Amyloidosis

1. Incidence, Prevalence

Amyloidosis is a heterogeneous group of diseases; they are characterized by deposition of insoluble substance called amyloid, which is stored in tissues and organs. The main component of amyloid deposits is fibrillar protein with β-sheet configuration, this lead to its resistance to proteolysis. So far more than 30 different amyloidogenic proteins have been identified. The deposit of amyloid can occur in multiple organs, e.g. heart, kidneys, liver, eyes, skin, lung and the nervous system.

The amyloidosis associated with long-term inflammatory disease may be decreased with focused biologic therapeutics and improved treatment. If we look at the overall incidence of the various types of amyloidosis, this has declined over the last 10 years, this is probably linked with the increased knowledge of amyloidosis and better treatment and prevention for the underlying disease, e.g. use of target biological therapy. The first study to prove this drop was from Finland, showing that the overall number of patients requiring renal replacement therapy associated with amyloidosis has decreased over 50% in the last 10 years and the use of methotrexate has increased almost 4-fold. However 2013 a study showing that the incidence of renal amyloidosis is increasing.

Certain types of renal amyloidosis are decreasing, e.g. HIV-related renal amyloid, which only contains a small part of the HIV-related renal disease.

In the most common type of amyloidosis, AL amyloidosis, we can see approximately 3000 of new cases each year in the United States.

Other types of amyloidosis, e.g. ATTR amyloidosis (transthyretin amyloidosis), causing the disorder familial amyloidotic polyneuropathy (FAP) is more prevalent in Sweden, Portugal and Japan. In one study from 1993, show us that the age of onset of FAP is much later in Sweden than in other population. The geographical distribution of FAP in Sweden is more concentrated to the towns of Skellefteå and Piteå, the reason for this is unknown.

2. Etiology, pathogenesis

Amyloidosis can be differentiated into localized and systemic types and into hereditary and acquired types.

AL amyloidosis (Immunoglobulin light chain-associated)

Most common type of amyloid disease in developed countries (70% of all cases with amyloidosis). AL amyloidosis is included in a group of monoclonal gammopathies and can be

associated with Waldenström´s macroglobulinemia or multiple myeloma (10-20% of the cases).

This is a plasma cell dyscrasia, the clonal plasma cells which are situated in the bone marrow produce immunoglobulins that are amyloidogenic. The destabilization of the light chains could be because of the substitution of some particular amino acids in the light chain variable region. We can find a clonal dominance of amyloid light (AL) chains, this can be either from κ or λ isotype, these light chains can be excreted in urine as Bence Jones proteins. AL amyloidosis rarely occurs before the age of 40 years.

All the clinical symptoms are related to which type of organ that is involved. This can be from kidneys, which present with proteinuria and Nephrotic syndrome or from the heart, which present with heart failure. Another common feature is sensory and autonomic neuropathies. We can notice an absence of central nervous system involvement.

On examination of the patients we can find hepatomegaly and splenomegaly in rare cases, polyneuropathy, cardiomyopathy and bruising is possibly seen. In around 10-15% of the patients we can find macroglossia and periorbital purpura.

Hereditary amyloidosis

ATTR amyloidosis - (transthyretin-associated, ATTR). The diseases, which are included in this group, are autosomal dominant transmitted where the mutant protein transthyretin forms amyloid fibrils, this usually occurs in middle age patient. A tetrameric protein called transthyretin, which consists of 4 identical subunits, is a transport protein for retinol-binding protein and thyroxine, and the liver mainly synthesizes it. The amino acids substitution destabilizes the protein and cause different outcomes. There are over 100 different substitution described, one example is the substitution of methionine for valine at the position 30 in all racial groups, and alanine for threonine in Irish and English population.

Main forms of the ATTR amyloidosis are familial amyloid polyneuropathy (TTR-FAP) and familial amyloid cardiomyopathy (TTR-FAC). FAP is more common in Sweden, Portugal and Japan.

The clinical symptoms are autonomic and peripheral sensorimotor neuropathy, which are common, with symptoms of autonomic neuropathy, weight loss and diarrhea. The involvement of the heart causes disturbances of the cardiac conduction system. In some patients we can find family history of unidentified neurological disease.

Other hereditary disorders that are included to this group are caused by gene mutation

of various proteins – fibrinogen α, apolipoprotein A, apolipoprotein C, Lysozyme etc.

AA amyloidosis

This type of amyloidosis is due to the formation of amyloid from serum amyloid A (SAA), an acute phase protein. AA amyloidosis is usually related to chronic inflammatory disorders and chronic infection.

The clinical manifestations can be different, because it is dependent on the underlying disorder. Examples of chronic inflammatory disorders include inflammatory bowel disease (IBD), rheumatoid arthritis and untreated Mediterranean fever. In the developing countries it includes different infectious diseases such as osteomyelitis, bronchiectasis and tuberculosis. In AA amyloidosis it is often present with hepatosplenomegaly and chronic kidney disease. In this type no macroglossia is present and cardiomyopathy is rare. The outcome of the renal failure depends of the degree and level of the SAA.

Endocrine amyloidosis

Amyloid deposits can be found in some endocrine organs, e.g. in medullary carcinoma of thyroid gland and in the islets of Langerhans in patients affected with Diabetes mellitus type 2. The amyloid protein seems to have their origin either from unique proteins (e.g. islets amyloid polypeptide) or polypeptide hormones (medullary carcinoma).

Senile systemic amyloidosis

This type of disease is caused by wild-type transthyretin protein (not mutated) and occurs with aging, it is a systemic deposition of amyloid in elderly persons (usually patients between 70-80 years). The heart is involved and it results in restrictive cardiomyopathy and arrhythmias. This for is called *senile cardiac amyloidosis.* A common finding in patients with wild-type ATTR amyloidosis is also carpal tunnel syndrome.

Localized amyloidosis

Amyloid fibrils of various types that deposit in various tissues or organs (e.g. heart, brain and skin). This can be of nodular (tumor-forming) deposits; frequently there are infiltrates of plasma cells and lymphocytes in the periphery of these amyloid masses.

Dialysis-related amyloidosis

This type is related to chronic dialysis patients, they produce β2-microglobulin, which create amyloid fibrils in these patients. Clinically the patients usually present with carpal tunnel syndrome.

3. The main symptoms

In amyloidosis that accompanies chronic inflammatory disorder are typically affected tissues of kidney, spleen, lymph nodes, liver, adrenals and thyroid. The AL type of amyloidosis cannot be distinguished from the AA amyloidosis only by its organ distribution; it is affecting the heart, respiratory tract, gastrointestinal tract, skin, tongue and peripheral nerves. In the hereditary amyloidoses the localization of the amyloid deposit varies. Amyloidosis may or may not be visible grossly. The small amounts of amyloid deposit are not recognizable until the surface of the cut organ is painted with sulfuric acid or iodine. When larger amounts of amyloid accumulate the tissue appears gray, with a waxy, firm consistency and the organ is enlarged.

As amyloidosis can affect a wide range of different organs, the clinical presentation is widely variable. The nonspecific complains include fatigue, weakness and weight loss is the most common presentation. The involvement of kidneys is the most serious and the most common feature especially of the AA amyloid disease. The patient can feel discomfort due to the abnormally large and firm kidney. The glomeruli develop focal deposits, causing nodular or diffuse thickenings of the basement membrane causing nephrotic syndrome and severe proteinuria, leading to consequences for the patient (e.g. edema, hypercholesterolemia, hypercoagulability and infection).

The cardiac involvement of amyloidosis can manifest as fatigue, dizziness, dyspnea, chest pain and syncope. This is mainly from cardiac arrhythmias and this is an important cause of death in cardiac amyloidosis.

4. Examination

To diagnose a patient with amyloidosis, we base this on clinical suspicion and always on tissue histology from biopsies. The amyloid present in tissues appear as amorphous, homogenous substance, it stains pink with eosin and haematoxylin and stains red with Congo red with red-green birefringence under polarized light microscopy. Amyloid can also have a green fluorescence in polarized light. We can obtain the tissues from different noninvasive sites (e.g. rectum, fat pad and gums), for biopsy and are positive in 80%. A sample from the bone marrow may show a lymphoproliferative disorder or plasma cells in amyloidosis. Proteinuria with Bence Jones proteins and paraproteinaemia is seen in AL amyloidosis. In AA amyloidosis there will be an underlying disorder. We can use scintigraphy with 123I-labelled serum amyloid P (SAP) component, used for AL, AA and ATTR amyloidosis, this is not available everywhere and it is an expensive procedure.

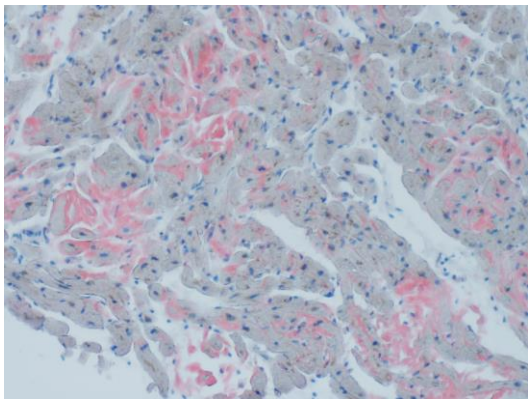

Fig. 1: Microscopic appearance of amyloid deposits (pink) in a heart. Special histological staining – Congo red, original magnification 100×.

5. Treatment

We try to treat the symptoms and treatment of the underlying associated disorders. Congestive heart failure and nephrotic syndrome is treated according to their relevant therapies. Treatment of infection and inflammatory diseases is important to avoid AA amyloidosis. For familial Mediterranean fever colchicine may help. To slow the decrease in renal function in AA amyloidosis, we can use Eprodisate, which interferes with the interactions between glucosamineoglycans and amyloid protein and inhibits the polymerization of amyloid fibroids.

In AL amyloidosis, optimize nutrition chemotherapy with oral melphalan plus dexamethasone/prednisolone extend the median survival from 13 months following diagnosis to 17 months. Autologous peripheral blood stem cell transplantation with high-dose IV melphalan may be better.

In ATTR amyloidosis the main problem is tranthyretin, which is predominantly synthesized in the liver, a liver transplantation is considered to be the definitive therapy.

6. Complications

Amyloidosis tends to manifest in several ways: by splenomegaly, hepatomegaly, renal disease or cardiac abnormalities.

The renal disease is mainly by nephrotic syndrome causing severe proteinuria, leading to complications like edema, recurrent infections etc. The renal involvement is usually caused by the AA amyloidosis. The long-term progression of renal disease may lead to renal failure; this is an important cause of death in patients with amyloidosis.

The cardiac amyloidosis is manifested by restrictive cardiomyopathy and conduction disturbances. An important cause of death in cardiac amyloidosis is the cardiac arrhythmias.

In one large series of patients, 40% of them with AL amyloid died of cardiac disease.

Prognosis of the patients with amyloidosis differs, but the median survival is 1-2 years. Those patients with myeloma and amyloidosis have shorter survival than those with only myeloma.

7. Practical advices for the patients

Considering the variability of amyloidosis, it is not possible to provide a single advice to all patients. Every type of the disease brings different difficulties and complaints for the patient, also the therapy and therapy-related problems differs very much. In general, it can be emphasized the benefit of healthy life style, this means quality food, adequate physical exercise and plenty of rest. Good adherence to specific treatment increases the chance of a more successful treatment. Patients should visit the doctor in cases of new difficulties and in every deterioration of their health condition. For better understanding, patients and their families should be informed about their disease as much as possible, they should not be afraid to ask the doctor about everything they care about.

8. List of literature

Abbas, Abul K., Jon C. Aster, Vinay Kumar, and Stanley L. Robbins. Robbins Basic Pathology. Philadelphia, PA: Elsevier/Saunders, 2013.

Longmore, Murray, Ian B. Wilkinson, Andrew Baldwin, and Elizabeth Wallin. Oxford Handbook of Clinical Medicine. Oxford: Oxford University Press, 2014.

Kumar, Parveen, and Michael L. Clark. Kumar & Clarks Clinical Medicine. Edinburgh: Saunders Elsevier, 2015.

9. List of articles

Kai Immonen, Patrik Finne, Markku Hakala, Hannu Kautiainen, Tom Pettersson, Carola Grönhagen. ”No Improvement in Survival of Patients with Amyloidosis Associated with Inflammatory Rheumatic Diseases — Data from the Finnish National Registry for Kidney Diseases.” The Journal of Rheumatology July 2008, 35 (7) 1334-1338.

Sousa, Alda, Rune Andersson, Ulf Drugge, Gösta Holmgren, and Ola Sandgren. "Familial Amyloidotic Polyneuropathy in Sweden: Geographical Distribution, Age of Onset, and Prevalence." Human Heredity 43, no. 5 (1993): 288-94.

10. List of photographs, pictures

Fig. 1 Microscopic appearance of amyloid deposits (pink) in a heart.