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REVIEW

Cardiac amyloidosis: Updates in diagnosis and management

Actualités dans le diagnostic et la prise en charge de l'amylose cardiaque

Dania Mohty[a,*,b], Thibaud Damy[c], Pierre Cosnay[d], Najmeddine Echahidi[a], Danielle Casset-Senon[e], Patrice Virot[a], Arnaud Jaccard[b,f]

[a] *Service de cardiologie, pôle cœur-poumon-rein, hôpital Dupuytren, CHU de Limoges, 87042 Limoges, France*
[b] *Service d'hématologie clinique et de thérapie cellulaire, pôle onco-hématologie, centre national de référence pour l'amylose AL et autres maladies de dépôts d'immunoglobulines monoclonales, CHU de Limoges, Limoges, France*
[c] *Service de cardiologie, CHU Henri-Mondor, Créteil, France*
[d] *Service de cardiologie, CHU Trousseau, Tours, France*
[e] *Service de médecine nucléaire, CHU Trousseau, Tours, France*
[f] *UMR, CNRS 7276, CRBL, laboratoire d'immunologie, Limoges, France*

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Summary Amyloidosis is a severe systemic disease. Cardiac involvement may occur in the three main types of amyloidosis (acquired monoclonal light-chain, hereditary transthyretin and senile amyloidosis) and has a major impact on prognosis. Imaging the heart to characterize and detect early cardiac involvement is one of the major aims in the assessment of this disease. Electrocardiography and transthoracic echocardiography are important diagnostic and prognostic tools in patients with cardiac involvement. Cardiac magnetic resonance imaging better characterizes myocardial involvement, functional abnormalities and amyloid deposition due to its high spatial resolution. Nuclear imaging has a role in the diagnosis of transthyretin

Abbreviations: 2D-GLS, Two-dimensional global longitudinal strain; AL, light-chain amyloidosis; ASCT, Autologous stem cell transplantation; ATTR, Hereditary transthyretin-related amyloidosis; cMRI, Cardiac magnetic resonance imaging; ECG, Electrocardiogram; LC, Light-chain; LGE, Late gadolinium enhancement; LS, Longitudinal strain; LV, Left ventricular; LVEF, Left ventricular ejection fraction; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; RV, Right ventricular; SSA, Systemic senile amyloidosis; TTE, Transthoracic echocardiography; TTR, Transthyretin; ^{99m}Tc-DPD, ^{99m}Tc-3-3-diphosphono-1-2-propanodicarboxylic acid.

* Corresponding author. Fax: +33 5 55 05 63 34.
E-mail addresses: dania.mohty@chu-limoges.fr, dania.mohty@gmail.com (D. Mohty).

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amyloid cardiomyopathy. Cardiac biomarkers are now used for risk stratification and staging of patients with light-chain systemic amyloidosis. Different types of cardiac complications may occur, including diastolic followed by systolic heart failure, atrial and/or ventricular arrhythmias, conduction disturbances, embolic events and sometimes sudden death. Senile amyloid and hereditary transthyretin amyloid cardiomyopathy have better prognoses than light-chain amyloidosis. Cardiac treatment of heart failure is usually ineffective and is often poorly tolerated because of its hypotensive and bradycardiac effects. The three main types of amyloid disease, despite their similar cardiac appearance, have specific new aetiological treatments that may change the prognosis of this disease. Cardiologists should be aware of this disease to allow early treatment.

MOTS CLÉS
Amylose ;
Chaînes légères ;
Transthyrétine ;
Atteinte cardiaque ;
Traitement

Résumé L'amylose est une maladie systémique grave. Les 3 principaux types d'amylose avec atteinte cardiaque sont l'amylose à chaînes légères, l'amylose héréditaire à transthyrétine et l'amylose sénile à transthyrétine non mutée. L'atteinte cardiaque conditionne le pronostic dans ces 3 formes. L'électrocardiogramme et l'échographie cardiaque sont indispensables pour le diagnostic et l'évaluation du risque de ces patients. Les biomarqueurs cardiaques sont utilisés depuis quelques années pour la stratification du risque en particulier dans l'amylose à chaînes légères. L'IRM cardiaque est de plus en plus utilisée pour évaluer ces patients mais son rôle n'est pas encore bien défini. L'imagerie nucléaire est intéressante chez les patients avec suspicion d'amylose à transthyrétine. Les complications cardiaques peuvent être principalement hémodynamiques (dysfonction diastolique puis systolique), ou électriques (arythmies atriales ou ventriculaires malignes; BAV de différents degrés), avec risque de mort subite. Le pronostic de l'amylose à transthyrétine héréditaire ou sénile est meilleur que celui des amyloses à chaînes légères. Malgré une certaine similarité dans la présentation clinique et l'imagerie, un traitement étiologique spécifique existe pour chaque type d'amylose systémique, dont il peut modifier le pronostic. En raison de l'atteinte cardiaque fréquente, les cardiologues devraient être sensibilisés au diagnostic rapide de cette maladie afin qu'un traitement précoce puisse être institué.

Introduction

Amyloidosis is due to extracellular tissue deposition of insoluble fibrils composed of a variety of serum proteins (amyloid), resulting in tissue involvement. Deposition of amyloid can be localized or systemic (in virtually all organs except the brain). Clinical manifestations are based on the site of the amyloid deposits and are related to the type of precursor protein involved.

There are many types of precursors that may affect the heart: light-chain (LC) immunoglobulin, mutant hereditary transthyretin (TTR), wild-type TTR, mutant apolipoprotein AI, amyloid atrial natriuretic peptide localized to the atrium, fibrinogen alpha type [1] and serum amyloid A protein. Secondary amyloidosis is typically a consequence of chronic inflammatory conditions, such as rheumatoid arthritis [2], Crohn's disease or other chronic inflammatory/infectious diseases, familial Mediterranean fever or idiopathic amyloid A amyloidosis [3].

The organs involved are typically the liver, kidney, gastrointestinal tract, nervous tissue and heart. The presence of amyloid deposits in the heart varies with the type of amyloidosis: systemic senile amyloidosis (SSA) and some forms of hereditary TTR-related amyloidosis (ATTR) affect the heart almost invariably, whereas cardiac involvement in LC amyloidosis (AL) is present in about 50% of cases. In secondary amyloidosis, cardiac involvement is rare or minimal or clinically non-significant [4].

The present review focuses on the three main types of systemic amyloidosis (AL, ATTR and SSA) and describes cardiac involvement.

Light-chain amyloidosis

AL is not rare, with a reported incidence in USA of 8.9 per million person-years, and is probably underdiagnosed [5]. The estimated incidence of AL in France is roughly 500 patients per year. AL is caused by the extracellular deposition of fibril-forming monoclonal immunoglobulin LCs, usually secreted by a small plasma cell clone. The fibrils consist of monoclonal kappa or lambda LCs [5]. A serum and/or urine monoclonal component is detectable by immunofixation and/or immunoelectrophoresis in 80—90% of patients. With the use of sensitive techniques, such as nephelemetric measurement of serum free LCs, an abnormal concentration of serum free LCs is found in > 90% of patients, with an over-representation of the lambda isotype compared with the kappa isotype [6]. Plasmocytosis is present in the bone marrow in > 50% of patients.

The diagnosis of AL is always based on histological findings using light microscopic examination, showing amorphous extracellular Congo red positive deposits (Fig. 1A), which display characteristic dichroism and apple green birefringence under polarized light (Fig. 1B) Non-invasive biopsies of abdominal fat and minor salivary glands should

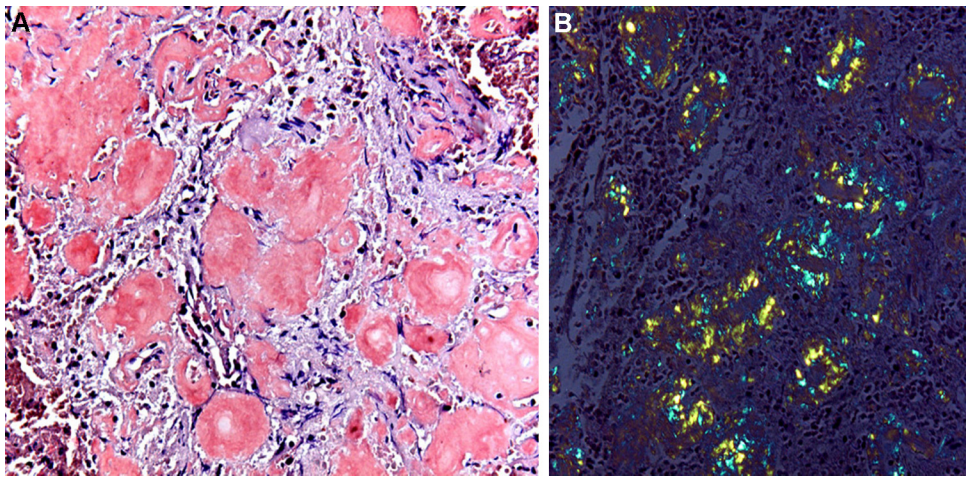

Figure 1. Typical amorphous extracellular Congo red-stained positive deposits under fluorescent light source showing important amyloid depositions (A), which display characteristic dichroism and apple green birefringence under polarized light (B).

be performed initially; the latter biopsy is usually positive in 80% of patients. If necessary, i.e. when tissue biopsies fail to demonstrate amyloid deposition, biopsy of a clinically affected organ (kidney, gastrointestinal tract or endomyocardial tissue) should be considered. Electron microscopy may be useful to confirm the presence of amyloid deposits, which typically display the ultrastructural appearance of randomly arranged fibrils (Fig. 2), 7—10 nm in external diameter. Immunohistological typing is indispensable to make the differential diagnosis between different types of amyloid disease (AL versus ATTR wild-type, mutant or with other precursors).

Diagnostic criteria for cardiac involvement

Cardiac involvement is one of the most frequent types of solid organ manifestation [5]. In patients with cardiac involvement, the lambda LC isotype is the most frequent and is observed in 70% of cases.

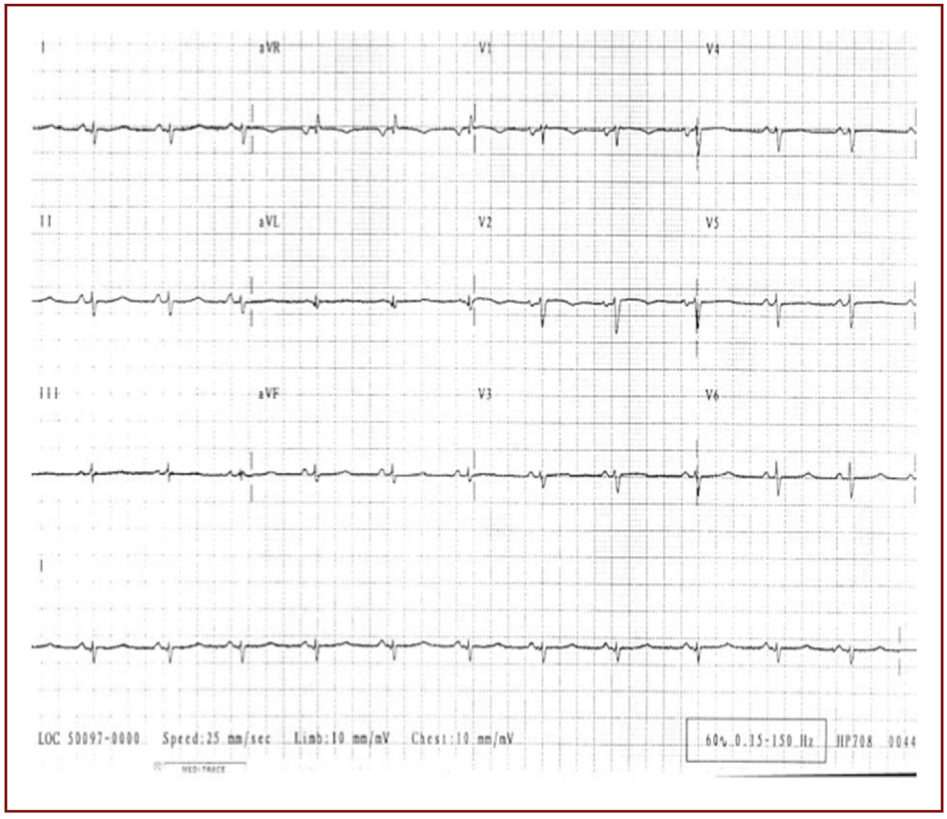

Figure 2. Typical electrocardiogram appearance of amyloidosis of the heart, showing a sinus rhythm, very low voltage with an abnormal axis and poor R-wave progression in the precordial leads.

Since 2005, organ involvement in systemic AL has been defined by consensus criteria [7], which were updated at the 2010 meeting of the International Society of Amyloidosis in Rome. Cardiac involvement is characterized by an increase in mean wall thickness in end-ventricular diastole of $\geq$ 12 mm by echocardiography, with no other obvious cardiac cause, associated with an increase in the concentration of *N*-terminal prohormone of B-type natriuretic peptide (NT-proBNP) to > 332 ng/L (in absence of renal failure).

Cardiac biomarkers

NT-proBNP and cardiac troponin have been used widely since 2004 for assessing cardiac involvement severity and prognosis in AL [8,9] and a current staging system—the Mayo Clinic staging—has been established, based on NT-proBNP (cut-off value = 332 ng/L; BNP = 100 ng/L) and cardiac troponin (cut-off value = 0.035 μg/L), in order to stratify patients into three groups:

- high risk (stage III: both biomarkers are increased);
- intermediate risk (stage II: at least one biomarker is above the cut-off value);
- low risk (stage I: both biomarkers are below the cut-off values).

This Mayo Clinic staging is now used by the medical community before the choice of therapy is made.

Recently, ultrasensitive troponin has emerged as a more sensitive biomarker of cardiac injury; thus, another classification has been proposed by Kristen et al. [10], using the same cut-off value for NT-proBNP and a cut-off value of 50 ng/L for ultrasensitive troponin.

Another biomarker —midregional proadrenomedullin, which is produced by many organs, including the heart— was tested in an Italian study in 2011 [11], in 130 patients with confirmed de novo AL. The authors found that a high concentration of midregional proadrenomedullin was associated with a higher early mortality rate of 40% at 6 months when its value was > 0.75 nmol/L.

Electric disturbances

Electrocardiograms (ECGs) are abnormal in 90% of cases with cardiac involvement. The largest study that reported ECG findings consisted of 127 patients with AL and biopsy-proven cardiac involvement seen at the Mayo Clinic [12]. The study confirmed that the two most common abnormalities were low voltage QRS complex (defined as all limb leads < 5 mm in height) and a pseudoinfarct pattern on the precordial leads (Fig. 2), which were seen in roughly 50% of the patients included. Right and left bundle branch block are uncommon. Other changes that may occur include conduction abnormalities (such as second and third degree atrioventricular block), more frequently atrial fibrillation in about 15% of patients [13] and, rarely, ventricular tachycardia in about 5% of patients. A recent study [14] that included a large number of patients with AL with and without cardiac involvement, reported that a fragmented QRS (notches and RsR' pattern in the absence of QRS prolongation) was significantly more frequent in patients with cardiac amyloidosis (28.5% vs. 11.7%; $P = 0.0008$). Moreover, the group with fragmented QRS had a significantly higher mortality rate compared with the 'normal' QRS group ($P = 0.0008$). According to the authors, fragmented QRS had a prognostic value independent of QRS duration, QTc interval, NT-proBNP serum concentration and LV wall thickness. However, these ECG findings are not specific to cardiac amyloidosis and any severe cardiomyopathy with severe myocardial injury may be responsible for a fragmented ECG, irrespective of its aetiology.

Twenty-four-hour Holter ECG monitoring might help to identify asymptomatic ventricular/supraventricular arrhythmias in > 75% of cardiac AL patients. Complex ventricular arrhythmias have been reported to be prognostic determinants for survival, but only couplets correlated with sudden cardiac death and were independent predictors of survival [15]. A 24-hour Holter ECG may also show the absence of heart rate variability due to autonomic dysfunction, which is frequent in cardiac amyloidosis [16].

Regarding endocavitary conduction disturbance, a large study [17] that included patients with confirmed AL found that they all had normal sinus function. However, the infra-Hisian conduction time was significantly prolonged (79 ms) and was independently associated with the occurrence of sudden death; the authors concluded that HV prolongation may be a marker of significant infiltration of myocardium by amyloid fibrils, which may be responsible not only for ventricular tachycardia, but also for severe atrioventricular conduction abnormalities with high degree atrioventricular block or asystole.

Echocardiographical findings

Cardiac involvement is usually characterized by the presence of an infiltrative/restrictive cardiomyopathy with classical echocardiographical findings, which have been well described [18,19], but also by new echocardiographical findings identified using strain imaging.

Transthoracic echocardiography (TTE) (Fig. 3A) typically shows the following features:

- increased LV wall thickness $\geq$ 12 mm with 'brilliant' speckled appearance of the myocardium (amyloid fibrils deposits are more echogenic than normal myocardium); a mean LV wall thickness > 15 mm was independently associated with worse outcome [20];
- normal or small LV cavity;
- preserved LV ejection fraction (LVEF) > 50% (at least in the early stage of the disease), but reduced S and E' waves at the basal, septal or lateral myocardium level, reflecting the poor longitudinal function and altered LV relaxation;
- abnormal mitral filling pattern, due to mild or moderate LV diastolic dysfunction (type I mitral or pseudonormalized pattern); and at a later stage, a typical severe restrictive mitral filling pattern with E/A ratio > 2, increased E/E' and small A wave due to atrial dysfunction;
- the elevated LV filling pressure may lead progressively to left atrial enlargement (diameter > 23 mm/m^2, area > 20 cm^2 or maximal volume > 28 mL/m^2), which seems not only to be helpful for differential diagnosis [21], but also to be independently associated with worse outcome in AL [22];

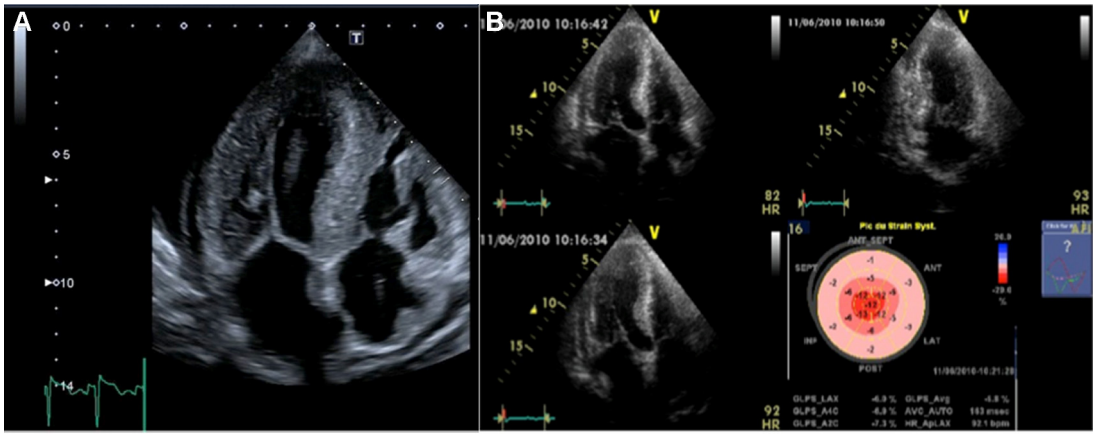

Figure 3. A. Typical echocardiography findings in cardiac amyloidosis: thickened and sparkled left ventricular (LV) walls, thickened interatrial septum, mitral and tricuspid valves, thickened right ventricular free wall, small pericardial effusion, normal LV cavity size and atrial enlargement. B. Example of a patient with light-chain amyloidosis and advanced cardiac involvement with two-dimensional altered global and basal longitudinal strain, despite a relative preservation of the apical longitudinal strain, named 'the apical sparing'.

- right atrial enlargement and dilated vena cave reflecting right ventricular (RV) filling pressure;
- increased interatrial septal thickness (it must be emphasized that this variable is much easier to measure by cardiac magnetic resonance imaging [cMRI] than by echocardiography);
- increased RV free wall thickness (> 7 mm) with RV systolic and diastolic dysfunctions associated with worse survival [23];
- left and right valve thickening, usually responsible for mild regurgitation;
- reduced aortic ejection time (< 273 ms), described as a prognostic factor [24];
- small pericardial effusion in 50% of cases, the presence of which is independently associated with worse survival [24]; exceptionally, an aspect of large pericardial effusion with tamponade may reveal the systemic disease [25];
- atrial thrombi may be seen, despite the presence of sinus rhythm; one large study that analysed the presence of atrial thrombi in patients with confirmed AL [13] found that AL patients were younger and had less atrial fibrillation than those with other types of amyloidosis; however, the AL group had significantly more intracardiac thrombi (51% vs. 16%; $P < 0.001$) and more fatal embolic events (26% vs. 8%; $P < 0.03$).

Diagnostic and prognostic value of new echocardiographical techniques

A large study recently published by Buss et al. [26], which included 200 consecutive patients with AL with systematic assessment of LV longitudinal function, showed that: longitudinal strain (LS) and 2D global LS (2D-GLS) were strongly correlated with NT-proBNP in patients with AL; reductions in LS and 2D-GLS were both independently associated with prognosis in AL, including overall survival, compared with standard TTE variables; and LS and 2D-GLS provided incremental value over NT-proBNP, cardiac troponin and all other clinical variables assessed.

Another recent study [27] was designed to show the diagnostic importance of two-dimensional speckle-tracking imaging in differentiating cardiac amyloidosis from other causes of LV hypertrophy. Using 55 patients with confirmed AL, the authors found that the amyloid heart is characterized by reduced basal strain and regional variations in LS from base to apex (Fig. 3B), and that a relative 'apical sparing' (average apical LS/[average basal LS + mid-LS]) pattern of LS is an easily recognizable, accurate and reproducible means of differentiating cardiac amyloidosis from other causes of LV hypertrophy.

Therefore, this technique appears useful not only for diagnosis but also for the independent assessment of prognosis in patients with AL.

Cardiac magnetic resonance imaging

cMRI is often performed when cardiac amyloidosis is suspected because it has an excellent spatial resolution for tissue characterization and is very sensitive for detecting the presence of infiltrative cardiomyopathy, even in cases of normal LV wall thickness.

cMRI allows precise measurement of the LV walls, the interatrial and RV free walls, biatrial enlargement and pericardial effusion (Fig. 4). cMRI is also useful for tissue characterization of the myocardium [28], by showing different patterns: transmural late gadolinium enhancement (LGE) or, more typically, a large diffuse annular LGE; less often a global heterogeneous LGE or rarely diffuse LGE, called 'patchy LGE'. Indeed, gadolinium has an interstitial distribution, and in patients with cardiac amyloidosis there is an increase in interstitial cardiac volume because normal myocardium is replaced by amyloid fibrils. Thus, gadolinium stays longer in the tissue, which explains the late gadolinium enhancement.

The prognostic significance of LGE or suboptimal nulling time (i.e. the determination of the optimal inversion time required to have the myocardium completely black in T1) is not yet clear. Maceira et al. [29], in a cohort of 29

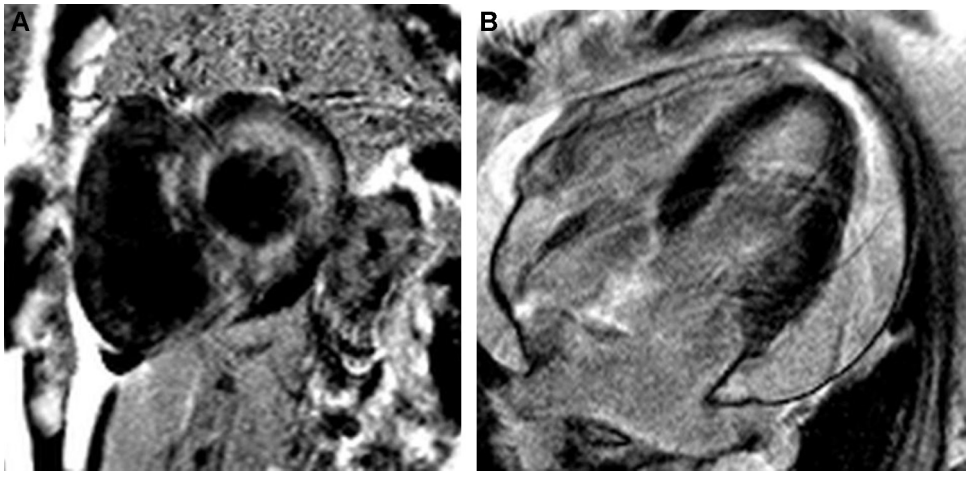

Figure 4. Cardiac magnetic resonance imaging. A. Short-axis section of a patient with hereditary transthyretin-related amyloidosis (ATTR) Val122Ile mutation, showing thickening and diffuse late gadolinium enhancement (LGE) of the left ventricular wall. B. Horizontal long-axis in an ATTR Val30Met late-onset patient, showing pericardial effusion, evidenced by diffuse LGE of the left and right ventricles, the interatrial septum and the left atrium.

patients, suggested that T1 mapping may have greater ability to predict outcome than LGE per se, possibly because it more accurately reflects the myocardial interstitial amyloid load. A small study by Mekinian et al. in 2010 [30] showed that the presence of LGE was a univariate predictor of outcome in patients with cardiac AL; however, it did not come out as an independent predictor of survival after adjusting for the presence of heart failure and high BNP concentrations.

Therefore, the additive value of this technique to existing prognostic indicators requires confirmation in larger series. cMRI may offer promise for the early detection of cardiac involvement using LGE, but this has yet to be proved.

Nuclear imaging

Several single-photon emission computed tomography tracers are used to visualize myocardial amyloid deposits: ^{99m}Tc-aprotinin, ^{99m}Tc-labelled phosphate derivatives and the serum amyloid P component. The latter is labelled with ^{123}I, a glycoprotein that binds in a calcium-dependent manner to all amyloid deposits, independent of the protein of origin; however, this tracer is useful for systemic amyloidosis but not for identifying cardiac involvement and is not available in all European countries. The phosphate derivative single-photon emission computed tomography tracers, labelled with ^{99m}Tc, have been used to detect cardiac involvement of amyloidosis; the mechanism of uptake seems to be related to the high calcium content in amyloid deposits. Among these bone tracers, ^{99m}Tc-3-3-diphosphono-1-2-propanodicarboxylic acid (^{99m}Tc-DPD) has been proven to be very useful in the differential diagnosis of ATTR and AL aetiologies. In AL, ^{99m}Tc-DPD uptake is absent or weak [31].

Although metaiodobenzylguaninine does not bind directly to amyloid deposits, ^{123}I-metaiodobenzylguaninine scintigraphy has been proven to be useful for revealing the impairment of cardiac nerve endings due to amyloid deposition; this scintigraphy seems attractive for the objective evaluation of cardiac sympathetic level, in relation to autonomic dysfunction [32].

Cardiac complications of myocardial amyloid fibril deposition

Symptoms are non-specific: dyspnoea due to heart failure, syncope, vertigo due to rhythm or conduction disorders and, rarely, chest pain. This is the reason why diagnosis is delayed. Cardiac involvement may have many serious consequences [5,33]:

- severe congestive heart failure with initially preserved LVEF and decreased LV compliance due to amyloid deposit, and advanced diastolic dysfunction;
- decreased LVEF may follow diastolic dysfunction, leading to terminal and fatal heart failure;
- chronic elevated LV filling pressure leads to left atrial enlargement then to paroxysmal or persistent atrial fibrillation; atrial thrombi are frequent in cardiac amyloidosis, even in patients with sinus rhythm, and can cause systemic embolic events;
- non-sustained or sustained ventricular arrhythmias are also potential complications of cardiac amyloidosis;
- conduction disturbances are more frequently encountered in cardiac ATTR and are prevented and treated by pacemaker implant;
- orthostatic hypotensive episodes are due to autonomic dysfunction and/or neurovegetative involvement or have a hypovolemic cause; severe dysautonomia can cause syncope and hypotensive cardiac treatment (angiotensin-converting enzyme inhibitors) should be avoided in these patients;
- autonomic dysfunction can be also expressed by the loss of heart variability; indeed, an SDNN < 50 ms on a 24-hour Holter ECG was found to be an independent predictor of short-term mortality in AL patients [16];
- chest pain may occur in rare cases where amyloid deposits affect the microcoronary circulation, whereas

the macrocoronary vessels are usually free of significant stenosis [34].

Management and treatment of light-chain amyloidosis

Treatment of AL focuses on the use of chemotherapy directed against the underlying B-cell clone-secreting amyloid-forming immunoglobulin LCs.

The decrease in or halting of the production of amyloidogenic proteins moves the balance towards the elimination of deposits. Therefore, treatment of AL is equal to treatment of the underlying plasma cell, lymphoplasmocytic or lymphoproliferative disorder to rapidly reduce the supply of the amyloidogenic monoclonal LCs, while using supportive measures to sustain the function of the organs involved.

All treatment strategies efficient in multiple myeloma or in lymphoproliferative disorders can be used, adapted to the type of haematological disease and the nature and number of affected organs, taking into account their potential toxicity. The goal of treatment should be the achievement of a haematological response, which is an important predictor of prolonged survival.

Conventional chemotherapy and intensive treatment with stem cell transplantation

Several studies have shown the efficacy of high-dose dexamethasone-based regimens in inducing haematological responses and prolonging survival. Impressive efficacy, with > 60% haematological response, has been reported with melphalan-dexamethasone regimens [35], with median survival up to 5 years.

In experienced centres, intensive treatment and autologous stem cell transplantation (ASCT) obtains a similar haematological response rate [36]. However, ASCT remains restricted to selected patients who are generally without advanced cardiac amyloidosis. In 2007, a French multicentre randomized prospective trial showed that, compared with ASCT, melphalan-dexamethasone had similar efficacy with less toxicity, resulting in increased survival (22.2 months in the ASCT group and 56.9 months in the group with oral melphalan-dexamethasone; $P = 0.04$) [35]. Whereas ASCT is still commonly used in the USA in patients without severe disease, it is no longer used in most European countries, except Germany; melphalan-dexamethasone has become the first-line treatment in France for the majority of patients.

Novel agents

Thalidomide, lenalidomide and the proteasome inhibitor bortezomib have been used in several studies with excellent results [37—39]. Bortezomib combined with dexamethasone produced clonal response rates of 70—90%, with 40% complete response, even in previously treated patients with refractory disease. The combination of melphalan-dexamethasone plus bortezomib was compared with melphalan-dexamethasone in an international ongoing randomized trial. Bortezomib may also be combined with cyclophosphamide and dexamethasone with good tolerance and impressive response rates [38,39], and this combination, due to its very rapid efficacy, is now the treatment of choice for patients with Mayo Clinic stage III patients in France.

Prognosis

In AL, survival depends mainly on the extension and severity of organ involvement, particularly the presence of amyloid heart disease, and on the haematological response to therapy. Prognosis is influenced relatively little by the underlying, usually non-proliferating, monoclonal plasma cells, even though bone marrow plasma cell infiltration > 10% has been associated with poorer outcome [40]. Only 15 years ago, overall survival in AL was poor, with a median overall survival of 18 months [41]. Since then, the disease prognosis has been transformed with the development of new strategies that efficiently suppress secretion of amyloid-forming LCs, giving a median survival of > 5 years. Early diagnosis is therefore a critical step to avoid irreversible damage, especially to the heart.

Cardiac supportive treatment

Apart from specific treatment of the underlying haematological disease, symptomatic treatment and supportive care are necessary in patients with organ failure. Most drugs commonly used for the treatment of congestive heart failure are inefficient or appear to be dangerous in patients with AL, ATTR or SSA [42]. Beta-blockers are deleterious because they decrease heart rate, which is the only mechanism that can maintain cardiac output in this disease; they may also aggravate autonomic dysfunction like angiotensin-converting enzyme inhibitors. In an in vitro study, digitalis has been shown to accumulate in cardiac amyloid deposits [43]; for this reason, digitalis is not recommended in patients with cardiac amyloidosis. Loop diuretics, given at high dosage in patients with severe fluid retention, are the mainstay of management. Amiodarone should be considered as first-line therapy for arrhythmia. Anticoagulation therapy is mandatory in patients with supraventricular arrhythmia but needs to be discussed in patients with sinus rhythm and severe contractile atrial dysfunction. Pacemaker implantation may be indicated in patients who develop symptoms of bradycardia or conduction disorders. A heart transplant should be considered in selected young patients with advanced amyloid cardiomyopathy [44,45], free from other comorbidities.

Hereditary transthyretin-related amyloidosis

ATTR—also named 'familial amyloid polyneuropathy' — was initially reported by the neurologist Corino da Costa Andrade in two coastal villages of Portugal in 1950 [46]. Since that time, the disease has been described as endemic in Japan (1968) and Sweden (1976), and sporadic cases have been reported in many countries. TTR is a transport protein mainly synthesized by the liver. The TTR gene is localized on chromosome 18 (18q23). The disease is transmitted as an autosomal dominant trait with high penetrance. More

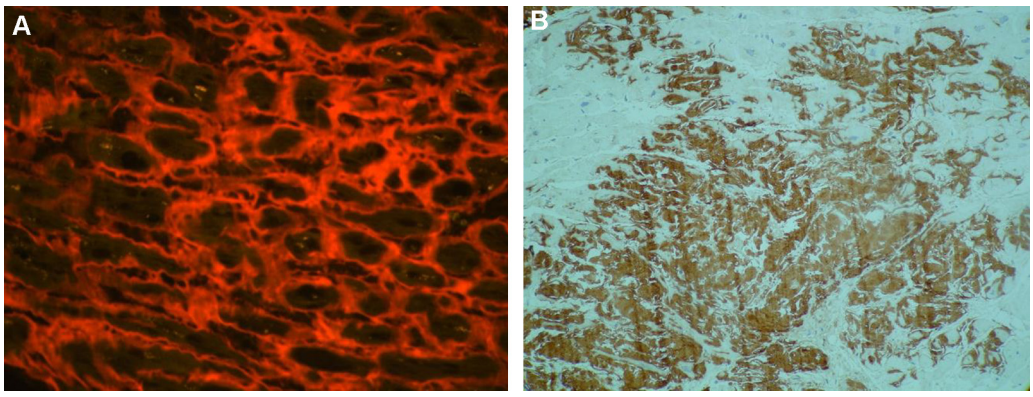

Figure 5. Patient with cardiac hereditary transthyretin-related amyloidosis. A. Congo red staining under fluorescent light source showing important amyloid deposition. B. Positive transthyretin immunostaining.

than 100 pathogenic mutations have been described. The most commonly found mutation is the replacement of valine by methionine at position 50 (Val50Met), first described in the Portuguese population. The variant TTR destabilizes the TTR tetramer and monomers aggregate in amyloid fibrils (Fig. 5).

The main clinical manifestations are neurological and cardiac. Neurological symptoms (due to TTR deposits) are sensory-motor peripheral neuropathy and autonomic dysfunction. The motor deficit involves the large sensory and motor nerve fibres. Walking becomes increasingly difficult, with neuropathic pain, leading to death within 10 years on average [47]. Autonomic dysfunction affects the cardiocirculatory (orthostatic hypotension), gastrointestinal and genitourinary systems. Gastrointestinal dysautonomia aggravates postural hypotension and progressive weight loss. Cardiac manifestations include episodes of arrhythmias, syncope or even sudden death due to severe conduction disorders, and dyspnoea and heart failure due to the restrictive cardiomyopathy as described above [48].

Clinical manifestations and age of onset vary depending on the TTR mutation, sex, parental gene transmission and geographical area [47]. For example, the Val50Met ATTR mutation in Portuguese patients occurs in their second or third decade, with peripheral neuropathy and cardiac conductive disorders. In other geographical areas, the same Val50met ATTR mutation has a late-onset (at age 50—70 years) and the clinical manifestations combine peripheral neuropathy, cardiac conductive disorders and heart failure [49]. In other ATTR mutations (Thr80Ala and Val142Ile), cardiac involvement is predominant.

ECGs, TTE and cMRI of cardiac ATTR show similar findings to cardiac AL, as described above. In asymptomatic ATTR carriers, cMRI may detect early cardiac involvement by focal myocardial LGE.

^{99m}Tc-DPD scintigraphy is useful for imaging amyloid deposits in the myocardium of patients with TTR-related amyloidosis. Positive phosphate scanning correlates with high amounts of amyloid fibrils in the heart. Absent in control subjects, ^{99m}Tc-DPD uptake is strong in ATTR amyloidosis, in both mutant and wild-type ATTR [31] (Fig. 6). The ^{99m}Tc-DPD uptake is reported to be a prognostic determinant of cardiac outcome in ATTR, either alone or in combination with LV wall thickness [50]. Cardiac two-photon excitation imaging with an amyloid-specific tracer (11C-BF-227) revealed significantly robust retention of tracer in myocardial amyloid deposition, promising future developments [51].

The diagnosis strategy for ATTR combines pathology and molecular genetic testing. ATTR is a gene of small size (7 kB), including four exons, and its screening by full sequencing of the coding parts is now easily accessible.

Cardiac medical supportive treatment is limited and is similar to that for AL. The specific treatment of ATTR is a liver transplant with or without a heart transplant, depending on phenotypic presentation and the age of the patient. The liver transplant eliminates the mutated TTR from the blood, but, for some patients, continued amyloid deposition can occur from wild-type (normal) TTR, particularly in the heart.

A new treatment has been developed to stabilize the tetramer and slow down the progression of the neuropathy (Vyndaquel®; tafamidis) [52]. So far, this treatment is limited to patients with mild or moderate neuropathy and the cardiac effects of this drug are going to be assessed shortly. New gene therapies (with antisense oligonucleotides to suppress hepatic TTR synthesis) are also going to be tested in ATTR.

Systemic senile amyloidosis (also called wild-type ATTR)

SSA is derived from native TTR, which results in the deposition of TTR mainly in the heart. The prevalence of cardiac TTR amyloid deposits is estimated at around 10% in people aged > 80 years and 50% in those aged > 90 years [53].

A study of 85 consecutive autopsies in patients aged > 80 years found amyloid deposits with positive TTR staining in 25% of cases [54]. SSA affects 25% of the very aged and is associated with genetic variation in alpha-2-macroglobulin [55]. The clinical significance of these limited deposits is not clear. In contrast, in some rare cases, TTR deposition in the heart results in an important increase in ventricle walls, mimicking concentric hypertrophic cardiomyopathy. Surprisingly, SSA occurred more than 90% in men (aged > 70

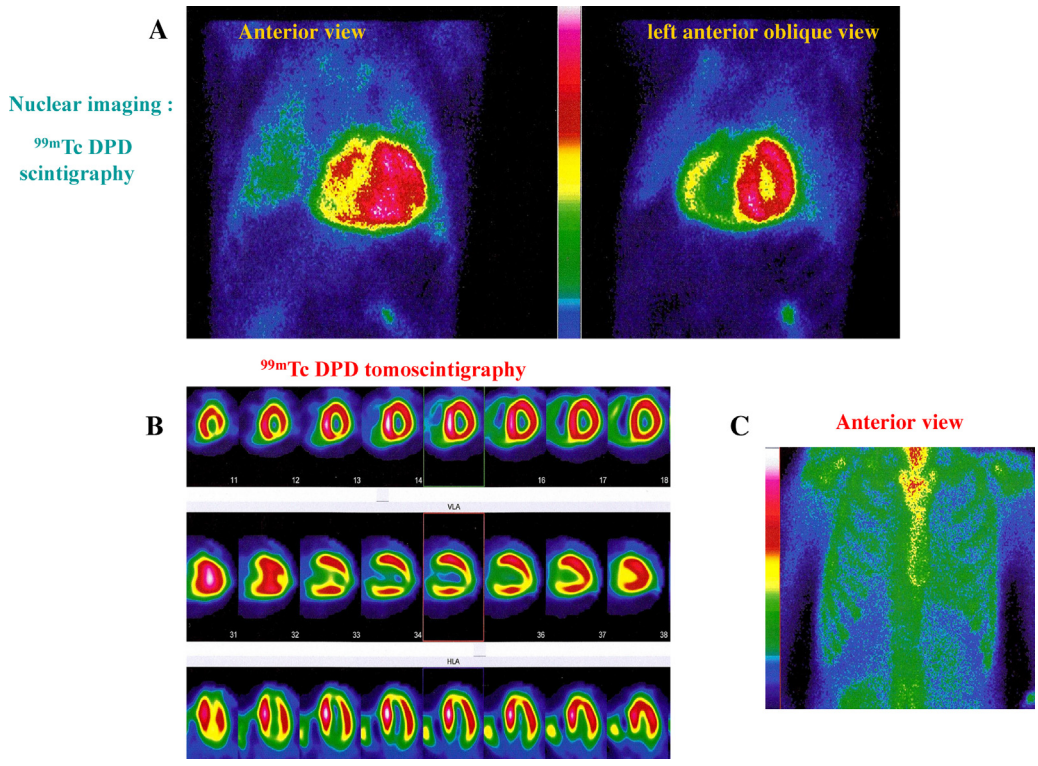

Figure 6. ^{99m}Tc-3-3-diphosphono-1-2-propanodicarboxylic acid (^{99m}Tc-DPD) nuclear imaging. A. Patient with cardiac systemic senile amyloidosis showing important ^{99m}Tc-DPD uptake in the heart. B. Cardiac ^{99m}Tc-DPD tomoscintigraphy in the same patient (the red colour corresponds to amyloid deposition). C. Patient with cardiac light-chain amyloidosis without heart uptake of ^{99m}Tc-DPD.

years). The mechanisms of normal TTR deposition in the heart are unknown.

Amyloid deposition in SSA is generally localized in the heart and the carpal tunnel. Salivary glandular, rectal or fat abdominal biopsies should be normal. ATTR gene sequencing is normal in SSA. SSA is characterized by an important symmetric increase in LV wall thickness (significantly thicker than that in AL and ATTR). History of myocardial infarction, arrhythmia and/or bundle branch block are present in one third of patients [48].

There is no specific, consistent sign on TTE and/or cMRI that allows the three main types of amyloid heart disease to be distinguished accurately. Endomyocardial biopsy is the only way to definitively diagnose SSA, through demonstration of ATTR deposits with no amyloidogenic TTR mutation. However, endomyocardial biopsies are invasive in elderly patients and are not performed for ethical reasons.

Nevertheless, ^{99m}Tc-DPD scintigraphy can accurately diagnose SSA cardiac amyloid deposition (Fig. 6A and B), in addition to normal TTR sequencing and normal serum free LC measurement [56]. Cardiological treatment is similar to ATTR; however because patients don't have symptomatic neuropathy, as seen in ATTR, cardiac therapeutic agents (angiotensin-converting enzyme inhibitors, beta-blockers), generally already prescribed for previous myocardial infarction or hypertension, are better tolerated than in other types of amyloidosis. Pacemaker implantation should be discussed, depending on symptoms and abnormalities on ECGs, 24-hour Holter ECGs and electrophysiological findings, if necessary.

Comparison between AL, SSA and ATTR cardiac amyloidosis

It is not possible to differentiate AL, ATTR and SSA accurately by TTE (Table 1).

A large longitudinal study [48] that included 233 patients with a clear-cut diagnosis by type of amyloid precursor (AL, $n = 157$; ATTR, $n = 61$; SSA, $n = 15$), compared the diagnostic/clinical profiles of the three different types of systemic cardiac amyloidosis. The main findings were that:

- average age at diagnosis was higher in AL than in ATTR; all SSA patients except one were elderly men;
- mean LV wall thickness was higher in SSA than in ATTR and AL;
- LVEF was moderately depressed in SSA but not in AL or ATTR;
- ATTR patients displayed low QRS voltage less often (25% vs. 60% in AL; $P < 0.0001$);
- AL patients had greater haemodynamic impairment.

Moreover, by multivariable analysis, AL was independently associated with worse survival, whereas SSA predicted freedom from major cardiac events. The authors concluded that AL, ATTR and SSA should be considered as three different cardiac diseases, characterized by different pathophysiological substrates and courses. Other studies showed that cardiac AL was associated with a worse prognosis and more rapid progression of heart failure than SSA [57]. The difference in survival, despite evidence of more

Table 1 Comparison of light-chain, hereditary transthyretin-related and systemic senile amyloidosis.

	AL	Hereditary ATTR			SSA
		Val30Met early onset	Val30Met late-onset and other mutation	Val122Ile cardiac mutation	
Clinical					
Average age (years)	60	30	> 50	> 50	> 75
Ethnic or country	White and black	Portuguese	French	White and black (Val122Ile prevalence in black population: 3—4%)	(90% in men)
Extracardiac manifestations	Myeloma or monoclonal gammopathies; renal insufficiency; CTS	Neuropathy; autonomic dysfunction; CTS	Neuropathy; CTS	CTS	CTS
Orthostatic hypotension	++	++	++	—	—
ECG					
Low QRS voltage	+++	—	++	+++	++
Pseudoinfarct pattern	+++	+	+++	+++	++
Biomarkers					
BNP, troponin	+++ for risk stratification	+	++	+++	+++
TTE					
Wall thickness	+ ++ (usually asymmetric)	+	+++	+++	+++ (concentric)
LVEF	Normal or ↓ (late)	Normal	Normal or ↓ (late)	Normal or ↓ (late)	Normal or ↓ (late)
LV strain[a]	↑↑↑	↑	↑↑	↑↑↑	↑↑↑
Restrictive mitral pattern	+++	—	++	++	++
Other features	RVH; pericardial effusion	—	RVH; inconstant pericardial effusion	RVH; inconstant pericardial effusion	RVH; inconstant pericardial effusion
cMRI					
Annular subendocardial	++	—	++	++	+

Table 1 (*Continued*)

	AL	Hereditary ATTR			SSA
		Val30Met early onset	Val30Met late-onset and other mutation	Val122Ile cardiac mutation	
LGE localization					
Patchy	+++	+	++	+++	+++
Nuclear imaging					
DPD scintigraphy	+ (not significant)	+	+++	+++	+++
Biopsy					
Positive Congo red biopsy; appropriate staining (TTR, kappa, lambda)	Immunoelectrophoresis: positive light-chains	Biopsy: positive TTR	Biopsy: positive TTR	Biopsy: positive TTR	Myocardial biopsy: positive TTR; negative light-chains
Genetic					
Mutation		ATTR mutation	ATTR mutation	ATTR mutation	No ATTR mutation

AL: light-chain amyloidosis; ATTR: hereditary transthyretin-related amyloidosis; BNP: B-type natriuretic peptide; cMRI: cardiac magnetic resonance imaging; CTS: carpal tunnel syndrome; DPD: 3-3-diphosphono-1-2-propanodicarboxylic acid; ECG: electrocardiogram; LGE: late gadolinium enhancement; LV: left ventricular; LVEF: left ventricular ejection fraction; RVH: right ventricular hypertrophy; SSA: systemic senile amyloidosis; TTE; transthoracic echocardiography; TTR: transthyretin.

[a] Increase in LV strain means decrease in left ventricular contractility.

myocardial disease in the senile group, suggests that heart failure in cardiac AL may have a toxic component, related to the direct toxicity of the circulating monoclonal LC [58] on the myocyte. Another study [59], focusing on survival analysis of patients with amyloid cardiomyopathy, showed that the hereditary ATTR aetiology appeared as an independent predictor of better survival compared with AL patients.

Clinical implications

There are three main questions that the clinician should be aware of: how to detect cardiac amyloidosis; when to think about it; and to whom to refer the patient?

In fact, a patient with dyspnoea, unexplained fatigue and LV hypertrophy on TTE contrasting with the microvoltage of QRS amplitude should alert the clinician to an infiltrative process rather than a classical sarcomeric hypertrophic or hypertensive cardiomyopathy; in this case it is important to refer the patient to a specialist in internal medicine and/or a haematologist to perform more specific biological and/or genetic testing, as described above.

Conclusion

Cardiac involvement in amyloidosis remains difficult to diagnose and treat. Extracardiac signs, in addition to unexplained LV thickening on echocardiography in the absence of increased voltage on ECG, favour amyloid cardiomyopathy. Confirmation of amyloid type is now possible in most cases, using different modern methods. The cMRI pattern of LGE appears to be very characteristic. ^{99m}Tc-DPD scintigraphy is an interesting technique for revealing the cardiac deposits of ATTR and SSA.

Unlike other causes of heart failure, supportive treatment is usually very limited and can be dangerous. Despite important developments in chemotherapy for AL, the prognosis of patients with advanced cardiac involvement remains poor. SSA is probably often underdiagnosed but has a better prognosis than AL and ATTR.

Finally, a variety of novel specific therapies are on the horizon, which can inhibit new amyloid formation and enhance clearance of existing deposits.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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