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TRANSTHYRETIN AMYLOIDOSIS. FUNDAMENTALS OF PATHOGENESIS, DIAGNOSIS, TREATMENT, PROGNOSIS

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Among the 42 human amyloidoses described to date the so-called systemic transthyretin amyloidosis, which comprises hereditary forms (more than 140 variants in accordance with the number of identified mutations in the transthyretin gene) and a sporadic form without structural changes in the gene and the protein, is of particular interest. This review summarizes modern understandings of pathogenesis of transthyretin amyloidosis. The symptoms of different forms of transthyretin amyloidosis, issues of early diagnosis, differential diagnosis (including within the group of amyloidoses), advanced therapy and prognosis are considered. Special attention is given to the non-mutant form of transthyretin amyloidosis, the so-called senile amyloidosis, which significantly complicates the course of underlying pathologies in the age group older than 70 years and is still poorly diagnosed. A quite high occurrence of non-mutant form of transthyretin amyloidosis makes it to be considered as a socially significant disease.

Keywords: amyloidoses; systemic transthyretin amyloidosis; non-mutant form of transthyretin amyloidosis; amyloidosis with mutational damage of transthyretin; transthyretin; amyloid; cardiomyopathies; familial amyloid polyneuropathy; neuropathic hereditary transthyretin amyloidosis.

ТРАНСТИРЕТИНОВЫЙ АМИЛОИДОЗ. ОСНОВЫ ПАТОГЕНЕЗА, ДИАГНОСТИКА, ЛЕЧЕНИЕ, ПРОГНОЗ

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Из 42 описанных к настоящему времени амилоидозов человека особый интерес представляет так называемый системный транстиретиновый амилоидоз, который включает наследственные формы (более 140 вариантов в соответствии с числом выявленных мутаций в гене транстиретина) и спорадическую форму без структурных изменений гена и белка. В обзоре суммированы современные представления о патогенезе транстиретинового амилоидоза. Рассмотрены симптоматика разных форм транстиретинового амилоидоза, вопросы ранней диагностики, дифференциальной диагностики (в том числе в группе амилоидозов), современной терапии и прогноза. Особое внимание уделено немутантной форме транстиретинового амилоидоза, так называемого старческого амилоидоза, который в значительной степени осложняет течение основных патологий в возрастной группе после 70 лет и все еще плохо диагностируется. Достаточно частая встречаемость немутантной формы транстиретинового амилоидоза заставляет рассматривать его как значимое для современного здравоохранения заболевание.

Ключевые слова: амилоидозы; системный транстиретиновый амилоидоз; немутантная форма транстиретинового амилоидоза; амилоидоз с мутационным повреждением транстиретина; транстиретин; амилоид; кардиомиопатии; семейная амилоидная полинейропатия; нейропатический наследственный транстиретиновый амилоидоз.

List of abbreviations

ATTR amyloidosis — transthyretin amyloidosis; ATTRwt amyloidosis — amyloidosis without mutations in the transthyretin gene; ATTRv amyloidosis — amyloidosis with mutational damage to transthyretin; AL amyloidosis — light-chain amyloidosis; THAOS, Transthyretin Amyloidosis Outcomes Survey — an international registry of patients with transthyretin amyloidosis; CHF — chronic heart failure; IG — immunoglobulins; MGUS — monoclonal gammopathy of undetermined significance.

Amyloidoses as an independent group of diseases were first described in the second half of the 19th century [1, 2], and were referred to as one type of amyloidosis, namely a secondary systemic lesion associated with inflammation. Much later, similar pathologies affecting both the nervous system and visceral organs were included in this group.

It currently includes 42 nosological entities [3–5]. All amyloidoses are characterized by a similar pathogenetic mechanism associated with the formation of amyloid, a special substance with a complex structure, whose main component is a protein capable of fibrillogenesis. In addition, tissue amyloid includes immunoglobulins (IGs), proteoglycans, serum amyloid P, and others [6]. The designation "amyloidosis" reflects the name of the primary protein on which amyloid is based. To date, 42 human proteins are known to be capable of amyloid formation and thus, there is an equal number of nosological entities, amyloidoses. They are distinguished into neurodegenerative, systemic, and localized. The most well-known neurodegenerative amyloidosis is Alzheimer's disease. Type 2 diabetes-associated local amyloidosis of the pancreas is significant for modern healthcare since the incidence rate of diabetes is constantly increasing [7]. Light-chain and transthyretin amyloidoses (AL and ATTR amyloidoses) are considered the most important of all systemic amyloidoses. These diseases, although rare, affect the middle-aged population, are quite severe, and, as a rule, have a very poor prognosis.

A modern understanding of the basics of amyloidosis pathogenesis and the role of individual proteins in their occurrence may have begun in the second half of the 20th century. One of the first described hereditary systemic amyloidoses is ATTR amyloidosis. The basic mechanisms of amyloidogenesis in general and ATTR amyloidosis in particular were established based on prion diseases and confirmed by numerous *in vitro* studies on amyloidogenesis [8–10].

General characteristics of the various forms of transthyretin amyloidosis

Hereditary ATTR amyloidosis was first described in 1952 and termed "familial amyloid polyneuropathy" [11]. The familial nature indicated the role of genetic factors in disease development and the disease met all the signs of a hereditary pathology. Indeed, in patients with familial amyloid polyneuropathy, a protein, transthyretin with an altered structure circulating in the plasma was subsequently discovered. Transthyretin was identified in 1942 [12]. It was initially named, prealbumin, since during electrophoresis it migrated to the anode ahead of serum albumin and was then conferred the present name "transthyretin" per its physiological activity. In the blood plasma, it transports thyroid hormones and, as was established later, a small retinol-binding protein saturated with vitamin A. Thus, a transport function is typical for transthyretin, but in itself, is not vital. Simultaneously, mutations in the gene encoding this protein lead to the synthesis of transthyretin with changes that facilitate the formation of fibrillar structures with the outcome being amyloids.

Transthyretin is a conserved protein and is encoded by a gene located on chromosome 18 (18q11.2-12.1), which consists of four exons and five introns. The mature protein is a 55 kDa homotetramer of small subunits with a molecular weight of 14 kDa, each consisting of 127 amino acid residues [13]. It does not possess any unique structural features. It is synthesized mainly in the liver and meagerly in the choroid plexus and retina. The components transported by transthyretin affect the stability of its quaternary structure, enhancing the inter-subunit interactions. Therefore, the removal of these components promotes the dissociation of transthyretin into monomers, which is related to the fibrillogenesis ability. The non-mutant transthyretin forms fibrils *in vitro* only under extreme conditions, at pH 2.0–4.5. In turn, mutant forms dissociate easily and form fibrils (the basis of amyloid) under physiological or experimental conditions.

To date, 140 mutations of the transthyretin gene are known (http://amyloidosismutations.com/mut-attr.php), most of which are fibrillogenic. The most common mutation, detected in different regions of the world, corresponds to the substitution of methionine with valine at position 30 of the mature protein (Val30Met or V30M, the three-letter abbreviation will be used hereinafter). In the USA, the pathogenic mutation Val122Ile is most common among African Americans [14]. Interestingly, the nature of the mutation is reflected in the course of amyloidosis. Based on clinical manifestations, mutations are distinguished that predominantly damage the nervous system, myocardium, and other tissues. For example, in patients with the most common Val30Met mutation, amyloid is predominantly formed in various parts of the nervous system, so they primarily exhibit symptoms of damage to the peripheral nerves and autonomic nervous system [15]. Polyneuropathy is most often the first sign of the development of ATTR amyloidosis. In this case, disease progression is accompanied by myocardial damage, which entails a sharp deterioration in the prognosis. The Val122Ile mutation, characteristic of African Americans, primarily contributes to the deposition of amyloid in the myocardium with the development of severe restrictive cardiomyopathy [16]. Other mutations are manifested by varying degrees of injury to the nervous system and myocardium [14]. In the Thr60Ala carriers, the disease demonstrates a mixed phenotype with damage to the nervous system, myocardium, and gastro-

intestinal tract. A satisfactory explanation for the different structural variants of transthyretin having a certain tropism concerning amyloidogenesis is still lacking. In fact, different protein variants differ in their *in vitro* fibrillogenicity, which does not explain their tropism. The tropism of some variants in local ATTR amyloidoses can be assumed to be associated with the peculiarities of extrahepatic synthesis to some extent. Another possible explanation is the altered ability of protein variants to undergo limited proteolysis [17], which can induce the onset of amyloidogenesis. This process may depend on the activity of tissue proteases.

Genetically determined ATTR amyloidosis is inherited in an autosomal dominant manner. Its distinctive characteristic is a variation in the penetrance of carriers. For example, in Portugal, almost all carriers of Val30Met developed amyloid polyneuropathy, which often precedes myocardial damage. In Sweden, the same mutation clinically manifested much less frequently; >30% of carriers do not develop amyloidosis even at the age of 90 years. The penetrance assessment depends on the average life expectancy in a particular region since the onset of the disease manifests itself quite late. In this regard, a longer life expectancy indicates a higher probability of hereditary amyloidosis. Age is particularly important in non-hereditary ATTR amyloidosis (ATTRwt amyloidosis) [18], the cause of which remains unresolved. Its relatively late development indicates special conditions for initiation. Such severe amyloidoses as prion diseases are often characterized by a long latent course, which is probably associated with prionization mechanisms and is due to the slow emergence of fibrillar structure embryos. In other amyloidoses, the same mechanism with a long latent period is possible, as a result of which the true onset of amyloidogenesis does not manifest clinically for a long time, and symptoms appear only at the formation stage of histologically determined amyloid accumulations. Another interesting feature is the genetic anticipation noted in Portuguese families with an increase in the maternal line [19]. Though an effect similar to genetic imprinting is possible, the reason underlying this phenomenon has not yet been established.

Our studies obtained information on the prevalence of hereditary ATTR amyloidosis in patients with restrictive cardiomyopathies in St. Petersburg, Russia. Mutations in the transthyretin gene were detected in three out of the 270 patients examined (cardiomyopathy) [20]. The spectrum of mutations is presented in [21]. Particular attention is paid to Val30Met and ATTRwt amyloidosis, and a case history of a patient with Val30Met amyloidosis is presented [22]. The cases on the clinical manifestation and diagnostics of ATTRwt amyloidosis dealt with by us are presented in [23–25].

Clinical manifestations of ATTR amyloidosis

The symptoms of amyloidosis before the full clinical presentation are highly diverse and simulate other types of pathology that diagnostics, especially early, is very challenging in many cases. Moreover, physicians often are not alert regarding these diseases. The average time from the onset of symptoms to diagnosis establishment, for example, in ATTRwt is ~5 years.

There are four clinical phenotypes of ATTR amyloidosis depending on the predominant clinical symptoms (data from the largest international patient registry, Transthyretin Amyloidosis Outcomes Survey [THAOS], which includes >5,000 patients as of 2022; the frequency of phenotypes is presented at the time of inclusion in the registry) [26]. These include

1. Predominantly neurological phenotype is represented in a majority of the patients with non-Val30Met and Val30Met with early onset. In Europe, among the ATTRwt patients, there are 0.4% cases.
2. Predominantly cardiac phenotype. In North America and Europe, a majority of the patients with this phenotype are ATTRwt patients, and up to 10% are ATTRv patients with cardiac mutations (Val122Ile, Leu111Met, Thr60Ala, and Ile68Leu).
3. Mixed (cardio-neurological) phenotype in Europe is represented by patients with ATTRwt (12.8%) and ATTRv (up to 20%) (non-Val30Met and Val30Met with early or late onsets).
4. Unclassifiable phenotype is represented by patients with a clinical manifestation that does not correspond to any of the listed categories. In Europe, this phenotype accounts for 0.9% of ATTRwt patients [27].

Neurological phenotype

First identified 70 years ago, transthyretin familial amyloid polyneuropathy is currently referred to as neuropathic hereditary transthyretin amyloidosis [19]. The age of polyneuropathy onset is 20–70 years, and progression is slow, taking over 10–20 years.

The main manifestation of the damage to the peripheral nervous system is sensorimotor polyneuropathy, namely pain in the distal parts of the limbs, paresthesia, burning sensation in the skin of the fingers, impaired temperature control, superficial pain, and deep sensitivity, as well as weight loss and weakness of the thenar muscles. Sensory ataxia is manifested by changes in gait and coordination of movements and impaired determination of limb position.

Damage to the autonomic nervous system includes impaired sweating (anhidrosis in the skin);

orthostatic hypotension, tachycardia in the cardiovascular system; constipation alternating with diarrhea, impaired motility in the gastrointestinal system; urinary retention or incontinence, neurogenic dysfunction of the bladder, and erectile dysfunction in the genitourinary system. Autonomic dysfunction develops at an average of ten years later than the first symptoms in ATTRwt, and 3.5 years later in ATTRv [28, 29]. Orthostatic hypotension (a decrease in systolic blood pressure by more than 20 mmHg or diastolic blood pressure by more than 10 mmHg upon standing up from a lying or sitting position) was registered in 12% of patients included in the registry, the vast majority of them were ATTRv patients (98.8%).

Cardiac phenotype

The most adverse sign during the development of ATTR amyloidosis is the appearance of life-threatening cardiac symptoms. Cardiomyopathy can develop independently and be the only manifestation of ATTR amyloidosis (cardiac phenotype) or have an onset against damage to other systems (mixed cardiac-neurological phenotype). In ATTRv amyloidosis, myocardial damage depends on a specific mutation in the transthyretin gene. As a result of amyloid deposition in the myocardium, the contractile function of the heart is impaired according to the type of restrictive cardiomyopathy with thickening of the ventricular walls (per cardiomyopathy classifications with mixed hypertrophic and restrictive phenotype). The latter circumstance suggests differential diagnostics with hypertrophic and other restrictive cardiomyopathies. With ATTRwt, 93% of patients have a cardiac or cardio-neurological phenotype.

Cardiac symptoms with ATTRwt included [30] symptoms of chronic heart failure (CHF) with a cardiac phenotype in 90% of the patients (including grades II–IV of heart failure per the classification of the New York Heart Association in 80% of them); with a mixed phenotype (cardio-neurological) CHF 0/I registered in 53% and CHF II–IV in 47% of cases. In this case, the median left ventricular ejection fraction in the entire group of patients was 61%; it was <50% in 28% of the entire group; and was <40% in 9% of the patients. Changes in the electrocardiograms included conduction abnormalities in 83% of the cases (complete atrioventricular block or electrocardio stimulation in 42% and left or right bundle branch block in 15 or 26%), and atrial fibrillation or flutter in 37% of the patients.

Mixed (cardio-neurological) phenotype

It often occurs as the initial cardiac phenotype gradually progresses. In this case, autonomic and sensory neuropathies are detected in 18% and 14% of cases, respectively. Involvement of other organs and systems included renal damage in 1%, carpal tunnel syndrome in 55%, biceps tendon rupture in 1%, and spinal stenosis in 7% of the patients [31]. Echocardiography indicated a restrictive type of left ventricular filling in 28% of the patients. ATTRwt predominantly affects men (>80%).

Heart damage in cardiac amyloidosis is characterized by the deposition of amyloid deposits in the myocardial interstitium, perivascularly (around the intramural small coronary arteries), and in the heart valves [32]. The consequences of these morphological changes are myocardial thickening in the left and right ventricles (hypertrophy is identified macroscopically and pseudohypertrophy is detected histologically), and an enhancement in the extracellular volume of the myocardium. Deposits in the interstitium impair myocardial extensibility (compliance), which causes diastolic dysfunction, and increased pressure in the left atrium, reflected in Doppler echocardiography by a restrictive type of left ventricle filling. Slight thickening and rigidity of the valve cusps lead to valvular regurgitation.

Cardiomyocytes adjacent to amyloid deposits, including cells of the conduction system, undergo atrophy and degeneration [33], which leads to rhythm and conduction disorders. As the number of deposits in the myocardium enhances, not only compliance but also contractile function decline, which is manifested in a reduction in the left ventricular ejection fraction.

More than half of patients with cardiac amyloidosis have pleural and pericardial effusion (more often with AL amyloidosis) [34]. This symptom is caused not only by right ventricular failure but also by a multifactorial genesis, including amyloid deposition in the visceral and parietal layers of the pericardium and local inflammation [35].

Amyloid lesions of other organs and systems

1. Lesions of the musculoskeletal system.

When amyloid is deposited in the ligamentous apparatus, bilateral carpal tunnel syndrome develops (as a result of median nerve compression in the carpal tunnel), as well as the rupture of muscle tendons (tear of the biceps tendon is typical), and stenosis of the spinal canal. These disorders can be the initial manifestations of ATTR amyloidosis, especially in patients with mutations p.Leu78His (Leu58His with numbering according to the mature protein), p.Leu78Arg (Leu58Arg), p.Lys90Asn (Lys70Asn), p.Ile104Ser (Ile84Ser), p.Ile127Val (Ile107Val), and p.Tyr134His (Tyr114His) [33]. Carpal tunnel syndrome occurs in 4% of the general population, and in 14% and 25% of patients with ATTRv and ATTRwt cases, respectively, but is extremely rare in

AL amyloidosis. The THAOS registry indicates that carpal tunnel syndrome is noted 5–9 years earlier than heart disease. In addition, to the listed bone and joint diseases, in ATTRwt patients, the diagnosis of amyloidosis was preceded by knee (19%) and hip (26%) joint replacement [36].

2. Kidney damage in amyloidosis.

The kidneys are affected by many amyloidoses, almost 100% in cases of inflammatory and AL amyloidosis. The incidence of kidney damage is registered in 5%–63% of patients depending on the type of ATTR amyloidosis [37, 38], namely more often with mutant (ATTRv) (up to 34%), less often with acquired (ATTRwt) [39], but with the latter, since these are older patients with evident comorbidity, kidney damage can be caused by concomitant pathology, in particular previous arterial hypertension. Nevertheless, since ATTR amyloidosis is systemic, there is always some involvement of the kidneys, as indicated by studies that describe kidney biopsy data for ATTR amyloidosis. For example, a previous work [40] presents kidney biopsy data for four patients (two each with ATTRv and ATTRwt), where all of them had amyloid depositions with different distributions (pericapsular, perivascular, in the interstitium of the medulla and cortex, and peritubular).

In 15%–30% of patients with ATTRv, kidney damage progresses to stage 5 chronic kidney disease, and it may precede polyneuropathy symptoms [41]. According to one study [42], 56% of ATTRwt patients showed a reduction in the estimated glomerular filtration rate <60 ml/min, and 6% had a decrease of <30 ml/min; in some of them, ATTRwt was combined with monoclonal gammopathy of undetermined significance (MGUS).

Laboratory indicators of kidney damage in amyloidosis are albuminuria or proteinuria and decreased estimated glomerular filtration rate. Calculation of glomerular filtration rate based on creatinine may underestimate kidney damage, since these patients may have low creatinine levels due to decreased muscle mass. A more accurate indicator of kidney function in amyloidosis is the glomerular filtration rate calculated by applying the CKD-EPI creatinine-cystatin C equation [43], which includes cystatin C and creatinine contents [44–46].

3. Eye damage.

The main manifestations are dry eyes, keratoconjunctivitis, vitreous opacity, and glaucoma. Scalloped pupil, according to clinicians, is a specific sign of ATTR amyloidosis [15, 47].

4. Combination of ATTR amyloidosis and MGUS, lymphoid system involvement.

The incidence of MGUS increases with age. In a study [40], MGUS was detected in 39% of patients with ATTRwt amyloidosis, i.e. a slight increase in IG light chains in the blood does not exclude ATTRwt amyloidosis. In this combination, the kidneys are involved in >50% of the patients.

5. Involvement of the gastrointestinal system.

Gastrointestinal symptoms such as constipation alternating with diarrhea, nausea, impaired motility, and weight loss are more often noted with ATTRv (63%) than with ATTRwt (15%) [48].

Diagnostic algorithm for ATTR amyloidosis

A diagnostic algorithm includes many sequential measures that confirm or refute the diagnosis of ATTR amyloidosis of the heart. The key link is to suspect ATTR amyloidosis in a patient based on clinical symptoms and other data. Further actions of the physician are described in detail in the clinical guidelines [49–52]. For the earliest possible detection of amyloidosis, the clinical guidelines provide "red flags" that help suspect the disease in a patient (regardless of the type of amyloidosis and clinical phenotype):

- CHF in a patient ⩾65 years old, more often with a preserved ejection fraction;
- an increase in the thickness of the left ventricular walls ⩾12 mm during echocardiography;
- aortic stenosis in a patient ⩾65 years old, more often with low-flow low-gradient;
- hypotension or normotension, in case of a history of hypertension;
- peripheral neuropathy (sensory and motor);
- proteinuria (in ATTRv and AL amyloidosis);
- easily generated subcutaneous hemorrhage;
- bilateral carpal tunnel syndrome or a history of biceps tendon rupture;
- disproportionate increase in N-terminal precursor of brain natriuretic peptide and/or slight persistent elevation in high-sensitivity troponin;
- electrocardiogram reveals reduced voltage of the *QRS* complex compared to the left ventricle mass (with the exclusion of extracardiac causes), pathological *Q* wave (in the absence of hemodynamically conspicuous stenosis of the coronary arteries), insufficient increase in the amplitude of the *R* wave in the chest leads, conduction abnormalities (atrioventricular blocks of varying degrees and right bundle branch block);
- atrial fibrillation/flutter;
- macroglossia (in AL amyloidosis);
- anamnesis a family history of the disease is possible in ATTRv (ATTRwt, AL, or HL amyloidosis are not hereditary);
- changes in echocardiography/magnetic resonance imaging (see below).

The listed symptoms are characteristic of severe systemic amyloidosis. The difficulty in diagnosing ATTRwt amyloidosis is the possible absence of many of the "red flags" in a particular patient or explained

by other causes, such as comorbidity since the patients are predominantly elderly and senile.

CHF, even with a cardiac phenotype, is present in only 90% of patients, with a low ejection fraction in some, which is considered uncharacteristic for cardiac amyloidosis. According to a study [30], 7% of patients, when included in the THAOS registry, i.e. when the diagnosis was made, had systolic blood pressure ⩾ 140 mmHg (no hypotension) and restrictive type of left ventricular filling (ratio of early and late left ventricular filling velocities on Doppler echocardiography >2) was registered in only 3.5% of cases, the average ratio of early left ventricular filling velocity to early mitral annulus velocity on echocardiography (E/e′) was >15 in 1%, low *QRS* voltage was noted in 28%, and thickening of aortic and mitral valve cusps was revealed in 21% and 30% of cases, respectively. Similar data from the THAOS registry were presented in later publications [53].

Echocardiography revealed left ventricular hypertrophy (a criterion that raises a suspicion of cardiac amyloidosis is a ⩾12 mm increase in the thickness of the left ventricular walls and ⩾5 mm right ventricular hypertrophy), grades II–III diastolic dysfunction (pseudonormal or restrictive type of left ventricular filling, E/e′ > 15), atrial dilation, slight thickening of the valve cusps, slight pericardial effusion, characteristic pattern of left ventricular deformity during the examination (decline in global longitudinal deformity with relative preservation of the deformity of the left ventricular apex), myocardial granularity and luster.

Magnetic resonance imaging revealed a characteristic pattern of late gadolinium (subendocardial/transmural) accumulation, and increased extracellular volume fraction.

Cardiac scintigraphy with osteotropic drugs is one of the key noninvasive diagnostic methods of ATTR amyloidosis [27]. Scintigraphy utilizes 99mTc-3,3-diphosphono-1,2-propanedicarboxylic acid, 99mTc-hydroxymethylene diphosphonate, and 99mTc-pyrophosphate. The study included planar scanning and single-photon emission computed tomography. There are four degrees (0–3) of radiopharmaceutical accumulation in the heart. Degrees 2 and 3 of the agent accumulation in the heart, provided that AL amyloidosis was excluded, allowing for the diagnosis of ATTR amyloidosis with high sensitivity (86%) and specificity (99%), without resorting to endomyocardial biopsy. False-positive scintigraphy results are rare and are caused by the presence of another type of amyloid in the myocardium of the patient (AApoAI, AApoAII, and AApoAIV). In AL amyloidosis, as a rule, the degree of drug accumulation in the myocardium is 0–1. False-negative scintigraphy results may be due to weak involvement of the heart in the pathological process during the initial stages of the disease and in the non-cardiac clinical phenotypes of ATTR amyloidosis.

If cardiac/cardio-neurological amyloidosis is suspected, the following algorithm is recommended for diagnosing ATTR amyloidosis.

Step 1: tests to rule out AL amyloidosis (determination of free IG chains in the serum or by immunofixation in the serum and urine).

Step 2: scintigraphy with osteotropic drugs.

Step 3: A — the degree of isotope uptake by the heart "0," IG light chains are not detected → cardiac amyloidosis is unlikely; if IG light chains are detected → cardiac magnetic resonance imaging + histological confirmation and amyloid typing (endomyocardial biopsy);

B — the degree of isotope uptake by the heart is "1" → regardless of the result of IG light-chain analysis, cardiac magnetic resonance imaging + histological confirmation and amyloid typing (endomyocardial biopsy);

C — cardiac uptake level "2–3," positive IG light-chain tests → see point B. If IG light-chain tests are negative → ATTR diagnosis.

Step 4: amyloidosis typing based on biopsy material (Congo red staining, polarized light examination, immunohistochemical examination of biopsy material, and microdissection with mass spectrometry). Genetic testing to verify ATTRwt or ATTRv amyloidosis [49–52].

Combination of aortic stenosis and ATTRwt

ATTRwt is diagnosed in 4%–16% of aortic stenosis cases [54, 55]. Several causes of such a frequent combination are discussed, namely, both diseases are age-dependent, and amyloid is deposited in the aortic valve leaflets and in the myocardium, which causes degenerative changes and thereby accelerates the development of aortic stenosis. Additionally, with aortic stenosis, an enhancement in the left ventricular wall stress (shear stress) may contribute to amyloid deposition in the myocardium [56]. This necessitates the identification of patients with aortic stenosis who require additional testing to confirm or rule out ATTRwt. "Red flags" of ATTRwt in patients with aortic stenosis are the following:

— severe left ventricular hypertrophy;
— low-flow low-gradient aortic stenosis;
— right ventricular myocardial hypertrophy (>5 mm);
— grades II–III diastolic dysfunction (E/e′ > 15);
— pronounced atrial dilation;
— decreased S′-wave in tissue Doppler ultrasonography of the mitral annulus;
— reduced global longitudinal deformity of the left ventricle with relative preservation of the apical deformity.

The RAISE scale is proposed; the authors suggest cardiac scintigraphy with osteotropic drugs if the

patient has aortic stenosis ⩾2 points (with ⩾3 points above the scale sensitivity). The RAISE scale includes the following:
— left ventricular hypertrophy and/or diastolic dysfunction (1 point);
— age over 85 years (1 point);
— serum troponin I >20 ng/l (1 point);
— manifestations from other systems (carpal tunnel syndrome — 3 points);
— electrocardiogram changes: right bundle branch block (2 points), low *QRS* voltage (1 point) [57].

Confirmation of amyloidosis diagnosis

Histological examination

The gold standard for confirming amyloidosis is the morphological detection of amyloids in biopsy samples of adipose tissue, salivary glands, myocardium, and tendon sheaths using Congo red staining [58] or analogs such as the fluorene derivative, thioflavin [59, 60]. The unique value is that the complexation of Congo red with amyloid protein fibrils rotates the plane of light polarization, due to which they appear apple-green. This phenomenon is associated with optical rotation dispersion, which in this case maximally corresponds to the green color range wavelengths. Other stains that selectively bind to amyloids have been recently described. A positive staining result for amyloids enables amyloidosis diagnosis with a high probability, but without detailing the nosological form.

Immunohistochemical analysis

Identification of the major amyloid protein is required for its determination and, therefore, to establish an accurate diagnosis. The major protein can be determined utilizing specific monoclonal antibodies. Therefore, it is desirable to have a panel of antibodies that react with various amyloid proteins. Notably, all amyloids, as a rule, contain some proteins of circulating blood, including IG, and, thus, monoclonal antibodies can interact with the light chains of IG, complicating the accurate identification of AL and ATTR amyloidosis using immunohistochemistry.

Mass spectrometry

Recent attention to the use of modern physicochemical approaches to diagnose amyloidosis is increasing. Microdissection of the stained amyloids from histological sections of biopsy material [61, 62] is already in use, followed by mass spectrometric identification of the proteins included. The study requires the usual staining of sections followed by laser dissection. The resulting material is dissolved in special detergents and hydrolyzed with trypsin or other specific proteases. Peptide fragments are analyzed using mass spectrometry and identified by comparing their molecular weights, with those in the database. The method is quite specific but requires special equipment and highly trained personnel.

Molecular genetic testing

If transthyretin or another protein capable of forming mutant amyloids is detected in amyloids, molecular genetic analysis with mutation identification is required. This problem can be partially solved using mass spectrometric testing. However, direct sequencing of the corresponding gene, preferably using the latest gene sequencing techniques is most effective.

ATTR amyloidosis therapy

Currently, several treatment options for ATTR amyloidosis have been proposed. Unfortunately, all of them are not completely effective. In addition, the therapy results for hereditary ATTR amyloidosis largely depend on the intra-protein localization of the mutation and the area of residence of the patients. The reason for this is not entirely clear. Perhaps, the protease status of the patient's tissues is significant, since reasonable assumptions mentioned above indicate that limited proteolysis of transthyretin promotes amyloidogenesis. In addition, modifier genes (region-specific manifestations of the same mutations) may exert influence.

Treatment of ATTR amyloidosis, like other amyloidoses, can be both general and highly specialized. Several approaches are possible:

Reducing the concentration of transthyretin by suppressing synthesis and secretion

A radical method of liver transplantation has been used for a long time to reduce the concentration of transthyretin in the blood plasma in hereditary ATTR amyloidosis. In this case, by definition, the mutant protein does not enter the bloodstream. Unfortunately, the success of the surgery depends on the nature of the mutation. The most promising results are registered in ATTR (Val30Met) amyloidosis and may be less satisfactory than with other mutations. In addition, success depends on the stage of the disease. Transplantation is most effective at the stages of polyneuropathy. The involvement of the heart in the process is an unfavorable factor. The reason for this is the ability of the non-mutant protein to form fibrils based on embryos that have included mutant transthyretin. Heart damage can only be avoided by transplantation. Recently, molecular approaches have been considered to reduce transthyretin synthesis. For this purpose, antisense RNAs are being tested. Preparations based on these compounds are capable of inhibiting the production of mutant and non-mutant transthyretin with an ef-

ficiency of ⩽80%. The drug patisiran, which suppresses transthyretin synthesis by RNA interference, has also been proposed.

Suppression of transthyretin tetramer dissociation to monomers

The transthyretin molecule consists of four subunits interacting non-covalently. The bond between the subunits is stabilized by ligands and thyroid hormones. There is a reliable correlation between the ability of the tetramer to dissociate into monomers and aggregate to form fibrils. Therefore, stabilization of mutant transthyretins reduces amyloidogenicity [12, 63]. Certain compounds interact with the ligand-binding center of the protein, stabilize the oligomeric structure, and prevent amyloid accumulation. Tafamidis is employed to treat ATTR amyloidosis, primarily transthyretin polyneuropathies [64]. It is indicated for use in the early stages of ATTR (Val30Met) amyloidosis. The non-steroidal analgesic, diflunisal is also effective in treating amyloid polyneuropathy. It acts at the stage during which amyloidogenic transthyretin subunits are formed.

Degradation of formed amyloids

Since amyloid deposits are undoubtedly one of the main causes of organ damage, suppression of amyloidogenesis and destruction of amyloids can be a crucial ATTR amyloidosis treatment method. The immunotherapy of amyloidosis under development includes two approaches. Monoclonal antibodies against transthyretin fragments are being tested, which enables a reduction in the concentrations of the protein in the plasma, which prevents amyloid generation. Another approach involves the use of antibodies against the serum amyloid P, a permanent component of any amyloid, including transthyretin [65, 66]. A compound that reduces the plasma levels of this protein is utilized to prevent the reactivity of antibodies with free serum amyloid P. Antibody preparations have been approved for use. Scintigraphy has established that immunotherapy can reduce the amyloid content in the organs. Unfortunately, its efficiency has not yet been sufficiently tested, and the results are ambiguous.

Conclusion

Most amyloidoses known to date are orphan diseases. In this regard, ATTR amyloidosis is no exception. Even though ATTR amyloidosis is, fortunately, a rare pathology, constant alertness of medical personnel is necessary in case of the appearance of the slightest symptoms indicating its possibility. Early diagnostics of hereditary ATTR amyloidosis can significantly improve the quality of life of patients and delay the onset of dangerous complications, in particular transthyretin cardiomyopathy. Although modern therapeutic approaches are incapable of eliminating the symptoms of ATTR amyloidosis, they are effective in some cases. Non-hereditary ATTR amyloidosis developing in elderly patients needs particular attention since the superposition of amyloidosis on an existing pathology markedly affects the course of underlying diseases. Therapy for amyloidosis can remarkably improve the effectiveness of treatment of age-related pathologies. Currently, relatively little attention is being paid to non-hereditary ATTR amyloidosis. An equally important factor in suspected amyloidosis is differential diagnostics which enables to distinction between various types of systemic amyloidosis. Diagnosis clarification is required for correct rational treatment since different amyloidoses require varying specific approaches.

Additional information

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Personal contribution of each author: *M.M. Shavlovsky* — analysis of literature on molecular basis of transthyretin amyloidosis, preparation of the manuscript, general guidance in writing and designing the article; *A.Ya. Gudkova* — analysis of literature on clinical aspects of transthyretin amyloidosis, preparation of the sections relating to diagnosis and treatment of transthyretin amyloidosis; *O.I. Antimonova* — selection of literature, editing of the manuscript, preparation of the article in accordance with the rules of the journal; *A.N. Krutikov* — preparation of the sections on clinical description of transthyretin amyloidosis, instrumental methods for examining patients, differential diagnosis.

Дополнительная информация

Источник финансирования. Работа выполнена по Госзаданию ФГБНУ «Институт экспериментальной медицины».

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, прове-

дение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Наибольший вклад распределен следующим образом: *М.М. Шавловский* — анализ литературы по молекулярным основам транстиретинового амилоидоза, подготовка рукописи, общее руководство написанием и оформлением статьи; *А.Я. Гудкова* — анализ литературы по клиническим аспектам транстиретинового амилоидоза, подготовка разделов, касающихся диагностики и терапии транстиретинового амилоидоза; *О.И. Антимонова* — подбор литературы, редактирование рукописи, оформление статьи в соответствии с правилами журнала; *А.Н. Крутиков* — подготовка разделов по клиническому описанию транстретинового амилоидоза, инструментальные методы обследования пациентов, дифференциальная диагностика.

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