REVIEW PAPER

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Amyloidosis – short review

Agnieszka Gaczkowska, Paweł P. Jagodziński, Adrianna Mostowska

Department of Biochemistry and Molecular Biology, Poznan University of Medical Sciences, Poznan, Poland

ABSTRACT

Amyloidosis is a heterogeneous group of disorders associated with pathological deposition of amyloid. We can recognize two major categories of amyloidosis: primary (AL) and secondary (AA) type. Systemic monoclonal immunoglobulin light-chain (AL) is the most common form of systemic amyloidosis. Systemic AA amyloidosis is associated with chronic inflammation or infective diseases and is the second common form of systemic amyloidosis. The golden standard in diagnosis of amyloidosis is biopsy. The model of treatment depends of type of amyloidosis. In some cases cell transplantation can be considered. In AA the purpose is to decrease inflammation.

Keywords: amyloidosis, amyloid, diagnostic, treatment.

The first description of the amyloidosis was probably reported by Nicolaus Fontanus in 1639. The autopsy of a young man showed ascites, jaundice, epistaxis, abscess in the liver and large spleen with stones. The term 'amyloid' was used the first time by a German botanist in 1838. This term means a normal amylaceous constituent of plants. In medicine this term appeared in 1854 and it was involved in the case of nervous system disease described by Rudolph Virchow. The amyloid substituted another terms: 'lardaceous' and 'waxy' changes [6].

Amyloidosis is a heterogeneous group of disorders associated with pathological deposition of protein (extracellular amyloid) in an abnormal fibrillar form. The extracellular amyloid deposits are present also in Alzheimer's, Huntington's and Parkinson's diseases, familial Mediterranean fever or dementia with Lewy bodies. The fibril type is the basis for the classification of amyloidosis. We can recognize two major categories of amyloidosis: primary (AL) and secondary (AA) type. There are other, less popular types, which include hereditary mutant transthyretin (ATTR), dialysis associated (with β_2-microglobulin β2M) disease, age-related (senile) systemic amyloidosis and organ specific amyloidosis (**Table 1**) [1, 3, 7, 8].

Types of amyloidosis

Systemic monoclonal immunoglobulin light-chain (primary type AL) is the most common form of systemic amyloidosis. It is characterized by systemic disease (primary amyloidosis, multiple myeloma, Waldenstrom's lymphoma) and local disease (skin, urinary tract, larynx, eyes). Onset of the disease may result in non-specific symptoms. This may be enlargement of the spleen or liver, edema (proteinuria, hypoalbuminemia, congestive heart failure), peripheral sensory neuropathy, carpal tunnel syndrome, diarrhoea, constipation (autonomic dysfunction), orthostatic hypotension, symptoms of cardiomyopathy (50% of patients), enlarged tongue, in appearance of blood around the eyes, nail dystrophy. In radiographic manifestations of systemic amyloidosis we can identify parenchymal findings: reticular nodular opacities, reticular opacities and diffuse alveolar opacities. Primary systemic amyloidosis can involve the kidneys, gastrointestinal tract, skin, respiratory system, heart, and other organs. However, there are known forms of localized amyloidosis affecting only one organ. The prognosis for patients is bad since this disease is rapidly progressive, affects multiple organs and median survival is 5 months from diagnosis [2, 4,

Type	Symbol	The most common symptoms	Therapy
Primary type	AL	Systemic or local disease: enlargement of the spleen and liver, neuropathy, cardiomyopathy	High-dose alkylator-based chemotherapy, stem cell transplantation, diuresis, serial thoracenteses, pleurodesis, bronchial repermeabilization
Secondary/reactive type	AA	Diseases of urinal system – proteinuria, splenomegaly, functional hyposplenism, amyloid deposits at the adrenal glands, liver and gastrointestinal tract	Immunosuppressants, colchicine, demethyl sulfoxide, immunotherapy
The hereditary types, the most common - transthyretin amyloidosis	ATTR (transthyretin amyloidosis) AFib (fibrinogen Aα chain) ALys (lysozyme) AApo AI (apolipoproteins AI) AApo AII (apolipoproteins AII) AGel (gelsolin)	Peripheral neuropathy, autonomic neuropathy, cardiomyopathy, ophthalmopathy	Early liver transplantation, possibility of hepatorenal or hepatocardiac transplantation
Dialysis-related/β2-microglobulin type	DRA	Carpal tunnel syndrome, bone cysts, destructive arthropathies, spondylarthopathies	Renal transplantation, hemodialysis with high-flux membranes and β2-microglobulin adsorption columns, steroids, non steroidal anti-inflammatory drugs
Senile systemic type	SSA	Heart failure, atrial arythmias and cardiomegaly	Drugs therapy (diuretics, beta blockers, angiotensin enzyme inhibitors, angiotensin receptor blockers, digoxin), ventricular assist devices, heart transplantation

Table 1. Amyloidosis review. The Table is based on articles cited in the text

5, 9]. There are also extremely rare types of amyloidosis: with heavy chains (AH) and heavy and light chains (AHL), both included in the Ig-related amyloidosis. All described cases of AHL had renal involvement, patients are less likely to suffer from cardiac type and there was better patient survival than with AL [12, 19].

Systemic AA amyloidosis (known also as reactive or secondary) is associated with chronic inflammation or infective diseases. It is the second common form of systemic amyloidosis and it is popular in Europe and in developing countries (30–40% of renal cases). Patients with AA are usual younger than those with AL. High risk factors of AA are: arthritis – the common reason, hereditary periodic fevers, inflammatory bowel diseases, chronic infections (e.g. chronic cutaneous ulcers and osteomyelitis), immunodeficiency states, systemic vasculitis, neoplasia, tuberculosis and sarcoidosis. Clinical signs usually involve urinal system, including proteinuria in 95% and nephrotic syndrome in more than 50% of cases. Other common symptoms are massive splenomegaly, functional hyposplenism, amyloid deposits at the adrenal glands, liver and gastrointestinal tract. Cardiac and neuropathic symptoms are extremely uncommon [10–13]. AA type is caused by reactant protein serum amyloid A (SAA). SAA is synthesized under the cytokine control and it can increase in acute injury, infection or inflammation. There are two isoforms of SAA – SAA1 and SAA2. AA can be a serious complication for patients with the hereditary periodic fever syndromes: familial Mediterranean fever, the TRAPS syndrome, Muckle-Wells syndrome, and hyperimmunoglobulinemia IgD with periodic fever syndrome [32–34].

The hereditary amyloidosis is a rare group of disorders. It is mainly inherited as autosomal-dominant disorder. The most common type of familial amyloidosis is transthyretin amyloidosis (ATTR), but we can recognise other types with proteins including fibrinogen Aα chain (AFib), lysozyme (ALys), apolipoproteins AI (AApo AI) and AII (AApo AII), and gelsolin (AGel) [13–16]. ATTR includes five phenotypes: familial amyloid polyneuropathy type I or II, familial amyloid cardiomyopathy, familial oculoleptomeningeal amyloidosis and familial leptomeningeal amyloidosis. It can be presented as peripheral neuropathy, autonomic neuropathy, cardiomyopathy and ophthalmopathy. The amyloid-producing pathway is associated with mutations in the amyloid-β domain. The mutations of Alzheimer amyloid precursor protein are associated with the systemic hereditary amyloidosis [22–31]. To date, more than 90 single nucleotide variants have been identified in the coding sequence of *TTR* (OMIM *176300) in individuals with this type of amyloidosis. Familial ATTR amyloidosis is inherited in an autosomal dominant manner. Prenatal diagnosis is offered to all pregnant women if the pathogenic *TTR* variant has been identified in their families [25].

Dialysis-related amyloidosis (DRA) is caused by deposition of β_2-microglobulin (β2M) in tissues during long-term dialysis in chronic kidney disease patients. The clinical sings include carpal tunnel syndrome – the most characteristic symptom, bone cysts, destructive arthropathies, spondylarthopathies and sometimes involve other organs like skin, liver, heart or spleen. Risk factors of DRA are: age, duration of dialysis, use of low-flux dialysis membrane and genetic factors, e.g. apolipoprotein alleles, which are correlated with Alzheimer disease. The genetic risk is the highest in the case of mutation in apolipoprotein ε4 allele [17, 18, 55, 59].

Senile systemic amyloidosis (SSA) is associated with elderly patients. This type of disease causes deposits of wild-type transthyretin molecules in myocardium and results in heart failure, atrial arrhythmias and cardiomegaly. The renal symptoms are rare. The prognosis is better than for patients with AL and it is usually few years of survival [19–21].

Diagnostic

The most frequent and the earliest sign in AA type is proteinuria leading to nephrotic syndrome. The only test, which can confirm amyloidosis is biopsy with histological demonstration of amyloid deposits [14]. Congo-red-positive biopsies observed with polarization microscopy are the golden standard in detecting the disease. Amyloid material can be recognised also by gentian violet or thioflavin T [35]. The good method to diagnose a systemic amyloidosis is the subcutaneous adipose tissue biopsy. This is of value in the AL, AA and ATTR, but it has some limitations: unequally distributed deposits, overstaining in Congo red samples with needle biopsies and relatively little involvement of subcutaneous fat tissue in some types of amyloidosis [36]. There are four techniques in typing of amyloid: immunohistochemistry, immunochemistry, mass spectrometry and chemistry. There are 14 proteins detected in samples of amyloidosis, which can be analysed by proteomics. These tests give the investigation of amyloidogenic protein precursors, the identification of the fibrillar deposited proteins, the characterization of the metabolic modifications in affected tissues and the detection of new biomarkers. Amyloid can be classified by antibodies, for example against amyloid P component, AA amyloid, apolipoprotein A-I, lyzosyme, fibrinogen, transthyretin and κ and λ light chains. The immunohistology is most useful for AA and ATTR. The mass spectrometry detects serum monoclonal immunoglobulin free light chains, which are secreted by plasma cells and circulate in plasma and it is useful in AL amyloidosis [37–40].

Treatment

The model of treatment depends on type of amyloidosis. At the 13th International Symposium on Amyloidosis in Groningen updated criteria were given which defined treatment for individual involved organs. The most important is early diagnosis and effective therapy [41].

Treatment of AL is individualized and determined by age, organ dysfunction, present biomarkers and cardiac response. One of the oldest methods is high-dose alkylator-based chemotherapy. It was melphalan with prednisone, later substituted for dexamethasone. Another options are thalidomide, lenalidomide, pomalidomide, bortezomib and colchicine. In some cases autologous stem cell transplantation with earlier chemotherapy has higher response rate than conventional chemiotherapy This method is the standard treatment for multiple myeloma and employed for AL. Medical treatment is also prescribed according to clinical indications and medical judgement and it includes diuresis, serial thoracenteses, pleurodesis, bronchial repermeabilization, avoid digitalis and calcium channel blockers, assessment for atrial thrombi, mechanical pacing [41–44].

AA is associated with other diseases with inflammation and the basis is a common_control of both diseases and decrease of the inflammation. The popular treatment is immunosuppressants: methotrexate, cyclophosphamide and chlorambucil. In some diseases, for example familial Mediterranean fever, the most effective drug is colchicine. The best prognostic factor of therapy is normal renal function. Another effective treatment is demethyl sulfoxide, especially in bowel's inflammatory diseases. There are tested new methods of immunotherapy, which may eliminate deposits from systemic and local amyloidosis [45–50].

In ATTR type the best option is early liver transplantation. The surgery can not prevent all symptoms, cardiomyopathy and neuropathy progress even after transplantation. In cases with advanced organ's damage there is possibility of hepatorenal or hepatocardiac transplantation [51, 52].

For patients with DRA the most important step is renal transplantation, which reduces β_2-microglobulin to the normal level in plasma. The surgery does not decrease radiologic and histologic lesions long time after transplantation. β_2-microglobulin can be removed by hemodialysis with high-flux membranes and

β_2-microglobulin adsorption columns. The established DRA can be treated with low-dose steroids and non steroidal anti-inflammatory drugs [53–55].

Treatment of amyloid cardiomyopathy is primarily the therapy of heart failure. It can involve pharmacotherapy, for example with diuretics, beta blockers, angiotensin enzyme inhibitors, angiotensin receptor blockers or digoxin. The next step is heart transplantation or ventricular assist devices. Anticoagulation decrease risk of intracardiac thrombus, which is associated with amyloid cardiomyopathy [56–58].

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Correspondence address:
Agnieszka Gaczkowska, MD
Poznan University of Medical Sciences
Department of Biochemistry and Molecular Biology
6 Swiecickiego St, 60-781 Poznan, Poland
phone: +48618546511
fax: +48618546510
email: gaczka@gmail.com