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CLINICAL AND BIOCHEMICAL MARKERS FOR EARLY DIAGNOSIS OF SYSTEMIC AMYLOIDOSIS

© Iskander A. Latypov[1], Sarng S. Purveev[1, 2], Kirill V. Chelnyntsev[3], Lev D. Balashov[1]

[1] Saint Petersburg State Pediatric Medical University. 2 Lithuania, Saint Petersburg 194100 Russian Federation
[2] Institute of Experimental Medicine. 12 Academician Pavlov str., Saint Petersburg 19702 Russian Federation
[3] Almazov National Medical Research Centre. 2 Akkuratov str., Saint Petersburg 197341 Russian Federation

Contact information: Sarng S. Pyurveev — Senior Assistant Department of pathological physiology with immunopathology course.
E-mail: dr.purveev@gmail.com ORCID: https://orcid.org/0000-0002-4467-2269 SPIN: 5915-9767

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Abstract. Amyloidosis is a group of systemic diseases characterized by the extracellular deposition of pathologic, insoluble fibrillar proteins in tissues and organs, potentially leading to multiple organ failure. In spite of the heterogeneity of systemic amyloidosis etiology, clinical signs and symptoms of various forms of amyloidosis considerably overlap and depend on the affected organs. Signs and symptoms suggestive of amyloidosis are often nonspecific, which makes it difficult for clinicians to diagnose amyloidosis early and prompts them to exercise increased clinical vigilance. In the article, we aimed to determine the most significant clinical and hematologic markers of the most common forms of systemic amyloidosis and to assess the potential of using standard diagnostic manipulations to confirm or rule out amyloidosis in high-risk patients. Amid the backdrop of population aging and an increase in the incidence of neurodegenerative diseases, the adoption of standardized and relatively low-cost methods of early diagnostics will enable clinicians to evaluate disease progression, select treatment strategies, and determine patient prognosis earlier on, thereby minimizing damage to the healthcare system.

Keywords: amyloidosis, modeling of amyloidosis

КЛИНИКО-БИОХИМИЧЕСКИЕ МАРКЕРЫ ДЛЯ РАННЕЙ ДИАГНОСТИКИ СИСТЕМНОГО АМИЛОИДОЗА

© Искандер Альбертович Латыпов[1], Сарнг Саналович Пюрвеев[1, 2], Кирилл Владимирович Челнынцев[3], Лев Дмитриевич Балашов[1]

[1] Санкт-Петербургский государственный педиатрический медицинский университет. 194100, г. Санкт-Петербург, ул. Литовская, 2
[2] Институт экспериментальной медицины. 197022, г. Санкт-Петербург, ул. Академика Павлова, 12
[3] Национальный медицинский исследовательский центр им. В.А. Алмазова. 197341, г. Санкт-Петербург, ул. Аккуратова, 2

Контактная информация: Сарнг Саналович Пюрвеев — ассистент кафедры патологической физиологии с курсом иммунопатологии.
E-mail: dr.purveev@gmail.com ORCID: https://orcid.org/0000-0002-4467-2269 SPIN: 5915-9767

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Резюме. Амилоидоз — группа системных заболеваний, вызванных внеклеточным депонированием патологических нерастворимых фибриллярных белков в тканях и органах, которые могут привести к полиорганной недостаточности. Несмотря на гетерогенность этиологии системного амилоидоза, клинические проявления различных форм этой нозологической группы во многом пересекаются и зависят от пораженных органов.

Знаки и симптомы, позволяющие заподозрить амилоидоз, чаще всего неспецифичны, поэтому у специалистов возникают трудности в ранней диагностике, что требует усиленного клинического наблюдения. В данной статье мы хотим определить наиболее значимые клинико-гематологические маркеры распространенных форм системного амилоидоза и оценить возможности использования стандартных диагностических манипуляций для подтверждения или исключения амилоидоза у пациентов из групп риска. В связи с активным старением населения и ростом заболеваемости нейродегенеративными заболеваниями внедрение унифицированных и относительно дешевых методов ранней диагностики позволит клиницистам на начальных этапах оценить течение заболевания, подход к лечению и прогноз для пациента, а также позволит минимизировать ущерб для системы здравоохранения.

Ключевые слова: амилоидоз, моделирование амилоидоза

HISTORY

In the XIX century, pathologist R. Virchow, studying the so-called sebaceous disease, discovered that the substance located in the affected organs, when stained with iodine, acquires a purple color, like starch, and called it amyloid (Latin *amylum* — a starch). In the XX century German doctor N.N. Bennhold created one of the first methods of lifetime diagnosis of amyloidosis by intravenous injection of amyloid-specific dye congo-rot and estimation of the rate of reduction of its concentration in the blood. With the development of electron microscopy, A.S. Cohen established that amyloid is a fibrillar protein with β-folded configuration, which is detected in X-ray diffraction and is apparently responsible for the typical coloring of this protein. The discovery was also that in primary amyloidosis fibrils are fragments of immunoglobulin light chains. Later it was found that fibrils consist of different types of protein chains, which was the beginning of the way to the development of etiotropic therapy of amyloidosis.

EPIDEMIOLOGY OF AMYLOIDOSIS

To date, the prevalence of amyloidosis has not been sufficiently studied due to rarely expressed and specific clinical symptoms, difficulties in diagnosis, and low vigilance of specialists. Various sources estimate the prevalence of amyloidosis from 0.1 to 6% in the population based on autopsy data [6, 22].

Because of the lack of documentation, estimates of the prevalence of amyloidosis vary widely depending on the study period, the State and the researchers' methods of estimating incidence. For example, in the United States of America, according to S.Y. Tan, the incidence of amyloidosis ranges from 5.1 to 12.8 cases per 100 thousand population per year [23]. In European countries, the incidence of amyloidosis in chronic diseases ranges from 1.4 to 5%, and in Japan it is 0.1% [7, 23]. Over time and with the development of genetic screening in the Russian Federation, the frequency of occurrence of certain forms of amyloidosis began to increase, and the structure of the detected forms of amyloidosis changed: for example, AA-amyloidosis was detected in 46 patients out of 152 before 2006 and in 90 among 153 patients after 2006, but at the same time the frequency of AL-amyloidosis significantly increased (in 53 out of 153 patients before 2006 and in 80 out of 152 after 2006), which is associated with the increased sensitivity of diagnostic methods [6, 12, 13].

AMYLOIDOSIS MORPHOLOGY

Amyloid fibrils are protein polymers up to 10 nm in diameter and 800 nm in length, having a cross-β conformation, which determines the special polarization ability of amyloid to double beam refraction. Histochemical studies have established that polysaccharides account for no more than 4% of the mass of total amyloid. Nevertheless, the historical name "amyloid" has been retained and is used in the International Classification of Diseases [4, 12].

In addition to fibrillar protein, the so-called P-component, which constitutes 10–15% of the total mass of amyloid, was found in the composition of amyloid. This protein is similar in structure to serum amyloid P-component (SAP), the increase in the amount of which in blood plays its role in the pathogenesis of amyloid accumulation [11, 12]. In addition, P-component protects amyloid fibrils from their lysis by macrophages-amyloidoclasts, which prevents the patient's immune system from effectively destroying the depot of pathological protein and, in turn, also plays an important role in the pathogenesis of amyloidosis [4, 12].

Some types of amyloid have a relationship with neurodegenerative processes such as Alzheimer's disease, Parkinson's disease, hemoblastosis (Rustitzky–Kahler disease), hemodialysis (β_2-microglobulin amyloidosis), chronic inflammatory diseases (tuberculosis, rheumatoid arthritis, gout, bronchiectatic disease, etc.), as well as some genetic defects (Aβ-amyloidosis, familial nephropathic amyloidosis, Finnish-type amyloidosis, American amyloidosis, etc.).

AMYLOIDOSIS CLASSIFICATION

According to the International Classification of Diseases and Related Health Problems (ICD-10), amyloidosis is of the following types:

E85.0 **Non-neuropathic heredofamilial amyloidosis**
Familial Mediterranean fever
Hereditary amyloid nephropathy
E85.1 **Neuropathic heredofamilial amyloidosis**
Amyloid polyneuropathy (Portuguese)
E85.2 **Heredofamilial amyloidosis, unspecified**
E85.3 **Secondary systemic amyloidosis**
Haemodialysis-associated amyloidosis
E85.4 **Organ-limited amyloidosis**
Localized amyloidosis
E85.8 **Other amyloidosis**
E85.9 **Amyloidosis, unspecified** Clinical and biochemical classifications of amyloidosis forms are now widely accepted (Fig. 1).

AA-amyloidosis group: the disease is characterized by extracellular deposition of serum amyloid A (serum amyloid A, SAA) fibrils. SAA is a normal serum acute-phase protein

Table 1

Clinical and biochemical classification of amyloidosis forms

Таблица 1

Клиническая и биохимическая классификации форм амилоидоза

Название амилоидного белка / Name of amyloid protein	Белок-предшественник/ Precursor protein	Клиническая форма / Clinical form
AA	Сывороточный амилоид А (SAA) / Serum amyloid A (SAA)	Вторичный амилоидоз при хронических инфекционных и воспалительных заболеваниях (реактивный), амилоидоз при периодической болезни и синдроме Макла–Уэллса / Secondary amyloidosis in chronic infectious and inflammatory diseases (reactive), amyloidosis in periodic disease and Muckle-Wells syndrome
AL	Λ, κ легкие цепи Ig	Амилоидоз, ассоциированный с плазмоклеточными дискразиями: идиопатический, при миеломной болезни и макроглобулинемии Вальденстрёма / Amyloidosis associated with plasma cell dyscrasias: idiopathic, in multiple myeloma and Waldenström's macroglobulinemia
ATTR	Транстиретин / Transthyretin	Семейные варианты полинейропатического, кардиомиопатического амилоидоза, системный старческий амилоидоз / Familial variants of polyneuropathic, cardiomyopathic amyloidosis, systemic senile amyloidosis
Aβ2M	β_2-микроглобулин / β_2-microglobulin	Диализный амилоидоз / Dialysis amyloidosis
AGel	Гелсолин / Gelsolin	Финская семейная амилоидная нейропатия / Finnish familial amyloid neuropathy
AApoAI	Аполипопротеин / Apolipoprotein	Амилоидная нейропатия (III тип по van Allen, 1956) / Amyloid neuropathy (type III according to van Allen, 1956)
AFib	Фибриноген / Fibrinogen	Амилоидная нефропатия / Amyloid nephropathy
Aβ	β-протеин / β-protein	Болезнь Альцгеймера, синдром Дауна, церебральная амилоидная ангиопатия / Alzheimer's disease, Down syndrome, cerebral amyloid angiopathy
APrPser	Прионный белок / Prion protein	Болезнь Крейтцфельдта–Якоба, болезнь Гертсманна–Штраусслера–Шейнкера / Creutzfeldt–Jakob disease, Gertsmann–Straussler–Scheinker disease
AANF	Предсердный натрийуретический фактор / Atrial natriuretic factor	Изолированный амилоидоз предсердий / Isolated atrial amyloidosis
AIAP	Амилин / Amilin	Изолированный амилоидоз островков Лангерганса при сахарном диабете 2-го типа, инсулиноме / Isolated amyloidosis of the islets of Langerhans in type 2 diabetes mellitus, insulinoma
ACal	Прокальцитонин / Procalcitonin	При медуллярном раке щитовидной железы / For medullary thyroid cancer
ACys	Цистатин С / Cystatin C	Церебральная амилоидная ангиопатия / Cerebral amyloid angiopathy

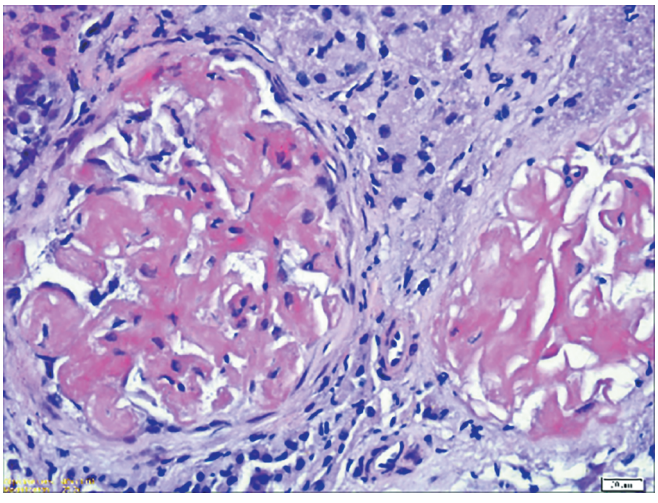

Fig. 1. Glomerular amyloid deposits in secondary amyloidosis. Light microscopia with kongo-rot colouring, ×40 [30]

Рис. 1. Гломерулярные депозиты амилоида при вторичном амилоидозе. Световая микроскопия с окраской конго-рот, ×40 [30]

synthesized by hepatocytes under the influence of pro-inflammatory protein-cytokines [15, 18]. Thus, a consistently high concentration of SAA in blood ensures the development of AA-amyloidosis by folding and stacking protein chains into the β-conformation and binding to glycosaminoglycans (GAGs) and the amyloid P component of serum [8, 21]. This group includes reactive amyloidosis, amyloidosis in periodic disease, and amyloidosis in Muckle-Wells syndrome. SAA levels in plasma have no significant difference according to sex and age and have been variously estimated to be between 5 and 20 mg/L using latex immunoturbidimetry, radioimmunoassay, and rapid quantitative test methods [9].

AL-amyloidosis develops as a result of massive systemic extracellular deposition of monoclonal immunoglobulin light chains secreted by plasmocyte clones [2–4]. It is known that λ-isotype and κ-isotype of light chains are predominantly amyloidogenic [8, 13, 21]. Diagnosis of this type of amyloidosis is based on morphologic examination of biopsy specimens of subcutaneous adipose tissue or salivary glands (at the initial stage), and if it is impossible to isolate it from these organs — from the affected organs: kidneys, liver, gastrointestinal tract organs, myocardium [5, 16, 25]. The presence of extracellular masses positively stained with congo red dye and giving green luminescence during microscopy in polarized light suggests the presence of amyloid deposits. Advanced methods of AL amyloidosis diagnostics may include immunohistochemical study on paraffin sections, immunofluorescence study using highly sensitive and specific anti-λ and anti-κ antibodies [14, 17, 20, 21]. It is necessary to perform differential diagnosis with other types of amyloidosis: for example, in the absence of positive staining of deposits, it is reasonable to analyze the level of serum amyloid A in plasma, β_2-microglobulin in patients on hemodialysis, as well as lysozyme, apolipoproteins, fibrinogen, gelsolin, transthyretin, the level of which may be increased in familial forms of amyloidosis [12, 14].

ATTR-amyloidosis (transthyretin, senile amyloidosis). This type of amyloidosis is an irreversibly progressive and disabling disease characterized by progressive polyneuropathy, as well as the development of heart failure, kidney and other organ damage. It includes familial amyloid polyneuropathy and systemic senile amyloidosis [10, 14, 26, 30].

In familial amyloid polyneuropathy, the amyloid precursor protein is transthyretin. It is a protein that provides transport of thyroxine and retinol and is synthesized in the liver, vascular plexus of the brain ventricles, and retinal epithelium. The development of ATTR-amyloidosis has two pathogenetic variants: genetic mutations associated with amino acid substitution or deletion in the *TTR* gene encoding transthyretin synthesis and located on the long arm of chromosome 18 [1, 24, 25]. Currently, more than 100 types of *TTR* gene mutations are known, but many remain unexplored. The prevalent *TTR* mutations are Val30Met and Val122Ile. Amyloidogenic mutations cause deposition of pathologic protein in the peripheral nervous system, heart, gastrointestinal tract, and lens [13, 22, 26].

ATTR-amyloidosis can be suspected in patients with progressive neuropathy and cardiomyopathy, constipation and diarrhea, and decreased visual acuity. Diagnosis is based on morphologic examination of a biopsy of the affected organ, as well as genetic testing for the presence of *TTR* gene mutations [10, 21, 24].

AN EXPERIMENTAL MODELING OF AMYLOIDOSIS

Many still unsolved problems of etiology, pathogenesis, diagnosis, treatment, and prevention of amyloidosis attract the attention of researchers to experimental models of amyloidosis [27]. Modeling amyloidosis in animals can provide the search for more effective methods of its prevention and treatment. There are many ways of experimental modeling of amyloidosis. Most of them are based on the administration of chemical or biological substances to animals. In the XXI century, the Russian Federation has developed its own methods: for example, for the first time a method was developed to obtain a model of systemic cardiac amyloidosis on the background of a single injection of rats with a mixture containing native egg albumin, complete Freund's adjuvant and rat myocardial homogenate. A method of modeling amyloidosis in white mice consisting in the administration of native egg albumin every other day for 30 days was also patented [3, 5, 7].

However, the disadvantages of these methods are: the small size of animals, the complexity of histological and chemical examination of organs due to their small size, the need to control daily diuresis, tubule reabsorption (by endogenous creatinine clearance) and the content of electrolytes in the urine of animals. The combination of these requirements significantly complicates experimental modeling, as well as increases its cost [3].

As a result of these studies, the authors found out that some pharmacological substances can have a therapeutic effect in amyloidosis: for example, succinic acid administered intragastrically through a probe at a rate of 1.5 mmol/kg for 60 days promoted the recovery of myocardium and stroma vessels and hemodynamics in tissues. Morphological study of the organs of rats treated with acisol (bis-1-vinylimidazole-zincdiacetate) showed a decrease in congophilia, the appearance of individual amyloidoclasts, and foci of revascularization [19].

Since one of the frequent links in the pathogenesis of amyloidosis is chronic inflammation, it is necessary to develop a system of measures allowing mass diagnostics of chronic inflammatory diseases in individuals at risk [6].

Currently, there are no massively implemented therapy protocols capable of inducing a sufficiently rapid process of destruction and excretion of amyloid deposits from tissues, and the available treatment methods are aimed at regulating the metabolism of amyloidogenic substances [29, 30].

The introduction of already available methods of searching for amyloidosis markers, such as C-reactive protein, β_2-microglobulin, serum amyloid A protein, and genetic studies (e.g., exon sequencing of the TTR gene) is feasible due to the possibility of performing such tests at a relatively low cost. Investigation of these markers will allow to detect or exclude the diagnosis of some amyloidoses in patients with unclear clinical picture associated with polyneuropathies, neurological syndromes, and cardiomyopathy of unclear genesis and/or in patients with the above symptoms and a history of chronic inflammatory diseases.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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