

**Abstract**

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**AMYLOIDOSIS OF CARDIOVASCULAR SYSTEM**

In most industrialized countries with a high level of urbanization diseases of the cardiovascular system are the leading cause of morbidity and mortality. Every year about 9.4 million people die from cardiovascular diseases. One of the causes of cardiovascular disease is an amyloidosis. Its incidence in the population, according to recent data, is 1 in 50 thousand of people, there is a tendency to more frequent detection of cases.

The aim of the study is to analyze the literature to determine different proteins' role in the etiopathogenesis of amyloidosis of the cardiovascular system.

Amyloid deposition in the heart may have different anatomical allocation, including atrial, ventricles, perivascular spaces such as heart valve leaflets, and in some cases – in the cardiac conductive system. Amyloidosis of the heart is established or by the help of positive cardiac biopsy with the presence of amyloid infiltration, or by an increase of left ventricular wall > 12 mm, in the case of arterial hypertension (AH) absence or absence of other potential causes of the genuine LV hypertrophy with a positive cardiac biopsy.

Among amyloid proteins, which affect a heart, there are such types: AL-amyloidosis (amyloid of light chains), family amyloidosis (F), senile systemic amyloidosis (SSA), isolated atrial amyloidosis (IAA) and the secondary (AA) amyloidosis.

Recently amyloidosis of heart went out of the category of rare diseases; it has become possible thanks to the different methods of research, including the possibility of studying the heterogeneity of the protein composition of amyloid fibril formation. However, systemic amyloidosis and particularly amyloidosis of the heart continue to belong to diseases, which are diagnosed difficult, considering the non-specific symptoms of disease, a small suspicion among physicians with regard to amyloidosis and multiple organ destruction.

**Keywords:** amyloidosis, cardiovascular system, amyloid proteins, heart failure, atherosclerosis, biomineralization.

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## Резюме

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## АМІЛОЇДОЗ В СЕРЦЕВО-СУДИННІЙ СИСТЕМІ

У більшості промислово розвинених країн з високим рівнем урбанізації перше місце серед причин захворюваності та смертності населення займають хвороби серцево-судинної системи. Щорічно в світі близько 9,4 мільйонів людей вмирає від серцево-судинних захворювань. Однією з причин розвитку серцево-судинних захворювань є амілоїдоз. Частота прояву його в популяції, за останніми даними, становить 1 на 50 тис. населення, відзначається тенденція до почастишання виявлення випадків захворювання.

Метою роботи є проведення аналізу літератури для встановлення ролі різних білків в етіопатогенезі амілоїдозу серцево-судинної системи.

Відкладення амілоїду в серці може мати різний анатомічний розподіл, включаючи передсердя, шлуночки, периваскулярні простори як листків серцевих клапанів, так і в деяких випадках – провідної системи серця. Амілоїдоз серця встановлюється або за допомогою позитивної кардіальної біопсії з наявністю амілоїдної інфільтрації, або при збільшенні стінки ЛШ > 12 мм, при відсутності артеріальної гіпертензії (АГ) або інших потенційних причин істинної гіпертрофії ЛШ з позитивною кардіальною біопсією.

Серед амілоїдних білків, які впливають на серце, виділяються такі типи: AL-амілоїдоз (амілоїд легких ланцюгів), сімейний амілоїдоз (F), старечий системний амілоїдоз (SSA), ізольований атріальний амілоїдоз (IAA) і вторинний (AA) амілоїдоз.

За останній час амілоїдоз серця вийшов з ряду рідкісних захворювань, це стало можливим завдяки різним методикам дослідження, в тому числі можливості дослідження гетерогенності білкового складу амілоїдних фібрил. Однак, з огляду на неспецифічність симптомів захворювання, малу настороженість серед лікарів щодо амілоїдозу і поліорганність ураження, системний амілоїдоз і амілоїдоз серця зокрема продовжує належати до захворювань, які важко діагностуються.

**Ключові слова:** амілоїдоз, серцево-судинна система, амілоїдні білки, серцева недостатність, атеросклероз, біомінералізація.

## Резюме

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## АМИЛОИДОЗ В СЕРДЕЧНО-СОСУДИСТОЙ СИСТЕМЕ

В большинстве промышленно развитых стран с высокой степенью урбанизации первое место среди причин заболеваемости и смертности населения занимают болезни сердечно-сосудистой системы. Ежегодно в мире около 9,4 миллионов людей умирает от сердечно-сосудистых заболеваний. Одной из причин развития сердечно-сосудистых заболеваний является амилоидоз. Частота проявления его в популяции, по последним данным, составляет 1 на 50 тыс. населения, отмечается тенденция к учащению выявления случаев заболевания.

Целью работы является проведение анализа литературы для установления роли различных белков в этиопатогенезе амилоидоза сердечно-сосудистой системы.

Отложения амилоида в сердце может иметь различное анатомическое распределение, включая предсердия, желудочки, периваску-



лярные пространства как листков сердечных клапанов, так и в некоторых случаях – проводящей системы сердца. Амилоидоз сердца устанавливается или с помощью положительной кардиальной биопсии с наличием амилоидной инфильтрации, или как увеличение стенки ЛЖ > 12 мм, при отсутствии артериальной гипертензии (АГ) или других потенциальных причин истинной гипертрофии ЛЖ с положительной кардиальной биопсией.

Среди влияющих на сердце амилоидных белков, выделяются такие типы: AL-амилоидоз (амилоид легких цепей), семейный амилоидоз (F), старческий системный амилоидоз (SSA), изолированный атриальный амилоидоз (IAA) и вторичный (AA) амилоидоз.

За последнее время амилоидоз сердца вышел из разряда редких заболеваний, это стало возможным благодаря различным методикам исследования, в том числе возможности исследования гетерогенности белкового состава амилоидных фибрилл. Однако, учитывая неспецифичность симптомов заболевания, малую настороженность среди врачей в отношении амилоидоза и полиорганность поражения, системный амилоидоз и амилоидоз сердца в частности продолжает относиться к трудно диагностируемым заболеваниям.

**Ключевые слова:** амилоидоз, сердечно-сосудистая система, амилоидные белки, сердечная недостаточность, атеросклероз, биоминерализация.

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## Introduction

In most industrialized countries with a high level of urbanization (which include also Ukraine) diseases of the cardiovascular system are the leading cause of morbidity and mortality. Every year about 9.4 million people die from cardiovascular disease [1]. It is estimated that only in 2012 17.5 million people died from heart diseases, this amounted 31% of all death cases in the world. According to WHO estimations about 23.6 million people will die from cardiovascular disease each year till 2030 that is why the only leading cause of death will be still heart diseases [2]. Over 75% of CVD deaths occur in low- and middle-income countries, to which Ukraine belongs. Diseases of the cardiovascular system (CVD) determine 66% of the total mortality level of our country population. They remain the leading cause of death (30%) also among people in working age [3].

One of the causes of cardiovascular disease is an amyloidosis [4]. It's incidence in the population, according to recent data, is 1 in 50 thousand of people, there is a tendency to more frequent detection of cases. Detection of amyloidosis is prognostically the most serious complication in patients with various rheumatic diseases, kidney and cardiovascular system diseases, it causes the develop-

ment of a functional organ failure and patients' death. A huge number of studies have been conducted to find out the pathogenesis of the disease, but today the issue of detection and, the most important, treatment of amyloidosis remains insufficiently studied [2].

**The aim** of the study is to analyze the literature to determine different proteins' role in the etiopathogenesis of amyloidosis of the cardiovascular system.

Amyloidosis is a heterogeneous group of clinical disorders, which are characterized by abnormal extracellular deposition of insoluble fibrils, which are formed by the aggregation of misfolded soluble proteins [2, 5].

Amyloid is composed approximately by 95% of the fibrils, which were formed by the aggregation of incorrectly composed protein, the other 5% are P-component (pentameric protein, it is from whey pentaxin protein family) and other glycoproteins, such as proteoglycans or sulfited glycoproteins [5, 6].

Protein fibrils consist of more than 28 different unrelated proteins, which are improperly stored parallel or in other alternative physiological way [2, 5]. P-component contributes to the deposition of amyloid by fibrils' stabilizing, reducing the possibility of its dissolution. During the light microscopy amyloid appears as amorphous eosinophilic sub-



stance in preparations stained with hematoxylin-eosin. Congo red staining of amyloid and formation of green glow in the polarization light is the gold standard in amyloidosis diagnostic [7].

The study of amyloid leads to the identification of previously unknown peptides and proteins, which are involved in a large number of important metabolic processes. These proteins include amyloid A and its precursor, cytokine-regulated serum amyloid A (SAA), more than 70 transthyretin variants (TTP), cerebral amyloid  $\beta$ -protein,  $\alpha\beta$  and their precursor A $\beta$ RR (previously not identified), which is associated with diabetes, islet amyloid peptide (IAAR) and prion proteins such as causative agent of scrapie and other neurodegenerative diseases (ARrR) [4, 5, 8].

Studies of amyloidosis are based on the ability of amyloid protein staining with Congo red. Affinity (binding ability) of Congo red is caused by the special  $\beta$ -shaped molecular conformation of amyloid, which can be determined by X-ray crystallography [7]. Ultrastructurally accidentally orientation fibrils with diameter 7.5–10 nm can be seen with electron microscopy [9]. Thioflavin T is another molecule that can bind to amyloid, but it is used less than Congo red. Staining with Congo red and ultrastructural studies are used for routine pathohistological diagnosis, but these methods don't give possibility to differentiate the various subtypes of amyloid. The classification of amyloid is based on the immunohistological technique with an antibodies panel against amyloidogenic proteins or proteomic technique [7]

Based on the spectrum of the affected organs by amyloidosis, the system localized forms with amyloid deposits can be identified [4]. The reasons of the diversity of organs and tissues, which are affected by amyloidosis, are unknown. Amyloid deposition in the heart may have different anatomical allocation, including atrial, ventricles, perivascular spaces such as heart valve leaflets, and in some cases – in the cardiac conductive system [2, 4, 9].

Despite the type of cardiac amyloidosis, the presence of a heavy amyloid cardiomyopathy is an important factor of influence on the patients' prognosis. According to the consensus (the 10th International Symposium about amyloidosis) heart amyloidosis is established or by the help of positive cardiac biopsy with the presence of amyloid infiltration, or by an increase of left ventricular wall > 12 mm, in the case of arterial hypertension (AH) absence or absence of other potential causes of the genuine LV hypertrophy with a positive cardiac biopsy [9, 10].

#### Types of amyloidosis

As amyloid fibrils can form different proteins, amyloidosis type is classified depending on the protein specificity and prevalence of amyloid deposits [12].

Among amyloid proteins, which affect the heart, there are such types: AL-amyloidosis (amyloid of light chains), family amyloidosis (F), senile systemic amyloidosis (SSA), isolated atrial amyloidosis (IAA) and the secondary (AA) amyloidosis [11–13] (Table 1).

**Table 1 – Total systematization of amyloids, which affect the heart**

Amyloid type	Protein	Synthesis place	Organs affected
AL	Light chains $\kappa, \lambda$	Bone marrow	Kidneys, heart, gastrointestinal tract, liver, nervous tissue, soft tissue
F (family)	Mutant transthyretin (TTR)	Liver	Nervous system, heart,
SSA (senile)	“Wild” type of TTP	Liver	Heart
AA (secondary)	Serum amyloid A	Liver	Kidneys, gastrointestinal tract, liver, spleen, nervous system, sometimes heart
IIA (isolated atrial)	Atrial natriuretic peptide (ANP)	Atrial	Heart

#### Systemic AL amyloidosis

Previously known as primary amyloidosis, systemic AL amyloidosis is the most diagnosed form of amyloid clinical disease in many countries. [5] Men and women complain of this disease at near

the same rate (with a slight prevalence of men over women). Mostly disease is diagnosed between the ages 55–60 years [13]. In primary amyloidosis abnormal plasma cells' clones of bone marrow produce amyloidogenic immunoglobulins. Some ami-



no acids in the variable regions of light chains of these immunoglobulins occupy an unusual position, this leads to their instability and causes the tendency to fibrilogenesis [14]. In patients with primary amyloidosis the content of plasma cells is increased to 5–10% in the bone marrow (normally less than 4%, in the case of myeloma – more than 12%), and they produce a particular isotype of immunoglobulin light chains, which is the predominant during immunohistochemical staining. AL fibrils are formed from the monoclonal immunoglobulin light chains and form the most amount of the variable domains (VL) [13]. Almost any B cell dyscrasia, including myeloma, macroglobulinemia and lymphoma, can be complicated by AL amyloidosis. In the case of AL amyloidosis the monoclonal population of plasma cells produces abnormal monoclonal light chains or, more often, their fragments, which are converted into amyloid in misfolding way. Free monoclonal light chains of predominant lambda or (rarely) kappa isotype are determined in blood and urine, but their content is lower than in the case of myeloma [13].

In the most cases (69%) all patient's organ systems are involved in amyloidogenesis (typical multiple organ infiltration), however, the most often heart, kidneys (approximately 74%), liver (approximately 27%), peripheral nervous (22%), and the autonomic nervous system (18%) are affected [9]. However, heart tissue can be unchanged visually [15]. In the presence of the amyloid depositions in the myocardium a variety of arrhythmias, progressive heart failure develop, which can be preceded by asymptomatic ECG changes in the form of reduced voltage peaks. Echocardiography reveals concentric wall thickening of the left and right ventricle, reducing of heart cavities volume, a moderate decrease in ejection fraction, diastolic dysfunction of the left ventricle [16].

The prognosis in the case of primary amyloidosis is worse than in other forms of this disease, life expectancy does not exceed two years. Patients die within a few months in the case of heart disease or multiple organ injury without necessary treatment. The most frequent causes of death are heart and kidney failure, sepsis, vascular complications and cachexia. Pathogenetic similarity with multiple myeloma can rely on the inhibition of disease progression during chemotherapy, which is carried out with the purpose monoclonal plasma cells' suppression [21].

#### **The hereditary systemic amyloidosis**

Hereditary systemic amyloidosis is caused by deposition of amyloid fibrils, which are derived

from genetic variants of the transthyretin (TTR), apolipoprotein AI, alpha-chains of fibrinogen and lysozyme, or other species [17, 18]. Family amyloidosis is usually associated with recurrent disease, which is transmitted in an autosomal dominant way. This variant is not rare; actually amyloidogenic TTR Val Ile 122 variant is present in 4% of all African-Americans and in 23% of African-Americans with heart amyloidosis [18]. There are nephropathic, neuropathic and cardiopathic types of hereditary amyloidosis. This amyloidosis can be the only one manifestation of the disease [19].

There are more than 80 mutations of the TTR gene, which cause diseases. Most TTR mutations are associated with damage of heart or nervous system [20]. Usually clinical symptoms don't debut earlier than 35–40 years. For transthyretin amyloidosis lesion of peripheral nerves with the development of amyloid polyneuropathy (sensory-motor or in the type of violations of autonomous vegetative functions), heart (amyloid cardiomyopathy), the gastrointestinal tract, the vitreous body, the development of carpal tunnel syndrome are typical. Prevalence of any symptoms depends on the type of gene mutations and on the type of family transthyretin amyloidosis. If the mutation is localized closer to the N-end of the protein transthyretin molecule, than the development of polyneuropathy (30Met) is more pronounced; if the mutation is located closer to the C-end, than the clinical picture of cardiomyopathy is more evident (121Met) [17].

The main manifestations of hereditary amyloidosis of the heart and cardiovascular system are the rhythm and conduction disturbances, false angina (it is caused by lesions of small coronary vessels) and progressive heart failure. During echocardiography a sharp compaction and thickening of the myocardium with a decrease of the size of the left ventricular cavity are revealed [21, 22].

Rare manifestations of a family non-TTR amyloidosis are mutations in genes, which encode fibrinogen, gelsolin, lysozyme and apolipoprotein A1 and A2 [23, 24]. Mutations of fibrinogen and apolipoprotein lead mainly to the amyloid kidney damage, progressive cardiomyopathy and severe heart failure can occur in some patients with discovered apolipoprotein A1 mutation (Ng, 2005) [20]. Gelsolin mutation, which is endemic in Finland and can be found rarely all over the world, almost always it is associated with diseases of cardiac conduction system [24].

The identification of pathological myocardial amyloid infiltration during endomyocardial biopsy



is necessary for the diagnosis of a family-type cardiac amyloidosis [25, 26].

#### **Senile systemic amyloidosis (SSA)**

SSA has been recognized as endemic in Japan (1968), Sweden (1976), and sporadic in many countries [27].

Senile systemic amyloidosis, which should be differentiated from AL-amyloidosis, is rare. Local forms of senile amyloidosis are dominant; they are presented as endocrine and not endocrine amyloidosis. Endocrine forms should include senile isolated atrial amyloidosis and senile amyloidosis of pancreatic islets, and not endocrine – senile aortic amyloidosis, senile cerebral amyloidosis, senile eye amyloidosis and senile amyloidosis of the prostate or seminal vesicles [20, 28–30].

In addition to the most frequently observed mono organ manifestations in the local senile amyloidosis, multiple organ manifestations are possible – multiple organ senile (matched) amyloidosis, which is not found in more than 5% of cases. Combinations of endocrine forms of amyloidosis with amyloidosis of aorta or pancreatic islets, with cerebral amyloidosis and associated eyes amyloidosis are the most common [20].

In the case of senile amyloidosis lesions of heart, arteries, brain and pancreatic islets are typical. These changes, as well as atherosclerosis, cause senile physical and mental degradation. Older people have a clear link between amyloidosis, atherosclerosis and diabetes, which combines age-metabolic disorders [31]. In the presence of senile amyloidosis the local forms (amyloidosis of atrial, brain, aorta, pancreatic islets) are most frequent, however a generalized senile amyloidosis can be observed with affecting mainly the heart and blood vessels, which is not much different from the generalized primary amyloidosis clinically [20].

SSA is caused by the deposition of amyloid fibrils, which were derived from normal transthyretin of "wild" type and presented always slowly progressive infiltrative amyloid cardiomyopathy. TTP is a transport protein, which is mainly produced in the liver. TTR gene is located on the 18<sup>th</sup> chromosome (18q23). The disease is transmitted in an autosomal dominant way with high penetrance [32]. Most often mutation is manifested in replace of valine into methionine at position 50 (Val50Met), firstly it was discovered in the Portuguese population. Cases of senile amyloidosis rarely occur in people younger than 60 years, but its prevalence ranges from 25% to 36% in patients older than 80 years and from 3.6 to 46.0% in patients older than

70 years. The predominance of male patients among the total number of patients is typical, also preferential cardiac lesions of SSA are noted [32].

In the presence of senile amyloidosis chest part of aorta is affected mainly, not the abdominal aorta, as in the case of atherosclerosis, which makes doubt on the role of hemodynamic factors in amyloidogenesis. But in the most cases there is a combination of amyloidosis and atherosclerosis in the same aorta parts. And this combination in different age periods has a different character: up to 80 years – a rare, from 80 to 89 years – a possible, but there are no correlations, over 90 years – frequent, and dominant amyloidosis [2, 33]. The combination of amyloidosis and atherosclerosis of aorta in old age has not univalent pathogenetic assessments and it is based on gerontological patterns [27]. The clinical manifestations of senile amyloidosis are extremely different: dysfunction of the myocardium, insulin dependent diabetes mellitus, presenile and senile dementia, cataract, glaucoma, age-related macular degeneration, etc. However, the senile amyloidosis is detected extremely rare during the life [2, 33].

#### **Isolated atrial amyloidosis (IAA)**

This is the most common variant of amyloidosis, which occurs mainly in old age – its prevalence exceeds 95% among people over 80 years and it is usually diagnosed as a random finding during autopsy. Typically, the disease has a benign course and is associated with atrial fibrillation [30, 34].

For IAA precursor protein is atrial natriuretic peptide (ANP), which forms the amyloid deposits only in the atrium. This disease is a representative of true localized forms of amyloidosis, which don't affect other organs. Thus, the IAA diagnosis can be established only during autopsy, an endomyocardial biopsy from a thin wall of the atrium is associated with an unacceptable risk of perforation. Unlike the SSA, this disease is typical for elder women [34]. According to the analysis of autopsies, increasing of IAA frequency occurs with age, reaching 95% in the 81–90 year old people [10]. Despite the high prevalence, IAA is not clinically significant type of amyloidosis, which is responsible for the occurrence ultimately heart failure. However, in some works a potential role in the development of atrial conduction disorders and atrial fibrillation in older patients is suggested [10, 34].

Besides the above information, the role of inflammatory proteins calgranulins A and B (S100A8 and S100A9) are considered in the formation of amyloid deposits in the cardiovascular system. These proteins belong to the family of S100 Ca<sup>2+</sup>-



binding proteins and in some studies their relation with pathology of cardiovascular system is indicated [35–39]. The presence of mRNA and S100A8 and S100A9 proteins are also expressed in the microvasculature in the areas of neovascularization. Monomeric and complex shapes of S100A9 were prevalent in the matrix vesicles, which were isolated from human aorta and carotid arteries, suggest-

### Conclusions

The studies of amyloid lead to the identification of previously unknown peptides and proteins, which are involved in a large number of important metabolic processes. These proteins include amyloid A and its precursor, cytokine-regulated serum amyloid A (SAA), more than 70 variants of the transthyretin (TTR), cerebral amyloid  $\beta$ - protein,  $\alpha\beta$  and their predecessor  $A\beta$ RR, associated with diabetes islet amyloid peptide (IAAR) and prion proteins such as an agent of scrapie and other neurodegenerative diseases (ARrR).

Currently more than 29 different proteins are learned, they are identified as the causative agents of amyloid diseases. Despite the heterogeneity of

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ing the role in the regulation of calcification in the case of complicated atherosclerosis [35, 36].

Co-localization of amyloidogenic protein  $A\beta$  and S100A9 was also detected in the aortic valve with degenerative aortic sclerosis [37]. As S100A9 is a calcium-binding protein, it can be indicative for its critical role in the calcification and transformation of fibroblast-like mesenchymal cells into the cells of osteoblastic type [37].

the structure and functions, all proteins form amyloid fibrils, which can't be distinguished from each other.

Recently amyloidosis of heart went out of the category of rare diseases; it has become possible thanks to the different methods of research, including the possibility of studying the heterogeneity of the protein composition of amyloid fibril formation. However, systemic amyloidosis and particularly amyloidosis of the heart continue to belong to diseases, which are diagnosed difficult, considering the non-specific symptoms of disease, a small suspicion among physicians with regard to amyloidosis and multiple organ destruction.

0116U006815), "Development of the diagnosis method of the reproductive organs tumors using cellular adhesion molecules of cancer-embryonic antigen" (state registration number 0117U003937) and "Morphogenesis of general pathological processes" (state registration number 013U003315).

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