTR* (formerly known as familial amyloid cardiomyopathy and senile cardiac amyloidosis, respectively). In this Review, we discuss the characteristics of cardiac amyloidosis, and present a structured approach to both the assessment of patients and treatment with emerging therapies and organ transplantation.

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Introduction

Amyloidosis is a clinical disorder that arises from the aggregation of insoluble fibrous deposits of misfolded proteins.[1] Deposition of fibrillar material and the toxic effects of precursor soluble intermediates result in progressive organ dysfunction, which manifest as heart failure with restrictive physiology. Amyloid deposits can be localized or systemic.[2,3] Cardiac deposition can lead to diastolic dysfunction, rhythm disturbances, and ischaemia. Delayed diagnosis of amyloidosis is a major reason for shortened survival of patients with this disorder.[4]

Although light-chain amyloid proteins can be directly toxic to cardiomyocytes,[5] amyloid deposits might not be responsible for cardiac dysfunction. Amyloidogenic light chains internalize into many cell types, including cardiac myocytes, and cause toxic effects. Soluble intermediates might, therefore, be more relevant to cardiac dysfunction than the finally formed amyloid deposits and might explain why patients improve clinically without anatomical evidence of amyloid regression.[6] Common to all forms of amyloidosis is a precursor protein or a fragment that can be detected in the bloodstream. However, the exact location where misfolding begins is unknown, and the nature of all the toxic species has not been fully characterized.[7]

In this Review, we aim to assist clinicians in the early recognition of cardiac amyloidosis before advanced failure occurs. We provide step-by-step recommendations for screening, diagnostic confirmation, classification, and prognostic assessment of patients with cardiac amyloidosis, and summarize current therapies.

Forms of cardiac amyloidosis

Immunoglobulin light-chain amyloidosis

The main forms of cardiac amyloidosis are summarized in Table 1. Immunoglobulin light-chain (AL) amyloidosis is the most common type of cardiac amyloidosis, with 0.3 cases per 100,000 people in the general population in England being diagnosed annually.[8] All patients with cardiac AL amyloidosis have a plasma cell dyscrasia.[9]

Although AL amyloidosis is a clonal plasma cell disorder, most patients do not have multiple myeloma and the average bone marrow plasma cell content is 5–7%; prognosis worsens with increasing accumulation of abnormal plasma cells in the bone marrow.[10] Nearly 80% of patients with cardiac AL amyloidosis have λ light chains rather than κ light chains, which suggests a greater susceptibility for λ chains to misfold.[11] Two-thirds of patients with AL amyloidosis are men, and the median age at diagnosis is 67 years. Cardiac AL amyloidosis is a systemic disorder, and ~50% of patients have renal involvement, ~16% have liver involvement, and ~10% have neurological involvement.[11] The only localized form of cardiac amyloidosis is atrial amyloidosis. The clinical presentations of AL amyloidosis and all other forms of systemic amyloidosis are similar, which makes distinction between types difficult by clinical assessment alone. Of note, tongue enlargement and purpura of the eyelids, face, and neck occur only in AL amyloidosis.

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Key points

- Cardiac amyloidosis should be suspected in any patient with heart failure and preserved ejection fraction or infiltrative cardiomyopathy
- Histological diagnosis of amyloid requires further investigation to determine the protein subunit type, because the therapies vary widely
- Preferred therapies for immunoglobulin light-chain amyloidosis involve standard-dose or high-dose chemotherapy with stem-cell rescue
- Investigational therapies for transthyretin-related cardiomyopathy are diflunisal or tafamidis, and multiple new therapies for transthyretin-related amyloidosis and antibody therapy for immunoglobulin light-chain amyloidosis are being developed

Table 1 | Classification of cardiac amyloid types

Amyloidosis type	Precursor	Comment
Light chain or light chain/heavy chain	Immunoglobulin light chain	Systemic plasma cell dyscrasia
Mutant transthyretin-related	*TTR* point mutation	Inherited autosomal-dominant mutation, expressed after fifth decade
Wild-type transthyretin-related	None	Formerly known as senile cardiac amyloidosis
Amyloid A	Serum amyloid A	Sustained inflammatory process, cardiac involvement rare
Isolated atrial amyloid	Atrial natriuretic factor	Diagnosis before death rare, features atrial fibrillation

Transthyretin-related amyloidosis

Mutant transthyretin-related amyloidosis

Transthyretin is the second most common protein subunit to cause cardiac amyloidosis. Among our patients at the Mayo Clinic, Rochester, MN, USA with amyloidosis, 72% have AL amyloidosis and 5% have *TTR* mutations. The first forms of amyloidosis to be recognized were those associated with amyloid neuropathy.[12,13] Overall, >100 *TTR* mutations causing transthyretin-related amyloidosis have been identified, and all are encoded on chromosome 18.[14,15] The symptomatic development of transthyretin-related amyloidosis is less prevalent and myocardial infiltration less severe in premenopausal women than in men or postmenopausal women.[16]

When transthyretin-related amyloidosis is suspected, sequencing of *TTR* is required to confirm the diagnosis and identify the specific mutation, each of which is associated with a different prognosis.[17] The three most common *TTR* mutations that we see in our patients are Thr60Ala, Val30Met, and Val122Ile. The Thr60Ala and Val122Ile variants are associated with dominant cardiac amyloidosis,[18] whereas Val30Met, which is the most common mutation worldwide, is associated with neuropathy at presentation, and development of cardiomyopathy later in the disease course. Patients with the Val122Ile variant are generally older and have a higher degree of cardiac infiltration than patients with the other two mutations.[19] The Val122Ile variant, which is autosomal dominant, is present in 3.5% of African-American individuals.[20] Nearly 90% of patients with the Val122Ile variant present because of cardiomyopathy.[17] Rarely, patients are homozygous for Val122Ile. In these patients, symptoms develop a mean of 8 years earlier than in those who are heterozygous (aged 64 years versus 72 years). The Val122Ile variant is predominantly seen in men.[21] The cardiac features of the other *TTR* mutations are indistinguishable from those of Val122Ile. In patients with the Val30Met variant, neuropathy is prominent, whereas in those with the Thr60Ala variant, neuropathy often occurs after the cardiac symptoms.

Another *TTR* variant, the Val94Ala substitution, has been associated with rapidly progressive amyloidosis that leads to disabling polyneuropathy and involvement of the gastrointestinal tract and heart after a long-term stable clinical course.[22,23] The thickness of the ventricular septum is frequently greater in patients with transthyretin-related amyloidosis than in those with AL amyloidosis, and often exceeds 20 mm. However, distinguishing between transthyretin-related and AL amyloidosis on the basis of clinical features alone can be difficult.

Wild-type transthyretin-related amyloidosis

Wild-type transthyretin-related amyloidosis (formerly known as senile cardiac amyloidosis or senile systemic amyloidosis) is more common than mutant forms. In 2012 at the Mayo Clinic in Minnesota, USA, 8.5% of all patients with amyloidosis had the wild-type transthyretin-related form of the disease (R. A. Kyle, personal communication). Wild-type disease is being increasingly recognized because of the willingness of cardiologists to perform endomyocardial biopsies in elderly patients now that treatment for amyloidosis is available through clinical trials. Patients with wild-type transthyretin-related amyloidosis seem to have a more indolent disease progression and longer survival than those with mutant disease[24] or AL amyloidosis.[19] In an observational study, the median survival of patients with mutant transthyretin-related amyloidosis was 25.6 months, compared with 43 months for those with wild-type disease.[20] Univariate predictors of mortality included bradycardia, left ventricular ejection fraction <50%, and stroke volume at baseline.[20] In a review of 272 patients with wild-type transthyretin-related amyloidosis, the mean age of patients was 77 years, and 89% were men.[25] In most patients, the diagnosis was made by assessment of endomyocardial biopsy samples. Median survival was 3.5 years.[25]

Wild-type transthyretin-related amyloidosis occurs rarely in patients aged <70 years, but is frequently detected during post-mortem myocardial evaluations of patients aged >80 years. Wild-type disease is associated with substantially fewer clinical symptoms than mutant transthyretin-related amyloidosis, and <10% of patients have symptomatic neuropathy or nephropathy. The youngest patient we have seen with biopsy-proven wild-type transthyretin-related amyloidosis was aged 58 years. Patients with clinically apparent disease typically present with progressive decline in energy and symptoms of congestive heart failure, but generally have normal systolic function. The diagnosis is often made after patients have been hospitalized multiple times for congestive heart failure owing to diastolic dysfunction. Increased myocardial thickness is often attributed to systemic hypertension, which is a highly prevalent condition in this age

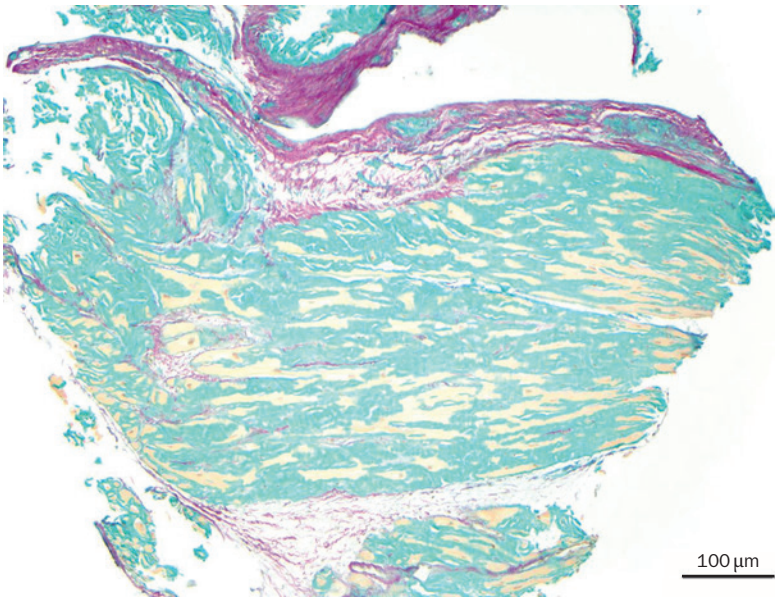

Figure 1 | Endomyocardial biopsy specimen. Amyloid is stained with sulphated Alcian blue.

group. For unknown reasons, symptomatic cardiomyopathy in wild-type transthyretin-related amyloidosis is seen almost exclusively in men (85%). Patients might have symptomatic median neuropathy that presents as carpel tunnel syndrome.[26]

Cardiac amyloidosis can sometimes be difficult to distinguish from hypertrophic obstructive cardiomyopathy with left ventricular outflow tract obstruction.[27] Although confusion arises primarily with AL amyloidosis, cardiac involvement that resembles hypertrophic obstructive cardiomyopathy also occurs with wild-type transthyretin-related amyloidosis.[28]

AA amyloidosis

AA amyloidosis, also known as reactive systemic amyloidosis, is characterized by deposition of serum amyloid A protein in the thyroid, gastrointestinal tract, liver, spleen, and kidney.[22] Cardiac involvement is uncommon—we see it in only 2% of our patients who have AA amyloidosis, although other investigators have reported higher incidence. For example, cardiac involvement was found in 6.5% of 46 patients with AA amyloidosis in one study[29] and in 14.6% of 41 patients in another.[30] By contrast, in a series of 75 patients with AA amyloidosis, cardiomyopathy was found in none.[31]

Isolated atrial amyloidosis

Isolated atrial amyloidosis is characterized by deposits of subunits of atrial natriuretic peptide.[32] The most common clinical manifestation is atrial fibrillation, and diagnosis before death is rare.[33] Isolated atrial amyloid deposition has been noted in patients aged as young as 40 years and can lead to severe congestive heart failure.[34] In an autopsy study, 14 hearts showed grade 3 isolated atrial amyloid; nine of the patients had had atrial fibrillation and one had had atrial flutter.[35]

Confirmation of diagnosis

A diagnosis of cardiac amyloidosis requires positive staining of biopsy samples with Congo red[36] and verification of the protein subunit associated with the amyloid deposits.[37] Endomyocardial biopsy (Figure 1) validates the diagnosis in virtually all patients, but might not be required.[38] Flail posterior leaflet of the tricuspid valve has been reported as a complication of biopsy.[39] In 85% of patients, aspiration of subcutaneous fat can validate the diagnosis of cardiac amyloidosis[40] when used in combination with bone-marrow biopsy. In a study of 131 patients who had positive results on endomyocardial biopsy, 73% also had positive results in noncardiac tissues.[41] Fat aspiration and bone-marrow biopsy are more sensitive tests for cardiac involvement in patients with AL amyloidosis than in those with transthyretin-related amyloidosis.[41]

After amyloidosis has been confirmed by biopsy, tissue typing of the amyloid deposits is required.[42] Immunofixation of serum and urine and the immunoglobulin free light-chain assay have traditionally been used to classify the type of amyloidosis, but are subject to misclassification because of the high prevalence of monoclonal gammopathy of undetermined relevance among elderly patients.[43] In one series of patients with cardiac amyloid deposits, transthyretin-related amyloidosis was diagnosed in 57% and AL amyloid in 43%.[44] Overall, 20 of the 81 patients with transthyretin-related amyloidosis had a monoclonal gammopathy and, therefore, the positive predictive value of the immunoglobulin free light-chain assay was only 74%. Techniques with improved sensitivity to classify amyloid deposits are required.[44]

Immunohistochemical diagnosis has been used to classify amyloidosis, but has major deficiencies.[45,46] Having antisera to the 40 different protein subunits associated with amyloidosis is generally not practical. In addition, AL amyloidosis is frequently not detected immunohistochemically because the amyloid deposits generally contain only the N-terminus of the immunoglobulin light chain, and commercial antisera are directed against the C-terminus.[47]

To improve diagnosis we recommend the routine use of mass spectroscopy. In a study of 15 patients who had monoclonal gammopathy and plasma cell dyscrasia, immunostaining of biopsy samples was performed.[48] Eight patients showed strong transthyretin staining in the cardiac amyloid deposits. However, mass spectroscopy on five of these eight specimens showed light-chain amyloid proteins in all, which indicates that immunohistochemical transthyretin testing alone can be inaccurate.[48] Laser-capture mass spectroscopic analysis of amyloid-laden tissue is sensitive and specific for typing of amyloidosis. In a training set of samples from 50 patients and an independent validation set of 41 samples from patients with confirmed cardiac amyloidosis, the amyloid type was identified by laser capture microdissection mass spectroscopy with 100% specificity and sensitivity in the training set and 98% in the validation set.[49] Patients who have AL amyloidosis might have deposition of immunoglobulin light and heavy chains. They cannot be distinguished

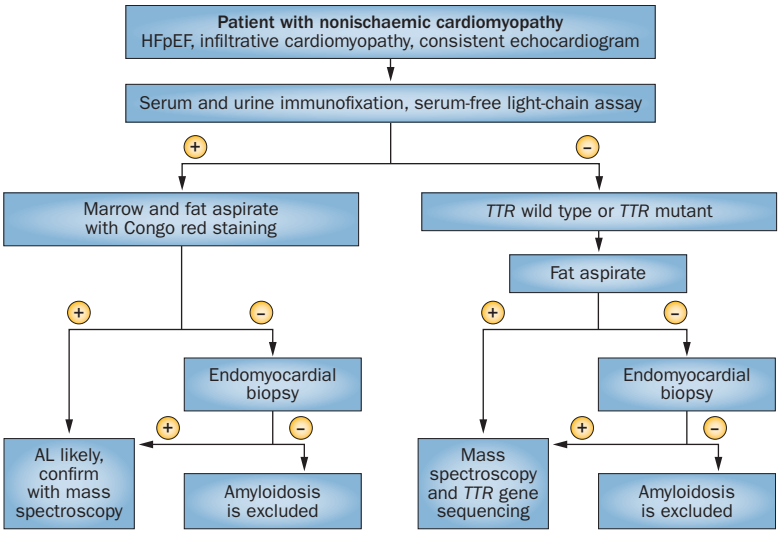

Figure 2 | Algorithm for diagnosis in patients with suspected amyloidosis. Abbreviations: +, positive test; –, negative test; AL, light-chain amyloidosis; HFpEF, heart failure with preserved ejection fraction.

from patients with only light-chain deposits without mass spectroscopic analysis, but the distinction is important because patients with heavy-chain amyloidosis are less likely to have cardiac involvement.[50]

Our standard of care is that all tissue sections positive for amyloid deposits, including fat, are assessed with mass spectroscopy.[51] Among 4,139 samples positive for amyloid fibrils using Congo red staining, with mass spectroscopy, 61% showed deposition of immunoglobulin light chains, 24.5% were positive for transthyretin, and 0.3% showed deposition of atrial natriuretic peptides.[52] We propose two algorithms for diagnosis: one for patients in whom amyloidosis is suspected (Figure 2), and one for patients in whom a diagnosis of amyloid has been established by biopsy (Figure 3).

Pathophysiology of cardiac amyloidosis

Mammalian stanniocalcin-1 is associated with several cellular processes, including oxidative stress and cell death, and is an important determinant of amyloidogenic light-chain cardiotoxic effects.[53] Deposition of amyloidogenic light chains provokes oxidative stress, cellular dysfunction, and apoptosis in isolated adult cardiomyocytes through activation of p38 mitogen-activated protein kinase.[54] Genetic silencing of stanniocalcin-1 prevents amyloidogenic toxic effects and cell death induced by light-chain deposition. The cardiotoxic effects of stanniocalcin-1 seem to be mediated via mitochondrial dysfunction, as indicated by loss of mitochondrial membrane potential.

The classic presentation of cardiac amyloidosis is heart failure with preserved ejection fraction.[55] When echocardiography shows thickening of the ventricular walls, this finding might be interpreted as hypertrophy rather than infiltration, leading to a misdiagnosis of hypertensive cardiomyopathy. Amyloidosis might create a pseudoinfarction pattern on electrocardiography[56] and be mistaken for ischaemic heart disease. The latter interpretation leads to unnecessary left-sided heart catheterization. When 127 electrocardiograms of patients with AL amyloidosis and biopsy-proven cardiac involvement were analysed, low voltage was found in 46%, but a pseudoinfarct pattern was found in 47%.[56] Overall, 16% of patients had symptoms that met the criteria for left ventricular hypertrophy, which suggests that voltage is not a sensitive criterion for suspecting amyloidosis.[56] Echocardiographically-determined ejection fractions remain normal until the amyloidosis is far advanced,[57] because patients have poor diastolic filling related to their noncompliant ventricle but normal systolic function. The resulting low left ventricular end-diastolic volume can lead to severely reduced cardiac output.[58]

Wild-type transthyretin-related amyloidosis is important to consider when assessing the pathophysiology of heart failure in patients with preserved ejection fraction.[55] The prevalence of wild-type transthyretin-related disease is higher in patients with heart failure and preserved ejection fraction than in control individuals (HR 3.8, 95% CI 1.5–11.3, $P = 0.03$).[55] In an autopsy study of 58 patients with AL amyloidosis, 97% had amyloid deposits in the epicardial coronary arteries, although the vessel was not obstructed in all instances (28% left anterior descending coronary artery, 29% circumflex artery, 34% right coronary artery).[59] However, patients with deposits in the vasa vasorum were at increased risk of obstructive intramural coronary amyloidosis.[59]

Imaging

Echocardiography

Cardiac amyloidosis is a classic infiltrative cardiomyopathy in which the ventricular walls become rigid and impede diastolic ventricular filling. The classic findings are increased wall thickness, low ventricular volume, and occasional dynamic left ventricular outflow obstruction that might be confused with hypertrophic cardiomyopathy.[60] Global mean values of peak systolic tissue velocity, systolic strain rate, and systolic strain are substantially lower in patients with cardiac amyloidosis than in those with amyloidosis and normal wall thickness or in healthy individuals. Longitudinal systolic strain echocardiography is the most accurate technique for detection of systolic dysfunction in amyloidosis.[61] Doppler myocardial imaging can be used to detect impaired left ventricular systolic function even when no evidence of cardiac involvement exists on standard 2D and Doppler echocardiography.[62] In 42 patients with normal ventricular wall thickness and normal velocity of the medial mitral annulus, peak longitudinal systolic strain rate and systolic strain were decreased.[63] When compared with diastolic colour Doppler myocardial imaging, pulsed-wave tissue Doppler imaging of the mitral annulus remains the most accurate diastolic measure to detect early left ventricular dysfunction in patients with AL amyloidosis.[64] Strain rate imaging allows for precise characterization of the mechanics of myocardial contraction and relaxation, which increases the sensitivity of this technique.[65]

In 249 consecutive patients with AL amyloidosis, the capacity of strain rate imaging to predict mortality was

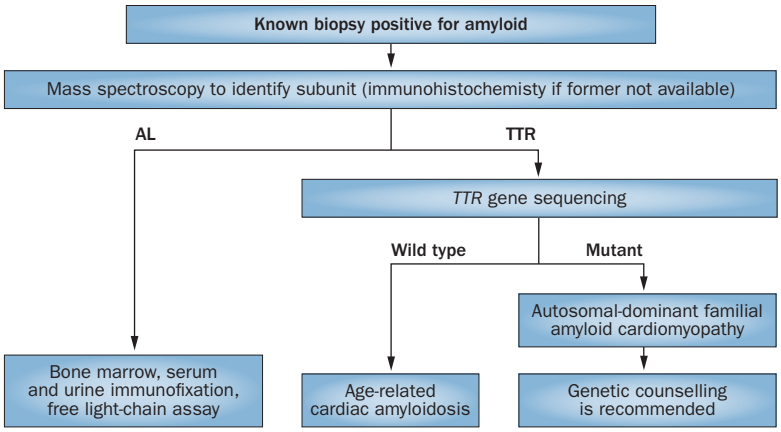

Figure 3 | Algorithm for diagnosis in patients with amyloidosis established by biopsy. Abbreviations: AL, light-chain amyloidosis; TTR, transthyretin-related amyloidosis.

investigated. Age, NYHA functional class III or IV, serum B-type natriuretic peptide level, and peak longitudinal systolic strain of the basal anteroseptal segment were independent predictors of survival. In the multivariable survival analysis, independent predictors associated with AL amyloidosis were NYHA functional class III or IV, pleural effusion, B-type natriuretic peptide concentration >493 ng/l, ejection time <273 ms, and a peak longitudinal systolic strain of the basal anteroseptal segment less negative than or equal to –7.5%.[66]

The strain rate of the right ventricle is also useful for making an early diagnosis of cardiac involvement in patients with AL amyloidosis. Independent predictors of death include male sex, level of B-type natriuretic peptide, troponin T level, pleural effusion, ratio of early-to-late ventricular filling velocities, right ventricular systolic pressure, and right ventricular strain rate of the middle segment.[67] Doppler myocardial imaging measures of the right ventricle can be used to identify impairment of cardiac function and are further predictors of death.[67] In one study, 36% of 70 patients with proven cardiac amyloidosis with a left ventricular wall thickness of ≤12 mm had a median survival of 729 days.[68] The predictors of survival in a multivariable analysis were age, N-terminal pro-B-type natriuretic peptide (NT-proBNP) level ≥1,800 ng/l, ratio of early transmitral flow velocity to early diastolic mitral annulus velocity, and a complete haematological remission. Finally, among an assessment of 255 patients with amyloidosis and a left ventricular ejection fraction of <40%, 3% had a normal ventricular wall thickness with histological confirmation of cardiac involvement.[69] Of these seven patients, six had AL amyloidosis and one had wild-type transthyretin-related cardiac amyloidosis. No significant difference existed in 1-year survival from tissue diagnosis in those with a normal thickness and those with increased thickness and an ejection fraction of ≤40% (21% versus 18%).[69]

Radionuclide imaging

Serum amyloid P component has been used to assess amyloidosis for nearly 20 years. All amyloid deposits contain serum amyloid P component and, therefore, radio-iodination allows visualization of the distribution of deposits.[70] Unfortunately, this technique is poorly suited to imaging of the myocardium because of the distribution of the radionuclide and the kinetics of cardiac function.[71]

^{99m}Tc-Phosphate derivatives can bind to transthyretin in the myocardium,[72] but not to immunoglobulin light chains. Positive scans on scintigraphic imaging of cardiac amyloid can, therefore, be used to identify wild-type and mutant transthyretin-related amyloidosis. By contrast, cardiac localization of amyloid deposits occurs in only a small proportion of patients with AL amyloidosis, and usually to a lesser degree than in patients with transthyretin-related amyloidosis. Consequently, negative scans are predictive of AL amyloidosis.[73] This technique is cheap and widely available, and might be a useful tool with which to distinguish transthyretin-related cardiac amyloidosis from other forms.[74] The most common technetium imaging compounds are ^{99m}Tc-3,3-diphosphoro-1,2-propanodicarboxylic acid and ^{99m}Tc-pyrophosphate.[75] One group of investigators has proposed that the utility of ^{99m}Tc-phosphate scintigraphy could be important in identifying wild-type transthyretin-related amyloidosis.[75] Nuclear imaging tracers, such as ^{99m}Tc-sestamibi and other ^{99m}Tc-based phosphate derivatives have not proven useful for detecting cardiac amyloidosis.

PET in conjunction with tracer ^{11}C-labelled Pittsburgh compound B (^{11}C-PiB) has been used to diagnose Alzheimer disease by detecting amyloid plaques in the brain.[76] Ten patients with either AL or transthyretin-related amyloidosis were investigated using ^{11}C-PiB and ^{11}C-acetate PET to measure Pittsburgh compound B retention.[77] Uptake of ^{11}C-PiB uptake was seen 15–25 min after injection in all patients and in no healthy controls. This significant difference in cardiac retention suggests that systemic amyloidosis can be visualized with the use of ^{11}C-PiB. No correlation was found between the ^{11}C-PiB retention index and myocardial blood flow, as measured using ^{11}C-acetate. Use of ^{11}C-PiB with PET might be a useful technique to study systemic amyloidosis affecting the heart.[77]

MRI

MRI can be used to diagnose cardiac amyloidosis.[78,79] In addition to its offering accurate evaluation of ventricular wall thickening and mass, highly characteristic patterns of late gadolinium enhancement are associated with cardiac amyloidosis.[80] However, in patients who have proteinuria in the nephrotic range and renal insufficiency, injection of gadolinium is contraindicated because of a high risk of systemic fibrosis.[81] In 38 patients with amyloidosis confirmed by biopsy and in sinus rhythm, simultaneous phase-contrast MRI and echocardiography showed highly correlated results for mitral inflow peak velocities, deceleration times, and ratios of early-to-late ventricular filling, and could be used to identify most patients (91%) with restrictive patterns.[82] Among 120 patients in whom cardiac MRI was performed after injection of gadolinium, of 35 patients with

histologically-detected cardiac amyloidosis verified with biopsy, late gadolinium enhancement was abnormal in 97%, and echocardiography showed increased left ventricular wall thickness 91%.[83] Transmural or subendocardial gadolinium enhancement was most common (seen in 83%) and was associated with increased amyloid deposition. Gadolinium enhancement was strongly associated with functional class, electrocardiographic voltage, left ventricular mass index, and levels of troponin T and B-type natriuretic peptide.[83]

MRI in patients with nondilated cardiomyopathies can be used to differentiate amyloidosis from hypertensive or hypertrophic cardiomyopathy.[84] Alterations in flow dynamics, such as mitral inflow peak velocities, deceleration times, and ratios of early-to-late ventricular filling velocities, can be reliably measured using phase-contrast MRI, with similar accuracy to that of Doppler echocardiography. One advantage of MRI is direct, high-contrast visualization of nonviable myocardium. Increased thickness of the mid-myocardium is often a symptom of hypertrophic cardiomyopathy, and subepicardial contrast enhancement might indicate acute myocarditis. Typically, expansion of the extracellular space that is indicative of amyloid deposition reveals a pattern of circumferential late shortening of the endocardium and thickening of the myocardial wall, when analysed using inversion-recovery-delayed, contrast-enhanced imaging. Focal areas of late gadolinium enhancement are nonspecific and might indicate conditions such as fibrosis, ischaemia, or inflammation. Diffuse, transmural late gadolinium enhancement generally correlates with a large degree of interstitial amyloid infiltration and clinical prognostic indicators, such as NYHA functional class, left ventricular thickness, and concentrations of troponin T and NT-proBNP.

Biomarkers

Most patients with cardiac amyloidosis have dyspnoea on exertion associated with oedema,[79] and a few patients have pleural effusions.[85] The symptoms of cardiac amyloidosis are nonspecific. Because of the poor diastolic filling, the low left ventricular end-diastolic volume, and reduced cardiac output, systolic blood pressure decreases as stroke volume declines.[86] Cardiac biomarkers can be sensitive indicators of the presence of cardiac amyloidosis and of survival.[87] Measurement of cardiac biomarkers is the most important feature of the staging system for AL amyloidosis.[88] Levels of troponin T and NT-proBNP can be used to determine safety margins for autologous stem-cell transplantation. Each biomarker can be used to identify a group of patients for whom high-dose therapy carries an excessive risk of death. Cardiac involvement is the major cause of death in patients with AL amyloidosis, including those who present because of renal,[89] hepatic,[90] or peripheral nerve involvement.[91] Measurement of cardiac troponin T by high-sensitivity assay can also be used for the staging of cardiac amyloidosis.[92]

In a multivariable model of >800 patients with AL amyloidosis, concentrations of cardiac troponin T and NT-proBNP independently predicted overall survival.[93] Accuracy of the model was improved when clonal free immunoglobulin light-chain burden (measured as the difference between the involved and uninvolved light chains) was included. A score of 1 point was assigned to each prognostic variable (cardiac troponin T level ≥0.025 μg/l, NT-proBNP level ≥1,800 ng/l, and clonal free light-chain burden ≥18 mg/dl) to create four stages (I, II, III, and IV, based on scores of 0, 1, 2, or 3, respectively). The median survival for each stage was 94.1, 40.3, 14.0, and 5.6 months.[93] This classification system applies only to AL amyloidosis.

Supportive care

Treatment with diuretics is the mainstay in patients with high left ventricular filling pressures,[94] but physicians should be aware that overdiuresis is possible and can lead to hypotension.[95] Tachycardia is common in patients with cardiac amyloidosis and most frequently is a reactive increase in heart rate to improve cardiac output. β-Blockers are often used to decrease heart rate and increase diastolic filling times, but in patients with amyloidosis these drugs have resulted in considerable symptomatic decline and impaired quality of life and, therefore, should be used sparingly.[96] The value of amiodarone for the treatment of cardiac amyloidosis and life-threatening ventricular arrhythmia is uncertain.[97]

Given that sudden death is common in patients with cardiac amyloidosis, the placement of an implantable cardioverter–defibrillator is rational, but the benefits are uncertain. This intervention was assessed in a study of 53 patients with cardiac amyloidosis: 33 with AL amyloidosis, 10 with wild-type and nine with mutant transthyretin-related disease, and one with AA amyloidosis.[98] The indication was primary prevention of cardiac arrest in 77% and secondary prevention in 23%. The rate of appropriate shocks was 32% in the first year, almost exclusively in patients with AL amyloidosis (12 of 15). Appropriate shocks did not translate into overall survival benefit, and the selection of patients who are appropriate candidates for implantable cardioverter–defibrillators is not well understood.[98] In an assessment at the Mayo Clinic in Rochester, MN, USA of four patients with cardiac amyloidosis who had an out-of-hospital cardiac arrest, and none of whom had an implanted device, only one survived to leave the hospital, despite prompt administration of cardiopulmonary resuscitation in all.[99] In nine patients fitted with left ventricular assist devices, two patients died before hospital discharge, three patients died after discharge with a median survival of 13.7 months, and four were alive at 16–24 months.[100] The most common adverse event was gastrointestinal bleeding (three patients). Although implantation of a left ventricular assist device is technically feasible in patients with cardiac amyloidosis, whether this approach has a beneficial role remains uncertain.[100]

The incidence of atrial thrombosis in patients with cardiac amyloidosis is high. Use of long-term prophylactic anticoagulation has been proposed in patients with cardiac amyloidosis. Among 116 autopsy patients with cardiac amyloidosis, 23 had one thrombus and

15 had between two and five thrombi.[101] More patients with cardiac AL amyloidosis than patients with other forms of cardiac amyloidosis had intracardiac thrombi (51% versus 16%; $P<0.001$), and more embolic events were fatal in these patients (26% versus 8%; $P<0.03$).[101] The presence of atrial fibrillation increases the risk of thromboembolism. Early anticoagulation might, therefore, reduce morbidity and mortality.[101] In a retrospective study of 49 patients with confirmed AL amyloidosis and ischaemic stroke, stroke was the initial presentation of amyloidosis in 26.5%, and median survival was 6.9 months.[102] Overall, 70% of patients had cardioembolic infarctions.[102] Thrombosis in both atrial appendages in patients in sinus rhythm has been reported.[103] The role of anticoagulation in the long-term management of patients with cardiac amyloidosis remains undefined.

Therapy

AL amyloidosis

Overall survival at 4 years from diagnosis improved in patients with AL amyloidosis for each of the 3 decades from 1977 to 2006 (from 21%, to 24%, to 33%).[104] Delay in diagnosis results in a persistently high 1-year mortality that has not improved over the past 30 years, and ranges from 30% to 40%.[104] Because the amyloid fibrils in AL amyloidosis derive from a clonal population of light-chain-producing plasma cells in the bone marrow, most patients require cytotoxic chemotherapy.[105] Patients who achieve a haematological response have resolution of cardiac symptoms and improvement of cardiac biomarkers, including histological regression of amyloid deposits.[106]

Haematological response is measured by the difference in concentration between involved and uninvolved immunoglobulin free light chains in serum. A partial response is defined as a decrease in the difference by >50%, a very good partial response as concentrations of free light chains <40 mg/l, and a complete response as normalization of the difference with negative immunofixation of serum and urine.[107] Cardiac response can be assessed on the basis of changes in NT-proBNP concentration. If the NT-proBNP level is >600 ng/l and is reduced by >30%, the criteria for cardiac organ response are satisfied.[107] Attempts to validate these response criteria with echocardiography have failed, and this approach is no longer part of the assessment of response. Haematological and cardiac responses can be seen as early as 3 months after the initiation of therapy and can be predictive of survival.[107]

The oral combination of melphalan and dexamethasone is effective in almost two-thirds of patients and results in a median survival of 5 years.[108] Cyclophosphamide, dexamethasone, and lenalidomide have been used for the treatment of AL amyloidosis. In a study of 35 patients, half of whom had stage 3 disease with cardiac involvement and 28% had three or more organs involved, the overall haematological response rate was 60%.[109] Organ responses occurred in 29% and were confined to patients who also had a haematological response. The median overall survival of the cohort was 37.8 months. Grade 3 or higher toxic effects were reported in 74% of patients, and 20% died during the study.[109] Lenalidomide is also associated with increases in NT-proBNP levels.[110]

Bortezomib

Our preferred drug therapy for patients with AL amyloidosis outside of trials is combined bortezomib, cyclophosphamide, and dexamethasone. In a phase II study, these three drugs were administered weekly (oral cyclophosphamide 300 mg/m^2, bortezomib 1.5 mg/m^2, and dexamethasone 40 mg) to 17 patients.[111] Overall, 10 of the patients had symptomatic cardiac involvement at baseline. Treatment responses were observed in 16 patients: 71% had complete haematological responses, with a median time to response of 2 months. Three patients previously unsuitable for stem-cell transplantation became eligible after treatment. Adverse effects were deemed tolerable.[111]

Stem-cell transplantation

For patients in whom transplantation can be performed safely, this approach is our preferred intervention. For patients who have only a small number of plasma cells in the bone marrow, we do not believe that cytoreduction before transplantation is required. Initial stem-cell transplantation followed by consolidation chemotherapy for patients who do not achieve a deep response has been used.[112] Patients with a troponin T level >0.06 μg/l should be excluded from stem-cell transplantation.[113] We also exclude patients with an NT-proBNP concentration >5,000 ng/l, which has substantially reduced mortality after transplantation in patients with cardiac amyloidosis, and improved 2-year survival to 82%.[114] Stem-cell transplantation is applicable in around 25% of patients with amyloidosis.[115] In patients who do receive autologous stem-cell transplantations, change in tricuspid regurgitant flow velocity predicts mortality.[116] Pulsed-wave tissue Doppler imaging should be performed before stem-cell transplantation.[116]

After autologous peripheral blood stem-cell transplantation, a high risk of supraventricular tachyarrhythmia exists. In one study, this complication developed in 9.4% of patients after transplantation (median 9 days).[117] Age and the presence of premature supraventricular complexes on echocardiography before the procedure were predictors of supraventricular tachycardia.[117]

In a study of patients with AL amyloidosis, the rate of cardiac dysfunction attributable to melphalan was 5.6%.[118] Left ventricular ejection fraction <60% before transplantation increased the risk of cardiac dysfunction related to the chemotherapy.[118] Therapy with high-dose melphalan and peripheral blood stem-cell transplantation was studied in 187 patients with cardiac AL amyloidosis.[119] The median overall survival was 66 months. All-cause mortality at day 100 was 16%. The haematological and cardiac response rates were 66% and 41%, respectively. Survival was predicted by both haematological response and decrease in NT-proBNP level.[119] By excluding patients with multiorgan involvement and an increased NT-proBNP concentration (>5,000 ng/l) and

Table 2 | Active nonchemotherapy trials for amyloidosis

Drug	Mechanism	Amyloidosis type	Trial registration number*	Comments
Tafamidis	Misfolding interference	Mutant (Val122Ile) and wild-type TTR	NCT00935012, NCT01994889	Double-blind, placebo-controlled trial
ALN-TTRsc	Suppress transthyretin expression	TTR wild type including cardiac involvement	NCT01981837	None
ISIS-TTR_{Rx}	Suppress transthyretin expression	TTR neuropathy in ambulatory patients (use only one walking stick)	NCT01737398	Placebo-controlled
Doxycycline and tauroursodeoxycholic acid	Misfolding interference	TTR	NCT01171859	None
Doxycycline	Fibril disruption	AL and TTR	NCT01677286	None
NEOD001	Antibody-mediated fibril dissolution	AL	NCT01707264	None

*From ClinicalTrials.gov. Abbreviations: AL, immunoglobulin light-chain amyloid; TTR, transthyretin-related.

troponin T level (>0.06 μg/l), we have reduced mortality after transplantation since 2009 to 1.1%.[120] A single-institution study performed in Toronto, ON, Canada, reported that transplantation-related mortality was 11.5% in 78 patients with AL amyloidosis.[121] Complete haematological and organ responses were achieved in 56% and 60% of patients, respectively.[121]

Immunomodulatory agents

Lenalidomide with or without dexamethasone is active in patients with amyloidosis. In a study of 23 patients, 64% of whom had cardiac involvement, 10 discontinued lenalidomide treatment within the first three cycles of therapy.[122] Of the remaining patients, 10 responded to treatment, including nine haematological and two cardiac responses. Haematological toxic effects were common. Increased NT-proBNP levels were associated with early discontinuation of lenalidomide.[123]

The third-generation immunomodulatory drug pomalidomide is also active in patients with AL amyloidosis. In a trial of 33 patients, 82% of whom had cardiac involvement, the haematological response rate was 48% and median overall survival was 28 months.[124] However, discordance was noted between haematological response and cardiac response measured by change in NT-proBNP level.[124]

Antibodies against amyloid aggregates

NEOD001 is a humanized monoclonal antibody designed to clear amyloid aggregates. This drug showed good safety data in a phase I study.[125] Cardiac biomarker responses were observed in five of nine patients. Placebo-controlled phase II and phase III trials are planned.

Organ transplantation

Cardiac transplantation can be beneficial in patients who have no organ involvement other than the heart and who achieve a complete haematological response to drug therapy. Normalization of immunoglobulin free light-chain ratio after chemotherapy suggests that the risk of disease recurrence is reduced.[126] Between 1994 and 2005, 11 patients underwent heart transplantation followed by autologous peripheral blood stem-cell transplantation for AL amyloidosis.[127] Two patients died during the latter procedure. Of the nine survivors, three died later of progressive amyloidosis. The 5-year survival for heart transplantation was 65%, and median survival from the time of heart transplantation was 76 months.[127] When these results were updated to November 2012 (B. S. Edwards, personal communication), 170 adults had been referred for cardiac transplantation, 76 of whom did not complete evaluation. Of the remaining 94 patients, 56 were deemed eligible for transplantation. A total of 31 patients received a heart, 22 of whom had AL amyloidosis, six had mutant transthyretin-related amyloidosis, and three had wild-type transthyretin-related amyloidosis. The 1-year survival of patients with amyloidosis after cardiac transplantation was 81.8%, and the 5-year survival was 47.6%. In comparison, the 5-year survival for patients without amyloidosis was 84%. In a study of 31 patients with cardiac AL amyloidosis, survival after orthotopic heart transplantation followed by autologous stem-cell transplantation was similar to that in patients with cardiomyopathy who undergo orthotopic heart transplantation. However, 35% of patients died awaiting heart transplantation. The only predictor of survival to heart transplantation was low BMI.[128] In another study, six patients underwent heart transplantation for cardiac amyloidosis.[129] All patients with AL amyloidosis received chemotherapy between heart transplantation and autologous haematopoietic stem-cell transplantation. Five patients were alive at 25 months after heart transplantation, without evidence of recurrent amyloid deposition. Therefore, a strategy of heart transplantation followed by chemotherapy before autologous hematopoietic stem-cell transplantation seems feasible for patients with AL amyloidosis.[129]

We have performed combined heart and liver transplantations in 11 patients with mutant transthyretin-related amyloidosis and found no increased risk of perioperative mortality.[130] Survival at 1, 5, and 10 years was 100%, 75%, and 60%, respectively. At a mean follow-up of 62 months, left ventricular ejection fraction was normal and liver allograft function was good. Simultaneous heart and liver transplantation for patients with mutant transthyretin-related amyloidosis is a feasible approach and achieves excellent results.

Transthyretin-related amyloidosis

Tafamidis has been approved for the treatment of mutant transthyretin-related amyloid polyneuropathy in Europe and Japan. The drug inhibits amyloidogenesis by stabilization of transthyretin (misfolding of the transthyretin tetramer into the insoluble amyloid conformation is prevented), and can delay neurological impairment in early-stage disease in patients with the Val30Met mutation.[131,132] In one study, estimated 15-year survival from symptom onset was 87%.[133] An open-label trial of tafamidis in patients with transthyretin-related amyloid cardiomyopathy included 31 patients with wild-type disease and four with mutant disease (Val122Ile variant).[134] Overall, 60% of patients withdrew because of an adverse event or death. Among the remaining 12 patients, the 5-year survival rate was 86% from symptom onset and 45% from the first dose of tafamidis.[134] In patients treated for 1 year, tafamidis was found to prevent neurological deterioration and decline in BMI and quality of life.[135]

The use of doxycycline plus tauroursodeoxycholic acid to treat transthyretin-related amyloidosis has been reported. Investigators in a study enrolled 40 patients, 25 with mutant and 13 with wild-type transthyretin-related amyloidosis, and two who had undergone liver transplantation.[136] Nine patients discontinued treatment because of adverse effects before 1 year, but treatment was well tolerated in the remaining 31 patients. A total of 24 patients completed 1 year of therapy, and 13 were evaluable for treatment response. NT-proBNP levels were stable in 18 (75%) and quality of life was maintained. This preliminary study indicates an acceptable safety profile with a trend for clinical benefit in patients with cardiomyopathy.[136]

Diflunisal has been shown to stabilize transthyretin. In a group of patients with neurological amyloidosis, 64 had cardiac involvement.[137] The use of diflunisal compared with placebo for 2 years reduced the rate of progression of neurological impairment and preserved quality of life. Diflunisal is well tolerated by most patients with transthyretin-related amyloidosis, although renal function and blood cell counts must be monitored, and the clinical effects are sustained after 2 years of therapy.[138]

ISIS-TTR_{Rx} is a second-generation antisense therapy for the treatment of transthyretin-related amyloidosis. Subcutaneous injections result in reduced concentrations of transthyretin in serum. In the phase I portion of a trial, the drug had an attractive safety profile, with toxic effects being limited to localized skin reactions.[139] Some patients had complete suppression of transthyretin levels (that is, below the measurable range). The current phase of this trial will complete enrolment in 2015.[139]

A phase II trial of patisiran, which uses RNA interference mechanisms, delivers small interfering RNA to the liver to inhibit synthesis of transthyretin.[140] In a study of 29 patients, serum transthyretin concentrations were reduced by >80% with a favourable safety profile. An open-label extension study was initiated in October 2013.[140] Other ongoing clinical trials of nonchemotherapy treatments for amyloidosis are summarized in Table 2.

Conclusions

Cardiac amyloidosis is a rare infiltrative disorder that leads to cardiomyopathy, and is primarily the result of misfolding of either clonal immunoglobulin light chains or mutant or wild-type transthyretin. Making the correct diagnosis is facilitated by a strong suspicion of amyloidosis in combination with echocardiography and measurements of immunoglobulin free light chains. New therapies are being developed at a rapid rate and survival is improving.

Review criteria

We searched the PubMed database for articles published in English or in other languages with English abstracts between January 1970 and May 2014. We used the search terms: “amyloid”, “amyloidosis”, “light-chain disease”, “transthyretin”, “wild-type transthyretin disease”, and “mutant transthyretin disease”. Abstracts were reviewed, and manuscripts focused on the diagnosis, pathophysiology, and treatment of cardiac amyloidosis were assessed. We gave preference to articles published from 2012 to 2014, and abstracts from the International Symposium on Amyloidosis, held from 27 April to 1 May 2014 in Indianapolis, IN, USA.

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Author contributions

M.A.G. researched data for the article, discussed its content, and wrote, reviewed, and edited the manuscript before submission. A.D. and T.S. also wrote the manuscript, and reviewed and edited it before submission.