

Cardiac amyloidosis: a review of the literature

N. de Marneffe^a, R. Dulgheru^b, A. Ancion^b, M. Moonen^b and P. Lancellotti^c

^aDepartment of Cardiology, University Hospital of Liege, Liege, Belgium; ^bHead of Clinic, Department of Cardiology, University Hospital of Liege, Liege, Belgium; ^cProfessor at the University of Liege, Head of the Cardiology Department, Director of the Cardiovascular GIGA, University Hospital of Liege

ABSTRACT

Cardiac amyloidosis is a rare disease associated with severe morbidity and mortality. There are three main types of amyloidosis associated with cardiac involvement: light chain (AL), familial or senile (ATTR) and secondary amyloidosis (AA). Cardiac amyloidosis often results in heart failure with preserved left ventricular ejection fraction, may display echocardiographic features of restrictive cardiomyopathy associated with left ventricular hypertrophy or mimic hypertrophic obstructive cardiomyopathy. However, left ventricular systolic dysfunction and normal wall thickness can sometimes be encountered. Imaging studies (echocardiography, bone scintigraphy, cardiac magnetic resonance) and blood and urine analysis are usually the main tools for the diagnosis. Sometimes, a tissue biopsy may be necessary. Treatment, which is constantly improving, will be carried out on two fronts: treatment of the symptoms and complications that the disease already caused and prevention of additional amyloid deposits while managing the concomitant complications. The purpose of this article is to review the management of cardiac amyloidosis.

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Introduction

Systemic amyloidosis is a very rare disease in which misfolded proteins (fibrils) become resistant to cellular catalytic processes and accumulate in tissues interstices, leading to organ dysfunction. Amyloid fibrils are derived from one and/or more precursor proteins called amyloidogens.

The disease presents itself in different forms. The most common are: immunoglobulin light chain amyloidosis (AL), secondary amyloidosis (AA), familial amyloidosis (TTR-h), senile/wild-type amyloidosis (TTR-wt) and dialysis associated amyloidosis [1].

Multiple organs can be affected: liver, kidney, lung, nerves, intestines and especially the heart. Organ type involvement depends on the protein causing amyloid deposition.

AL amyloidosis is one of the most common, but it affects only 12 people per million per year in the US population [2]. However, TTR amyloidosis seems to be more prevalent. It is often under-diagnosed, so its prevalence is probably even higher. Autopsy series have found amyloid deposits in 25% of patients over 85 years old [3].

In this article, we will mainly focus on the management of cardiac amyloidosis (CA) and on the 2 most common forms causing it, which are AL and TTR.

Physiopathology

It is important to determine the type of amyloidosis because treatment and prognosis vary according to the form.

The nomenclature for the different types of amyloidosis is AX, where 'A' indicates amyloidosis and 'X' represents the protein present in the fibrils.

The 2 major types of amyloidosis leading to cardiomyopathy are AL and TTR amyloidosis. Other types include the AA type, atrial natriuretic peptide (ANP), and immunoglobulin heavy chain (AH) type, but they represent only a minority (<5% of cases) [1] (Table 1).

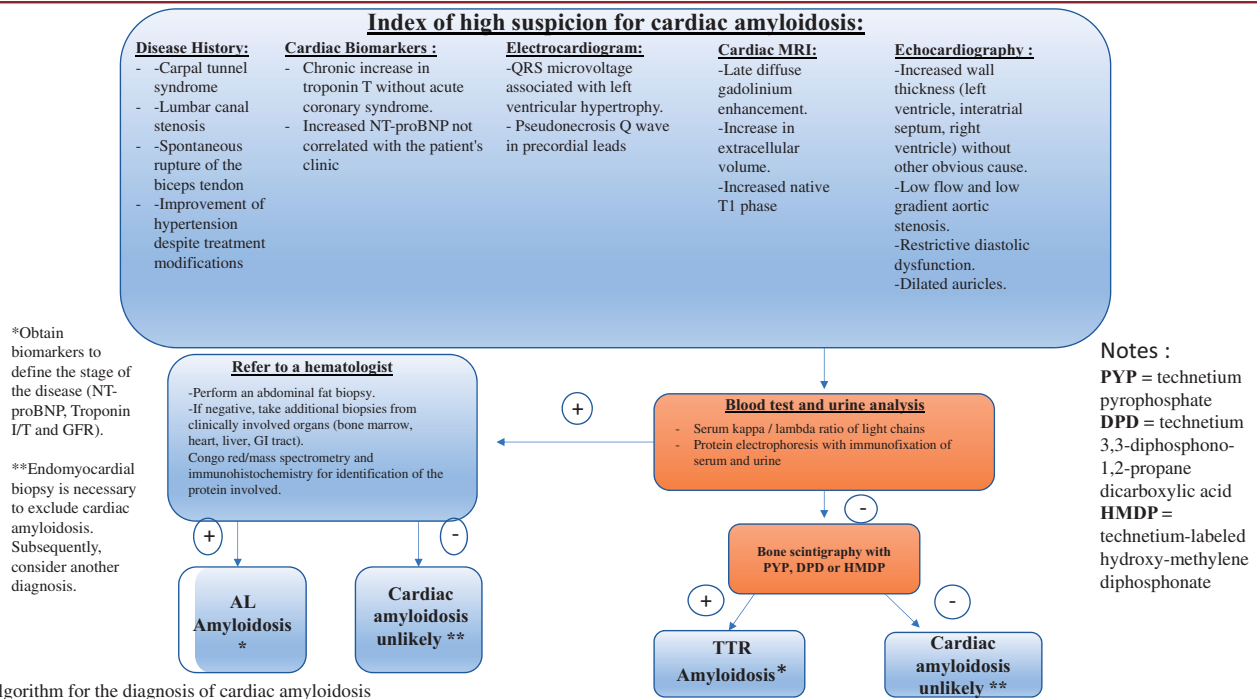
Physiopathology of AL amyloidosis

AL is the most severe subtype. It is generated by clonal plasma cells (multiple myeloma) or by a proliferative syndrome of the B lineage (Waldenström macroglobulinemia or lymphoma) and is characterised

Table 1. Characteristics of the different cardiac amyloidosis.

	AL Amyloidosis	TTR-hereditary Amyloidosis	TTR-wild Amyloidosis	Secondary Amyloidosis (AA)	Atrial natriuretic peptide Amyloidosis (ANP)
Incidence/age	<ul style="list-style-type: none"> • 3 to 12 people / million inhabitants • >50 years old (median age 63 years). Predominantly male. 	<ul style="list-style-type: none"> • Dependent on mutation. • Variable depending on the mutation (between 30 and 80 years with median age at 39 years). Slight male predominance. Mutations are endemic in some places (Ireland, Japan, sub-Saharan Africa). 	<ul style="list-style-type: none"> • Incidence unknown because underdiagnosed. • Generally > 60 years (median age 75) and more often African Americans 	<ul style="list-style-type: none"> • Decreased compared to inflammatory diseases. Increased due to chronic infections related to intravenous and subcutaneous drugs • 50 years or older (median age 50) Slight male predominance 	<ul style="list-style-type: none"> • Very rare • In the elderly, with a predominance of women. • Its prevalence increases linearly after the third decade.
Associated factors	<ul style="list-style-type: none"> • Multiple myeloma, MGUS, Lymphoma, Waldenström. 	/	<ul style="list-style-type: none"> • Age. 	<ul style="list-style-type: none"> • Infection, chronic inflammatory disease, cancer. 	<ul style="list-style-type: none"> • Persistent PNA production is most common in patients with long-standing heart failure.
Protein involved	<ul style="list-style-type: none"> • Immunoglobulin light chains and sometimes heavy chains. 	<ul style="list-style-type: none"> • Mutated transthyretin (Mutation at a nucleotide level). • Autosomal dominant disease. • Val30Met: The most common. Japan, Sweden, Portugal. • Val122Ile: USA, United Kingdom, West Africa. • Thr60Ala : USA, United Kingdom 	<ul style="list-style-type: none"> • Non-mutated transthyretin. 	<ul style="list-style-type: none"> • AA protein from the inflammation protein (SAA). 	<ul style="list-style-type: none"> • ANP protein.
Organ damage	<ul style="list-style-type: none"> • Kidney +++(50% to 60% of patients) • Peripheral/autonomic nerves (22%) • Liver (20%) • Spleen • Gastrointestinal • Lung • Muscle. • Periorbital ecchymosis or macroglossia is almost pathognomonic of AL 	<ul style="list-style-type: none"> • Nerves (peripheral and autonomic). • Eyes (Glaucoma, dry eyes). 	<ul style="list-style-type: none"> • Carpal tunnel syndrome (often bilateral) preceding the diagnosis by 5 to 10 years. • Lumbar stenosis. • Rupture of the biceps tendon. 	<ul style="list-style-type: none"> • Kidney +++ (Renal failure and proteinuria) • Liver ++ (Hepatomegaly) • Spleen (Splénomégaly). • Rare: nerves, digestive tract. 	/
Heart disease	<ul style="list-style-type: none"> • Diastolic dysfunction • Hypertrophic cardiomyopathy. 	<ul style="list-style-type: none"> • Conduction disorder • Atrial fibrillation (31 to 52%) • Heart failure. • Hypertrophic cardiomyopathy (sometimes asymmetric) • Aortic stenosis (low flow low gradient). 	<ul style="list-style-type: none"> • Atrial fibrillation (38–67%). • Conduction disorder. 	<ul style="list-style-type: none"> • Heart (2% of patients). 	<ul style="list-style-type: none"> • Atrial fibrillation.
Prognosis	Untreated, the median survival after the onset of heart failure is about 6 months, but modern therapies can put the disease into prolonged remission and extend life by several years	Median survival is approximately 10 years for those with polyneuropathy versus 2.5 years for those diagnosed with cardiomyopathy (Val122Ile).	The median survival was 3.6 years.	The median survival is 11 years.	?

Table 2. Modified algorithm for the diagnosis of cardiac amyloidosis from the article by Ruberg, F. L and al. Transthyretin Amyloid Cardiomyopathy. Journal of the American College of Cardiology.



by a secretion of fragments of light or heavy chain of immunoglobulin.

In AL, fibrils are formed and deposited in any organ at the extracellular level, with the exception of the central nervous system. The kidney is most frequently involved, leading to a nephrotic syndrome [4].

The heart is affected in 50–75% of cases; fibril deposits precipitate in the extracellular part of the myocytes, causing myocardial restriction and possibly leading to either systolic and/or diastolic dysfunction [5]. The cardiotoxic effect of light chains on cardiomyocytes has also been demonstrated. The light chains bind to the cardiomyocytes causing metabolic dysfunction of the cell without causing cell death which may explain the rapid progression of cardiac dysfunction in AL amyloidosis [6].

Symptoms of AL amyloidosis are non-specific. They may present as peripheral oedema, fatigue, weight loss, dysphagia, orthostatic hypotension - a sign of autonomic nervous system dysfunction or cardiac involvement -, as well as exertional dyspnea. Some signs are quite pathognomonic of AL amyloidosis such as periorbital ecchymosis or macroglossia. However, they are rare (<15% of cases).

Physiopathology of TTR amyloidosis

TTR amyloidosis is derived from a protein called 'transthyretin' produced by the liver and sometimes

by the choroid plexus or retinal epithelial cells (<5%). It allows the transport of thyroxine (T4) and retinol (Vitamin A) in plasma [7].

There are 2 distinct entities of TTR amyloidosis.

The hereditary form (ATTR-h) results from one of more than 130 mutations in the TTR gene (chromosome 18). Typically, a single amino acid modification in the protein's structure predisposes to instability of the TTR tetramer and enhances its dissociation into amyloid-forming monomers or oligomers [2].

It is a rare autosomal dominant disease with variable penetrance. A family investigation should therefore be systematically proposed in these patients. The most known mutation is the Val30met mutation: it is endemic in many regions (Japan, Sweden, Portugal, Cyprus).

In the United States and the United Kingdom, the Val122Ile mutation is the most common.

Generally, patients present first with peripheral and autonomic polyneuropathy, which can sometimes camouflage cardiac involvement. The latter comes in advanced stages of the disease and is a factor of poor prognosis [8].

Initially, cardiac conduction abnormalities (atrio-ventricular block or bundle branch block) or arrhythmia (atrial fibrillation) predominate, followed by heart failure with preserved ejection fraction [5].

In the wild-type form (ATTR-wt) there is no mutation in the protein encoding TTR.

Currently, there is no clear explanation for the mechanism of ATTR-wt amyloidosis. There seems to be some similarities with the hereditary form.

The disease is predominant in males (>90%) and is a disease of the elderly (mean age at diagnosis 74 years). It tends to affect Caucasians. The average survival is estimated at 3.6 years at diagnosis [5].

Patients with bilateral carpal tunnel syndrome, spinal stenosis, or spontaneous rupture of the biceps tendon (Popeye's sign) should be investigated for ATTR-wt, as these may be harbingers of cardiac involvement which has a poor prognosis [3].

Occasionally, in ATTR-wt there may be autonomic/peripheral neuropathy, but this is less common.

Cardiac involvement is more common in the wild type form than in the hereditary form. Conduction disorders (atrioventricular block, bundle branch block) are predominant, with the need for a pacemaker in one third of cases [5].

Atrial fibrillation alone may be one of the first signs of cardiac damage in ATTR-wt and its detection should prompt rapid anticoagulation. The infiltrative and rigidifying nature of amyloidosis in the atrium (reduced capacity of the atrium to expand during filling) leads to a so-called atrial myopathy and to a higher rate of thrombus formation, even in patients without documented atrial fibrillation.

Diagnosis

Treatments have improved in CA. It is important to make an early diagnosis of the disease so that treatment given in the early stages of the disease to improve patient's chances of survival.

CA is generally considered a form of restrictive cardiomyopathy, that is, a myocardial disease associated with increased parietal stiffness, causing elevated ventricular filling pressure and leading to congestive heart failure symptoms and signs.

There are many different phenotypes of cardiac involvement in amyloidosis. The differential diagnosis is quite broad and it is not uncommon to confound amyloidosis with hypertensive heart disease, with hypertrophic cardiomyopathy, aortic stenosis, ischaemic disease or heart failure with preserved ejection fraction [9]. Fabry disease, sarcoidosis, and hemochromatosis should also be considered in the differential diagnosis. Recently, a diagnostic algorithm has been proposed (Table 2).

In the following paragraphs, we are going to detail some findings allowing to guide us towards the final diagnosis:

- The electrocardiogram can exclude atrial fibrillation or conduction disorders. Microvoltage in the standard leads (I, II, III, AvF, AvL, AvR) coupled with signs of left ventricular hypertrophy increases the sensitivity and especially the specificity (91 to 100%) of detecting CA. Microvoltage is defined as a QRS amplitude < 5 mm in the standard leads, and below 10 mm in the precordial leads. This sign is found in 50% of AL amyloidosis cases, whereas it is present in one third of patients with TTR amyloidosis (40% senile or 25% hereditary) [1].
- Cardiac markers are used for the diagnosis of cardiomyopathy in suspected CA and for its follow-up.

In AL amyloidosis, NT-ProBNP is an excellent tool to detect cardiac damage well before cardiac decompensation disproportionately increased in the early stages of the disease.

On the other hand, NT pro BNP can be used to monitor treatment [10].

Troponin T coupled with NT-ProBNP allows to evaluate the severity of the disease. The European classification, derived from the old Mayo Clinic classification (2004), hierarchises the severity into 4 stages based on troponin T (lower or higher than 0.035 ug/L) and NT pro-BNP values (lower or higher than 332 ng/L).

In stage I (100% survival at 3 years), the values are below the norm. For stage II (52% 3-year survival), one of the values must be above or equal to the norm. In stage III (24% survival at 3 years), both values are equal or above the norm. And finally in stage IV (19% survival at 3 years), both values are equal or above the norm but NT-ProBNP is > 8500 ng/L [3].

- Echocardiography plays an important role in the diagnosis of CA but has unfortunately a low sensitivity and a low specificity.

The 'granular and scintillating' appearance of the myocardium, once described as a typical sign, has been shown to be a non-specific presentation [11].

Distinguishing between different types of hypertrophic cardiomyopathy and amyloidosis remains a challenge.

Left ventricular hypertrophy with a thickness >12 mm in the absence of other plausible causes of ventricular hypertrophy is one of the

echocardiographic criteria for suspecting CA. There is usually no left ventricular dilatation or very rarely mild dilatation. Patients with CA often have angina with nonobstructive epicardial coronary artery disease, and it is likely that the left ventricular systolic dysfunction and angina are manifestations of chronic myocardial ischaemia due to amyloid damage to small vessels with relatively less myocardial infiltration [12].

Atrial enlargement and dysfunction, thrombus or stasis in the left atrium or left atrial appendage, pericardial effusion, valve thickening, right ventricular and interatrial septal hypertrophy and restrictive diastolic dysfunction are all red flags for CA.

Typically, ejection fraction is preserved at baseline but may deteriorate with disease progression.

In 2010, a landmark study by Rapezzi et al. first noted the differences between echocardiographic findings and clinical course in patients with CA. In AL amyloidosis, there was instead impairment of diastolic function measures. Morphological involvement was not predominant (left ventricular thickness). Pericardial effusion was also more frequently found in AL amyloidosis [13].

In TTR amyloidosis, thickening of the mitral and tricuspid valves was most common.

Altered global strain with an apex-base gradient is very specific for CA (relative apical sparing pattern) and is often seen when the left ventricular ejection fraction is still preserved (Figure 1) [14].

- Cardiac nuclear magnetic resonance is useful for rapid diagnosis in the early stages of CA.

This is particularly true when serum biomarkers (Troponin T and NT-ProBNP) and electrocardiographic

and echocardiographic findings are not yet evident or typical of CA.

Because of the accumulation of amyloid deposits in the interstitial part:

1. **Unenhanced myocardial T1** values in CA are high compared with other diseases with hypertrophic patterns.
2. **Unenhanced myocardial T1** values exceeding certain thresholds (depending on equipment) are pathognomonic of CA.
3. **Late gadolinium enhancement** reflects extensive extracellular binding, thus protein accumulation. This is reflected not only in several enhancement patterns in the ventricles and atria, but also in increased values when the extracellular matrix is quantified.

Recent data have shown that **diffuse transmural late gadolinium enhancement** is more prevalent in TTR amyloidosis than in AL amyloidosis, ranging from 63% to 71% versus 27% to 50% of patients, respectively. However, because of the amyloid deposits, late subendocardial enhancement is more prevalent in AL amyloidosis (39%) whereas it is present in 12% to 24% of TTR amyloidosis [15].

More often in TTR amyloidosis, there is right ventricular free wall enhancement (96–100% of cases), in contrast to 72–77% of cases in AL amyloidosis [16].

The presence of late enhancement is a prognostic factor for the patient associated with other factors such as left ventricular ejection fraction, left ventricular mass index, NT-proBNP [15].

Another parameter is the **quantification of the extracellular volume**. This reflects the interstitial



Figure 1. Case of cardiac TTR amyloidosis. Image from left to right: (1) Alteration of the global Strain with an Apex-base gradient 'Apical sparing'. (2) Mild concentric hypertrophy (12 mm) with thickening of the mitral and tricuspid valve leaflets and thickened interatrial septum. The atria are dilated.

space fraction over the myocardium and can be calculated using the patient's haematocrit and the change in signal intensity after gadolinium administration in blood and myocardium. It is increased in patients with CA and is specific when it is above 0.40. When it is between 0.30 and 0.40, it is also useful for discovering early disease for both AL and TTR amyloidosis. At this stage, there is less cardiac involvement and early treatment could prevent disease progression [17].

- Cardiac scintigraphy using bone tracers, several studies have demonstrated that these ^{99m}Tc radio-labeled tracers, such as ^{99m}Tc-DPD, ^{99m}Tc-HDMP, and ^{99m}Tc-PYP, offer high specificity and sensitivity for the diagnosis of TTR amyloidosis in the absence of monoclonal gammopathy [18].

The intensity of cardiac uptake at 3 h after tracer injection is graded using a semi-quantitative visual scale compared with the bone signal. This is divided into 4 grades called "Perugini grading scale" (from grade 0 to 3). If there is no monoclonal gammopathy, scans with a visual score above or equal to 1.5 on planar images and above or equal to 2 on the 3-h SPECT are classified as positive for TTR amyloidosis if AL amyloidosis is excluded.

Blood and urine protein electrophoresis with immunofixation is always required when bone scintigraphy is suggestive of CA because AL cases may show bone tracer fixation in the myocardium. Cardiac scintigraphy is thus not specific for ATTR. Biopsy may be indicated [19] if the clinical, echocardiographic and/or CMR suspicion is high but cardiac scintigraphy is negative. A negative scintigraphy does not exclude TTR amyloidosis.

Scintigraphy is unable to differentiate senile from hereditary TTR amyloidosis [20].

- Biopsy: Endomyocardial biopsy remains the gold standard for diagnosis. However, this technique is invasive and of limited accessibility. Therefore, current diagnostic strategies are often based on clinical, laboratory and imaging findings. If this is not sufficient, a non-cardiac biopsy must be performed. This is often used for the diagnosis of AL amyloidosis. Samples are taken from certain tissues, such as the abdominal fat pad, the salivary glands on the inside of the lip (a less invasive procedure), the digestive tract during an endoscopic examination, a kidney biopsy or a bone marrow biopsy. In TTR amyloidosis, endomyocardial biopsy is not necessary if echocardiography

and DPD scintigraphy confirm amyloidosis and AL is ruled out by blood and urine electrophoresis with immunofixation [21].

On the other hand, genetic testing will be essential to see if the disease is an inherited form or not [3].

The biopsy is then analysed with Congo red with yellow-green birefringence in polarised light to distinguish the amyloid deposits. Amyloid typing will be performed by tissue mass spectrometry or immunohistochemistry by highly experienced clinicians. Mass spectrometry is the test of choice to detect the type of amyloid deposits.

Treatments

Treatment has two targets: treatment of diastolic heart failure (which has certain particularities) and targeted therapies (depending on the type of CA).

Treatment of heart failure

CA is a restrictive heart disease characterised by a small and less compliant left ventricle. Atrial contractility is important in order to preserve good ventricular filling in the setting of diastolic dysfunction associated with CA. To improve the patient's main symptom, which is dyspnea, one must therefore optimise the patient's blood volume and maintain the patient in sinus rhythm. Since the myocardium is rigidified by the infiltration of fibril deposits, it can no longer easily adapt to preload variation. There is therefore a difficult balance because of the narrow window between too high and too low filling pressures that can lead to syncope or orthostatic hypotension.

In patients with CA and heart failure, the general approach involves dietary advice. Fluid restriction and daily weight gain are necessary [22].

Congestive symptoms are treated primarily with loop diuretics sometimes combined with an aldosterone antagonist [22].

Treatment of heart failure in CA is different from other cardiomyopathies. In CA, optimal treatment of heart failure could result in mild side effects (hypotension) or adverse effects (syncope) in patients receiving neurohormonal blockade. In addition, cardiac output is rate-dependent, which, together with the tendency to orthostatic hypotension, may account for some of the intolerance or ineffectiveness of neurohormonal blocking agents [23].

Therefore, it is not recommended in these patients to prescribe beta-blockers, angiotensin-converting

enzyme inhibitors, and sartans. Sometimes it is necessary to use beta-blockers to achieve rhythm control in a patient with atrial fibrillation, but care should be taken. Digoxin, on the other hand, is rather contraindicated because of the risk of sudden death and an increased risk of arrhythmogenesis because it binds easily to fibrillar deposits increasing its concentration [24].

Non-dihydropyridine calcium antagonists are also contraindicated because of their negative inotropic effect, which can lead to severe hypotension and sometimes syncope [23].

Atrial fibrillation is a common arrhythmia in CA due to infiltration of the atria by fibril deposits, which decreases the initial compliance of the atria. It is necessary to maintain as much as possible a sinus rhythm as well as the 'atrial kick' in order to have a sufficient atrial mechanical function for good ventricular filling. In the early stages, it is necessary to propose ablation, especially in the case of atrial flutter [8]. In the later stages, ablation is often unsuccessful because of the high risk of recurrence [25].

Given the lack of compliance and contractility of the left atrium, even in sinus rhythm, the risk of thrombus formation is not low. Indications for anticoagulation include the presence of atrial thrombus, the presence of atrial fibrillation, and a weak or absent A wave on the Doppler study, suggesting impaired atrial contractility, even in sinus rhythm [26].

For anti-arrhythmic drugs, amiodarone is the safest drug.

In CA with severe conduction abnormalities, the indications for pacemakers follow the current pacing recommendations. However, caution should be exercised when initiating a pacemaker prophylactically in CA. This may lead to additional hemodynamic disturbances because of ventricular asynchrony or because of secondary tricuspid insufficiency related to the right lead that may cause right heart failure. A recent study done on TTR amyloidosis by Donallan et al., in patients with CA for whom there was an indication for pacemaker placement, showed that cardiac resynchronisation with biventricular pacing resulted in a better outcome than right ventricular pacing. Indeed, this resulted in improvement in mitral regurgitation, left ventricular ejection fraction, and dyspnea [27].

In either AL or TTR amyloidosis, the risk of sudden death is not low.

Nonsustained ventricular tachycardia is often found in AL amyloidosis (27% of cases). However, the number of deaths due to cardiac arrest is almost the same whether ventricular tachycardia is present or not [26].

It was noted that in most cases, the activity during sudden death was pulseless electromechanical activity. Primary prevention with a defibrillator is hence not recommended. It is therefore necessary to have had at least one history of sustained ventricular tachycardia or ventricular fibrillation and a life expectancy of at least 1 year (Class II a Evidence C) to benefit from a defibrillator [28].

Specific treatments

There are many specific treatments for AL and TTR amyloidosis. Their mechanisms are different according to the type of CA.

AL amyloidosis

The treatment of AL amyloidosis is based on blocking plasma cell, lymphoplasmacytic and lymphocytic proliferation which is responsible for the formation and production of the monoclonal protein. Whether it is an amyloidosis due to multiple myeloma (plasmacytoid involvement) or lymphoma (lymphocytic or lymphoplasmacytic involvement), the treatment will be different and the current protocols for these treatments are used. These are composed of chemotherapy that has changed dramatically over the last decade, with significantly improved response rates and prolonged survival. It is not the purpose of this review to discuss all chemotherapy protocols but to review the various new developments that have led to improved prognosis. With the institution of proteasome-inhibiting agents, particularly bortezomib, the prognosis of patients with light-chain CA has improved considerably. Bortezomib is relatively well tolerated, even in the presence of amyloid cardiomyopathy, and is usually combined with dexamethasone and frequently with low-dose cyclophosphamide [29].

High-dose chemotherapy with autologous stem cell transplantation is generally reserved for patients with CA in whom oral regimens have failed and can produce a complete haematologic response [29].

Cardiac transplantation was previously considered a contraindication in CA. However, with advances in chemotherapy and the discovery of specific therapies, outcomes are now acceptable in carefully selected patients.

In AL amyloidosis, heart transplantation is indicated only very rarely. Indeed, in view of the risk of recurrence of cardiac disease after transplantation, heart transplantation is chosen only for very specific cases. For example, patients with heart failure due to AL

amyloidosis who are not candidates for disease-specific therapies because of a significant cardiovascular disorder may be selected for transplantation in experienced centres. 6–8 months later, these candidates should receive an autologous stem cell transplant, so the indication should be made in consultation with haematologists.

Survival is 89% at 1 year and 76% at 5 years [30].

TTR amyloidosis

The treatment of TTR amyloidosis is increasingly complex in view of the discoveries and treatments currently under study.

The treatment is based on 3 aspects: **suppression of TTR secretion, destruction of fibrils** and **stabilisation of the tetramer**.

Treatment for suppression of TTR secretion

Inotersen is an antisense oligonucleotide directed against the messenger RNA synthesising transthyretin and interfering with hepatic TTR synthesis.

It is currently shown to be effective in the early stages of TTR neuropathies. It can cause glomerulonephritis in 3% of cases and rarely thrombocytopenia. Thrombocytopenia can be potentially fatal, especially in patients with atrial fibrillation who are treated with anticoagulants. Thus, frequent monitoring by blood tests is necessary to avoid these potential side effects. Several studies are currently underway to determine its effectiveness in cardiomyopathy [31].

Patisiran is a double-stranded RNA with a genetic sequence similar to that of the TTR gene, activating the destruction of the TTR messenger RNA and leading to the suppression of the synthesis of the protein in the liver. Its efficacy has been demonstrated mainly in neuropathies in TTR amyloidosis but has also shown good results in CA by improving the basal longitudinal strain of the left ventricle and the hypertrophy of the left ventricle. Improvement in NT-proBNP levels was also observed [32].

The last alternative to decrease TTR secretion in TTR amyloidosis is **liver transplantation**. Indeed, the liver produces the majority of transthyretin.

However, there are some indications for isolated heart transplantation in TTR amyloidosis, for example, in the setting of severe heart failure without or with limited extracardiac involvement.

Liver transplantation has been shown to prevent disease progression in patients with TTR-h amyloidosis.

Thus, in individuals without critical extracardiac manifestations, the **heart-liver combination** is an attractive and potentially curative alternative [30].

Destruction of fibrils

Doxycycline and **tauro-ursodeoxycholic acid** have been shown to be synergistically effective in degrading non-fibrillar TTR deposits. A study of 20 patients showed stabilisation of neurological and cardiac damage in both senile and hereditary amyloidosis [33].

A molecule extracted from green tea, Epigallocatechin-3-gallate, can inhibit the formation of TTR amyloid fibrils and break down amyloid deposits.

Two studies have shown improvement in left ventricular mass with a reduction of up to 13% in senile TTR amyloidosis. However, these studies were done on a small population and deserve further exploration [34].

Stabilisation of the tetramer

Tafamidis represents a huge advance in recent years in the treatment of senile and hereditary TTR amyloidosis, both neurological and cardiac. It allows stabilisation of the tetramer which binds with high affinity and selectivity to the thyroxine site of TTR, slowing down the dissociation of TTR tetramers into monomers and preventing aggregation into amyloid fibrils.

However, the optimal results with Tafamidis are achieved when the disease is discovered in its early stages in patient with senile or hereditary TTR amyloidosis. Class I and II restrictive heart failure according to New York Heart Association (NYHA) shown lower mortality and lower rates of hospitalisation for heart failure. For NYHA stage III patients, there was no improvement in morbidity and mortality. In this study of 441 patients, there was a 30% relative reduction in all-cause mortality and a 32% reduction in hospitalisations for cardiovascular causes. The study also showed an improvement in the 6-minute walk test and quality of life score on tafamidis [35].

Previously, no significant difference was shown between tafamidis 20 mg or 80 mg treatment in CA. A recent paper from October 2020 showed superiority at 51 months of tafamidis 80 mg treatment in terms of patient survival compared to tafamidis 20 mg [36].

Diflunisal is a non-steroidal anti-inflammatory drug. It also acts as a tetramer stabiliser like tafamidis. In a non-randomized study of TTR CA, diflunisal promoted a survival benefit similar to that of tafamidis. However, in view of its renal and platelet (thrombocytopenia)

side effects, its use is limited to patients with non-severe renal dysfunction, normal platelet counts, no evidence of fluid overload, or using high-dose diuretics and no evidence of recent hemodynamic or renal instability. The dosage will be 250 mg orally twice daily [5].

There are 2 molecules currently being studied. AG 10 and Tolcapone which is currently used in Parkinson's disease.

Conclusion

CA is a disease associated with significant morbidity and mortality when not caught early. The prevalence is constantly increasing thanks to the improvement of diagnostic tools and to the increasingly sophisticated knowledge of the disease. However, it is still underdiagnosed, leading to management that is sometimes too late for the patient. Early management is necessary in order to establish a rapid treatment that can reduce the patient's morbidity and mortality.

Disclosure statement

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