AL Amyloidosis (Amyloidosis Antibody Light).
Part 2 – Epidemiology, Clinical Symptoms, Diagnosis and Treatment of Amyloidosis AL

Abstract
Studies have shown that 10–20% of patients with multiple myeloma develop AL amyloidosis. AL amyloidosis can affect the kidney and the heart, as well as cause peripheral polyneuropathy and CNS impairment. The main diagnostic test to confirm amyloidosis is the staining of the adipose tissue from abdominal fat with Congo red, which demonstrates green birefringence when polarized light is used, or reveals nonbranching fibril structures with a diameter of 10 nm under an electron microscope. Oral melphalan and prednisone have been the leading drugs in the therapy of AL amyloidosis for 30 years. The patients qualified for megachemotherapy and stem cells transplantation had to be free from severe, burdening diseases and had to have less than three involved organs (Adv Clin Exp Med 2011, 20, 6, 771–788).

Key words: amyloidosis AL, epidemiology, clinical symptoms, diagnosis, treatment.

Epidemiology
The prevalence of amyloidosis is difficult to estimate, as the disease often remains undiagnosed or misdiagnosed. In AL amyloidosis, the estimations more often include mortality due to this complication, while estimations of the prevalence of the AA type are based on post mortem examinations [1]. In order to evaluate the incidence of AL amyloidosis, Kyle and colleagues analyzed the number of cases in one Minnesota county from 1952 to 1992. They found that the annual morbidity rate was 8.9 cases per million of the county residents [2, 3]. This was used as the basis for an estimation according to which there are 1275–3200 new AL amyloidosis cases diagnosed annually in the USA, which constitutes 5.1–12.8 cases per million residents. The studies have shown that systemic AL amyloidosis is a more common form among residents of the USA and western Europe. The incidence of this
disease is 0.8–1/100000 cases/year, with patients at the age of 50–70 [4].

In Europe, there are no centers that would keep a register of amyloidosis cases. Data reported from individual countries only provides information on the incidence of amyloidosis in a given region [5]. Studies have shown that 10–20% of patients with myeloma develop AL amyloidosis [6]. Vela-Ojeda et al. analyzed 201 newly diagnosed MM patients and found that 68 of them (34%) had amyloidosis AL and poorer disease prognosis [7]. Primary AL amyloidosis also affects 7% of patients suffering from non-hematologic malignancies [8].

Amyloidosis rarely occurs before the age of 40, patients aged 50–70 constitute 60% of cases, and it more often affects men (50–65%) [4].

Clinical Symptoms

The most common clinical symptoms associated with amyloidosis include: weight loss, ankle oedema, hoarseness, paraesthesia, tiredness, orthostatic hypotension, heart failure, enlargement of the liver and the tongue, and carpal tunnel syndrome [9]. The amyloidosis can also affect the kidney and the heart as well as cause peripheral polyneuropathy and CNS impairment [10]. According to Müller et al., kidney damage in the form of nephritic syndrome affects 28% of patients, heart failure and polyneuropathy 17%, carpal tunnel syndrome 21%, orthostatic hypotension 11%, and orbital purpura 15% of the subjects [11].

The Kidney

Studies have shown that in a group of 211 newly dialyzed patients, 2% developed systemic amyloidosis [12]. Kyle et al., analyzing 474 AL patients, revealed the presence of proteinuria in 73% of the subjects, out of which 28% met the criteria of nephritic syndrome and 50% developed renal failure [13]. Other authors reported Bence-Jones proteinuria in 60% of amyloidosis patients, while 10% of patients had amyloidosis without typical proteinuria. In these patients, proteinuria was replaced by fatigue and ankle oedema [14].

The Heart

17% of amyloidosis patients develop amyloid cardiomyopathy in the type of restrictive cardiomyopathy with the symptoms of right ventricular insufficiency. The low ejection fraction observed in 13% of patients may evolve into orthostatic hypotension [11]. Congestive heart failure is associated with shorter median survival and exertional syncope is a predictor of early death [15]. ECG (echocardiography) tracing shows low voltage QRS complex in standard leads, or traces corresponding to myocardial infarction, but without evidence of ischaemic disease. The deposits of amyloid in coronary vessels may also lead to arrhythmia, conduction blocks, angina pectoris, or myocardial infarction [16]. Unlike ECG, troponin I and N-terminal pro-brain natriuretic peptide (NT-proBNP) are objective parameters of cardiac involvement. According to these measurements, three stages of cardiac amyloidosis have been proposed. In patients with stage I of cardiac amyloidosis, troponin T, troponin I and NT-proBNP must be within normal values, while in stage II, one of them, and in stage III both of them, exceed normal values [17]. At the Mayo Clinic, the serum troponin T level was introduced as a criterion of the inclusion for stem cell transplantation (SCT) [18].

The Haematopoietic System

In AL amyloidosis, 18% of patients reveal above 20% plasmocytes in the bone marrow, and 60% – below 10% [19]. According to Merlini et al., the majority of patients with amyloidosis AL do not meet the criteria for myeloma [9]. A tendency to bleeding, ecchymoses, and periportal extravasations in the type of “raccoon eyes” results from amyloid deposition in the blood vessels, which increases their fragility. Moreover, the bleeding tendency is associated with the binding of the X factor by the amyloid, which leads to the formation of a faulty clot [20].

The spleen is involved in 10% of amyloidosis patients. Amyloid may be present in the white splenic pulp and less commonly in the red pulp [13]. Hyposplenism resulting from amyloid infiltration may cause thrombocythemia, and the presence of Howell-Jolly bodies has also been observed.

The Liver

Hepatomegaly is secondary to amyloid cardiomyopathy, or results from the accumulation of amyloid fibrils. Liver involvement is observed in 50% of amyloidosis patients. Laboratory studies reveal significantly elevated levels of alkaline phosphatase and slightly elevated levels of aminotransferases.

The Skin

Skin involvement affects 30–40% of patients and 10–15% of them develop spontaneous petechiae. Skin nodules in the form of flat, waxy, shiny,
scaling infiltrations are common. Mucous membranes present a similar picture. The sensation of dryness in the mouth (xerostomia) results from amyloid infiltration of the salivary glands. An evident balding tendency occurs.

**The Musculo-Skeletal System**

Amyloid accumulation in the muscles leads to pseudohypertrophy, such as enlargement of the tongue. Macroglossia affects up to 10% of amyloidosis patients. Arthropathy results from amyloid depositions in the joints.

**The Nervous System**

20% of patients with nervous system involvement develop polyneuropathy. Its peripheral form is associated with peripheral sensation disturbances, such as numbness, paraesthesia and piercing pains. The symptoms result from pressure exerted by the amyloid deposits on peripheral nerves, like in carpal tunnel syndrome in the course of AL amyloidosis. Orthostatic hypotension, impotence and digestive tract motor disturbances are associated with autonomic neuropathy.

**Diagnosis of Amyloidosis**

The main diagnostic test to confirm amyloidosis is the staining of adipose tissue from abdominal fat with Congo red, which demonstrates green birefringence when polarized light is used, or reveals nonbranching fibril structures with a diameter of 10 nm under an electron microscope. If the test is negative, it may be followed by a salivary gland, rectal mucosa, gingival, or bone marrow biopsy, or a biopsy from an organ which is assumed to contain accumulated amyloid fibrils [21]. The efficacy of amyloid identification in various loci varies: kidney, spleen and liver biopsies are positive in about 90% of cases, abdominal adipose tissue aspirates in 60–80%, rectal biopsy in 50–70%, bone marrow biopsy in 50–55%, and skin biopsy in 50–80% [22, 23]. The amyloid deposits may also be visualized by means of radioisotope methods with the use of Tc99m technetium, which is especially useful in the case of cardiac amyloidosis [24]. It is effective in very advanced cardiomyopathy, which, together with echocardiography, constitutes the basic diagnostic test.

Amyloid deposits may be diagnosed by means of another diagnostic method – scintigraphy, which is based on the coexistence of amyloid deposits with normal serum SAP protein, which may be tagged with technetium or iodine (I123). Scintigraphy using the radioisotope combined with SAP is able to determine the locations of amyloid deposits and amyloid fibril load in a very short time. This examination is especially useful in secondary amyloidosis and may be positive despite a negative tissue biopsy. Spleen scintigraphy may be positive in 100%, kidney in 80%, adrenals in 50% and liver in 25–50% of cases [25]. The method is of no use in cardiac amyloidosis due to the large amount of blood flowing through the organ, which may cause 100% false results [26]. In AL amyloidosis, a bone marrow aspiration biopsy is performed in order to demonstrate plasma cell infiltration. The clonal character of the plasma cells may be demonstrated by means of the immunohistochemical method with the use of anti-κ or anti-λ antibodies.

The use of electrophoresis and immunofixation of serum and urine proteins may help reveal the presence of light chains and monoclonal immunoglobulin in 90% of amyloidosis patients [6]. The serum level of free light chains (FLCs) is determined with the immunonephelometric method with the use of antibodies specific for κ and λ chains, which do not recognize light chains linked with heavy chains. The sFLCs test is more sensitive than protein electrophoresis and at least 500 times more sensitive that immunofixation [27]. With the immunofixation method, while the presence of light chains may be determined when their level is 100–500 mg/l, the immunonephelometric method revealed the presence of sFLCs at the level of 3–4 mg/l. According to Katzmann, a combination of 2 parameters, i.e. the kappa/lambda ratio and serum immunofixation, gives the highest sensitivity (99%) in diagnosed AL patients [28].

DNA examinations used in sequencing of the amino acids in the amyloid fibrils are indicated in patients who reveal the presence of monoclonal protein, and who at the same time present clinical symptoms of inborn amyloidosis [29]. In other forms of fibrilosis than AL amyloidosis, apart from a histological demonstration of amyloid deposits, other examinations are performed in order to identify the amyloid protein, immunohistochemical evaluation with the use of an electron microscope, or spectrophotometric examinations [30].

**Treatment of Amyloidosis**

All therapies for amyloidosis AL have focused on lowering clonal plasma cells and reduction of the synthesis of monoclonal FLC. There are: high dose chemotherapy with autologous hematopoietic stem cell transplantation, standard therapy with melphalan and prednisone Vel/dex, thalidomide, lenalidomide and bortezomib [31]. Therapy
for solubilizing the amyloid fibril is not known at the moment. The response criteria in patients with amyloidosis AL meet both the monoclonal protein, measured as a serum free light chains level, and an objective improvement in organ function [5]. The current study conducted by Kumar et al. supports the notion that FLC response is a more useful measure of hematological response than M-protein and achieving at least a 90% reduction in the FLC to improve the outcome of patients with light-chain AL [32]. According to Lachmann et al., there is a positive correlation between a hematologic as well as organ response to therapy and survival [33]. The hematologic response has been defined as a 50% reduction in the precursor monoclonal protein level (PR, partial response), and survival is better in patients who have at least 50% reduction of FLC compared with those who do not fulfill this criterion. The best outcomes were observed in patients with normalization of these parameters and negative immunofixation of the serum and urine (CR, complete hematologic response) [34]. An organ response has been defined as a 50% reduction in urinary albumin loss in patients with renal amyloidosis, a decrease in liver size (or a 50% lowering of alkaline phosphatase in serum) in persons with hepatic amyloidosis, and echocardiographic improvement (or a 30% abatement in the BNP level) in cardiac amyloidosis [35].

**Megachemotherapy and Stem Cells Transplantation**

In the Mayo Clinic, the patients who were qualified for megachemotherapy and stem cells transplantation had to be free from severe, burdening diseases and had to have less than three involved organs [35]. The conditioning therapy involved administration of high doses of melphalan. A multi-center study performed in the years 1998–2006 demonstrated that 25–67% of patients treated this way achieved remission of the disease, however the transplant-related mortality was high and ranged from 15 to 40% [36]. Bone marrow transplantation in patients with amyloidosis differs from the procedure performed in other plasma cell dyscrasias. Multi-organ dysfunction occurs more commonly in amyloidosis. This leads to post-transplantation complications, such as kidney failure requiring dialysis, as well as liver and heart failure. Studies have shown that the success of transplantation is affected by the high level of expertise of the transplantation center, with significantly better outcomes achieved in centers with over 5 years’ experience [37].

Stem cell transplantation is not a routine management in amyloidosis, despite the reported fact that remission of organ involvement was achieved in up to 50% of patients [38]. Studies performed by a multi-center French group involving 100 patients treated with melphalan and dexamethasone at standard doses, or megachemotherapy, revealed that the median survival for group I was 57 months, and in patients after transplantation – 49 months, and the therapeutic response was achieved in 64% and 65% of patients respectively [39]. However, according to the authors, the rejection of megachemotherapy as a therapeutic modality in amyloidosis seems premature.

**Treatment of Patients not Qualified for Transplantation**

Oral melphalan has been the leading drug in the therapy of AL amyloidosis for 30 years. The drug is administered in 4-day cycles every 28 days at a daily dose of 0.22 mg/kg, in combination with prednisone. In the study by Kyle et al. involving 219 patients, the median survival was demonstrated to reach 17 months, twice as much as in the case of colchicine-treated patients [40]. Promising outcomes were also achieved in 93 patients treated with dexamethasone with or without interferon: a complete hematological remission was achieved in 24% of patients, improved organ function in 45% of patients, and median survival was 31 months [41]. The above outcomes were confirmed in the study by Palladini et al. [42].

**Thalidomide, Lenalidomide and Bortezomib for Amyloidosis AL**

Like in myeloma therapy, amyloidosis is also treated with thalidomide, lenalidomide and bortezomib, in monotherapy or in combination with dexamethasone.

According to data provided by Palladini et al., thalidomide as a single agent is toxic and ineffective, but used with dexamethasone showed hematologic response in 48% patients with 19% CR and the organ response rate was 26% [43]. The results of the second phase of two trials that tested the efficacy of lenalidomide +/- dexamethasone therapy showed that 10 of 23 patients and 16 of 24 evaluable patients achieved the hematologic response.
Adverse events of grade 3 and 4, possibly related to lenalidomide, were neutropenia, thrombocytopenia and fatigue [44, 45]. In 2008, the National Amyloidosis Center in Great Britain presented data of a study conducted on 18 patients treated with bortezomib that had previously received thalidomide-based therapy [46]. Hematologic and organ response was observed in 77% and 27% of patients, respectively. Kastritis et al. reported on AL patients, who relapsed or progressed after previous therapy and persons with renal dysfunction, treated with bortezomib. This data as well as a study conducted by Lamm et al. in previously untreated patients has shown significant benefits in overall and progression-free survival [47, 48].

**New Therapeutic Options**

New drugs, the main aim of which is to inhibit amyloid fibril formation, are being investigated and tested clinically. They include:

1. Drugs diminishing the aggregation of fibrils and stimulating the resorption of amyloid. The effect is achieved by 4-iodo-4-deoxydoxorubicin (IDOX). Clinical trials have shown that a dose of 15 mg/m² is able to evoke a clinical response in 15% of patients [49].
2. R-1-[6-[R-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylicacid causes the elimination of SAP protein from the circulation and its secondary resorption from amyloid deposits [50].
3. Etaenercept – a TNF blocker, the use of which is associated with TNF-alpha activity in the development of amyloidosis [51].
4. Eprodisate (sulfated glycosaminoglycan), the use of which in the therapy for secondary amyloidosis is tested in ongoing phase II–III clinical trials [52].

**Supportive Care of Organ Involvement in the Course of Amyloidosis**

**Cardiac Amyloidosis**

The therapy for cardiac amyloidosis has two aims: it is directed against light chains, and it is aimed to protect the heart. Maintaining balance between the function of the amyloidosis-affected heart muscle and the volume of the vascular bed plays a key role, thus administration of diuretics, e.g. spironolactone and metholasonel, as well as a sodium regime are important measures [53]. Such management may be limited if there is coexisting orthostatic hypotension or nephritic syndrome. In case of recurrent fainting, the patients should be qualified for pacemaker implantation [54]. In patients with paroxysmal ventricular arrhythmias, defibrillator implantation is advisable. The use of angiotensin inhibitors is hampered due to large differences in blood pressure. Patients with low ejection fraction may use ICE, however with extreme caution, starting from low doses. Calcium-channel blockers are also advocated. Orthostatic hypotension is an important problem in patients with amyloid heart disease. In such cases, the use of compression stockings and midodrine may prove useful. In cases of extreme heart failure, trials were undertaken to transplant the heart, which gave a symptom-free survival rate of 32 months [55]. According to recommendations of the National Amyloidosis Center in Great Britain, and the Spanish Register for Heart Transplantation, heart transplantation should follow bone marrow transplantation and be reserved for patients with or without mild systemic AL [55, 56].

**Kidney Amyloidosis**

A crucial role in the therapy for kidney dysfunction in the course of amyloidosis is played by diuretics and a sodium regime. However this management proves insufficient in the case of nephritic syndrome and high loss of protein with urine. In these patients, in the terminal stage of kidney failure, ramipril remains the drug of choice [57]. The mean time lapse between the diagnosis of kidney amyloidosis to the onset of dialysis therapy is 14 months, and the mean survival rate of patients on renal replacement therapy is assessed at 9 months. Simultaneously coexisting cardiac amyloidosis significantly hampers the dialysis therapy. Researchers from the Mayo Clinic found out that institution of chemotherapy prior to renal transplantation ensures better tolerance of the transplant, however it requires the use of immunosuppressive drugs since the very onset. It was established that a positive therapeutic response to decreased doses of melphalan constitutes an indication to kidney transplantation in amyloidosis patients.

To summarize: In the past decade, significant progress in the diagnosis and treatment of patients with amyloidosis AL has been made. However, there still is an urgent need for education in order to promote the earlier diagnosis and proper therapy of this disease. The aim of the therapy of amyloidosis AL is to suppress the monoclonal plasma cell clone that produces the amyloidogenic FLC. The most important clinical endpoint of this treat-
ment is the improvement of organ response. For this reason, the definition of an organ response (PR, CR) was developed.

The introduction of thalidomide, lenalidomide and bortezomib, the new agents for the management of AL, have significantly expanded the possibilities of treatment of amyloidosis AL. Reduction of FLC level is associated with survival benefits, irrespective of the chemotherapy regimen used.

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