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PRACA POGLĄDOWA
REVIEW

Cardiac amyloidosis

Amyloidoza serca

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ABSTRACT

Amyloidosis is a rare disease characterized by an abnormal accumulation of the amyloid protein in tissues. Amyloidosis can be divided into two main subtypes: transthyretin amyloidosis (ATTR-CA) and immunoglobulin light chain amyloidosis (AL-CA). Accumulation of the amyloid protein in the heart muscle may lead to conduction disturbances, restrictive cardiomyopathy, and consequently, heart failure. The symptoms may include decreased exercise tolerance, shortness of breath, swelling and fainting. The diagnosis is based on laboratory tests, imaging and biopsy. Treatment focuses mainly on slowing the progression of the disease and treating the symptoms.

KEYWORDS

heart failure, imaging diagnostics, cardiac amyloidosis

STRESZCZENIE

Amyloidoza jest rzadką chorobą charakteryzującą się nieprawidłowym gromadzeniem się białka amyloidowego w tkankach. Amyloidozę można podzielić na dwa główne podtypy: amyloidozę transtyretynową (ATTR-CA) i amyloidozę łańcuchów lekkich immunoglobulin (AL-CA). Nagromadzenie białka amyloidu w mięśniu sercowym może doprowadzić do zaburzeń przewodzenia, kardiomiopatii restrykcyjnej i w konsekwencji niewydolności serca. Objawy mogą obejmować spadek tolerancji wysiłku, duszność, obrzęki oraz omdlenia. Rozpoznanie opiera się na badaniach laboratoryjnych, obrazowych oraz biopsji. Leczenie koncentruje się głównie na spowolnieniu postępu choroby oraz leczeniu objawowym.

SŁOWA KLUCZOWE

niewydolność serca, diagnostyka obrazowa, amyloidoza serca

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INTRODUCTION

Amyloidosis is a rare multi-system disease characterized by an abnormal accumulation of amyloid protein in tissues, leading to damage to multiple organs, including the heart.

Cardiac amyloidosis (CA) has two main subtypes: transthyretin amyloidosis (ATTR-CA) and immunoglobulin light chain amyloidosis (AL-CA). ATTR-CA can be caused by a misfolded age-related transthyretin protein and is called senile, age-related CA or wild-type transthyretin CA (ATTRwt-CA) or autosomal dominant transthyretin-familial CA or variant transthyretin CA (ATTRv-CA). The consequences of the accumulation of the amyloid protein in the myocardium may include conduction disorders, arrhythmias, restrictive cardiomyopathy (RCM), and consequently, heart failure (HF). The symptoms include decreased exercise tolerance, shortness of breath, edema, palpitations and fainting. The diagnosis of CA includes laboratory tests, imaging and biopsy. The treatment focuses on treating the symptoms, slowing the progression of the disease, and treating comorbidities. A change in lifestyle and supportive care are also important aspects. In some cases, a heart transplant may be necessary [1].

Although CA is a progressive process, early diagnosis and appropriate treatment can significantly slow down its course and improve the quality of life of people affected by the disease [2].

ETIOLOGY AND PATHOGENESIS

The pathogenesis of CA is extremely complex and varies depending on the subtype. The most common types of CA include:

Light chain amyloidosis (AL)

Light chain amyloidosis is the most common type of CA. It is caused by the build-up of abnormal immunoglobulin light chains, which are produced by plasma cells in the bone marrow. The nascent amyloid fibrils accumulate in many organs, including the heart.

Transthyretin amyloidosis (ATTR)

Transthyretin amyloidosis is caused by abnormal deposition of the transthyretin protein. Is divided into: familial CA (variant transthyretin CA, ATTRv-CA), which results from an autosomal dominant mutation of the transthyretin protein; senile CA (age-related CA, wild-type transthyretin CA, ATTRwt-CA), which is caused by a misfolded age-related transthyretin protein.

Misfolded proteins aggregate to form oligomers. The oligomers undergo further structural changes to form amyloid fibrils. On the other hand, they are released into the bloodstream and deposited in various organs, including the heart. By accumulating within the extracellular matrix of the myocardium, they cause structural damage and dysfunction of the myocardium. Diastolic function is impaired and cardiac output is reduced, resulting in HF.

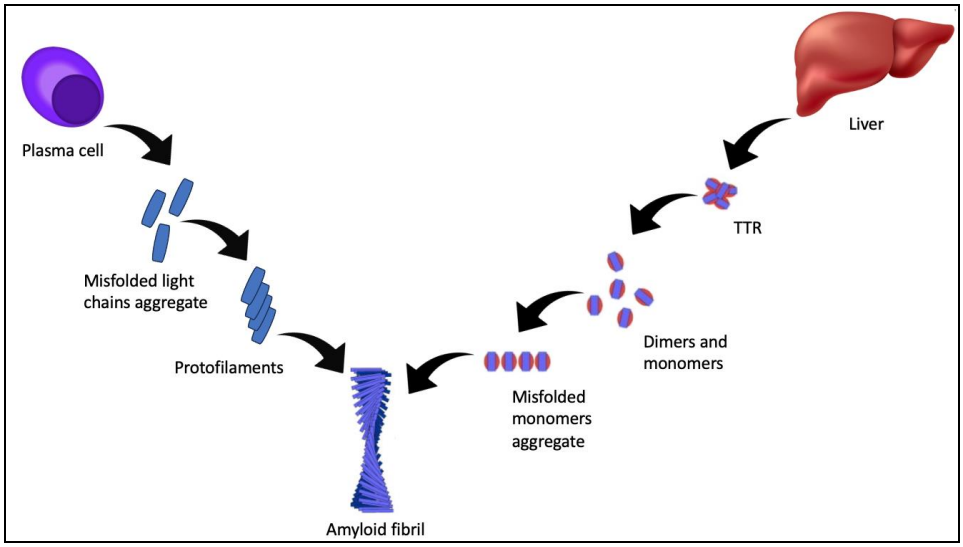

Fig. 1. Pathogenesis of amyloidosis (based on [50]).

Table I. Characteristics of types of cardiac amyloidosis

Characteristic	AL-CA	ATTRwt-CA	ATTRv-CA
Median age at diagnosis	5–9th decade of life	7–10th decade of life	3rd–8th decade of life
Predominant gender	no differences	male	male
Protein involved in pathogenesis	immunoglobulin light chains	transthyretin	transthyretin
Genetic basis	none	none	autosomal dominant
Most common extracardiac organs involved	nervous system, kidneys, liver, gastrointestinal tract, skin	lumbar section of spine, gastrointestinal tract	nervous system
Prognosis	depends on mutation and stage; median survival 4–6 months with advanced heart failure	depends on stage and mutation; median survival 2–6 years in absence of treatment	depends on mutation and stage; mean survival 3–12 years
Treatment	autologous stem cell transplant, anti-plasma cell therapy	afamidis, diflunisal	inotersen, patisiran, tafamidis, diflunisal

AL-CA – amyloid light-chain cardiac amyloidosis; ATTRwt-CA – wild-ype transthyretin cardiac amyloidosis; ATTRv-CA – variant transthyretin cardiac amyloidosis.

EPIDEMIOLOGY

The prevalence of amyloidosis varies by ethnicity and geographic region. The exact prevalence of CA is difficult to determine due to the lack of standardized diagnostic criteria.

However, ATTR-CA is considered to be the much more common subtype [3]. ATTRwt-CA is diagnosed mainly in men aged 70–75 [4,5] and is found more often in the African population [6]. According to one study of 120 patients with HF with preserved ejection fraction (HFpEF), ATRR-CA accounted for 13% of cases [7] and 16% of 151 patients with severe aortic stenosis [8]. ATTRv-CA usually occurs in younger people [6].

LA-CA is a rarer subtype diagnosed more frequently in the European population. LA-CAA is usually associated with plasma cell disorders and is thought to be only slightly more common in men than in women. It is usually diagnosed in younger patients [9].

SYMPTOMS

The symptoms of CA can vary greatly depending on the stage of the disease and the degree of organ involvement. In many cases, CA may be asymptomatic or develop for many years with mild symptoms, making diagnosis difficult. Nevertheless, it happens that the development of the disease is very rapid and leads to sudden cardiac death.

The cardiac symptoms and sequelae of CA include:

- symptoms of RCM and congestive HF: shortness of breath, decreased exercise tolerance, fatigue, peripheral edema
- conduction disorders and arrhythmias (mainly atrial fibrillation)
- pain in the chest
- weight loss
- orthostatic hypotension
- aortic stenosis symptoms, which comes from, especially in the ATTR subtype, lipid infiltration and inflammation, calcification and fibrosis of the valve leaflets.

CA can manifest with many of the above-mentioned symptoms and lead to several serious complications, which is why it is so important that diagnosis is made and appropriate treatment is introduced as early as possible [12,13,14,15,16,17].

It should also be mentioned that in the case of light chain amyloidosis, 5–10% of patients will have symptoms of multiple myeloma [9].

DIAGNOSTIC TESTS

Electrocardiography

The most specific of electrocardiographic (ECG) findings for CA constitute low-voltage QRS complexes (less than 0.5 mV in limb leads and < 1 mV in precordial leads) associated with left ventricle hypertrophy features. Moreover, the algorithm for transthyretin amyloid cardiomyopathy diagnosis refers to pseudo-infarction Q waves in precordial leads without significant stenosis of the coronary arteries or bundle branch blocks [18,19,20].

Biomarkers

Elevated cardiac biomarker levels correlate with progression of the disease. Raised levels of troponin T and I, as well as the N-terminal prohormone of the brain natriuretic peptide (NT-proBNP) occur in CA patients before the clinical symptoms of HF. Increased

troponin T and I indicate AL-CA to be more destructive than transthyretin amyloidosis. NT-proBNP proved to be elevated in over 75% of familial amyloidotic neuropathy patients and strongly correlates with interventricular septum thickening [18,21].

Echocardiography

Many echocardiographic presentations have been described for CA, and due to its noninvasive character, made it an important diagnostic tool. Nonetheless, it shows low sensibility and specificity.
Left ventricle wall and interatrial septum thickness coexist with progressive diastolic dysfunction with no other explanation of such myocardium changes. Left ventricle thickness ≥ 12 mm concomitance with other imaging abnormalities strongly suggests the diagnosis [22,35].
CA presentation is congenial to RCM with atria and right ventricle dilation and increased echogenicity [33]. The left ventricle enlargement and reduced left ventricular ejection fraction (LVEF) may appear in the advanced disease process [24]. Global longitudinal strain (GLS) assessment provides more accurate evaluation of left ventricle contractility impairment. It can expose an "apical sparing" sign with a decrease in the shortening of apical segments of the left ventricle. A specificity of 82% and sensitivity of 93% were demonstrated in differentiating CA from other reasons for left ventricle wall thickening [23,25].
Other findings include atrioventricular valve thickening and pericardial effusion. The sign of granular and scintillating myocardium can be suspicious, but a lack of it does not exclude the diagnosis.

Table II. Amyloidosis in transthoracic echocardiography (TTE)

Transthoracic echocardiography		
LVH	sensitivity: 100%	specificity: 0
LA dilatation	sensitivity: 44%	specificity: 93%
Bold AV and IAS	characteristic	non-specific
LV DD ≥ II	characteristic	non-specific
TDI – speed reduction	characteristic	non-specific
GLS ≥ -15	sensitivity: 88%	specificity: 72%
Bold AV and IAS	sensitivity: 38%	specificity: 93%

AV – aortic valve; GLS – global longitudinal strain; IAS – interatrial septum; LA – left atrium; LV DD – left ventricle diastolic disfunction; LVH – left ventricle hypertrophy; TDI – tissue doppler imaging.

Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) constitutes a great diagnostic method in CA because of its high sensitivity of 93%. Apart from the described echocardiographic findings, it reveals diffuse subendocardial and transmural late gadolinium enhancement (LGE) and foci of amyloid accumulation. Despite the fact that the type of amyloidosis cannot be differentiated on the basis of CMR only, transmural changes are more common phenomenon in TTR amyloidosis (63–71%) than in AL amyloidosis (27–50%) in contrast to subendocardial lesions (39% vs 12–24%) [29].
T1 mapping shows increased relaxation times and extracellular volume (ECV). These outcomes can also be detected before structural heart reshaping [26,27,28].

SPECT (single-photon emission computed tomography)

Cardiac scintigraphy using 99mTc and bone markers (^{99m}DPD, ^{99m}HMDP, ^{99m}PYP), because of its high sensitivity and specificity, plays a key role in detecting TTR cardiac amyloidosis. The diagnosis is made using the Perugini grading scale (0–3), in which the tracer saturation of the myocardium and ribs is visually compared. Grades 0 and 1 exclude TTR amyloidosis [30]. Grades 2 and 3 mean a positive test, although small tracer uptake was described in AL amyloidosis. The specificity of SPECT in ATTR was 83%, thus monoclonal gammopathy must be excluded by evaluation of the levels of plasma light chains (κ and λ) [23,26].

Endomyocardial biopsy

A histological examination directly confirms amyloid infiltration of the myocardium with great sensitivity of 100% if samples from at least 4 locations are taken. Congo red deposits are revealed in the process. Immunohistochemical tests or tandem mass spectrometry analysis are further examination methods required to confirm the precursors of the protein [31,34]. An endomyocardial biopsy was the gold standard of TTR amyloidosis diagnostics. Nowadays it is being replaced resulting from the development of noninvasive methods (SPECT) and their usage in diagnostic algorithms.
However, when AL amyloidosis is suspected, a biopsy of other probable involved organs (e.g. abdominal fat, kidneys or salivary glands) should be taken [32].

DIAGNOSIS

The beginning of CA diagnosis should consider suspicion of the disease on the basis of presenting symptoms. The ESC Working Group on Myocardial and Pericardial Diseases suggested the list of "red flags" including extracardiac symptoms, which frequently coexist with CA, especially with left ventricular thickness ≥ 12 mm [36,37].

Table III. Red flags of cardiac amyloidosis

Extracardiac symptoms	polyneuropathy, dysautonomia, skin bruising, skin discoloration, cutis laxa, macroglossia, deafness, bilateral carpal tunnel syndrome, ruptured biceps tendon, lumbar spinal stenosis, vitreous deposits, corneal lattice dystrophy, family history
Laboratory tests results	renal insufficiency, proteinuria, disproportionately elevated NT-proBNP to degree of HF, persisting elevated troponin levels
Cardiac symptoms	hypotension or normotension, if previous hypertension
Electrocardiography	pseudo infarct pattern, low/decreased QRS voltage to degree of LV thickness, AV conduction disease
Echocardiography	granular sparkling of myocardium, increased right ventricular wall thickness, increased valve thickness, pericardial effusion, reduced longitudinal strain with apical sparing pattern
Cardiac magnetic resonance	subendocardial LGE, elevated native T1 values, increased extracellular volume, abnormal gadolinium kinetics

NT-proBNP – N-terminal pro B-type natriuretic peptide; HF – heart failure; QRS – a complex on the electrocardiogram representing ventricular depolarization; LV – left ventricle; AV – atrioventricular; LGE – late gadolinium enhancement.

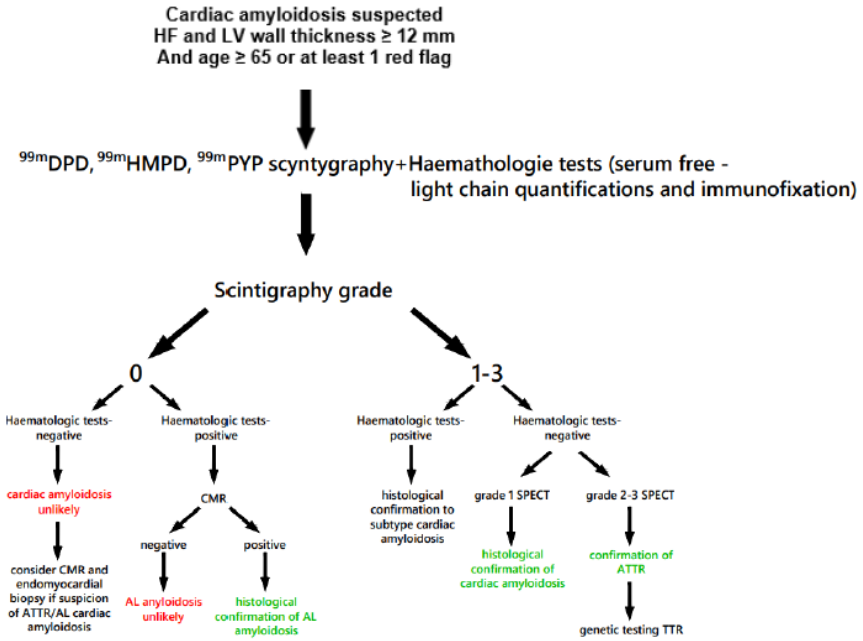

Fig. 2. Diagnostic algorithm of cardiac amyloidosis. HF – heart failure; LV – left ventricle; 99mDPD99mDPD – 99mTc99mTc-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid; 99mHMDP99mHMDP – 99mTc99mTc-labeled hydroxymethylene diphosphonate; 99mPYP99mPYP – 99mTc99mTc-labeled pyrophosphate; CMR – cardiac magnetic resonance; SPECT – single-photon emission computed tomography; ATTR – transthyretin amyloidosis; TTR – transthyretin.

CA may also appear in the progress of other conditions like nephrotic syndrome, chronic inflammatory diseases (e.g. tuberculosis, osteitis, arthritis, rheumatic diseases) and should be actively searched [39].

A diagnostic algorithm should be adhered to as soon as possible in the case of CA suspicion. The flowchart is focused on the diagnosis of AL and TTR amyloidosis.

The first step is to determine the concentration of serum monoclonal light chains, and simultaneously, perform ^{99m}DPD, ^{99m}HMDP, ^{99m}PYP scintigraphy. If both tests are negative, the diagnosis is unlikely. Negative laboratory test results and tracer uptake rated 2–3 confirm ATTR diagnosis. Grade 1 requires an endomyocardial biopsy. A positive hematologic test, but lack of cardiac uptake in SPECT should lead to CMR. Transmural and subendocardial LGE, increased ECV and native T1 constitute an indication for histological confirmation, which is also required when laboratory tests fulfill the criteria and SPECT 1–3 [35,36].

DIFFERENTIAL DIAGNOSIS

CA may cause difficulties in making the right diagnosis as a consequence of its resemblance to other conditions, which should be considered during the process.

The first diagnosis often made primarily in the course of CA is (HFpEF on the basis of typical signs and

symptoms with elevated NT-proBNP levels [39]. Nevertheless, poor tolerance of HF pharmacotherapy suggests extending the diagnostic process and questing the reason for such a condition [40].

CA should be differentiated with hypertrophic cardiomyopathy (HCM), which manifests itself with left ventricle wall and interventricular septum thickening, and in about 30% of cases, left ventricular outflow obstruction. Although changes in CA typically constitute diffuse hypertrophy, it can also present as isolated left ventricle involvement [41]. Studies suggest that TTR amyloidosis is the reason for myocardial hypertrophy only in 0.4% of HCM patients [42]. Left ventricle wall thickness in HCM is typically ≥ 15 mm, but at early stages it can be less and cause diagnostic dilemmas. Features that support the diagnosis are: systolic anterior motion and mitral valve-septal contact with a left ventricle outflow gradient, left ventricle hypertrophy, especially the apex, an anterolateral free wall and posterior septum. Genetic testing also plays a key role in the process [43].

Hypertensive cardiomyopathy should also be taken into account in differential diagnosis. It occurs as an early manifestation of long-lasting poorly controlled arterial hypertension [44]. Echocardiographic findings include greater diastolic dysfunction among CA patients compared to hypertensive patients. Both groups were characterized by an asymmetrical left ventricle wall and interventricular septum thickness. GLS assessment reveals decreased peak systolic left atrial strain values in both groups, but lower in CA patients (9.8–11.0% vs 24.8%) [45].

HFpEF with left ventricular wall thickness includes several conditions with infiltration of the myocardium, such as sarcoidosis and oxalosis and storage diseases, e.g. Fabry disease, Danon disease or other glycogen storage diseases [46].

Table IV. Differentiation of cardiac amyloidosis

Diagnostic tests	Hypertrophic cardiomyopathy	Fabry disease	Amyloidosis
Electrocardiography	features of left ventricular hypertrophy	PQ shortening, no delta wave, QRS widening, atrioventricular block	low QRS voltage, AV block, AF, FLA
Echocardiography	moderate to severe asymmetric hypertrophy, often obstructing outflow tract and SAM	concentric, moderate LV/RV hypertrophy; inferior/lateral wall dysfunction (reduction of longitudinal strain); circular deformation – correct; characteristic "binary sign" within IVS	concentric hypertrophy – both ventricles; thickening of IAS/valve leaflets; hyperechoic/speckled myocardium, pericardial effusion; advanced dysfunction of longitudinal fibers except the apex
Cardiac magnetic resonance imaging	LGE throughout muscle thickness is initially focal, then diffuses, typically in form of intramural linear areas in hypertrophic segments and punctate lesions in anterior and posterior walls of the RV	late subendocardial gadolinium enhancement mainly in basal segments of inferolateral wall; decreased signal intensity within IVS on T1 sequence	late subendocardial gadolinium enhancement mainly subendocardial (also within IAS)

PQ – PR interval (shortening); QRS – QRS Complex (widening); AV – atrioventricular block; AF – atrial fibrillation; FLA – atrial flutter; IAS – interatrial septum; RV – right ventricle; IVS – interventricular septum; LGE – late gadolinium enhancement.

TREATMENT

Heart failure management in amyloidosis

The main group of drugs used in patients with amyloidosis in heart failure are loop diuretics. Other drugs, such as angiotensin converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor neprilysin inhibitors, beta-blockers and mineralocorticoid receptor antagonists, are not used in this group of patients owing to the lack of evidence of improvement in the survival and quality of life of patients, and they are most often poorly tolerated by patients and may cause hypotension [1]. A possible explanation for this phenomenon is the complex pathophysiology of myocardial changes caused by amyloid infiltration; the combination of small and normal ventricular size, significant diastolic dysfunction, and impaired atrial contraction may result in a reduced stroke volume and cardiac output, while increasing intracardiac pressure.

Heart transplantation in these patients may be an effective therapeutic option [2].

Specific therapy for AL amyloidosis

In AL amyloidosis, the main treatments are chemotherapy and/or autologous stem cell transplantation targeting the primary plasma cell clone responsible for the formation of AL amyloid. The main chemotherapeutics used in treatment – bortezomib, cyclophosphamide and dexamethasone – are the most common initial chemotherapy regimens with satisfactory rates of hematological response.

Specific therapy for ATTR amyloidosis

For patients with New York Heart Association class I to III ATTR cardiomyopathy, tafamidis is the main treatment. Tafamidis is a drug that stabilizes the transthyretin tetramer, leading to a reduction in the formation of TTR amyloid. In a recent study, tafamidis was found to reduce cardiovascular-related mortality and hospitalizations while improving the quality of life and reducing declines in functional capacity [47].

Liver transplantation may be considered in patients with hereditary ATTR cardiomyopathy, thus removing the mutated amyloidogenic TTR in hereditary ATTR cardiomyopathy since the source of amyloidogenic protein is the liver. However, liver transplantation is not indicated in wild-type ATTR amyloidosis.

Research is underway on other drugs that could be used to treat ATTR amyloidosis. Great hopes are placed on RNA-targeted therapy that interferes with TTR synthesis in the liver and thus reduces the ability of the misfolded monomer to form amyloid deposits. Representatives of this group of drugs are patisiran and inotersen [36]. Tafamidis therapy is not registered in Poland, but it is registered for the treatment of ATTR amyloidosis in the European Union. In order to use the drug in Poland, consent of the bioethics committee and the patient's consent for treatment with tafamidis are required. After obtaining the consent of the bioethics committee and the patient, the doctor sends the appropriate documents to the company producing the drug and then, after approval of the documents, the company sends the drug to the hospital and then the drug is issued to the patient.

PROGNOSIS

The prognosis of CA is unfavorable. The median survival in untreated CA from the onset of HF is 6 months. Treatment can prolong life by several years. The prognosis also depends on other prognostic factors, including: the cause of the disease, the type of amyloidosis, the degree of organ involvement, the patient's clinical condition, and the presence of comorbidities.

In conclusion, it is extremely important that the diagnostic process is started as early as possible because early initiation of appropriate treatment can significantly improve the prognosis in this group of patients [9,48,49].

CONCLUSIONS

CA is a rare and serious disease. Inappropriate deposition of amyloid in the heart can cause many serious complications, including RCM, conduction disorders, HF, and sudden cardiac death.

There are two main types of CA: ATTR-CA and AL-CA. The symptoms may be non-specific and include shortness of breath, edema and arrhythmias. Diagnosis is usually based on a medical history, physical examination, imaging studies such as echocardiography and CMR, as well as biopsies of affected tissues. The treatment of CA depends mainly on the degree of organ involvement and includes drugs that reduce amyloid production and drugs for symptomatic treatment. In addition, a heart transplant may be considered in some cases. The prognosis is generally poor. Nonetheless, early diagnosis and appropriate treatment can significantly slow down the progression of the disease.

In conclusion, CA is a serious condition that requires proper diagnosis and treatment. A multidisciplinary approach involving many specialists helps to provide the best care for those affected by the disease.

Conflict of interest

None declared

Author's contribution

Study design – M. Niemiec
Data collection – B. Gruchlik
Manuscript preparation – M. Niemiec
Literature research – M. Balwierz
Final approval of the version to be published – K. Mizia-Stec

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