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Amyloid cardiomyopathy

The term "amyloidosis" encompasses a group of degenerative diseases characterized by extracellular deposition of fibrillar aggregates that are composed of a specific abnormally folded serum protein. While neurological amyloidosis, such as Alzheimer and Parkinson disease, has received the greatest attention, there is also systemic amyloidosis that affects many target organs, including the heart, kidneys, liver, and nervous system. More than 30 proteins have been reported to cause amyloid deposition. The frequency of cardiac involvement varies among the different types and is primarily associated with deposition of immunoglobulin light chains (AL) due to a clonal plasma cell dyscrasia or transthyretin (TTR). ATTR amyloidosis may be due to a variant in the TTR gene (hereditary ATTR amyloidosis; ATTRv) or results from normal wild-type amyloidogenic TTR protein as seen in the elderly male population (ATTRwt amyloidosis) However, cardiac amyloidosis may also occur in patients with AA amyloidosis due to chronic inflammatory diseases [1].

Cardiac amyloidosis often results in an aggressive form of heart disease that presents with progressive biventricular congestive heart failure with impaired ventricular filling, but typically with preserved systolic function. It is largely resistant to many common heart failure therapies or even worsened by general heart failure medication. In general, the prognosis of amyloid cardiomyopathy is poor with the highest mortality rates particularly for AL amyloidosis [2, 3].

Cardiac amyloidosis is claimed to be a rare disease although it appears in fact to be a widely underdiagnosed disease because of its ambiguous presentation and rapid mortality. Autopsy studies have identified cardiac wild-type ATTR deposition in over 25% of individuals >80 years of age [4]. Disease awareness programs and improved cardiac imaging modalities (echocardiography strain imaging, cardiac magnetic resonance imaging) as well as the use of skeletal scintigraphy have contributed to improved detection of this particular disease. Novel imaging techniques can also be used to screen people at elevated risk for developing cardiac amyloidosis, including patients after surgery for carpal tunnel syndrome, asymptomatic gene carriers, or patients with monoclonal gammopathy of undetermined significance.

Clinical signs and symptoms

The diagnosis of amyloidosis requires a high index of suspicion from multiple disciplines especially if the patient presents with symptoms in diverse organs. Non-cardiac clinical characteristics associated with cardiac amyloidosis may include male gender, sensorimotor polyneuropathy, carpal tunnel syndrome, lumbar spinal stenosis, low-flow low-gradient aortic stenosis, or family history of amyloidosis. Emergent screening for monoclonal gammopathy by serum/urine electrophoresis, immunofixation, and free-light chain assay is mandatory followed by histological confirmation of amyloid using Congo red staining and immunohistochemistry. Potential biopsy sites include abdominal fat (aspiration or biopsy), rectum, salivary gland, or any other obviously affected organ (**Fig. 1**). If the initial biopsy did not confirm deposition of amyloid, additional biopsies might be necessary to ultimately confirm or exclude systemic amyloidosis [5, 6].

In the absence of a monoclonal protein, the diagnosis of cardiac ATTR amyloidosis can also be made noninvasively with the use of skeletal scintigraphy (^{99m}Tc-DPD scintigraphy). This noninvasive diagnostic tool is more sensitive in detecting mild cardiac ATTR amyloidosis compared with echocardiography. However, in the presence of monoclonal gammopathy, histological confirmation by endomyocardial biopsy (or any other organ) including Congo red staining and immunohistochemistry is mandatory. If cardiac ATTR amyloidosis is confirmed either by histology or skeletal scintigraphy, molecular genetic testing is required to differentiate two distinct genetic forms of ATTR amyloidosis, namely, ATTRwt and ATTRv amyloidosis. In patients with a family history for ATTRv and symptoms compatible with this disease, it may be appropriate to proceed directly to genetic testing [7].

Two forms of cardiac ATTR amyloidosis

Cardiac ATTRwt is almost exclusively a disease of older males with predominant cardiac involvement. Some distinct clinical scenarios have been reported to be associated with cardiac ATTR amyloidosis. Half of the patients diagnosed with ATTRwt have undergone surgery for (bilateral) carpal tunnel syndrome 5–10 years prior to the diagnosis of cardiac manifestations. By contrast, ATTR amyloid deposition was found in 10–30% of the patients undergoing surgery for carpal tunnel syndrome without any evidence of systemic amyloidosis. Thus, carpal tunnel syndrome may identify patients

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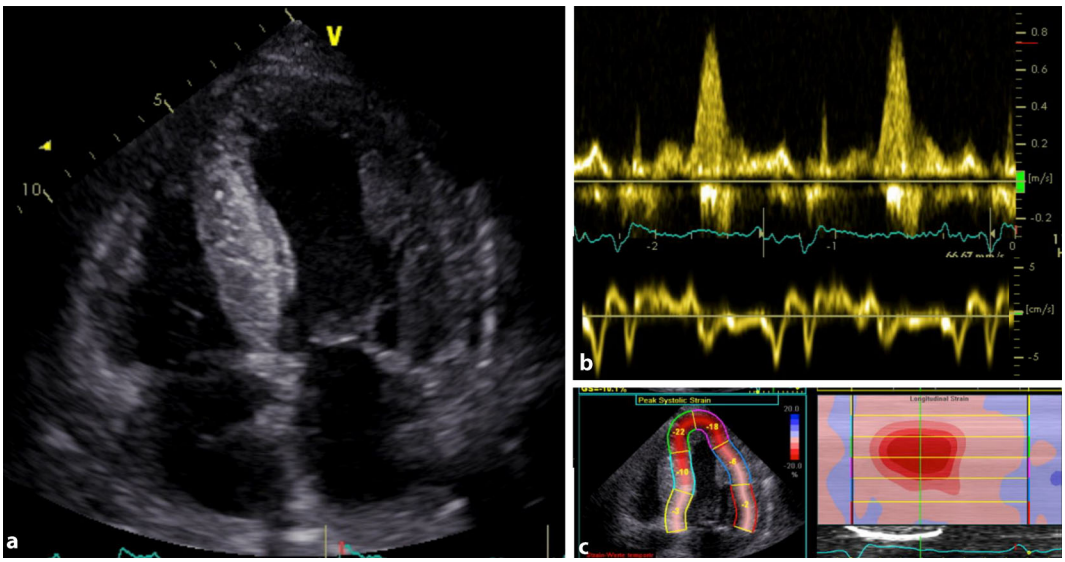

Fig. 1 ◀ Typical echocardiography features in cardiac amyloidosis patients. **a** Thickened LV wall, biatrial dilation, thickening of atrioventricular valves in apical 4-chamber view. **b** Doppler interrogation demonstrates a restrictive filling pattern in the mitral inflow study with high LV filling pressure (Calculation of *E*/*e*′ is estimated to >15). **c** A representative bull's eye plot of longitudinal strain. Note that the longitudinal strain of the apex is preserved in contrast to those of the other midventricular or basal segments

at risk for cardiac ATTR amyloidosis. Similarly, ATTR amyloid deposition in the ligamentum flavum as the underlying morphological substrate of lumbar spinal stenosis was observed in 50% of the patients. The prevalence of amyloid deposition in the ligamentum flavum depends on the patient's age and severity of the disease. Approximately 10% of the ATTRwt amyloidosis patients also present with signs or symptoms of peripheral and/or autonomic neuropathy. Whether this relates to amyloid deposition or is associated with other etiologies remains undefined. Moreover, 13% of patients hospitalized for heart failure with preserved ejection fraction were shown to have cardiac ATTRwt amyloidosis. Finally, retrospective studies reported a prevalence of up to 16% of concomitant cardiac ATTRwt amyloidosis in patients with severe aortic stenosis undergoing aortic valve replacement. The co-prevalence of aortic stenosis and cardiac amyloidosis with restrictive physiology may explain the phenomenon of low-flow–low-gradient aortic stenosis. The hereditary form of ATTR cardiomyopathy is caused by a gene mutation and can progress rapidly to end-stage diastolic heart failure. In general, the progression of ATTRwt cardiomyopathy is much slower [8, 9].

Diagnostics

The ECG pattern of cardiac amyloidosis may include a pseudo-infarction pattern, bundle branch block, low-voltage pattern, and/or conduction disturbances. Although at least one of them is present in almost all patients with cardiac amyloidosis, initial specific evidence derives from echocardiography. Biventricular wall thickening, left and right atrial enlargement (◘ **Fig. 1a**) due to a restrictive filling pattern (grade III or IV diastolic dysfunction, ◘ **Fig. 1b**), and/or pericardial effusions are frequently present in patients with advanced cardiac amyloidosis. Impairment of longitudinal function and regional longitudinal strain pattern with reduction of strain in basal and midventricular segments in combination with normal strain in apical segments ("apical sparing") are typical findings of cardiac amyloidosis (◘ **Fig. 1c**). Besides precise morphological and functional characterization, cardiac magnetic resonance imaging may raise suspicion of cardiac amyloidosis on the basis of diffuse subendocardial or transmural late gadolinium enhancement with inability to suppress myocardial signal with phase sensitive inversion recovery late gadolinium enhancement imaging as well as increased native T1 and extracellular volume fraction. Cardiac biomarkers including N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitive (hs) troponins give important information on potential cardiac involvement and on the prognosis of patients. The broader use of bone scintigraphy resulted in a much higher number of patients diagnosed with ATTR amyloidosis, mainly wild-type.

Differentiation of the amyloid type, including definition of ATTRv and ATTRwt, in patients with cardiac amyloid detected via skeletal scintigraphy and evaluation for noncardiac involvement, including neuropathy in ATTRv, is crucial for initiation of specific treatment [10].

Treatment

Symptomatic treatment

Treatment of cardiac amyloidosis includes symptomatic therapy of heart failure as well as of the underlying disease. Heart failure treatment in cardiac amyloidosis differs from the medication generally recommended for patients with heart failure with reduced ejection fraction. It is primarily based on the use of diuretics. The clinical benefit of common heart failure medication including beta-blockers and angiotensin-converting enzyme inhibitors has not been proven yet, and may even be harmful. Similarly, calcium channel blockers and digitalis are contraindicated in amyloid cardiomyopathy. Only if tachyarrhythmia is present might the use of beta-blockers be helpful.

Cardiac amyloid infiltration, especially of the AL type, is associated with a high incidence of cardioembolic events even in sinus rhythm. Grade II or III diastolic dysfunction on echocardiograms, atrial size, and a reduction in the atrial ejection velocity (A wave less than 19–23 cm/s) are independently associated with an increased risk of intracardiac thrombus formation. Thus, anticoagulation is recommended if a peak transmitral inflow velocity of less than 20 cm/s using spectral Doppler during early diastole (E-wave) and no other contraindications are present [11].

Specific treatment

In general, there are more therapeutic options addressing the underlying disease in AL amyloidosis than in ATTR amyloidosis. Causative treatment of AL amyloidosis is aimed at removing the amyloidogenic light chains. Treatment regimens are according to regimens used for multiple myeloma. The oral alkylator melphalan and dexamethasone are considered standard therapy for patients with AL amyloidosis who are ineligible for autologous stem cell transplantation owing to extended survival and minimal toxicity [12]. In relapsed/refractory patients, the use of the proteasome inhibitor bortezomib and dexamethasone showed high hematologic response rates. In patients without severe heart failure (NYHA III or IV) and with NT-proBNP levels of <8500 ng/l, a significant survival benefit was observed for first-line treatment with bortezomib, oral melphalan, and dexamethasone [13]. However, no treatment has specifically been approved for AL amyloidosis. In highly selected patients, heart transplantation might be helpful to improve cardiac function and allow for effective treatment of plasma cell dyscrasia, e.g., by subsequent high-dose chemotherapy and autologous stem cell transplantation that has been reported as the most effective treatment to control plasma cell dyscrasia. If the plasma cell dyscrasia can be controlled, there is often a relatively rapid decrease in serum biomarkers of heart failure [14].

For many years, the only therapy for ATTRv amyloidosis was (combined heart and) liver transplantation to eliminate altered transthyretin production. This would improve sensory and motor impairment especially in patients with early onset p.Val50Met amyloidosis with short disease duration and unremarkable nutritional status (modified body mass index). The 10-year post-transplantation survival rate in these cases exceeds 70% for some patients with ATTRv [15]. Despite reports of successful outcomes with liver transplantation, progression of peripheral and autonomic neuropathy and cardiomyopathy have occurred following liver transplantation [16]. More recently, effective medical treatment approaches including RNA inhibition and TTR stabilization have been approved for ATTRv amyloidosis. None of these drugs is cur-

Abstract · Zusammenfassung

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Amyloid cardiomyopathy

Abstract

Cardiac amyloidosis is a heterogeneous group of diseases characterized by extracellular deposition of amyloid fibrils in many different organs finally resulting in organ failure. Cardiac involvement is common for immunoglobulin light chain amyloidosis (AL) or transthyretin amyloidosis (ATTR); the latter is caused by a transthyretin gene variant or wild-type protein. Precise diagnostic assessment including laboratory tests, electrocardiography, echocardiography, cardiac magnetic resonance imaging, biopsy, and/or bone scintigraphy is mandatory for definition of the amyloid type and finally for treatment initiation. Treatment of cardiac amyloidosis includes symptomatic therapy of heart failure as well as the underlying disease. Causative treatment of AL amyloidosis is according to regimens used for multiple myeloma. For many years, orthotopic liver transplantation was the only treatment available for hereditary ATTR amyloidosis, but important advances have been made after approval of a novel class of medication, namely, RNA silencers. However, currently no treatment is available to remove amyloid deposited in the tissue. Thus, early diagnosis is still critical to afford the best efficacy of available therapies.

Keywords

Amyloidosis · Transthyretin · RNA silencing · TTR stabilizer · Heart failure

Kardiale Manifestation bei Amyloidosen

Zusammenfassung

Die kardiale Amyloidose ist eine heterogene Gruppe von Krankheiten, die durch eine extrazelluläre Ablagerung von Amyloidfibrillen in vielen verschiedenen Organen gekennzeichnet ist und letztendlich zum Organversagen führt. Eine kardiale Beteiligung liegt häufig bei der Immunglobulin-Leichtketten-Amyloidose (AL) oder Transthyretin-Amyloidose (ATTR) vor. Letztere kann durch eine Transthyretin-Genvariante verursacht werden oder auch ohne Genvariante vorliegen. Eine genaue diagnostische Beurteilung, einschließlich Labortests, EKG, Echokardiographie, Magnetresonanztomographie des Herzens, Biopsie und/oder Knochenszintigraphie, ist für die Definition des Amyloidtyps und den Beginn der spezifischen Behandlung erforderlich. Die Behandlung der Herzamyloidose umfasst neben einer symptomatischen Therapie der Herzinsuffizienz auch die Therapie der Grunderkrankung. Die kausale Behandlung der AL-Amyloidose erfolgt nach den beim multiplen Myelom angewendeten Behandlungsschemata. Eine orthotope Lebertransplantation galt jahrelang die einzige verfügbare Behandlung für die hereditäre ATTR-Amyloidose. Durch die Zulassung einer neuen Medikamentenklasse, nämlich der RNA-Silencer, wurden wesentliche Fortschritte für die medikamentöse Behandlung der Patienten mit hereditärer ATTR-Amyloidose erzielt. Weiterhin ist jedoch keine Behandlung verfügbar, um im Gewebe abgelagertes Amyloid zu entfernen. Daher ist eine frühzeitige Diagnose immer noch von entscheidender Bedeutung, um die beste Wirksamkeit der verfügbaren Therapien zu erzielen.

Schlüsselwörter

Amyloidose · Transthyretin · RNA-Inhibition · TTR-Stabilisierung · Herzinsuffizienz

rently approved for treatment of cardiac ATTR amyloidosis.

Tafamidis is a selective small molecule that stabilizes the transthyretin homotetramer and subsequently avoids the rate limiting step of tetramer dissociation. Less neurologic deterioration with an excellent safety profile has been demonstrated in patients with early-stage hATTR polyneuropathy [17]; however, outcomes are mixed for patients with mid- to late-stage Val30Met ATTRv and patients with non-Val30Met ATTRv amyloidosis. Neuropathy progression and increasing disability in patients with late-stage Val30Met ATTRv [18] and worsening neurologic function in patients with non-Val30Met ATTRv disease have been demonstrated [19]. It was approved in 2011 for treatment of ATTRv amyloidosis with stage 1 polyneuropathy (walking ability without any support). Recently, the efficacy and safety of tafamidis were shown in ATTRwt and ATTRv cardiomyopathy. After 30 months, a significant reduction in all-cause mortality by 30% and cardiovascular-related hospitalizations by 32% was observed for tafamidis (20 and 80 mg once daily pooled) compared with placebo. This effect was superior in patients with early-stage cardiac disease (NYHA class 1 or 2). Patients receiving tafamidis experienced a significant reduction in the decline of functional capacity assessed via the 6-min walk test and quality of life compared with patients receiving placebo. In general, tafamidis was well tolerated [20]. Therefore, tafamidis was approved for the treatment of wtATTR or hATTR cardiomyopathy by the Food and Drug Administration. European Medicines Agency (EMA) approval is expected in 2020.

Diflunisal is a nonsteroidal anti-inflammatory drug with TTR-stabilizing properties. In a randomized, placebo-controlled, double-blind, investigator-initiated study, the difference in Neuropathy Impairment Score +7 neurophysiologic tests composite score (NIS +7) between diflunisal 250 mg twice daily and placebo indicated decreased neuropathy progression and improvement of quality of life at 2 years [21]. However, owing to potential side effects, the use of diflunisal in patients with ATTR amyloidosis is limited.

Patisiran is an RNAi therapeutic agent composed of a small interfering RNA formulated as a lipid nanoparticle that enables delivery to hepatocytes. After intracellular release, the small interfering RNA blocks production of mutant and wild-type TTR protein by inducing cleavage of TTR messenger RNA resulting in lowering of TTR blood levels up to 80% when administered intravenously every 3 weeks [22]. Improvements in neuropathy as well as polyneuropathy, quality of life, ambulatory function, and autonomic symptoms have been demonstrated when compared with placebo. Furthermore, the APOLLO study demonstrated an acceptable safety profile for patisiran [23]. Moreover, improvement in several important measures of cardiac structure and function—including reduction in LV wall thickness and NT-proBNP compared with both baseline and placebo—and relative improvement in global longitudinal strain have been reported in a prespecified subpopulation of patients with cardiac ATTR at study entry, as well as cardiac safety in the overall APOLLO patient population [24].

Inotersen is an antisense oligonucleotide specific for transthyretin mRNA that suppresses TTR in blood up to 80% when administered subcutaneously once a week. It was tested for safety and efficacy in patients with ATTRv amyloidosis polyneuropathy (NEURO-TTR study). Inotersen demonstrated a highly significant benefit for both primary endpoints in the mNIS +7 ($p < 0.0001$) and Norfolk QOL-DN ($p < 0.0006$) compared with placebo. Adverse events included thrombocytopenia and glomerulonephritis, which were managed by close monitoring [25]. Both drugs were approved by the EMA for treatment of ATTRv with polyneuropathy stage 1 and 2 in 2018. Importantly, in Germany TTR silencer therapies are not approved for treatment of hereditary or for wild-type ATTR amyloidosis. Moreover, direct comparison of inotersen and patisiran is not possible given differences in the NEURO-TTR and APOLLO study designs, endpoints, and patient populations. Similarly, direct comparison of inotersen and patisiran with tafamidis for patients with cardiac disease is not possible. Currently no treatment is available to remove amyloid deposited in the tissue. Thus, early diagnosis is still critical to afford the best efficacy of available therapies.

Conclusion

Treatment of cardiac amyloidosis includes symptomatic therapy of heart failure as well as the underlying disease. Causative treatment of amyloid light-chain amyloidosis is according to regimens used for multiple myeloma. For many years, orthotopic liver transplantation was the only treatment available for hereditary transthyretin amyloidosis, but important advances have been made after approval of a novel class of medication, namely, RNA silencers. To date, however, there is no treatment available to remove amyloid deposited in the tissue. Thus, early diagnosis is still critical to afford the best efficacy of available therapies.

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Compliance with ethical guidelines

Conflict of interest. A.V. Kristen points out the following relationships. AlnylamPharmaceuticals: study investigator (APOLLO, APOLLO OLE, ENDEAVOUR, HELIOS-A, HELIOS-B), advisory boards, travel support, honoraria. AkceaTherapeutics: travel support, honoraria, advisory boards. IONIS Pharmaceuticals: study investigator (NEURO-TTR), advisory board. PfizerInc./Pharma GmbH: study investigator (THAOS registry, ATTR-ACT, ATTR-ACT OLE), research support (ASPIRE 2015), member of THAOS Scientific Board and advisory boards, travel support, honoraria.

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