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АМИЛОИДОЗ СЕРДЦА: ВЗГЛЯД ТЕРАПЕВТА И КАРДИОЛОГА

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Cardiac Amyloidosis: Internist and Cardiologist Insight

Резюме

Амилоидоз сердца (амилоидная кардиомиопатия) — поражение сердца, обусловленное внеклеточным отложением амилоида. В ряде случаев может быть локальное поражение структур сердца, например, предсердий, чаще поражение сердца является частью системной (генерализованной) патологии. В зависимости от белка-предшественника амилоида выделяют 36 типов амилоидоза, среди которых — наследственные и приобретенные формы. Амилоидоз сердца необходимо диагностировать как при выявлении амилоидной инфильтрации при эндомиокардиальной биопсии, так и при утолщении стенки левого желудочка >12 мм в отсутствии артериальной гипертензии или других причин для развития гипертрофии левого желудочка при выявлении амилоида внесердечной локализации. Сердце чаще всего поражается при AL-, ATTR-, AA-, AANF-типах амилоидоза. Скрининговое обследование на амилоидоз необходимо при хронической сердечной недостаточности неясной этиологии (особенно с сохраненной фракцией выброса левого желудочка), рефрактерной к терапии, в сочетании с протеинурией и хронической болезнью почек 4-5 стадии; идиопатической фибрилляции предсердий и нарушениях проводимости, утолщении стенки левого желудочка неясной этиологии, наличии низкого вольтажа зубцов при электрокардиографии, необъяснимой артериальной гипотензии и легочной гипертензии. Скрининг на амилоидоз должен включать как неинвазивные методы, в т.ч. электрофорез и иммунофиксацию белков крови и мочи, исследование на свободные легкие цепи иммуноглобулинов лямбда и каппа, ^{99}Tc-DPD-сцинтиграфию, генетическое тестирование (при подозрении на наследственные варианты

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амилоидоза), так и морфологическое исследование биоптатов различной локализации с окраской Конго красным и поляризационной микроскопией.

Ключевые слова: *амилоидоз сердца, амилоидная кардиомиопатия, хроническая сердечная недостаточность с сохраненной фракцией выброса левого желудочка, фибрилляция предсердий, гипертрофия левого желудочка, хроническая болезнь почек, альбуминурия, нефротический синдром*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Cardiac amyloidosis (amyloid cardiomyopathy) is a disease damage to the heart caused by extracellular amyloid deposition. In some cases, there may be local damage to the structures of the heart, for example, the atria; more often, heart damage is part of a systemic (generalized) pathology. Depending on the amyloid precursor protein, 36 types of amyloidosis are described, among which hereditary and acquired forms are distinguished. Cardiac amyloidosis is diagnosed 1) in the case of the amyloid infiltration in the myocardial bioptates or 2) in the case of non-cardiac amyloid deposition and the left ventricular wall thickening >12 mm without arterial hypertension and other reasons. The heart is most often affected in AL-, ATTR-, AA-, AANF-types of amyloidosis. Cardiac amyloidosis should be considered in patients with a heart failure with an unclear etiology, especially with preserved left ventricular ejection fraction, refractory to treatment, with proteinuria and CKD 4-5, in patients with idiopathic atrial fibrillation and conduction disturbances, in patients with left ventricular wall thickening of unclear etiology, low ECG voltage, unexplained arterial hypotension and pulmonary hypertension. Screening for cardiac amyloidosis should include non-invasive methods such as electrophoresis and immunofixation of blood and urine proteins, the free light lambda and kappa chains of immunoglobulins, 99Tc-DPD scintigraphy, genetic testing (if hereditary variants of amyloidosis are suspected), as well as a histological examination of biopsy samples stained with Congo red and polarizing microscopy.

Key words: *cardiac amyloidosis, amyloid cardiomyopathy, chronic heart failure with preserved ejection fraction, atrial fibrillation, left ventricular hypertrophy, chronic kidney disease, albuminuria, nephrotic syndrome*

Conflict of interests

The authors declare that this study, its theme, subject and content do not affect competing interests

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ACEI — angiotensin-converting enzyme inhibitor, AH — arterial hypertension, CHF — chronic heart failure, CHFpEV — chronic heart failure with preserved ejection fraction, CMP — cardiomyopathy, ECG — electrocardiogram, EchoCG — echocardiography, EV — ejection fraction, ICD — implantable cardioverter defibrillator, LV — left ventricle, MRI — magnetic resonance imaging, NSAID — non-steroidal anti-inflammatory drug, NT-proBNP — N-terminal prohormone of cerebral natriuretic factor, PET — positron emission tomography, RNA — ribonucleic acid, TTP — transthyretin

Introduction

Amyloidosis is a group of diseases characterized by extracellular deposits of a specific glycoprotein (amyloid) [1]. Amyloid infiltration of tissues and organs can result in their enlargement, damage/death of their cells and impaired functioning [2, 3]. The clinical picture can be quite different; it depends on organs damaged by amyloid deposits and on the type of their functional impairment. Although amyloidosis is quite common in clinical practice, unfortunately, this disease is remained unaddressed by Russian science societies, scientific journals and medical specialists who, despite their vast experience and expertise, not diagnose amyloidosis, especially cardiac amyloidosis. This review touches on the issues of modern-day classification, clinical picture, diagnosis and management of patients with cardiac amyloidosis.

Classification of amyloidosis

Based on different amyloid precursor proteins, there are currently 36 types of amyloidosis (Table 1) [4]. For clinical purposes, we can identify local and systemic (generalized) types of amyloidosis: local types are characterized by one organ involved, and systemic types — by several organs and systems [5].

Table 1. *Classification of amyloidosis [4]*

Type	Precursor protein/place of its synthesis in systemic forms	Systemic (S) and/or localized (L)	Acquired (A) or hereditary (H)	Target organs
AL	Λ and κ-immunoglobulin light chain/ Bone marrow	S, L	A, H	All organs, usually except CNS, macroglossia and periorbital purpura are almost pathognomonic
AH	Immunoglobulin heavy chain	S, L	A	All organs except CNS
AA	Serum amyloid A (SAA-protein) / liver	S	A	All organs except CNS
ATTP	Transthyretin, wild type/liver	S	A	Heart mainly in males, Lung, Ligaments, Tenosynovium
	Transthyretin, variants/liver	S	H	PNS, ANS, heart, eye, leptomen
$A\beta_2M$	b2-Microglobulin, wild type	S	A	Hemodyalisis associated: Musculoskeletal System
	b2-Microglobulin, variant	S	H	Hemodyalisis associated: ANS
AGel	Gelsolin, variants	S	H	PNS, cornea
AApoAI	Apolipoprotein A I, variants	S	H	Heart, liver, kidney, PNS, testis, larynx (C terminal variants), skin (C terminal variants)
AApoAII	Apolipoprotein A II, variants	S	H	Kidney
AApoAIV	Apolipoprotein A IV, variants	S	A	Kidney
AApoCII	Apolipoprotein C II, variants	S	H	Kidney
AApoCIII	Apolipoprotein C III, variants	S	H	Kidney

Table 1. *[The end].*

Type	Precursor protein/place of its synthesis in systemic forms	Systemic (S) and|or localized (L)	Acquired (A) or hereditary (H)	Target organs
ALys	Lysozyme, variants	S	H	Kidney
ALECT2	Leukocyte Chemotactic Factor-2	S	A	Kidney
AFib	Fibrinogen a, variants	S	H	Kidney
ACys	Cystatin C, variants	S	H	PNS, skin
ABri	ABriPP, variants	S	H	CNS
Adan	ADanPP, variants	L	H	CNS
Aβ	Ab protein precursor, wild type	L	A	CNS
	Ab protein precursor, variant	L	H	CNS
AαSyn	α-Synuclein	L	A	CNS
Atau	Tau	L	A	CNS
APrP	Prion protein, wild type	L	A	CJD, fatal insomnia
	Prion protein variants	L	H	CJD, GSS syndrome, fatal insomnia, PNS
Acal	(Pro)calcitonin	L	A	C-cell thyroid tumors
AIAPP	Islet amyloid polypeptide	L	A	Islets of Langerhans, Insulinomas
AANF	Atrial natriuretic factor / atria	L	A	Cardiac atria
APro	Prolactin	L	A	Pituitary prolactinomas, aging pituitary
AIns	Insulin	L	A	Iatrogenic, local injection
ASPC	Lung surfactant protein	L	A	Lung
AGal7	Galectin 7	L	A	Skin
ACor	Corneodesmosin	L	A	Cornified epithelia, hair follicles
AMed	Lactadherin	L	A	Senile aortic media
Aker	Kerato-epithelin	L	A	Cornea
ALac	Lactoferrin	L	A	Cornea
AOAAP	Odontogenic ameloblastassociated protein	L	A	Odontogenic tumors
ASem1	Semenogelin 1	L	A	Vesicula seminalis
AEnf	Enfurvitide	L	A	Iatrogenic
ACatK	Cathepsin K	L	A	Tumor associated

Determination of cardiac amyloidosis

Diagnosis of cardiac amyloidosis (amyloid cardiomyopathy) can be established if endomyocardial biopsy reveals amyloid infiltration or if there are extracardiac sites of amyloid and a thickened left ventricular (LV) wall > 12 mm with no arterial hypertension (AH) or any other conditions that can cause LV hypertrophy [6]. Heart damage occurs in connection with systemic AL, ATTR, AA, Aβ2m, AApoAI amyloidosis and local atrial AANF amyloidosis (Table 2) [1]. The most common types of amyloidosis associated with heart damage are AL (70–80% of cardiac amyloidosis), ATTR (15–25%), and AA amyloidosis (2–7%) [5, 6].

Table 2. *Main types of amyloidosis with cardiac involvement [2, 7]*

Type	Age, years	Gender	Laboratory data	Treatment
AL	>50	M≥F	Increase of free lambda or kappa chains in serum with an abnormal ratio (norm 0.26-1.65). M-gradient in serum and / or urine. Decreased normal immunoglobulins. Proteinuria.	Chemotherapy Stem cell transplantation in selected patients
Дикий ATTR	60-80	M:F > 250: 1	No	1.Suppression of TTP synthesis (liver transplantation; TTP gene «switches») 2.Stabilization of TTP (tafamidis, diflunisal, green tea, AG10) 3. Cleavage of amyloid fibrils (doxycycline with taurursodeoxycholic acid, monoclonal antibodies)
Наслед-ственный ATTR	Depends of mutation: V122I in afroamericans — 60-65 years; 20-30 years in Portugale, Shweden, Greese, Kipr; >40 years in Great Britain	50-72% M	No	
AA	20-30 years after the onset of the chronic inflammatory disease	M=F	Increased ESR, C-reactive protein, SAA protein in the blood. Proteinuria.	Treatment of the underlying disease Cytostatics Monoclonal antibodies Dimethyl sulfoxide Eprodisate Heparin Statins Fibrillex
AANF	Oderly	>F	No	
Aβ2M	Hemodyalisis patients and severe predyalisis CRF		Increase in the level of β2-microglobulin in the blood, antibodies to it	

Note: F — women, M — men, ESR — erythrocyte sedimentation rate, CKD — chronic kidney disease

Epidemiology

Until recently, amyloidosis was considered a rare disease; this diagnosis was often established during autopsy. According to the National Amyloidosis Center, the prevalence of amyloidosis in the UK is 0.8/100,000 population [8]. Among Medicare (National Health Insurance Program) patients in the United States who were hospitalized for chronic heart failure (CHF) in 2000–2012, there was a significant increase in the prevalence (from 8 to 17 per 100,000 people per year) and the incidence (from 18 to 55 per 100,000 people per year) of cardiac amyloidosis; the most pronounced growth was observed after 2006 [9].

Unfortunately, there are no statistics on amyloidosis on the website of the Federal State Statistics Service (www.gks.ru). At the V. M. Buyanov State Clinical Hospital of the Department of Health of Moscow, the detection frequency of amyloidosis was low for the period from 2008 to 2017; in 2018–2019 it amounted to 30–53 per 100,000 people per year [10].

AL amyloidosis

AL amyloidosis develops as a result of extracellular deposition of fibrils formed by monoclonal immunoglobulin light chains (gamma globulins; most often lambda, less often kappa) secreted by a pathological clone of plasma cells or B lymphocytes [2, 11]. AL amyloidosis belongs to the group of monoclonal gammopathies [6, 12]. Monoclonal gammopathies are often found in people aged

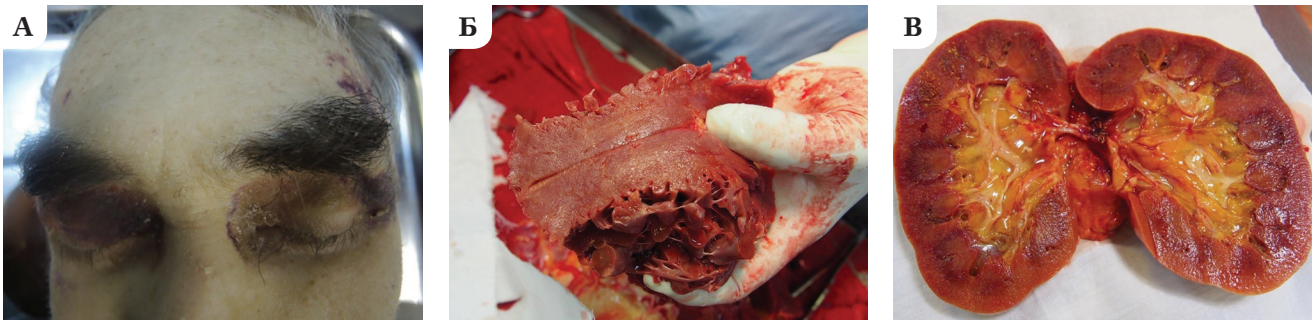

Figure 1: A. *Periorbital hemorrhages of the different ages («panda eyes», «raccoon eyes»).* ***B*** *and* ***C****. Damage of the heart and the kidney in the patient with amyloidosis, macropreparations. Large volume of amyloid deposits leads to the tissue compaction usually. The affected organ acquires a yellowish tint, «waxy» or «greasy» appearance (photos from the archive Dr Stepanova E.A.).*

over 50, which is the reason for screening this age group for gammopathies. However, monoclonal gammopathy does not always indicate AL amyloidosis: it can be found in 40% of patients with ATTR amyloidosis [2, 13–15].

The formation of an abnormal clone of plasma or B cells in the bone marrow is called plasma cell or B cell dyscrasia [5]. All patients with plasma cell dyscrasia and lymphoproliferative diseases are at risk of AL amyloidosis [5]. They also should be tested for AL amyloidosis. The formation of an abnormal cell clone outside the bone marrow can result in local amyloidosis (amyloidosis of the trachea, bronchi, larynx, bladder, etc.) [5, 16].

Cardiac amyloidosis is found in 33–60% of patients with AL amyloidosis [6]. Heart failure associated with AL amyloidosis develops relatively early — in 22% of patients as early as the onset of disease [5]. Heart damage in AL amyloidosis almost always occurs in connection with damage to other organs, most often, kidneys, blood vessels, the peripheral nervous system, liver, gastrointestinal tract, soft tissues [2]. Isolated cardiac involvement occurs in less than 5% of cases [6]. Eleven percent of patients with AL amyloidosis have orthostatic hypotension at diagnosis [5].

Despite a smaller increase in LV mass, the prognosis for AL amyloidosis with cardiac damage is worse than for ATTR amyloidosis. On average, cardiac AL amyloidosis with clinical signs of chronic heart failure (CHF) without treatment results in a fatal outcome within six months after the onset of symptoms [17]. Heart damage is the main predictor of a poor prognosis; the management strategy should be chosen depending on the severity of this damage [6] (Figure 1).

ATTR amyloidosis

Transthyretin amyloidosis (ATTR) is caused by the deposits of an abnormal transthyretin protein [15]. Transthyretin (TTR) is a carrier protein of thyroxine (T4) and complex retinol-binding protein/vitamin A; it is a tetramer and consists of four identical subunits. About 95% of transthyretin is synthesized in the liver, less than 5% — in the vascular plexus of the brain and retinal pigment epithelium. Less than 1% of transthyretin carries thyroxine in human serum; most of the circulating transthyretin is unconjugated [18, 19].

ATTR amyloidosis can be divided into family type (mutant, hereditary, with autosomal dominant type of inheritance with incomplete penetrance; it is caused by mutation in the gene encoding transthyretin synthesis) and senile type (not caused by mutations; in the English literature sources, it is called “wild type,” or “Alzheimer’s heart disease”) with no mutations in the transthyretin gene. In both cases, transthyretin tetramers decompose to amyloidogenic monomers [5].

“Wild type” ATTR amyloidosis is more common in men aged over 65. Its prevalence in people aged over 75 is 1–3%, in people aged over 80 — 20–30% [6], in patients with CHF — 11–13.3% [20], with degenerative aortic stenosis — 16%, and with carpal tunnel syndrome — 7–8% (Table 3) [15, 21].

The most important sign is cardiac involvement with a developing pattern of restrictive or hypertrophic cardiomyopathy (CMP) and heart failure (HF), rhythm and conduction disorders [6]. Carpal tunnel syndrome is a frequent comorbidity [6].

Table 3. *Prevalence of ATTR amyloidosis [20, 22-26]*

Patient group	Frequency of proven ATR amyloidosis	Type of the ATTR-amyloidosis
Afroamericans	3,4%	Hereditary Val122Ile
Population of Northwest Ireland	1%	Hereditary Thr60Ala
CHFpEF with LV wall thickness ≥12 mm	13,3%	Wild ATTR-amyloidosis
CHFrEF with LV wall thickness ≥12 mm	11%	Wild ATTR-amyloidosis
CHF (RF, Almazov's centre)	4,6%	Hereditary ATTR-amyloidosis
Hypertrophic cardiomyopathy	5%, у лиц старше 55 лет — у 7,6%/ 5%, older 55 years — 7,6%	Hereditary ATTR-amyloidosis
Aortic stenosis in patients with the transcatheter aortic valve implantation	16%	NA
Aortic stenosis in persons > 65 years in patients with the aortic valve replacement	6%	NA
Conduction disturbances requiring the installation of a pacemaker	2%	Wild ATTR-amyloidosis
Patients with carpal tunnel syndrome	7-8%	Both types
Older 75 years old	1-3%	Almost all with wild ATTR-amyloidosis
Older 80 years old	20-30%	Wild ATTR-amyloidosis

Note: CHFpEF — chronic heart failure with preserved left ventricular ejection fraction, CHFrEF — chronic heart failure with low left ventricular ejection fraction

Hereditary ATTR amyloidosis is less common: 7–9% of all cases of amyloidosis [6]; 40,000–50,000 diagnosed patients in the world [15]. Recent studies revealed ~~it~~ hereditary ATTR amyloidosis in 5% of patients with hypertrophic cardiomyopathy [22]. Hereditary ATTR amyloidosis developed due to gene mutations and replacement of amino acids in the transthyretin molecule. At present, there are more than 120 different mutations in the transthyretin gene; 110 of them are amyloidogenic [26]. Mutations lead to the dissociation of the transthyretin tetramer into monomers (destabilization), prone to improper folding and aggregation with the formation of toxic amyloidogenic intermediate products [18, 19, 27]. Most patients are heterozygotes. Therefore, they have not only mutant but also normal non-mutant transthyretin.

The phenotype of hereditary ATTR amyloidosis can be predominantly neurological, or predominantly cardiological, or mixed. The most common mutation, *Val122Ile* (found in 3–10% of African Americans), is characterized by predominant cardiac symptoms. The most frequent sign of *Val30Met* mutation is amyloid polyneuropathy. However, its late onset may be manifested by cardiomyopathy. The *Thr60Ala* mutation (found in 1% of the population in Northwest Ireland) is characterized by a mixed cardiac and neurological phenotype combined with gastrointestinal damage [28–33].

Screening for ATTR amyloidosis should be performed in elderly patients with definite clinical signs of CHF, especially with chronic heart failure with preserved LV ejection fraction (CHFpEF) (with no history of arterial hypertension (AH)), hypertrophic, restrictive cardiomyopathy, degenerative aortic stenosis and thickness of the interventricular septum (T_{IVS}) ≥ 12 mm in patients with CHF, hypertrophic, restrictive cardiomyopathy, degenerative aortic stenosis and LV wall thickness ≥ 12 mm for no clear reason for left ventricular hypertrophy (LVH) (Table 4).

Life expectancy for patients with «wild type» ATTR amyloidosis after diagnosis/manifestation of heart failure (HF) is 2–6 years [15]. The prognosis for patients with hereditary ATTR amyloidosis depends on the mutation and is determined by cardiac involvement.

AA amyloidosis

AA amyloidosis (reactive, secondary amyloidosis) develops in connection with chronic inflammatory diseases that are usually difficult to manage [5, 6].

Table 4. *Diagnostic keys (indications for screening) ATTR amyloidosis [14]*

Anamnesis/physical examination	Imaging	Clinico-instrumental data
➢ Right ventricular heart failure of unclear etiology ➢ CHFpEF, especially in men ➢ Intolerance to ACE inhibitors or beta-blockers ➢ Carpal tunnel syndrome (bilateral) ➢ Spinal stenosis ➢ Ruptured biceps tendon ➢ Unexplained peripheral neuropathy (loss of heat / cold sensitivity, postural hypotension, unstable stool) ➢ Unexplained atrial rhythm and conduction disturbances, incl. requiring pacemaker installation	➢ Accumulation of PYP, DPD or HMDP isotopes in the myocardium during scintigraphy ➢ Signs of symmetric LV (and RV) hypertrophy in the absence of aortic stenosis or long-term hypertension ➢ Infiltrative phenotype (biventricular hypertrophy, pericardial effusion, thickened leaflets, atrial septum) ➢ Diffuse subendocardial or transmural late accumulation of gadolinium or increased extracellular volume on MRI ➢ Apical sparing on longitudinal strain imaging ➢ Decreased contractility ➢ Restrictive type of diastolic dysfunction ➢ Reducing the ECG voltage ➢ Pseudoinfarction pattern in the absence of violations of local contractility during echocardiography	➢ HF with unexplained thickening of the LV wall without dilatation ➢ Concentric thickening of the LV wall, possibly with a mismatch between QRS voltage and LV wall thickness ➢ Decreased longitudinal LV function despite normal LVEF ➢ Aortic stenosis with RV wall thickening, especially with low pressure gradient

Note: LV — left ventricle, RV — right ventricle, HF — heart failure, EF — ejection fraction, CHFpEF — chronic heart failure with preserved left ventricular ejection fraction, DPD- ^{99m}technetium-3,3-diphosphono- 1,2-propanodicarboxylic acid; HMDP — hydroxymethylene diphosphonate; PYP- technetium pyrophosphate

AA amyloid is formed from the SAA serum precursor (serum amyloid A), which is an acute-phase protein produced by the liver in response to inflammation [1, 4, 5]. Since SAA is actively produced by the synovial membrane of joints, an additional risk factor for amyloidosis is the manifestation of an inflammatory disease with joint syndrome [1, 4, 5].

Any chronic inflammatory disease can be considered a risk factor for AA amyloidosis. Screening for AA amyloidosis should be carried out in cases of chronic seropositive and seronegative polyarthritis (rheumatoid arthritis, ankylosing spondylitis, juvenile chronic arthritis, psoriatic arthropathy, Reiter's syndrome, etc.), chronic inflammatory bowel diseases (Crohn's disease, ulcerative colitis), chronic suppurative diseases (bronchiectasis, osteomyelitis, etc.), tuberculosis, solid malignant tumors, autoinflammatory diseases (Table 5) [5].

Adequate management of the underlying disease should be performed to prevent AA amyloidosis [5, 34]. Assessing the risk of the development and progression of AA amyloidosis requires monitoring SAA,

Table 5. *Autoinflammatory diseases [60, 61]*

Polygenic	Monogenic		
	Pathology	Inheritance type	A gene with a mutation
Osteoarthritis Gout Pseudogout Sarcoidosis Erythema nodosum Accumulation diseases Atherosclerosis, etc.	Periodic illness (familial Mediterranean fever)	AR	*MEFV*
	Hyperimmunoglobulinemia D with periodic febrile syndrome	AR	*MVK*
	Tumor necrosis factor α receptor-associated periodic syndrome (TRAPS)	AD	*TNFRSF1A*
	Familial cold urticarial	AD	*NLRP3 (или CIAS1)*
	Macle-Wells syndrome (familial nephropathy with urticaria and deafness)	AD	
	Neonatal Onset Multisystemic Inflammatory Disease — NOMID, hronic Infantile Neurological Cutaneous and Articular syndrome — CINCA	AD	

Note: AR — autosomal recessive, AD — autosomal dominant, MEFV — Mediterranean fever, MVK — mevalonate kinase, TNFRSF1A — tumor necrosis factor receptor superfamily 1A, NLRP3 — Nod-like receptor family NALP, the main component of NLRP3-inflammasome, recognizes molecular fragments associated with damage (DAMP; uric acid crystals, mitochondrial DNA, S100 proteins, etc.) or pathogens (PAMP; lipopolysaccharides, peptidoglycans, bacterial nucleic acids) and initiating the process of inflammation

C-reactive protein, ferritin, calgranulin (S100A12 serum marker of neutrophilic activity) levels [5].
AA amyloidosis most often causes kidney damage with the development of nephrotic syndrome and/or renal failure. Heart is rarely involved (in 2–3% of patients) [6].

AANF amyloidosis

AANF is a local amyloidosis with atrial damage. It is more common in elderly women (aged over 80) but can also occur in younger patients with valve abnormalities or atrial fibrillation [35, 36]. Atrial natriuretic peptide (ANP) is the precursor protein. It is most commonly found during autopsy. It is extremely rarely found during lifetime due to the risk of atrial perforation with endomyocardial biopsy [6].

Clinical picture of amyloidosis

Most patients with amyloidosis have multiple organ damage (Figure 1, Table 6).

Table 6. *Possible manifestations of amyloidosis [6, 45]*

Clinical picture	Involvement of the cardiovascular system	Features
	Left, right ventricular, or biventricular heart failure	Shortness of breath, choking Weakness, fatigue Heartbeat Swelling of the neck veins Pathological III tone Edema Hepatomegaly Hydrothorax Hydropericardium Ascites
	Presyncope / syncope, orthostatic hypotension	Caused by low cardiac output, rhythm and conduction disturbances, amyloidosis of the nerve plexuses of blood vessels
	Angina pectoris syndrome, myocardial infarction	Caused by amyloid infiltration of coronary vessels
	Signs of tricuspid and mitral valve insufficiency	Caused by amyloid infiltration of valves and subvalvular structures
	Rhythm disturbances	In 50% of patients Most often atrial fibrillation Supraventricular tachycardia Less commonly, ventricular tachycardia Premature Ventricular Excitation Syndrome
	Conduction disorders	Atrioventricular block Sinoatrial block His bundle branch block
	Sudden cardiac death	Due to arrhythmias, electromechanical dissociation
	Damage to the nervous system	**It is detected in 17% of patients with AL-amyloidosis, in many patients with hereditary amyloidosis**
	Progressive symmetric distal sensorimotor polyneuropathy	It is caused by degeneration of the myelin sheath of nerves, as well as compression of the nerve trunks by amyloid deposits and ischemia as a result of amyloid deposits in the walls of blood vessels. First, pain and temperature are disturbed, then vibration and positional sensitivity, later motor disturbances join. Early symptoms are paresthesias, painful dysesthesias (numbness). The lower limbs are involved more often than the upper ones, the ability to move is impaired

Table 6. *[Continuation].*

Erectile dysfunction, impotence	Caused by dysfunction of the autonomic nervous system
Urinary retention, bladder dysfunction	May be complicated by recurrent urinary infection
Sweating disorders	Caused by dysfunction of the autonomic nervous system
Tunnel Syndrome	In 20% of all patients, early sign; pain and paresthesia in fingers I-III of the hand with gradual atrophy of the thenar muscles
Gastrointestinal manifestations	**Observed in 70% of patients with amyloidosis**
Dysphagia	Caused by amyloid infiltration of the esophagus
Nausea, vomiting	
Early satiety	
Ulceration, gastrointestinal perforation, bleeding	Amyloid infiltration of the esophagus may manifest as dysphagia stomach and intestines
Chronic diarrhea, malabsorption	Caused by infiltration of the intestinal wall with amyloid, dysfunction of the autonomic nervous system
Severe constipation	
Alternating constipation and diarrhea	
Prepiloric obstruction of the stomach, mechanical intestinal obstruction	
Unintentional weight loss	Due to malabsorption, autonomic dysfunction
Macroglossia	Pathognomonin for AL-amyloidosis, observed in 15% of patients, is due to pronounced infiltration of the tongue with amyloid. Often visible are imprints of teeth on the lateral surfaces of the tongue, abnormal phonation, difficulty in swallowing, speaking, breathing
Hepatomegaly, cholestasis; rarely intrahepatic portal hypertension, severe jaundice, hepatic failure, hepatic coma	In AA and AL amyloidosis, liver damage is observed in almost 100% of cases
Spleen involvement	
Splenomegaly	Macroscopically, the spleen may appear as «sago» (amyloid deposits in lymphoid follicles) or «sebaceous» (diffuse amyloid deposits).
Hyposplenism	May lead to thrombocytosis, thrombosis
Spontaneous rupture of the spleen	Seldom
Nephropathy	**In AA amyloidosis, the kidneys are affected in 100%, in AL — in 80-90% of patients**
Albuminuria, proteinuria, nephrotic syndrome	In nephrotic syndrome, antithrombin III deficiency is common, with an increased risk of thrombosis
Azotemia, renal failure	
Increased kidney size	It persists even with the development of end-stage renal failure
Chronic kidney disease	
Acute kidney injury	

Table 6. [Continuation].

	Respiratory system damage	More common in AL amyloidosis
	Hoarseness or change in tone of voice	Caused by the deposition of amyloid in the vocal cords
	Cough, shortness of breath	Обусловлены отложением амилоида в альвеолярных перегородках/ Caused by the deposition of amyloid in the alveolar septa
	Recurrent pleural effusion	It is caused by amyloidosis of the pleura, does not depend on the effectiveness of the treatment of edematous syndrome, often contains an admixture of blood
	Loss of the musculoskeletal system	**It rarely occurs, in 5-10% of patients with AL-amyloidosis, it is associated with amyloid deposition in bones, articular cartilage, synovia, ligaments and muscles**
	Carpal tunnel syndrome, manifested by intense pain and paresthesias in fingers I-III of the hand with atrophy of the thenar muscles	It is caused by compression of the median nerve by amyloid, which is deposited in the wrist ligaments. Detected in 20% of patients with AL-amyloidosis
	Pseudohypertrophy (hypertrophied muscle relief with a decrease in muscle strength) or muscle atrophy, difficulty in movement, pain syndrome	
	Lumbar spinal stenosis	
	Ruptured biceps head	
	Skin lesions	**Observed in almost 40% of patients with AL-amyloidosis**
	Periorbital purpura («raccoon eyes», «panda eyes»)	Occur at the slightest stress (cough, straining), the result of vascular fragility
	Papules, plaques, nodules, vesicular eruptions, induration of the skin, similar to scleroderma, pigmentation disorders (from pronounced intensification to total albinism), alopecia, trophic disorders, perspiration disorders	
	Other clinical manifestations	
	Clouding of the vitreous humor leading to gradual loss of vision; obstruction of the lacrimal canal leading to chronic open-angle glaucoma, keratitis, abnormal blood vessels in the eye	With AL and ATTR types
	Cachexia	Due to lesions of the gastrointestinal tract, autonomic dysfunction with trophic disorders
	The defeat of the thyroid gland with the development of the clinical picture of hypothyroidism	Described in AL amyloidosis
	The defeat of the adrenal glands with the development of their failure	More often with AA amyloidosis
	Lymphadenopathy	

Table 6. *[The end].*

	Sjogren's syndrome	
	Hemorrhagic syndrome, bleeding	Caused by the deposition of amyloid in the vascular wall, sometimes in combination with a deficiency of coagulation factors (X, less often V or IX)
ECG	Reducing the voltage of the ECG teeth Pseudo-infarction pattern	
ECHO	Thickening of the LV wall (> 12 mm) in patients without hypertension and a history of aortic stenosis, sometimes with thickening of the RV wall	Nonspecific trait
	Grainy or glowing myocardium	In 26% of patients
	Preserved LVEF	Decreased LVEF in the late stages of the disease
	Normal or reduced volume of the LV cavity	
	Diastolic dysfunction, restrictive type of transmitral flow on Doppler	
	Dilation of the left atrium	As the disease progresses, dilatation of both atria
	Thickening of the interatrial septum, atrioventricular valves	
	A small amount of fluid in the pericardial cavity	
	LVEF to global longitudinal strain ratio >4	
CMI	Diffuse transmural or subendocardial late gadolinium enhancement (LGE) in LV, RV	
	Enhanced myocardial uptake on T1-weighted images	
	Increased extracellular volume fraction (usually> 0.4)	
	Failure to suppress myocardial signal during PSIR (phase-sensitive inversion recovery)	
Scintigraphy	Increased accumulation of the isotope in the heart	
Laboratory data	Disproportionately high NT-proBNP values, chronic mild troponin elevation with normal ECG	
	Monoclonal gammopathy	AL amyloidosis
Genetic testing	Mutations in hereditary ATTR and other types amyloidosis	Differential diagnosis of familial and hereditary ATTR amyloidosis
Biopsy	The gold standard of diagnostics, allows for histological verification and typing of amyloid	

Cardiac amyloidosis

Clinical picture

The clinical picture of cardiac amyloidosis is nonspecific. First, patients have complaints of weakness, fatigue, decreased exercise tolerance, palpitations, dyspnea during exercise; later — at rest, a suffocating feeling at night [15]. Later stages are characterized by frequent development of right ventricular HF (edema of lower limbs, hepatomegaly, ascites, hydrothorax, hydropericardium, anasarca). A specific feature of HF is its resistance to management.

Amyloidosis should be suspected in patients with a history of AH, whose BP normalizes with time and with intolerance to angiotensin converting enzyme inhibitors (ACEI), angiotensin II or beta-blockers receptor antagonists due to hypotension. Orthostatic hypotension often develops due to decreased cardiac output and dysfunction of the autonomic nervous system (amyloidosis of vascular plexuses). In severe cases, orthostatic hypotension is accompanied by syncopal conditions. Fainting, as well as palpitations, can also be caused by cardiac arrhythmias and conduction disorders: atrial fibrillation, supraventricular, rarely ventricular tachycardia, pre-excitation syndrome, sinoatrial or atrioventricular blocks, sick sinus syndrome [6].

Obstruction of the intramural branches of coronary arteries is often found; it leads to ischemia, right up to myocardial infarction [37]. Increased risk of thrombosis and antithrombin III deficiency in connection with nephrotic syndrome may contribute to it [6].

The most common causes of death associated with cardiac amyloidosis are refractory CHF, rhythm and conduction disorders, electromechanical dissociation [6].

Electrocardiography

Electrocardiogram (ECG) reveals low *QRS* voltage (< 0.5 mV in limb leads and/or < 1.0 mV in precordial leads, Figure 2) in 46–66% of patients with amyloidosis [6].

Typical echocardiography (EchoCG) demonstrates a combination of low ECG voltage and thickened heart walls. The signs of LV hypertrophy on ECG should not be a reason for excluding cardiac amyloidosis [15]. In some patients, the following can be observed: QS complex in at least two chest leads («pseudo-infarct pattern») [5], T wave inversion or ST depression in lateral chest leads, often with no local contractility disorders on EchoCG.

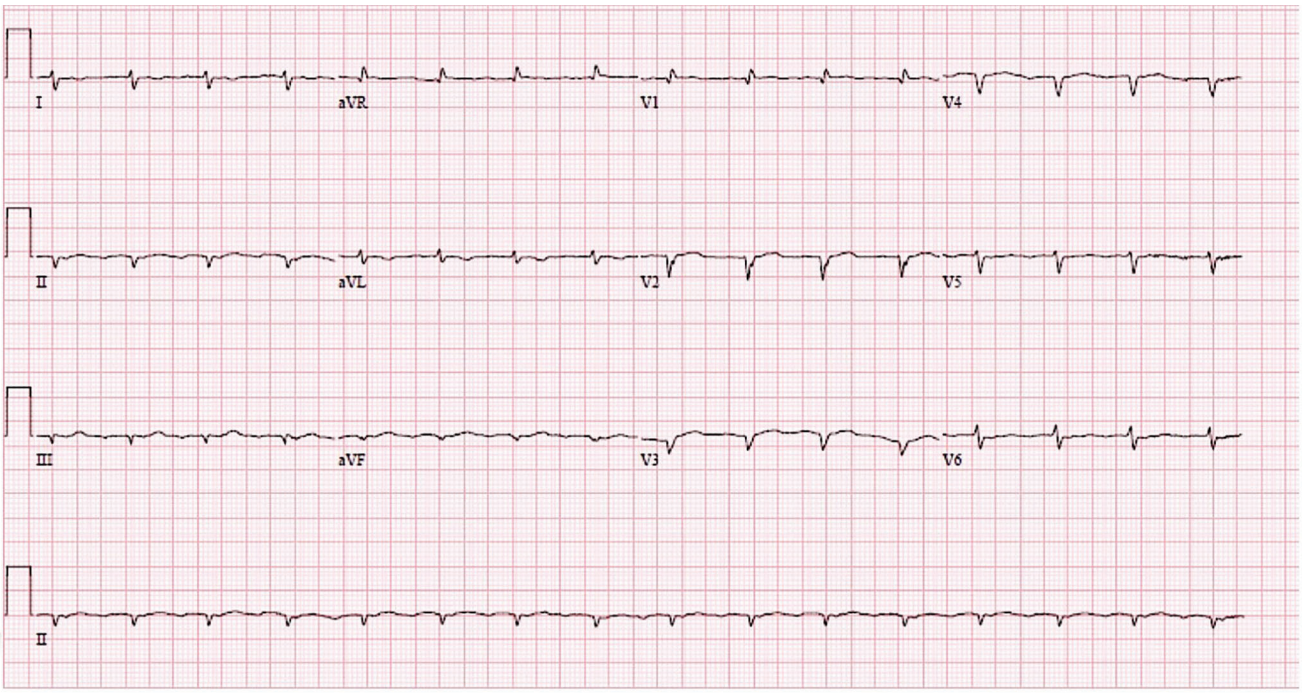

Figure 2. *ECG of a patient with cardiac amyloidosis (photos from the archive of authors)*

Holter ECG monitoring

Holter ECG monitoring can help to identify episodes of rhythm and conduction disorders and low heart rate variability, which indicates dysfunction of the autonomic nervous system [6].

Echocardiography

Imaging examinations of patients with cardiac amyloidosis demonstrate a picture of restrictive or hypertrophic cardiomyopathy (CMP) [5].

EchoCG-signs of amyloid CMP include symmetrical thickening of LV walls (> 12 mm) with no reason for hypertrophy, normal size and diastolic volume of LV, increased systolic size. The term «myocardial hypertrophy» is incorrect in this case [6]. LV wall thickness > 15 mm is rarely observed in cases of AH. Therefore, if there is a thickening of heart walls of unknown etiology, LV wall thickness > 15 mm, even with AH, discrepancies between wall thickness and QRS voltage on ECG, cardiac amyloidosis should be suspected [2].

Thickened interatrial septum, diffuse or local LV hypokinesis are also typical for amyloidosis (Figure 3) [38].

LV ejection fraction (EF) is often within normal but may decrease as the disease progresses. Myocardial

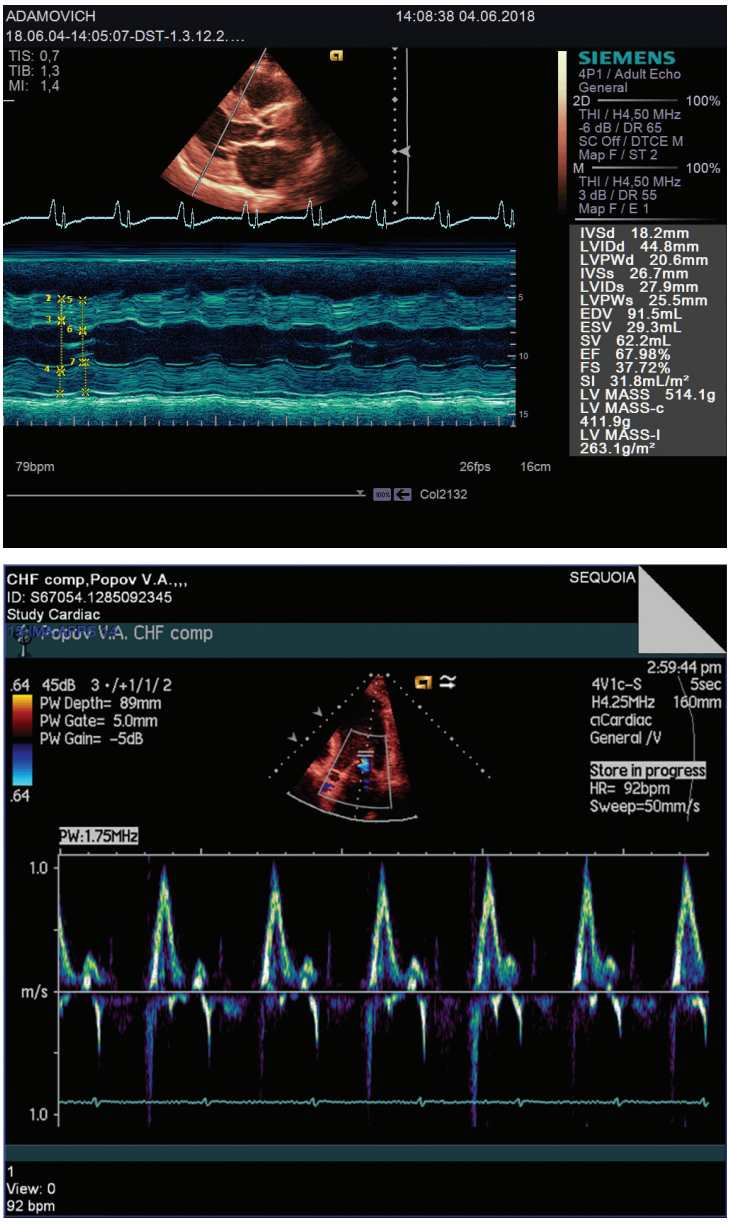

Figure 3. *Transthoracic echocardiography of a patient with cardiac amyloidosis. In the upper part, there is a thickening of the walls of the left ventricle, B-mode, apical four-chambered position. In the lower part, restrictive type of diastolic dysfunction, transmitral flow, pulse wave Doppler (photos from the archive Dr Reznik E.V.)*

granularity or fluorescence occurs in 26% of patients due to the higher echogenicity of amyloid deposits in comparison with normal myocardium [5, 38].

Disorders of longitudinal contractility, especially of LV basal segments, are typical for amyloidosis. Impaired LV diastolic function from mild relaxation impairment to severe restriction, and atrial dilatation are also typical [6].

Amyloidosis is also characterized by a thickening of the RV free wall and its dysfunction, as well as a thickening of valve cusps with blood regurgitation. Mitral and tricuspid insufficiency develops more often. Pericardial effusion is observed in 50% of patients; in some cases, cardiac tamponade may develop [6].

Specific ECG and EchoCG parameters have low sensitivity and specificity in cases of cardiac amyloidosis. EchoCG can not help to establish a definite diagnosis of amyloid CMP [6].

Cardiac MRI

Cardiac magnetic resonance imaging (MRI) in patients with amyloidosis reveals a symmetrically thickened LV wall, most often without obstruction of the outflow tract, sometimes — a thickened right ventricle (RV), atrial dilatation. Contrasting in delayed phase typically shows diffuse damage of all segments of ventricles and sometimes also of atria (Figure 4).

Deposits are most often of subendocardial or transmural type. In such cases, LV systolic function remains within normal [39, 40]. The new myocardial T1-mapping method allows a more precise assessement of myocardial damage caused by amyloidosis, and calculating the volume of the amyloid deposit in intercellular space, which is a marker of disease severity ("amyloid burden") and correlates with the survival rate [41]. Despite its high accuracy, MRI cannot be used as the only method for establishing cardiac amyloidosis diagnosis [15].

Scintigraphy and positron emission tomography

In cases of ATTR amyloidosis, there is active uptake of several isotopes in the heart. However, there is no or minimal uptake thereof in cases of AL amyloidosis [2]. This allows diagnosing ATTR-CMP at the early stages (Table 7).

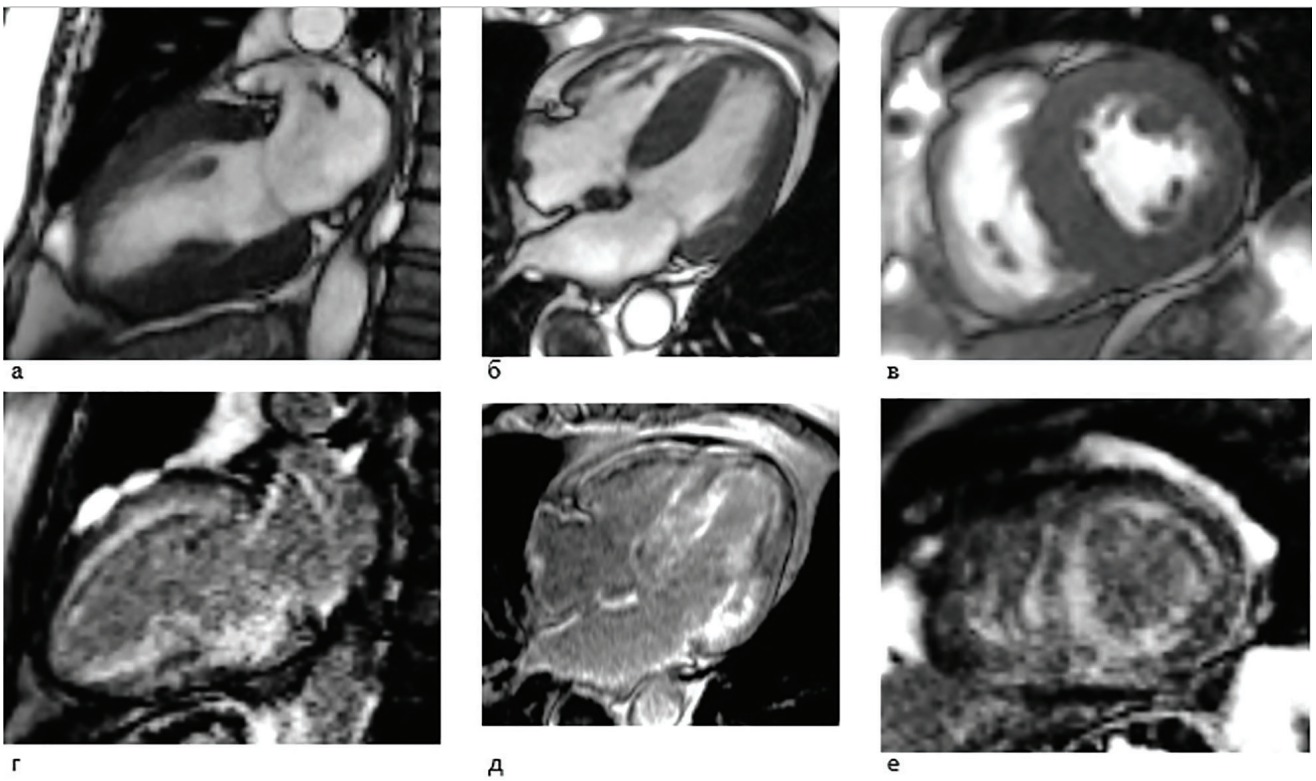

Figure 4. *MRI of a patient with cardiac amyloidosis (photos from the archive Dr Ustyuzhanin D.V.)*

Table 7. *Radioisotopes for Imaging TTR-Amyloid in the Heart*

Radiotracer	Imaging Modality	Mechanism of Uptake	Amyloid Subtype Uptake	Imaging Capability	Considerations
Bone avid tracers primarily used in the United States					
^{99m}Tc-PYP	Planar/SPECT	Bone tracer	ATTR-CM	Diagnostic; possibly early detection	Some uptake in patients with AL amyloidosis, less than ATTR amyloidosis
Bone avid tracers primarily used outside the United States					
^{99m}Tc-DPD ^{99m}Tc-HMDP	Planar/SPECT	Bone tracer	ATTR-CM	Diagnostic; possibly early detection	Some uptake in patients with AL amyloidosis, less than ATTR amyloidosis
Amyloid-binding radiotracers					
^{11}C-PIB	PET	Amyloid deposits	ATTR-CM, AL amyloidosis	Possibly quantitation of amyloid burden, disease monitoring	Short half-life, expensive isotope relative to SPECT tracers
^{18}F-флорбетапир	PET	Amyloid deposits	ATTR-CM, AL amyloidosis	Possibly early detection, quantitation, and disease monitoring	Expensive isotope relative to SPECT tracers
^{18}F-флорбетабен	PET	Amyloid deposits	ATTR-CM, AL amyloidosis	Possibly early detection, quantitation, and disease monitoring	Expensive isotope relative to SPECT tracers
^{18}F-NaF	PET	Bone tracer	Equivocal ATTR-CM	Possibly early detection, quantitation, and disease monitoring	No uptake in patients with AL amyloidosis, equivocal uptake in patients with ATTR-CM

Note: The tracers ^{99m}Tc-MDP and ^{99m}Tc-aprotinin are not recommended. ^{11}C-PIB indicates Pittsburgh compound B; ^{18}F-NaF, sodium fluoride; ^{99m}Tc-DPD, ^{99m}technetium-3,3-diphosphono-1,2-propanodicarboxylic acid; ^{99m}Tc-HMDP, hydroxymethylene diphosphonate; ^{99m}Tc-PYP, technetium pyrophosphate; 123I, iodine-123; AL, amyloid light chain; ATTR-CM, transthyretin amyloidosis with predominant cardiomyopathy (either wild-type or hereditary); PET, positron emission tomography; and SPECT, single-photon emission computed tomography

Positron emission tomography (PET) allows differentiating amyloidosis from cardiac pathology of another etiology [15].

Biomarkers

Patients with amyloidosis should be tested for the levels of troponin T/I and N-terminal prohormone of cerebral natriuretic factor (NT-proBNP) [6]. NT-proBNP of over 1,800 ng/l and troponin T over 0.025 ng/ml are nonspecific, but the most informative parameters that indicate the severity of cardiac amyloidosis [5]. The presence of amyloid CMP can be almost excluded if NT-proBNP level is < 332 ng/l. When troponin and NT-proBNP levels are high for no specific reason, cardiac amyloidosis should be excluded [15]. A decrease in the NT-proBNP level is a cardiological criterion for the response to treatment and remission (Table 8) [6].

The diagnostic value of a new biomarker, circulating retinol-binding protein 4, was recently demonstrated [15].

Diagnosis of cardiac amyloidosis

The gold standard for amyloidosis diagnosis is a histological examination with Congo red staining and polarized microscopy (Figure 5). In cases of systemic forms of amyloidosis, subcutaneous fatty tissue and endoscopic biopsy samples from the gastrointestinal tract are taken for screening. If screening biopsy gives a negative or equivocal result, the material is taken from a clinically affected organ. The sensitivity of myocardial biopsy is about 100%, rectal submucosa — 75–85%, salivary glands — 58%, abdominal subcutaneous fatty tissue — 75% (79–100% in cases of AL amyloidosis, in samples > 700 mm^2 — 100%).

Table 8. *Stages of cardiac amyloidosis [14, 44, 62]*

Biomarker		Threshold (*)
Troponin	Troponin T	<0,035 мкг/л (0,05 нг/мл)/ <0,035 mcg/l (0,05 ng/ml)
	Troponin I	<0,1 мкг/л/ <0,1mcg/l
	hs-Troponin T	<77 нг/л/ <77 ng/l
Brain natriuretic peptide	NT-ProBNP	<332 нг/л (3000 пг/мл)/ <332 ng/l (3000 pg/ml)
	BNP	<100 нг/л/ <100 ng/l
Stage	**Definition**	**Median survival, months (% over 4 years*)**
I	Troponin T, Troponin I, NT-proBNP < than threshold	26,4 (57%)
II	or Troponin T > than threshold, or Troponin I > than threshold, or NT-proBNP > than threshold	10,5 (42%)
III	Troponin T > than threshold, or Troponin I > than threshold, AND NT-proBNP > than threshold	3,5 (18%)

Note: * NT-proBNP — N-terminal of the prohormone brain natriuretic peptide; hs — high sensitive

The incidence of severe complications (including perforation of the right ventricle, cardiac tamponade) during endomyocardial biopsy is 1%. Therefore it should not be performed if amyloid is found in biopsy samples of another location [5].

If the presence of amyloid deposits in tissue is confirmed, amyloid typing with a panel of antisera is required. The most effective typing method is an immunohistochemical study based on the reaction of antibodies with a precursor protein [5]. A more reliable but less accessible method is mass spectrometry, which allows identifying a specific protein [6].

Diagnosis of cardiac AL amyloidosis

If AL amyloidosis is suspected, screening for monoclonal gammopathies and B cell or plasma cell dyscrasia should be performed (Figure 6). Monoclonal gammopathy can be found by electrophoresis and immunofixation of proteins from serum and daily urine. The most sensitive and cheap method for detecting monoclonal gammopathy is a quantitative Freelite method using immunoglobulin free lambda and kappa light chains [5]. If a monoclonal gammopathy is found, then a trephine biopsy should be performed to confirm the presence of plasma cell B cell dyscrasia. Twenty percent of patients with AL amyloidosis at the time of diagnosis have multiple myeloma as comorbidity, which is associated with a lower survival rate: 1 year for 39% and 81% in the case of presence and absence, respectively. Multiple myeloma in patients with AL amyloidosis can be excluded using the PET method. Clonality and malignancy of the pathological cell clone should be defined using cytogenetic tests and immunophenotyping; FISH test (fluorescence in-situ hybridization) should also be performed. The most common cytogenetic abnormality in cases of AL amyloidosis is translocation t(11;14), which is found in approximately 40–60% of patients. Trisomy, deletion 17p, or abnormal t(11;14) are associated with an unfavorable prognosis [42].

Figure 5. A. *Massive deposits of amyloid in the liver, macropreparation.* ***B.*** *«Sebaceous spleen», macro preparation.* ***B–I*** *Microscopic picture of amyloidosis. Amyloid deposits are characterized by the ability to birefringence and dichrosis with the glow of apple-green and yellowish-green colors when studying preparations stained with Congo red in polarized light. Micropreparations with liver tissue, Congo red staining, × 20:* ***B*** *– polarized light, crossed polaroids,* ***G*** *– bright field. Micropreparations with heart tissue:* ***D.*** *Clusters of amorphous eosinophilic masses in the interstitium, stained with hematoxylin eosin, × 20.* ***E.*** *Congophilic deposits in the interstitium, stained with Congo red, × 20.* ***F, I.*** *Characteristic apple-green glow of amyloid deposits when examined in polarized light, different crossing angle of polaroids, × 20 (photos from the archive Dr Stepanova E.A.)*

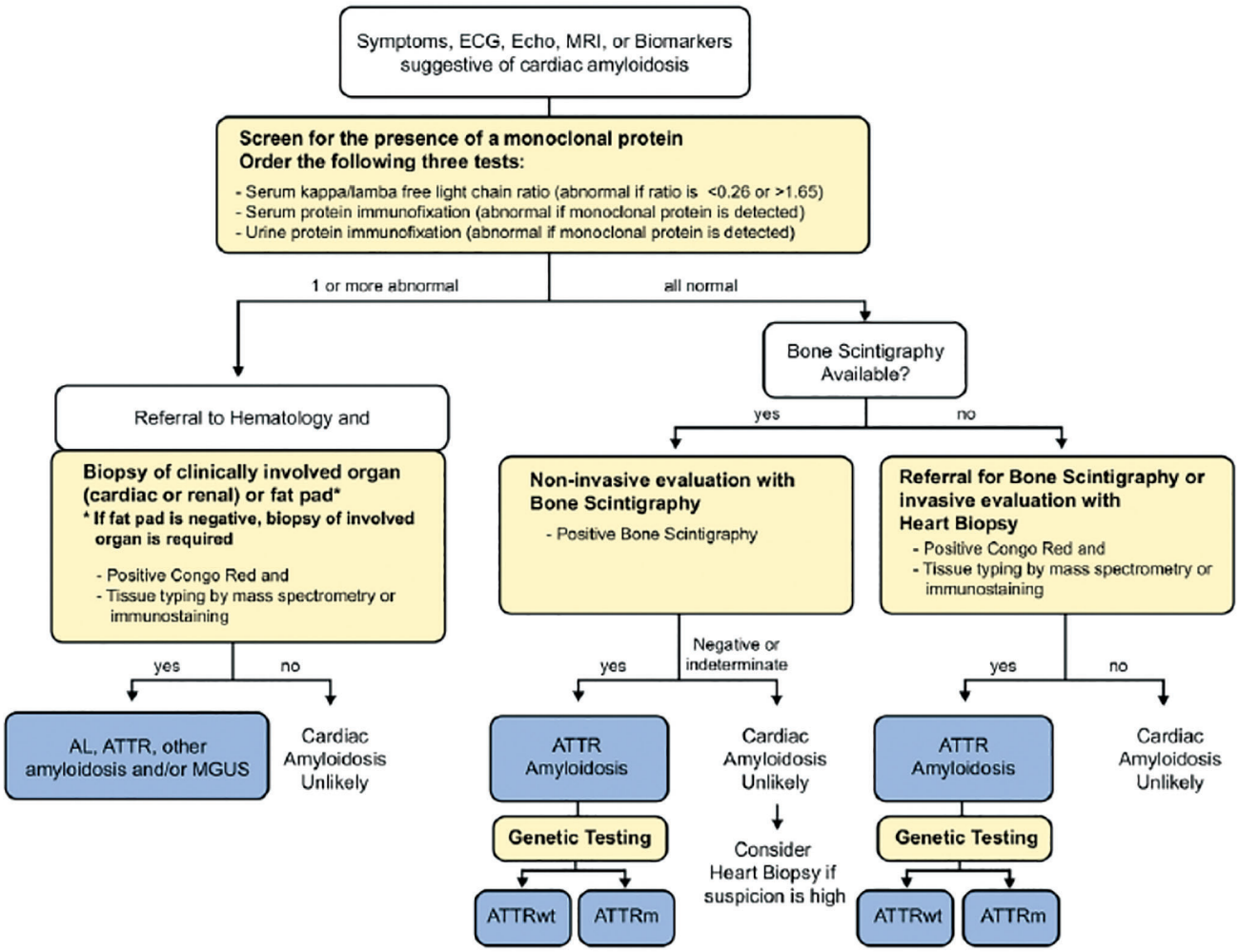

Figure 6. *Algorithm for the diagnosis of cardiac amyloidosis [15]*

ECG — electrocardiogram; Echocardiography — echocardiography; MRI — magnetic resonance imaging; EMB — endomyocardial biopsy; SCF — subcutaneous fatty tissue; MGUS, monoclonal gammopathy of undetermined significance; ATTR-AC — ATTR-cardiac amyloidosis, AC — cardiac amyloidosis

Diagnosis of ATTR amyloidosis

Diagnosis of ATTR amyloidosis can be established used scintigraphy, single-photon emission tomography with different isotopes that allow non-invasive diagnosing with very high specificity (> 99%) and sufficient sensitivity (86%) and avoiding endomyocardial biopsy [43–45]. A visual three-point scale was proposed for assessing the results of scintigraphy based on isotope accumulation in the myocardium: 0 — no isotope accumulation in the myocardium, from 1 to 3 (grade) — increasing accumulation. It was demonstrated that moderate absorption of 99mTc-DPD (grade 1) can also be observed in cases of AA and AApoA1 amyloidosis; in cases of diagnosed AL amyloidosis, a slight isotope accumulation (grade 1 and in 10% of cases — grade 2) is often recorded. Diagnosis of ATTR amyloidosis can be established in a non-invasive way using DPD scintigraphy if there is moderate or significant isotope accumulation (grade 2–3) and no plasma cell dyscrasia and immunoglobulin free light chains. Scintigraphical changes appear earlier than changes on EchoCG and can be considered as an early sign of ATTR CMP (Figure 7) [43–45].

Subcutaneous tissue biopsy for ATTR amyloidosis is associated with a minimum risk of complications, although its sensitivity amounts to 45% for ATTR amyloidosis of the mutant type and 15% for the wild type. In the case of negative biopsy of non-affected organs (subcutaneous tissue, bone marrow) and persisting suspicion of cardiac ATTR amyloidosis, endomyocardial biopsy is indicated [15].

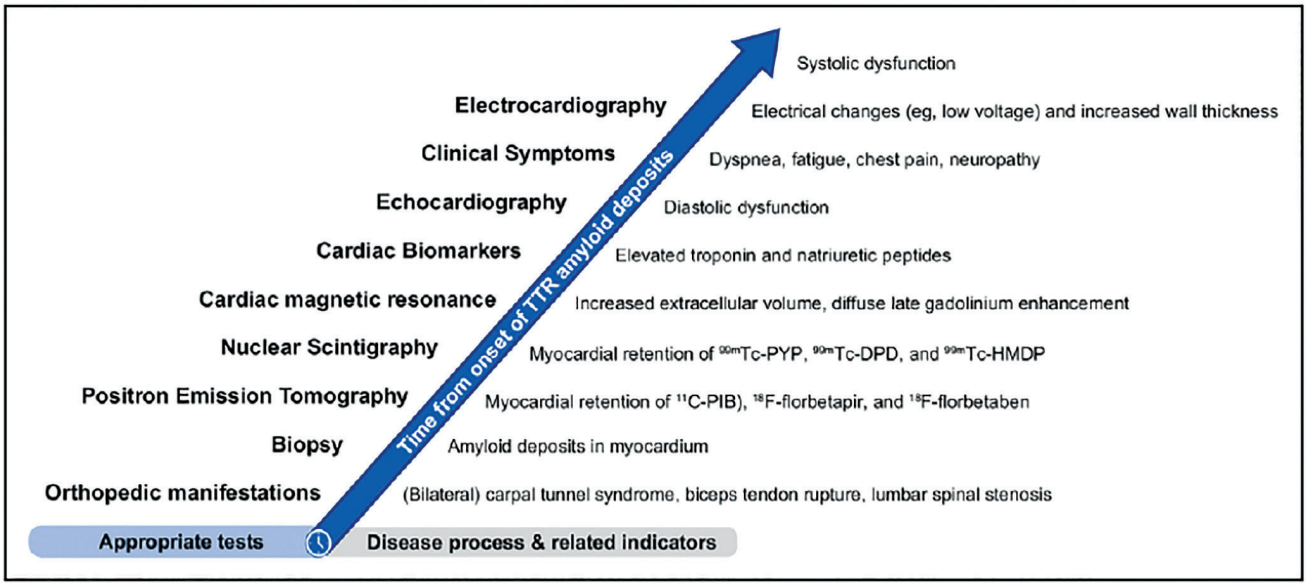

Figure 7. *Progression of ATTR-amyloid cardiomyopathy [14]*

ECG — electrocardiogram; PNP — polyneuropathy, CHF — chronic heart failure; ^{11}C-PIB — indicates Pittsburgh compound B; ^{99m}Tc-DPD — ^{99m}technetium-3,3-diphosphono-1,2-propanodicarboxylic acid; ^{99m}Tc-HMDP — hydroxymethylene diphosphonate; ^{99m}Tc-PYP — technetium pyrophosphate

If signs of ATTR amyloidosis are found during scintigraphy or in biopsy results, genetic tests should be performed [15]. The genetic test alone is enough to diagnose ATTR amyloidosis in patients with typical clinical symptoms and family history. Precise identification of the mutation helps to assess the prognosis and effectiveness of treatment [43, 46].

Cardiac ATTR amyloidosis is often not diagnosed or is misdiagnosed as hypertrophic or restrictive CMP, or CHFpEF with unknown etiology. Heart Failure Bridge Clinic (USA) has developed and implemented criteria for screening for cardiac amyloidosis in cases of CHFpEF and the algorithm for its diagnosis. The following are the criteria for screening for amyloidosis:

1. Age 50+ years;
2. Thickness of interventricular septum (T_{IVS}) ≥ 12 mm;
3. Body mass index (BMI) ≤ 30 kg/m^2;
4. Low QRS voltage on ECG;
5. Central or peripheral neuropathy, carpal tunnel syndrome.

If a patient has ≥ 2 of these criteria, a diagnostic procedure should be performed in order to exclude/confirm cardiac amyloidosis (Figure 8). This algorithm helped diagnose cardiac amyloidosis in 15% of patients with CHFpEF [47].

Management of amyloidosis

According to the modern view, management of amyloidosis of any type can be pathogenetic (anti-amyloid, aimed at reducing the production or elimination of precursor proteins) and syndrome-based [5].

Pathogenetic management of ATTR amyloidosis

Tremendous success was achieved in recent years in the management of ATTR amyloidosis. The following are the main management aspects:

1. Suppression of transthyretin synthesis (liver transplantation; transthyretin gene switches).
2. Stabilization of transthyretin (tafamidis, diflunisal, green tea, AG10 TTR-stabilizer).
3. Cleavage of amyloid fibrils (doxycycline/ taurodeoxycholic acid (TUDCA), monoclonal antibodies) [48].

Liver transplantation

For many years, the only effective way to slow the progression of hereditary ATTR amyloidosis was liver transplantation, which led to the synthesis of less amyloidogenic wild transthyretin instead of

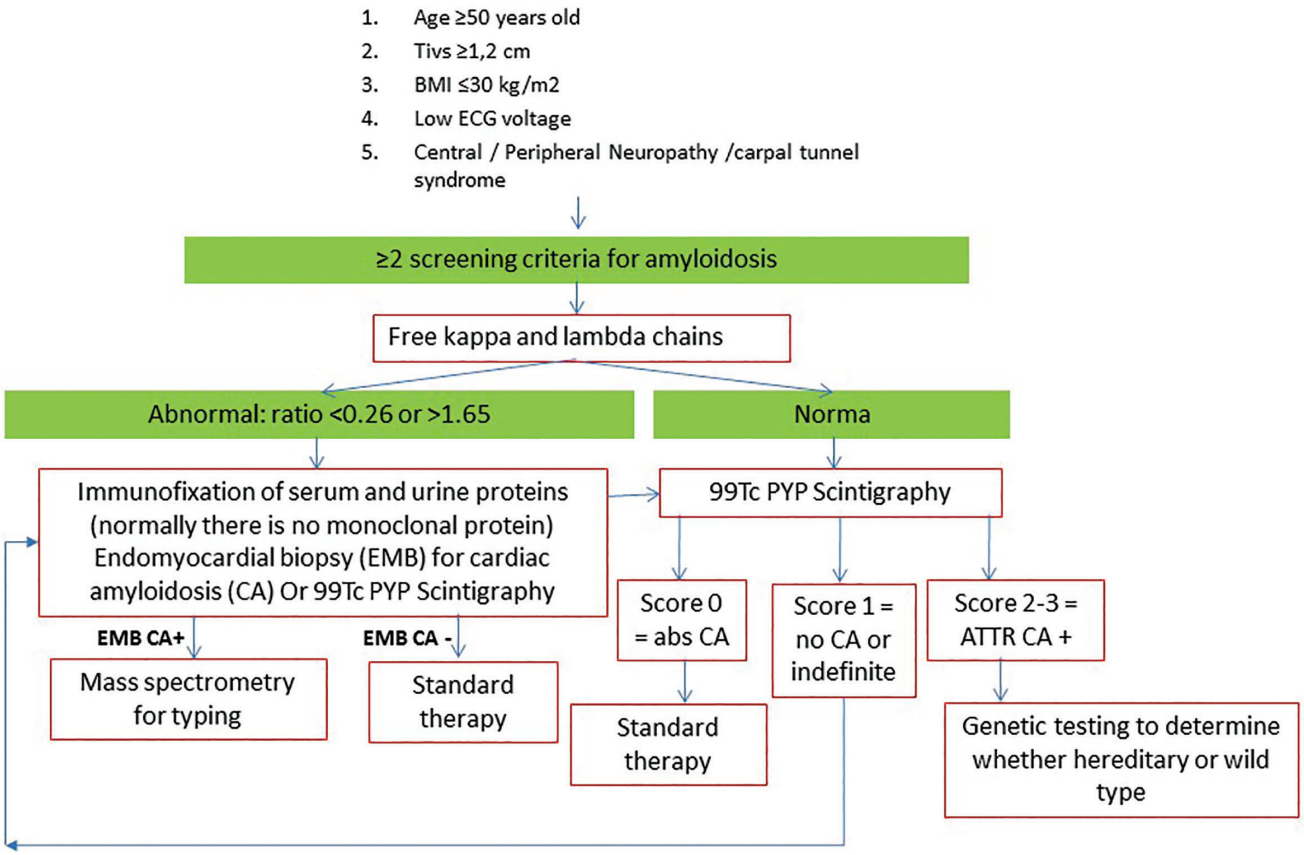

Figure 8. *Algorithm for the diagnosis of cardiac amyloidosis in CHFpEF [43].*

CHFpEF — chronic heart failure with preserved ejection fraction; EMB AS — endomyocardial biopsy for cardiac amyloidosis; ^{99m}Tc-PYP — ^{99m}technetium pyrophosphate

the mutant one. Ten-year survival after liver transplantation reaches 70%. However, progressive deposition of amyloid in the nervous system and the heart due to wild transthyretin continues [6]. Heart transplantation in cases of wild type ATTR amyloidosis is very rarely accompanied by repeated amyloid deposition. However, it is rarely performed due to the elderly age of patients [42].

Transthyretin stabilizers

Transthyretin stabilizers (tafamidis and diflunisal) prevent the dissociation of the transthyretin tetramer, preventing amyloid deposition in tissues.

Tafamidis

Tafamidis is a benzoxazole derivative that stabilizes the transthyretin tetramer by slowing down monomer formation, incorrect folding and amyloidogenesis. Long-term efficacy and safety of tafamidis in slowing disease progression and improving the survival rate of patients with ATTR polyneuropathy, hereditary transthyretin-amyloid cardiomyopathy, and also CMP in connection with wild type ATTR amyloidosis was confirmed [49, 50]. Tafamidis should be considered in patients with clinically evident CHF due to ATTR amyloidosis (both hereditary and wild) in order to improve exercise tolerance and the quality of life and reduce the frequency of hospitalizations for cardiovascular reasons and cardiovascular mortality rate [21].

Diflunisal

Diflunisal is a nonsteroidal anti-inflammatory drug (NSAID) with the ability to stabilize transthyretin. Slower progress of neuropathy during two years of treatment with diflunisal compared with the placebo, as well as improved quality of life was demonstrated. Side effects of diflunisal are the same as those of other NSAIDs [49].

ATTR gene switches (Transthyretin protein knockdown (reduction) agents (gene silencing))

Inotersen and patisiran reduce the synthesis of both wild and mutant transthyretin by 75–81% through the destruction of transthyretin mRNA (inotersen — by nuclear RNaseH1 (ribonuclease H1), patirisan — by cytoplasmic RNA-induced silencing complex). This slows or stops disease progression and results in new neurological signs. Inotersen can cause thrombocytopenia, bleeding, glomerulonephritis, and decreased kidney and liver function. The safety profile of patisiran is more favorable [49]. It may be the agent of choice in patients with atrial fibrillation (AF) taking anticoagulants [48].

Further lines of research for the management of ATTR amyloidosis

In future, it will be wise to reduce the cost of treatment with tafamidis, to continue studies of diflunisal, to study the combination of taursodeoxycholic acid (TUDCA) with doxycycline, which affects the destruction of amyloid masses, to study new selective stabilizers of transthyretin (epigallocatechin-3-gallate (EGCG), catechin from green tea), AG-10, CHF5074 (a NSAID derivative that does not block cyclooxygenase and has no corresponding side effects), to study monoclonal antibodies against incorrectly folded transthyretin (PRX004), the second generation of gene silencers transthyretin (AKCEA-TTR-LRx, vutrisiran — ALNTTRsc02) [21], and combinations of stabilizers and switches of the transthyretin gene [49].

Pathogenetic management of AL amyloidosis

The synthesis of immunoglobulin light chains is stopped using [5, 51] various chemotherapeutic agents (alkylating agents, steroids, proteasome inhibitor — bortezomib) and/or immunomodulating drugs combined with autologous stem cell transplantation. Treatment regimens are similar to those used for multiple myeloma but usually include the use of dexamethasone [13, 51]. Melphalan in combination with prednisolone or dexamethasone in large doses also yields a good result but can also cause acute leukemia or myelodysplasia. After remission in 20% of patients (who have no severe comorbidities), high-dose chemotherapy is conducted, followed by the injection of autologous blood stem cells. Subsequent administration of growth factors can increase CHF and hypotension. Injection of stem cells may be associated with ventricular arrhythmias due to the toxic effects of cryoprotectant dimethyl sulfoxide [51]. New agents, ixazomib and carfilzomib, have several advantages over bortezomib, but their evidence base is currently limited. [13].

Doxycycline has also demonstrated an antiamyloid effect *in vivo* and *in vitro*. Its addition to standard treatment for cardiac AL-amyloidosis reduced short-term mortality. An international phase III study is currently underway, where the efficacy of bortezomib with doxycycline is compared to that of the standard treatment scheme (NCT03474458) [48].

Phase III study of RNA-interference drug (resuviran) showed increased mortality in patients with amyloid CMP (ENDEAVOR; NCT02319005). Therefore, this study was stopped [48].

Young patients with isolated heart damage can be treated with orthotopic heart transplantation (1-yr survival is 50–89.5%, 5-yr survival is 20–65%) combined with high-dose chemotherapy (1-yr survival reaches 75%) [51]. Indications include good hematological remission with persisting severe HF. Contraindications are the following: diarrhea (weight loss, malabsorption), autonomic nervous system involved, impaired nutritional status, damage to the gastrointestinal tract, kidneys, respiratory tract [48].

Recommended treatment strategy for AL CMP includes 3 stages [48]:

1) Induction of chemotherapy: in most cases includes schemes with bortezomib that are aimed at minimizing or stopping the production of immunoglobin light chains.
2) Cardiac transplantation usually after 6 months to ensure cardiovascular stability during high-dose chemotherapy.
3) High-dose chemotherapy with melphalan, followed by autologous stem cell transplantation 6 months after stage 2.

New drugs for management of AL amyloidosis

Daratumumab is a monoclonal antibody against CD38 (differentiation cluster 38). After treatment with this agent, 129 patients with refractory AL amyloidosis showed a good hematological response without significant toxic effects [42]. Venetoclax, a BCL-2 (B-cell lymphoma 2 protein) inhibitor, was recently used for the management of multiple myeloma, especially in cases of mutation t(11; 14), which also occurs in connection with AL amyloidosis [42].

Pathogenetic management of AA amyloidosis

Pathogenetic management of AA amyloidosis includes management of the underlying disease in accordance with clinical recommendations and also management for amyloid deposits. Cytostatics used in patients with AA amyloidosis can help achieve clinical improvement; in some patients, they prevent or slow down renal failure and improve the prognosis.

Management for amyloid deposits

Tocilizumab, a monoclonal antibody against interleukin-6, demonstrated its efficacy in reducing the level of circulating SAA protein and controlling the progression of amyloidosis in cases of several joint diseases. This effect does not depend on the underlying disease [34].

Dimethyl sulfoxide is a derivative of the intracellular low-density lipoprotein molecule that causes amyloid resorption [34]. It should be used in high doses (at least 10 g/day), which is hardly possible due to its extremely unpleasant odor [5].

Eprodisate is a low molecular weight molecule, similar to heparan sulfate. Competitively binding with glycosaminoglycans, it inhibits the polymerization of amyloid fibrils and prevents the stabilization of amyloid deposits [52].

Heparin can slow the progression of AA amyloidosis by disrupting the stabilizing bonds between glycosaminoglycans and SAA in deposits; its action is similar to that of eprodisate [53]. Statins can also have a positive effect by inhibiting the isoprenoid pathway through specific blocking of farnesyl transferase [54].

Fibrillex is a new agent that contributes to amyloid resorption and destruction. It can be prescribed as an addition to the management of the underlying disease or treatment with colchicine [5].

New therapeutic targets

R-1-[6-[R-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid (CPHPC) is a small molecule that can bind to two subunits of serum amyloid P component (SAP) thereby reducing its concentration in serum. Thirty-one patients with amyloidosis demonstrated its positive effect on kidney function without significant side effects [55].

Dezamizumab, an antibody against SAP, is safe and reduces the amount of amyloid in the liver, although it showed no effect on amyloid deposits in the heart and kidneys [42].

Monoclonal antibodies against amyloid (11-1F4) that opsonize fibrils and facilitate their removal demonstrated a positive cardiac response in 8 of 12 treated patients [56].

The possibility of inhibition of SAA protein transcription with antisense oligonucleotides was shown using mouse models; it reduced the level of SAA in blood by 50% and significantly reduced amyloid deposits [56]. Clodronic acid, also used in mouse models, demonstrated the capacity for the prevention and management of amyloidosis [57].

Syndrome-based management

Syndrome-based management of amyloidosis is aimed at reducing the severity of symptoms and signs of HF, correction of rhythm and conduction disorders, correction of hypertension and hypotension, etc. (Table 9).

Management of CHF

Management of CHF in cases of amyloidosis is based on a low-salt diet, loop diuretics (preferably with high bioavailability, i.e., torasemide and bumetanide) and mineral corticoid receptor antagonists. In cases of severe CHF and/or nephrotic syndrome, large doses of diuretics are

Table 9. *Syndromic therapy of cardiac amyloidosis [63]*

Clinical situation	Medicine	Note
Fluid retention, edema syndrome, orthopnea	A loop diuretic, often in combination with a mineralocorticoid receptor antagonist	Careful dose titration, prevention of hypovolemia
Supraventricular arrhythmias (atrial fibrillation / flutter)	β-blocker	Indicated only in cases of tachycardia, in most cases should be avoided due to heart rate-mediated maintenance of cardiac output
	Amiodarone	Generally, well tolerated. Able to maintain sinus rhythm
	Verapamil, diltiazem	Contraindicated, because toxic effect develops rapidly due to binding to amyloid fibrils
	Digoxin	Contraindicated due to the possibility of rapid development of glycosidic intoxication due to binding to amyloid fibrils
	Anticoagulant therapy	Should be administered even with sinus rhythm or low CHA2DS2VASC score due to high risk of atrial thrombosis
Prolongation of the QT interval		It is necessary with extreme caution to prescribe drugs that prolong the QT interval with careful monitoring of its duration, incl. antipsychotics (haloperidol, quetiapine, olanzapine), tricyclic antidepressants (amitriptyline, nortriptyline, citalopram), antiemetics (metoclopramide, ondansetron), antibiotics (ciprofloxacin, azoles)

often required to maintain euvolemia. However, this can lead to the underfilling of the decreased and rigid LV with a decrease in cardiac output and the development of hypotension, dizziness, fainting, and prerenal acute kidney damage. In this regard, it is extremely important to evaluate the balance between fluid taken and lost and to titrate the dose of diuretics carefully [6].

There is no separate evidence base for using ACE inhibitors, angiotensin II receptor antagonists, and neprilysin inhibitors (ARNI) in patients with cardiac amyloidosis. These drugs can be poorly tolerated due to hypotension (probably due to concomitant dysfunction of the autonomic nervous system). Therefore, they should be prescribed in patients with CHF and amyloidosis with great caution, and their dose should be carefully titrated.

Patients with amyloidosis usually do not tolerate beta-blockers, especially in high doses and those with alpha-blocking effect, because they reduce heart rate and, consequently, cardiac output and blood pressure. In later stages, compression stockings and midodrine may be beneficial.

Non-dihydropyridine calcium channel antagonists (verapamil, diltiazem) are contraindicated in patients with amyloidosis due to their accumulation in amyloid deposits, leading to heart block.

Mechanical support of blood circulation in patients with cardiac amyloidosis is technically possible but is a low class (IIB) recommendation. Two-year survival of patients with cardiac amyloidosis treated with mechanical support of blood circulation is lower than in those without amyloidosis; however, in some patients, it may become a way to move towards heart transplantation [5].

Management of arrhythmias

Cardiac glycosides are contraindicated in patients with amyloidosis due to the possible accumulation in amyloid of a toxic dose with the development of paradoxical reactions [5].

Among antiarrhythmic agents used for restoring sinus rhythm, only amiodarone is relatively safe in cases of paroxysmal AF and amyloidosis. Rhythm control strategy in these patients may be of lesser importance than in the general population since atrial work aimed at filling ventricles is minimal or absent.

Ablation and/or implantation of cardioverter defibrillator (ICD) is indicated in some patients due to the high risk of fatal tachyarrhythmias. Data on the results of catheter ablation in cases of cardiac amyloidosis are limited. Long-term results are probably worse than in patients without amyloidosis. If life expectancy is less than one year, ICD is not recommended for the primary prevention of sudden death. Sudden death in cases of amyloid cardiomyopathy is often associated with electromechanical dissociation, which is also an argument against inserting ICD in these patients. ICD should be considered in every individual case for secondary prevention in patients with frequent unstable or persistent ventricular tachycardia.

Patients with severe cardiac amyloidosis have an increased risk of developing intracardiac thrombi. Left atrial thrombosis was found in 33% of patients with ATTR CMP by means of transesophageal echocardiography; most of these patients took anticoagulants [5]. Due to the high risk of thrombosis in patients with cardiac amyloidosis, anticoagulant treatment should be prescribed (warfarin or oral anticoagulants that are not vitamin K antagonists). They are indicated not only for the management of intracardiac thrombosis, AF (regardless of CHA2DS2-VASc scale points), atrial arrhythmias but also when there is sinus rhythm with echocardiographic signs of mechanical left atrial dysfunction [5]. AL amyloidosis is often accompanied with coagulation factor X deficiency and hemorrhages. Therefore, anticoagulants should be prescribed with caution [5, 59, 60].

Management of conduction disorders

Heart blocks, sick sinus syndrome, chronotropic incompetence are often found in cases of cardiac amyloidosis and require implantation of a permanent pacemaker. Permanent right ventricular apical pacing can cause interventricular dyssynchrony and further decrease in stroke volume and cardiac output. In this regard, biventricular stimulation is preferred. With the development of CHF, the lower limit of stimulation frequency can be increased to maintain cardiac output.

Management of orthostatic hypotension

Mineralocorticoids or glucocorticoids for continuous administration are recommended for orthostatic hypotension, but this therapy increases the risk of HF decompensation [5].

Conclusion

Understanding pathogenesis has led to successful diagnosis and management of all forms of amyloidosis, including cardiac amyloidosis. Clinical alertness of cardiologists regarding the possibility of cardiac amyloidosis is extremely important for its timely diagnosis. Screening for amyloidosis should be performed in patients with CHF of unknown etiology, idiopathic AF, low ECG voltage, especially in combination with left ventricular myocardium thickness of 12 mm or more, proteinuria, chronic kidney disease stage 4–5, arterial hypotension and pulmonary hypertension. Early diagnosis allows achieving the best treatment results. Therefore, the disease that was previously considered incurable may soon become treatable or, at least, a slowly progressing condition.

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication.

E.V. Reznik (ORCID ID: https://orcid.org/0000-0001-7479-418X): review design development; writing the text of the manuscript; review of publications on the topic of the article; interaction with the editors in the process of preparing a publication for printing

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