Cardiac amyloidosis — state-of-the-art diagnosis and emerging therapies

Amyloidoza serca — właściwe rozpoznanie i nowe terapie na horyzoncie

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Abstract

Cardiac amyloidosis (CA), which used to be considered a rare disease, is now increasingly recognised due to increased clinical awareness and the availability of advanced diagnostic techniques. CA can occur unexpectedly frequently in particular patient populations: among patients with heart failure with preserved left ventricular ejection fraction, as a phenocopy of hypertrophic cardiomyopathy, and among older patients with severe aortic stenosis. The deposition of abnormally folded, insoluble proteins in the extracellular matrix of tissues and organs plays a key role in the pathogenesis of amyloidosis. Despite the large number of pathogenic molecules, two types account for more than 95% of CA cases: immunoglobulin light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR). A recent paradigm shift in the diagnosis of CA, without the need for performing endomyocardial biopsy, has occurred as a result of technological advances in imaging and the development of new scintigraphy protocols. A combination of positive scintigraphic examination performed with bone-avid tracers and the absence of detectable monoclonal protein in serum or urine justifies a non-invasive diagnosis of ATTR. Early identification of affected patients remains crucial in order to improve prognosis, especially in patients with AL, in whom progression of the disease from the moment of heart involvement is extremely swift without causal treatment. There has recently been an exponential development of novel agents designed for patients with cardiomyopathy in the course of ATTR, which as a result, hopefully, in the future could become a curable disease. In the following article we present recent advances in the diagnosis and treatment of CA.

Key words: amyloidosis, light-chain amyloidosis, transthyretin amyloidosis, transthyretin, cardiomyopathy, heart failure

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Introduction

In the past, cardiac amyloidosis was considered a rare disease; nowadays, however, owing to increased clinical awareness and the availability of advanced diagnostic methods, it is being diagnosed more and more frequently.

The deposition of misfolded, insoluble proteins in extracellular matrix of various tissues and organs is the key element in the pathogenesis of amyloidosis. Currently, over 30 different precursor proteins, native or mutated, that have the potential to form amyloid fibrils, are known; by accumulating in tissues, they can lead to the development

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of systemic amyloidosis [1–3]. Despite such a high number of pathogenic proteins, two types are responsible for over 95% of cases of cardiac amyloidosis (CA): immunoglobulin light-chain (AL) amyloidosis and transthyretin amyloidosis (ATTR) [4]. Other, very uncommon, amyloid types that can lead to CA are amyloid A, apolipoprotein AI, heavy chain and atrial natriuretic peptide (ANP). On the one hand, accumulation of amyloid in the heart causes calcium metabolism disorders, which leads to dysfunction of mitochondria and cell membrane, activation of oxygen free radicals and, ultimately, cell death [3, 4]. On the other hand, amyloid fibrils accumulating in the extracellular space of the myocardium cause progressive diastolic dysfunction, and, in more advanced stages, systolic dysfunction too. This leads to the development of hypertrophic or restrictive cardiomyopathy phenotype [5–8].

Epidemiology and clinical presentation

The incidence of AL, the most common subtype of systemic amyloidosis (70–80%), is approx. 1–1.5 cases/100,000 persons per year [9]. The disease is most often seen in men aged over 65 [10]. Monoclonal free light chains (FLCs) type lambda or kappa, produced by pathological plasma cell growth in the bone marrow, are the precursor protein [11]. AL is more aggressive than ATTR; median survival of untreated patients who present symptoms of cardiomyopathy is less than six months. Early identification of such patients is thus crucial for prolongation of life [12].

Transthyretin (TTR), also known as prealbumin, physiologically synthesised in the liver, is a transport protein for thyroxine and retinol. Misfolding of TTR leads to amyloidogenesis. There are two distinct forms of ATTR: acquired wild-type ATTR (ATTRwt), also known as senile amyloidosis, and hereditary ATTR (ATTRm).

Recently published findings have shown that the disease may occur more frequently in specific patient populations: in 13% of ones with heart failure with preserved left ventricular ejection fraction (HFpEF), in 5% of cases of hypertrophic cardiomyopathy (HCM), and in 16% of patients with severe aortic stenosis qualified for transcatheter aortic valve implantation (TAVI) [13–15]. ATTRwt typically affects older men with heart failure, and is often comorbid with carpal tunnel syndrome and lumbar spinal stenosis [16]. The inherited in an autosomally dominant manner ATTRm form develops as a result of TTR gene mutation. Currently, over 120 pathogenic TTR variants are known; as they exhibit ethnic and geographical variability, the clinical picture and prognosis of the disease vary. ATTRm patients present symptoms of cardiomyopathy at the age of approx. 30–50, depending on the type of mutation, and the clinical picture can frequently include sensorimotor polyneuropathy [17]. Average survival from the date of diagnosis is 2–6 years [18].

Currently, there is no reliable epidemiological data concerning ATTR occurrence in Poland, and published reports are limited to a small number of cases [19].

Current diagnostic procedure for cardiac amyloidosis

Electrocardiography

Patients with cardiomyopathy in the course of amyloidosis may develop characteristic electrocardiogram (ECG) changes as the disease progresses. There is low QRS complex voltage — below 0.5 mV in limb leads and below 1.0 mV in precordial leads. ST-T segment changes similar to those which occur in the course of myocardial ischaemia — a pseudoinfarction pattern with no significant narrowing of coronary arteries — are typical. Unexplained hypertrophy of the left ventricular muscle identified via echocardiography coupled with simultaneous low QRS complex voltage in ECG is a characteristic feature of amyloid cardiomyopathy. Although the above cardiographic phenomena are treated as red diagnostic flags, they are not sufficiently sensitive to provide a definitive confirmation of diagnosis [21]. Furthermore, due to fibrosis of atrial walls and the electrical conduction system, conduction disorders and relatively frequent (7–25%) development of atrial flutter and fibrillation, are observed [21].

Echocardiography

Echocardiographic examination plays a very important role in CA diagnosis. At the early stages of the disease, the examination reveals progressive left ventricular diastolic dysfunction; systolic function is also severely reduced at very advanced stages of the disease. Classic CA phenotype corresponds to restrictive cardiomyopathy and is characterised by increased thickness of the left ventricular muscle, non-enlarged left ventricular chamber, dilated atria and features of elevated filling pressure. Left ventricular ejection fraction (LVEF) decreases as the disease progresses, which means that HFpEF can also progress into a much more severe heart failure form with reduced LVEF (HFrEF). Other features of CA include left ventricular hypertrophy, pericardial effusion, thickening of the interatrial septum, thickening of the heart valves, and intracardiac thrombi [17].

Owing to the development of advanced technology in the field of echocardiography, longitudinal strain assessment has become the standard tool for assessing myocardial deformation, which was initially assessed via magnetic resonance imaging (MRI) of the heart. Speckle tracking enables assessment of both global longitudinal strain (GLS) and segmental longitudinal strain (SLS), with relative left ventricular apical sparing of longitudinal strain considered to be a defining characteristic of CA (Figure 1). Relative apical longitudinal strain index makes it possible

to differentiate CA from other causes of left ventricular hypertrophy (with 93% sensitivity and 82% specificity) [22].

Magnetic resonance imaging

MRI is a useful diagnostic tool for patients with suspected CA. Typically, beyond morphological features of the heart, diffuse, subendocardial late gadolinium enhancement (LGE) is observed after administration of a contrast agent. Occurrence of this image is characterised by excellent sensitivity of 93% for CA, but it fails to differentiate between different types of the amyloid itself [23].

Radioisotope diagnostics
— a new diagnostic algorithm

Single-photon emission computed tomography (SPECT) has become a key technique for identifying ATTR patients. It utilises technetium-99m radioisotope and markers traditionally used for examining bones: 3,3-disphono-1,2-propanodicarboxylic acid (DPD), methylenediphosphonic acid (MDP), and pyrophosphate (PYP). It should be noted

that the procedure is carried out on the basis of various bone imaging protocols, using various diagnostic criteria, which may hinder direct comparisons of results of research conducted thus far [24–27].

The use of this non-invasive method for differentiating AL and ATTR cardiac amyloidosis was validated by Perugini et al. [24]. Moreover, the authors also introduced a four-point scale based on assessment of marker uptake in the bones, heart and soft tissue (Figure 2), which is still used today [24]. During the study, which involved 1,217 patients and included both SPECT with ^{99m}Tc-PYP and with 99mTc-DPD, a negative result excluded TTR amyloidosis with a probability of 99%. A positive image had a specificity of 86%, which was caused by a slight marker uptake in patients with the AL form [28]. Combining a positive bone scintigram result with the absence of monoclonal protein in blood or urine was proposed; this caused specificity to increase to 100% [24]. Similarly, SPECT with PYP has a sensitivity and specificity of 88% in detecting ATTR cardiac amyloidosis; following introduction of heart-to-contralateral ratio, with
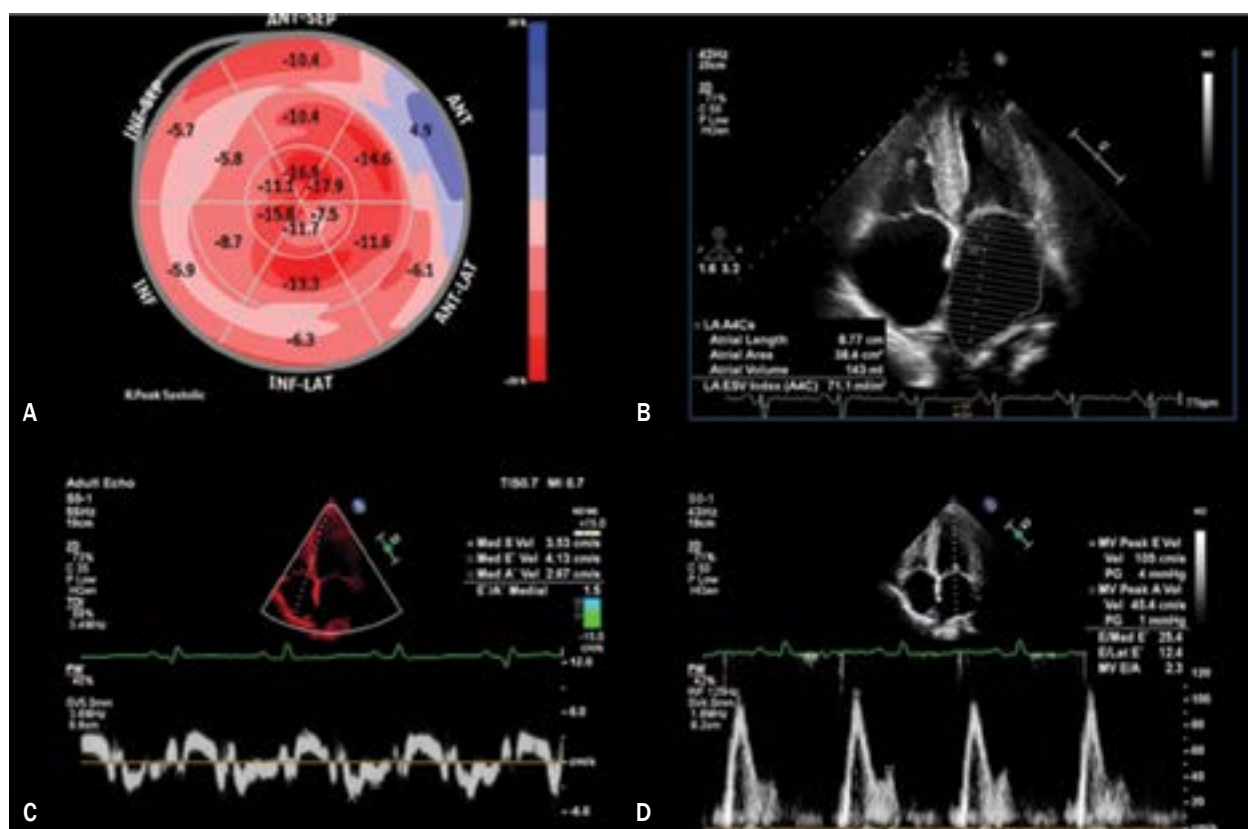

Figure 1. Echocardiographic features of cardiac amyloidosis; **A.** Speckle-tracking, visible preserved apical segmental strain and reduced basal segmental strain — apical sparing; **B.** Four-chamber apical view, visible classic features of cardiac amyloidosis — non-enlarged left ventricle, enlarged atria, thickening of left ventricular muscle, granular echostructure of muscle. **C.** Tissue Doppler echocardiography — slow early diastolic speed of septal part of mitral annulus; **D.** Flow through mitral valve recorded using pulsed-wave Doppler imaging — grade 3 left ventricular diastolic dysfunction

a cut-off point of > 1.6, sensitivity increased to 91%, and specificity to 92% [29]. Currently, it is known that marker uptake in SPECT correlates with the left ventricular muscle hypertrophy observed in echocardiographic examination; however, scintigraphic changes can be observed at earlier stages of the disease, when the thickness of the muscle is not greater than the cut-off point of 12 mm [30]. Development of this imaging technique lead to introduction of a non-invasive diagnostic approach of the unexplained left ventricular muscle hypertrophy in larger populations — in a study involving 12,521 patients who underwent bone SPECT, the prevalence of cardiac amyloidosis was estimated to be 0.36% [31].

A recent paradigm shift in CA diagnosis is the result of technological advances in imaging. Positive bone SPECT imaging, specifically a marker uptake score of 2 or 3, with no detectable monoclonal protein in the serum or in the urine, enables a non-invasive diagnosis of ATTR (Figure 3) [28]. Conventional histopathology and amyloid type determination are still necessary in cases which do not meet these diagnostic criteria.

Histology

Abdominal fat biopsy is a procedure which directly confirms the presence of amyloid; less frequently, biopsies are taken from other sites, mainly in cases where symptoms of involvement of these organs also occur. Low sensitivity of abdominal fat aspiration, respectively 84% for AL, 15% for ATTRwt, and 45% for ATTRm, can delay diagnosis [32]. To confirm deposition of amyloid in the myocardium, a right ventricular biopsy is performed; currently, due to the introduction of the non-invasive diagnostic algorithm, this procedure is carried out less and less frequently.

During histopathological examination, deposits of amyloid are detected with Congo red staining. In polarised light, amyloid presents apple-green (birefringence). Further amyloid type determination may be performed on the basis of analysis of the structure of amyloid deposits using immunohistochemistry, mass spectrometry or immune electron microscopy. This is important for diagnosing the type of amyloidosis and, consequently, choosing appropriate therapy. It should be noted, however, that the availability of amyloid typing techniques is limited to few highly-specialized pathomorphological laboratories, thus they are performed relatively rarely in clinical practice in Poland.

Therapy in cardiac amyloidosis

Treatment of cardiovascular complications

Both interstitial amyloid accumulation and subendocardial fibrosis secondary to ischaemia lead to morphological and functional changes in the heart. Amyloid infiltration leads to simultaneous thickening of walls, with normal or even reduced volume of the left ventricle, and consequently
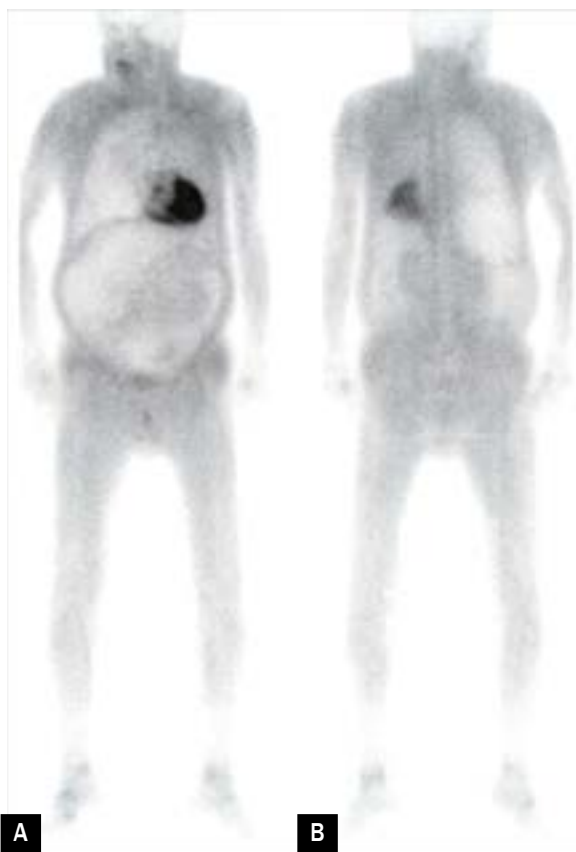

Figure 2. This figure presents a planar scintigraphic examination following administration of a Tc-99m-DPD tracer. Study shows increased radiotracer cardiac accumulation, specifically in grade 3 with strong uptake in cardiac region and decreased or absent bone signal. This scan is consistent with ATTR cardiac amyloidosis, in this case caused by TTR mutation

to the development of severe diastolic dysfunction. Atrial dysfunction can also lead to diastolic ventricular filling disorders. The above pathological changes cause reduced ejection fraction with significantly elevated intracardiac pressure [17].

Most drugs used in HFrEF may be harmful due to the unique pathology of amyloidosis. Angiotensin-converting-enzyme inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs) entail a risk of severe hypotension caused by activation of the renin-angiotensin-aldosterone axis due to autonomic dysfunction. Beta-blockers can also be harmful, as they reduce cardiac output secondary to heart rate reduction and negative inotropic effect. Calcium channel blockers, as well as digitalis, should be avoided, as they bind irreversibly to amyloid fibrils and can cause severe side effects [33, 34]. Diuretics remain a first-line drug. A combination of loop diuretics and mineralocorticoid receptor antagonists has shown efficacy [17]. During the course of atrial fibrillation, which affects a large proportion of CA patients, rhythm control is very important. Calcium
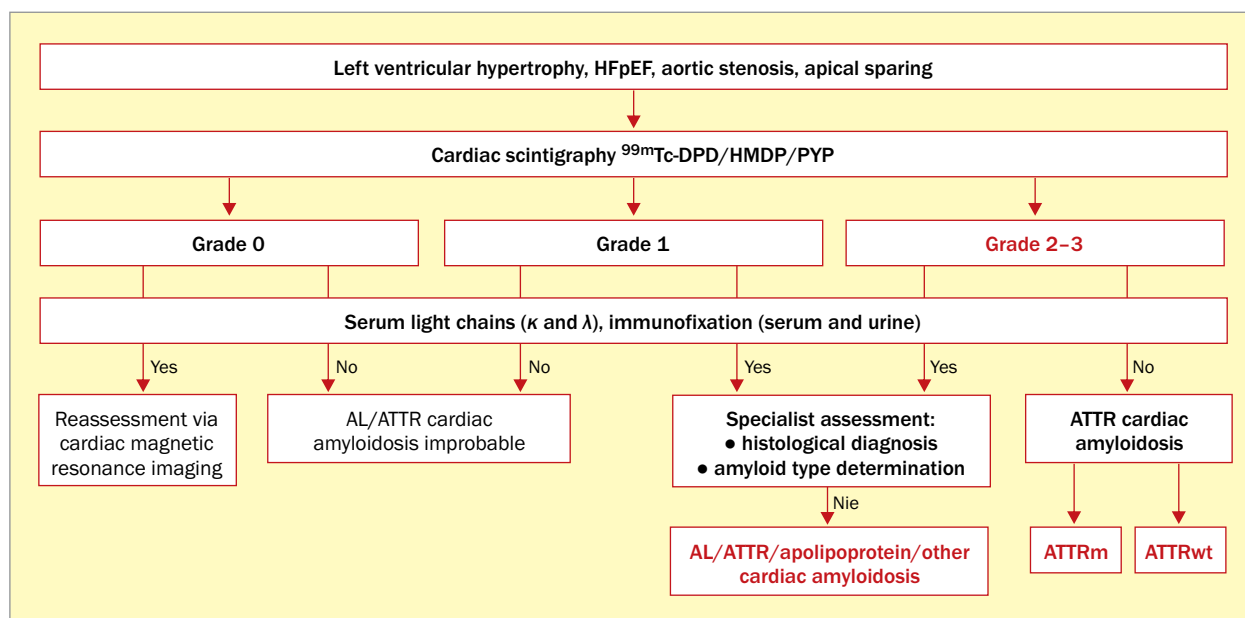
Figure 3. Authors' modification of the algorithm of non-invasive diagnosis of cardiac amyloidosis (based on [28]); HFpEF — heart failure with preserved ejection fraction; ^{99m}Tc-DPD — technetium-99m-3,3-diphosphono-1,2 propanodicarboxylic acid; HMDP — acidhydroxymethylene diphosphonate; PYP — pyrophosphate; CMR — cardiac magnetic resonance; AL — light chain amyloidosis; ATTR — transthyretin amyloidosis; ATTRm — ATTR mutant; ATTRwt — ATTR wild-type

channel blockers and beta-blockers should be avoided, while on the other hand, amiodarone shows the highest safety of use [17].

Treatment of light-chain amyloidosis

The goal of AL amyloidosis treatment is to eliminate the clonal plasma cells which produce the immunoglobulin light chain [35]. Classification of patients into risk groups before commencing treatment is of the utmost importance; this is usually done in accordance with the Mayo Clinic scale, which takes into account cardiac enzyme concentrations and the difference between serum concentrations of kappa and lambda FLCs [36]. In the low-risk group, for younger patients, experts recommend therapy using large doses of melphalan, supported by bone marrow autologous haematopoietic stem cell transplantation with possible consolidation therapy using bortezomib. For the most numerous (70% of patients) mid-risk group, chemotherapy using melphalan and dexamethasone as well as bortezomib-based regimens are the standard for haematological treatment. Finally, for the high-risk group, reduced-intensity chemotherapy is recommended. In treatment of recurrent and resistant forms of AL amyloidosis, therapeutic regimens are based on immunomodulatory drugs, as well as new generation proteasome inhibitors, bendamustine and monoclonal antibodies [35]. In specific cases, AL amyloidosis patients can undergo organ transplantations, such as kidney and heart transplantations [35].

Treatment of transthyretin amyloidosis

Organ transplantation
Great expectations were placed on liver transplantation as a promising strategy for ATTRm treatment, which could remove the source of circulating pathogenic TTR protein [37]. Unfortunately, it was shown that an isolated liver transplantation entails a very high risk of the development of progressive amyloid cardiomyopathy [38, 39]. For this reason, according to the International Society for Heart and Lung Transplantation, simultaneous heart and liver transplantation should be considered for young ATTRm patients in order to prevent progression of a systemic disease. For older patients with dominant heart failure symptoms (wild-type or Val122Ile variant), isolated heart transplantation should be considered [39].

Gene therapy
Patisiran is a short interfering RNA (siRNA) molecule which targets TTR expression. The randomised 18-month-long phase 3 APOLLO trial (NCT01960348), which evaluated the efficacy and safety of patisiran in a group of 225 patients with neuropathy, showed that, compared to the control group, ATTRm patients treated with patisiran presented with improved quality of life and reduced neurological symptoms. Moreover, in the subgroup of patients with cardiomyopathy, the drug reduced NTproBNP natriuretic peptide levels and had a positive effect on left ventricular

remodelling. It has to be noted, however, that the APOLLO trial concerned patients with neuropathic ATTRm variants, and the efficacy and safety of the drug in the cardiomyopathy patient group is yet to be verified [40–42].

Inotersen is a TTR antisense oligonucleotide, which inhibits TTR synthesis in hepatocytes. The randomised 66-week-long phase 3 NEURO-TTR (NCT01737398) trial evaluated the efficacy and safety of the drug administered subcutaneously at a dose of 300 mg once per week in a group of 172 patients with familial amyloid polyneuropathy. The trial showed that inotersen reduces neurological symptoms and improves quality of life, but also that the drug has adverse effects, the most frequent of which were glomerulonephritis (3%) and life-threatening thrombocytopenia (3%) [43].

Tetramer stabilisation therapy

2018 saw the publication of results from a groundbreaking trial — ATTR-ACT (NCT01994889) — in which patients with the cardiac form of ATTR were treated using tafamidis [44]. Tafamidis is a benzoxazole derivative which selectively and strongly binds to native tetrameric TTR, preventing its dissociation into monomers. The trial enrolled 441 patients with amyloid cardiomyopathy in the course of ATTR, who were randomly assigned (2:1:2) to treatment using tafamidis at a dose of 80 mg, or treatment using tafamidis at a dose of 20 mg, or treatment using a placebo, and then observed for 30 months. Study reported significant reduction in mortality and urgent hospitalisations rates in the group treated with tafamidis. Furthermore, patients treated actively were characterised by better physical fitness and enjoyed improved quality of life. The introduction of tafamidis into treatment provides the first real chance to prolong the life of patients with the cardiac form of ATTR, given that no other causal therapy in the course of this disease is available. Tafamidis is also already registered for the treatment of patients with symptomatic ATTR polyneuropathy [45].

Diflunisal is a nonsteroidal anti-inflammatory drug which has the ability to stabilise TTR tetramers *in vitro*. In a randomised phase 3 trial, 130 patients with ATTR with symptomatic polyneuropathy were randomly assigned to diflunisal at a dose of 500 mg/day or to a placebo, and then observed for two years [46]. The trial showed that diflunisal reduced the progression of neurological symptoms; however, no beneficial effect with respect to cardiomyopathy was identified. Although this relatively large dose of diflunisal was well-tolerated in this trial, its effect as a cyclooxygenase inhibitor can potentially lead to kidney and gastrointestinal tract injury, as well as fluid retention and difficulties in arterial pressure management. Potential adverse effects remain a serious therapeutic problem. The AG10 is a new TTR-stabilising compound. The AG10 drug has a similar structure of the thyroxine-binding site as the anti-amyloidogenic protective Thr119Met variant and specifically binds to the TTR tetramer, hampering its dissociation. An *in vitro* trial showed that the preparation caused increased tetrameric stability of TTR compared to tafamidis and diflunisal [47]. A randomised phase 2 trial (NCT03458130) confirmed the safety and efficacy of AG10 in patients with ATTRwt and ATTRm cardiomyopathy; a phase 3 trial is currently underway [48].

Amyloid degradation affecting therapy

Doxycycline and tauroursodeoxycholic acid (TUDCA) degrade TTR deposits; moreover, a few reports on their mitigating effect on ATTR progression have already been published [49, 50]. A trial (NCT01855360) which evaluated the tolerance and efficacy of a combination of doxycycline (100 mg orally twice daily) and TUDCA (250 mg orally thrice daily) in 38 patients with cardiomyopathy in the course of ATTRm or ATTRwt for a period of observation of 18 months was recently completed, but its results have not yet been published.

Epigallocatechin gallate is an organic chemical compound classified as a flavonoid found in large quantities in green tea, which may inhibit the formation of TTR amyloid fibrils and disaggregate amyloid deposits [51]. Two small, 12-month-long observation trials showed that consumption of green tea reduced the mass of the left ventricle by 6–13%, as assessed via magnetic resonance imaging in ATTRwt patients [52, 53]. Antibodies which selectively bind to amyloid molecules, which could be utilised via immunotherapeutic removal of deposits from key organs, including the liver, in patients with systemic amyloidosis, are also being studied [54].

Conclusions

Both correct diagnosis and treatment of CA are challenging, even for multidisciplinary teams dedicated to the heart failure treatment. The development of new imaging techniques, and as a result the change of diagnostic algorithm, have in recent years given rise to numerous reports stressing higher prevalence of ATTR in specific patient subpopulations: those with aortic stenosis, and older people with unexplained left ventricular hypertrophy, HCM or HFpEF. Early identification of patients is vital in terms of improved prognosis, especially with respect to AL patients, in whom progression of the primary disease is extremely rapid without causal treatment. Furthermore, novel emerging ATTR therapies are currently underway; in particular, the effects of tafamidis have been demonstrated with respect to improved survivability of patients with cardiomyopathy, which thus may have the potential to become a curable disease in the future.

Streszczenie

Amyloidoza serca (CA), uważana w przeszłości za chorobę rzadką, obecnie jest coraz częściej rozpoznawana dzięki zwiększonej świadomości klinicznej oraz dostępnym zaawansowanym metodom diagnostycznym. Może ona występować zaskakująco często w szczególnych populacjach pacjentów — wśród osób z niewydolnością serca z zachowaną frakcją wyrzutową, jako fenokopia kardiomiopatii przerostowej oraz wśród starszych pacjentów z ciężką stenozą aortalną. Kluczową rolę w patogenezie amyloidozy odgrywa odkładanie się w macierzy pozakomórkowej tkanek i narządów depozytów nieprawidłowo sfałdowanych, nierozpuszczalnych białek. Mimo dużej liczby patogennych cząsteczek, to dwa ich rodzaje odpowiadają za ponad 95% przypadków CA — amyloidozę łańcuchów lekkich immunoglobulin (AL) i amyloidozę transtyretynową (ATTR). Niedawna zmiana paradygmatu w diagnozowaniu CA bez konieczności wykonywania biopsji endomiokardialnej dokonała się wraz z postępem technologicznym w obrazowaniu i rozwoju nowych protokołów badania scyntygraficznego. Pozytywne obrazowanie scyntygraficzne z użyciem znaczników klasycznie stosowanych w obrazowaniu układu kostnego, w przypadku braku wykrywalnego białka monoklonalnego w surowicy lub moczu, pozwala na nieinwazyjną diagnozę ATTR. Wczesna identyfikacja chorych jest kluczowa w kontekście poprawy rokowania, zwłaszcza pacjentów z AL, u których postęp choroby podstawowej od czasu zajęcia serca jest dramatycznie szybki. Obserwuje się ogromny rozwój nowych leków przeznaczonych dla pacjentów z kardiomiopatią w przebiegu ATTR, która w przyszłości ma szansę stać się chorobą uleczalną. W poniższym artykule przedstawiono ostatnie postępy w diagnostyce i leczeniu CA.

Słowa kluczowe: amyloidoza, amyloidoza łańcuchów lekkich immunoglobulin, amyloidoza transtyretynowa, transtyretyna, kardiomiopatia, niewydolność serca

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