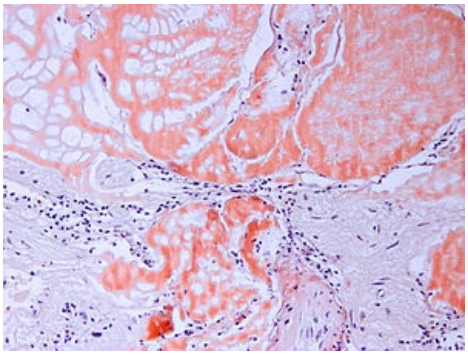
Amyloidosis/PGS

Amyloidosis (amyloid dystrophy) is a designation for the main symptom of a group of diseases caused by amyloid deposition in many organs. Amyloid is an insoluble degradation product of some proteins, its name is derived from the fact that it behaves similarly to starch when stained with Lugol's solution. Amyloid deposits can impair organ function to such an extent that renal failure, malabsorption syndrome or dementia are clinically manifested. The immediate cause of deposition may be pathological conditions, usually chronic inflammatory disease, but there are also inherited forms of the disease in which some mutant proteins show a higher susceptibility to amyloid deposition. The molecular basis of the properties of amyloid is the precipitation of fragments rich in the secondary structure of β sheet and their folding into characteristic unbranched fibrils.

History

The oldest described case of probable secondary amyloidosis is from 1639, when Nicolaus Fontanus described a "large spleen filled with stones" during the autopsy of a young man with ascites, jaundice and epistaxis. It was probably a sago spleen. In the book Historiarum Anatomicarum Rariorum (1654), Thomas Bartholin described the autopsy findings of a woman whose spleen was so stiff that it was difficult to cut with a knife. Here, too, it could have been a saga spleen. Primary amyloidosis was first described probably by Samuel Wilks in 1856 as an autopsy finding in a 52-year-old man with "speckled" organ changes. Wilks was convinced of the proteinaceous origin of amyloid. In 1967, Hermann Weber described the first case of myeloma-associated amyloidosis.



Amyloidoma

The term amyloid was first used in 1838 by the German botanist Matthias Schleiden to describe the normal component of plant tissue. German pathologist Rudolf Virchow used the term amyloid in 1854 to find that corpora amylacea stained with iodine similar to starch. Virchow assumed that these were indeed starch or glycogen deposits. He strongly disagreed with the findings of Carl Friedrich and August Kekul, who in 1859 found a high nitrogen content in spleen amyloid, and thus that it was more of a proteinaceous nature.

Independently, in 1875, Anderé-Victor Cornil (Paris), Richard Heschl (Vienna) and Rudolf Jürgens (Berlin) described the use of aniline dyes to stain amyloid. In 1878, Paul Ehrlich used the term metachromasia introduced by William Ackroyd to describe the behavior of amyloid in aniline dying, especially methyl violet. It was methyl violet that replaced iodine reactions on microscopic detection of amyloid. In 1922, Hermann Bennhold described the coloring of Congo red amyloid. It is not without interest that the very term Congo red (Congo red) has nothing to do with Congo, at the time of the synthesis of the new aniline dye, diplomatic conferences of colonial powers were held in Berlin concerning the Congo region in particular, and Congo became so fashionable the color originally used for dyeing textiles is also marked. Bennhold administered Congo red to patients intravenously as a diagnostic test because healthy tissues stained natively, but the staining washed away relatively quickly, so a biopsy performed at an appropriate distance made it possible to detect amyloid as a stained substance in a frozen section preparation. He later found that if the tissue was exposed to a solution of lithium carbonate in 80% alcohol after staining Congo red, only amyloid stained, and the color was washed from the healthy tissue. Finally, the characteristic birefringence was described by the Belgians Divry and Florkin in 1927.

In 1959, Cohen and Calkins described amyloid in an electron microscope as a fibrous non-branching structure. The same pattern has been reported for amyloid from different sites in both primary and secondary amyloidosis. Pras et al. described in 1968 a method of extracting amyloid from tissues. In 1968, Eanes and Glenner studied the X-ray diffraction pattern of amyloid, which led to a high proportion of amyloid β structures. In 1971, Glenner et al., Reported that primary amyloidosis amyloid contained amino acid sequences corresponding to immunoglobulin light chains. In the same year, Benditt et al. secondary amyloidosis amyloid sequence. Costa et al. in 1978 and Skinner and Cohen in 1981 described prealbumin (transthyretin) as another possible protein base for amyloid in familial amyloid polyneuropathy. Gradually, other proteins capable of participating in amyloid formation were discovered.

Morphology

Macroscopically, amyloid is usually yellowish-gray-white, semi-translucent, and the consistency is usually brittle to brittle, but it can also be relatively flexible. Amyloid-infiltrated organs tend to be stiffer, sometimes more flexible, and are then dullly shiny on the incision in a way that reminded old pathologists of bacon. In conventional hematoxylin and eosin staining, amyloid is amorphous and turns pinkish-red. When viewed with an electron microscope, amyloid has a fibrillar structure, consisting of unbranched fibrils usually 8–10 nm in diameter (according to some sources 6–12 nm), which form a relatively dense felt-like structure.

Detection of amyloid

- **macroreaction** - detection of amyloid in a macroscopic tissue sample
  - ***Virchow I*** – Lugol's solution stains the tissue mahogany brown
  - ***Virchow II*** – after transfer from Lugol's solution to sulfuric acid, it turns blue-green

- **microscopic detection**
- **Reaction with Congo Red** (Benhold's) - orange-red color. It is interesting that the color itself does not matter, because it depends, among other things, on the thickness of the preparation, the presence of birefringence and dichroism is significant.
- **Reaction with crystal violet** (Cornilov-Weigert r.) - red-violet metachromatic staining
- **Reaction with thioflavin S or T** - yellow-green fluorescence, sensitive but less specific method.
- **immunochemical detection** of building protein - The use of paraffin blocks is less suitable because fixation reduces sensitivity, so it is more appropriate to use frozen preparations (cryostatic sections). The method is suitable for the diagnosis of amyloidosis based on SAA and β2 microglobulin, in the case of amyloid based on λ chains of immunoglobulins it is less sensitive.

Disability of individual organs

In the adrenal gland, amyloid is deposited between the sinusoidal capillaries and the beams of the spongiocytes, mostly in the zona fasciculata, leading to cell atrophy. In the spleen, amyloid can be bound mainly to the follicles, then it forms an image of the sago spleen, it can also be bound to the red pulp, an image of the ham spleen. In the kidneys, amyloid is first deposited in the glomerular loops, and as the disease continues, it is also deposited in the interstitium. Clinically, kidney disease leads to renal failure. In the liver, amyloid is deposited in Disse's spaces. In the gut, amyloid is deposited in the basement membrane of the intestinal epithelium. Bowel dysfunction can lead to malabsorption syndrome.

Pathogenesis

Amyloid is formed by fibrils formed mainly by the starting protein. Dozens of proteins that may give rise to amyloid have been described. The formation of fibrils from a protein is a spontaneous process controlled by the physicochemical properties of the precursor protein. The formation of fibrils is similar to crystallization, fibrils are best formed on the basis of existing nuclei, ie clusters of pathological precursor proteins. The dynamics of the amyloid formation process are influenced by the concentration of nuclei, on which amyloid fibrils can form more rapidly. In terms of process dynamics, three phases of amyloid formation can be distinguished:

1. **nucleation** (lag phase) - slow oligomerization of proteins, resp. protein fragments, with a pathological conformation
2. **elongation** - a sufficient concentration of condensation nuclei leads to the fact that proteins with a normal conformation can sometimes be incorporated into the emerging amyloid fibrils, fibrils grow rapidly
3. **steady-state** - there is no further growth of fibrils in the steady-state.

Although at least 27 different precursor proteins have been described in human pathology, the appearance and formation of fibrils are relatively uniform. Fibrils form protofilaments with a diameter of 25 nm from protein residues rich in β-sheet structure. Protofibrils have a diameter of 25 nm and can twist around or adhere to each other laterally. In principle, five possible mechanisms can be identified that can lead to amyloid formation:

1. **Propagation of conformational changes** - A pathologically conformed protein induces a conformational change even in a normally conformed protein. This mechanism is mainly used in prion diseases.
2. **Failure of the proteolytic process** - The proteolytic process of a malformed protein may proceed abnormally, leaving a poorly degradable protein residue. This mechanism is used, for example, in the pathogenesis of Alzheimer's disease.
3. **Precursor protein gene mutation** - In some cases, the pathological conformation is due to a germline mutation in the gene. This is a case of hereditary amyloidoses.
4. **Overproduction** - Excessive production of physiological protein may in itself increase the risk of condensation nuclei of amyloid fibrils. It is involved in the pathogenesis of localized amyloidoses in particular.
5. **Assembled protein quality control disorder**

Amyloid fibrils

The process of amyloid fibril formation is still poorly studied because the detailed analysis of the structure of amyloid is very difficult. It has been shown that a number of proteins, under specific in vitro conditions, can assume a non-physiological misfolding that leads to aggregation; however, only a few proteins assume such a conformation even under in vivo conditions.

Proteins that can give rise to amyloid are a heterogeneous group of proteins with various functions and structures. A common feature of these proteins is the high proportion of β-leaf, α-helix and β-helix secondary structures, although only β structures are detectable in amyloid. During the formation of amyloid, the original protein fragments, physiologically, complete degradation is common at this stage.

Analysis of the X-ray diffraction pattern of amyloid led to the finding in the late 1960s that amyloid is rich in β structures, a similar pattern was obtained from amyloid formed from various precursor proteins. From a biochemical point of view, amyloid is a non-covalently bound polymer whose monomeric units are β-sheet rich peptides. The result of protein misfolding is a high proportion of β-sheet in their secondary structure. Under certain circumstances, β-sheets can interact with a relatively strong bond, not only within a single molecule but also between molecules. The bond between the individual molecules gives rise to the so-called cross-β structure. It is important for other properties of amyloid that the resulting structures are relatively hydrophobic. This is probably responsible for the high stability of amyloid in vivo, most likely including the fact that amyloid practically does not stimulate the inflammatory response. The interaction between several β-sheets leads to the formation of protofibrils, along the long axis of which the β-sheets of the individual peptides are oriented longitudinally. The

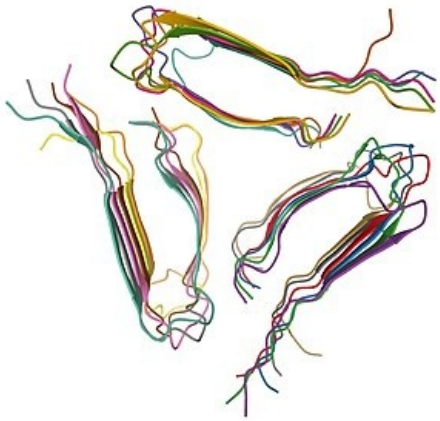
protofibrils are again side-by-side, but as a result, they are folded so that they are rotated at the same time. In the amyloid fibril, the protofibrils are then placed perpendicular to the long axis of the fibril but are not in a row. Interestingly, amyloid fibrils are not uniform. This is probably due to the fact that several conformations and several protofibril assemblies are energetically possible.

It is not without interest that the molecular and microscopic structure of amyloid gives amyloid a material with high strength, high modulus of elasticity and resistance to chemical degradation. Therefore, attempts are being made to synthesize material with an amyloid-derived structure for use in, for example, molecular electronics or tissue engineering.

Coprecipitated components

Amyloid deposits are not only amyloid fibrils, they also contain a number of other more or less tightly bound substances, so-called coprecipitated components:

- Serum amyloid protein (SAP) - is a bulky complex that is a common part of the extracellular matrix. SAP appears to be involved in amyloid resistance to proteolysis. SAP binds to growing and definitive amyloid fibrils, so radiolabeled SAP can be used for diagnosis.
- Glycosaminoglycans in all types have been shown especially heparan sulfate
- Apoproteins - apparently play an important role in pathogenesis, because, for example, Apo E4 is a significant risk factor for the development of Alzheimer's disease.



Protofilament of Beta Amyloid

Cellular and tissue toxicity

From the point of view of tissue biology, amyloid is not just a passive substance. Although it does not cause a cleaning reaction, it is toxic to adjacent cells. It was originally thought that amyloid was primarily the physical barrier that significantly affected the exchange of substances necessary for cell metabolism. This effect could be potentiated by the macrophages present. More recently, however, it has been shown that the soluble amyloid precursor components are at least as toxic, i.e. that the toxic effects of amyloid are much more complex. For example, soluble amyloid fragments of light chain origin added in the experiment induce cardiomyocyte apoptosis in tissue culture.

Classification of amyloidosis

The classification of amyloidosis may seem confusing because it has evolved from a descriptive clinical and pathological point of view to a molecular basis, both of which have their advantages.

Classification according to clinical and pathological picture

It is a classic classification, which is based primarily on the clinical picture. Each group shares common characteristics but is not homogeneous.

1. secondary amyloidosis
2. primary amyloidosis
3. localized amyloidosis

Secondary amyloidosis

Secondary amyloidosis occurs on the basis of a well-defined primary disease, which usually has the character of chronic inflammation. It usually occurs in chronic osteomyelitis, chronic abscess, rheumatoid arthritis, cancer or tuberculosis or syphilis. Amyloid deposition is not affected by the location of the primary disease, the following organs are most often affected (sorted by frequency of involvement):

- adrenal gland
- spleen
- lymphatic nodes
- kidney
- liver
- intestine

Primary amyloidosis

The defining feature of primary amyloidosis is the lack of an underlying disease that would explain amyloid formation. The location of the disability also differs, the myocardium and tongue are most often affected, the lungs and skin are less common, and other organs may also be affected. The amyloid may not stain completely, then the finding is referred to as achromatic amyloidosis, atypical amyloidosis or paraamyloidosis. Clinically primary amyloidosis usually progresses rapidly. There are also hereditary forms.

Plasmocytoma amyloid differs from the spectrum of affected organs, which is more similar to primary amyloidosis. It was classically classified as secondary amyloidosis precisely because it is (pathologically) clearly evoking the disease.

Localized amyloidosis

- **Tumor amyloid** is not cancer, although it may be associated with plasmacytoma. This is a significant local accumulation of amyloid, which presents itself as a tumor resembling a nodule. It most often occurs in the conjunctiva, skin, tongue and bladder, less common in the airways, for example.
- **Amyloid** in the tumor stroma occurs most often in tumors that produce certain hormones, such as nesidioma.
- The above groups can be considered "classical" (Bednář, 1981). Amyloidosis-like changes, even at the molecular level, occur in a number of neurodegenerative diseases, for example (Alzheimer's disease, Parkinson's disease, Lewy body dementia or prion diseases).

Molecular classification

Molecular classification is based on the determination of an amyloid-forming protein. It is usually an acquired disease, but there are also hereditary forms. The following table summarizes the most common types:

disease	precursor protein	specification
AL amyloidosis	immunoglobulin light chain	acquired mutation and overproduction
AH amyloidosis	immunoglobulin heavy chain	overproduction in myeloma
Senile systemic amyloidosis	transthyretin	accumulation of a common type of transthyretin
Familial amyloid polyneuropathy	transthyretin	congenital disorder
AA amyloidosis (secondary and.)	SAA protein	SAA overproduction in inflammatory disease
Aβ2M amyloidosis (a. Dialyzed)	β2-microglobulin	chronic hemodialysis
Lysozyme amyloidosis (ALyz)	lysozyme	congenital disorder
Apo AI amyloidosis (AApoI)	apolipoprotein AI	congenital disorder
Apo AII amyloidosis (AApoII)	apolipoprotein AII	congenital disorder
Apo AIV amyloidosis (AApoIV)	apolipoprotein AIV	congenital disorder
Fibrinogen amyloidosis (AFib)	α chain of fibrinogen	congenital disorder
Finnish hereditary amyloidosis (AGel)	gelsoline	congenital disorder
Icelandic type amyloid angiopathy (ACys)	Cystatin C	congenital disorder
Familial British Dementia (BriPP and.)	BRI2 gene product	congenital disorder, stop codon
Acquired renal amyloidosis (ALECT2)	leukocyte chemotactic factor 2	acquired disorder
Aortic media amyloidosis (AMed)	lacadherine	
Atrial amyloidosis (AANF)	atrial natriuretic factor	sometimes in patients with fibrillation
Amyloidosis associated with medullary carcinoma of thyroid gland	calcitonin	limited to the tumor
spongiform encephalopathy (AScr)	prion	acquired change, limited to the brain
Langerhans islet amyloidosis	Langerhans islet amyloid polypeptide	localization on the islets of Langerhans, sometimes in type 2 DM or in the nesidioma
Lactoferrin-based amyloidosis (ALac)	lactoferrin	familial corneal involvement
Alzheimer's disease	amyloid β precursor protein	acquired disorder
Hereditary cerebral angiopathy (Aβ)	amyloid β precursor protein	congenital disorder

Individual forms

AL amyloidosis

Amyloid is made up of fragments of light chain immunoglobulins. It practically corresponds to primary amyloidosis in the pathological classification, therefore the names AL amyloidosis and primary amyloidosis are usually used as synonyms.

It is the most common form of systemic amyloidosis, the incidence in Western countries is about 1 / 100,000 cases per year. It usually occurs in patients over 45 years of age, with a maximum incidence around age 67. According to published results, the median survival is between 10 and 42 months.

The actual cause is the monoclonal proliferation of plasma cells with the overproduction of light chains. Current therapy is primarily aimed at suppressing monoclonal proliferation, but this therapy is not curative in the sense that suppression of light chain overproduction usually does not lead to regression of the disease. Amyloid deposits can occur virtually anywhere in the body, but most commonly occur in the following locations:

- kidney
- gastrointestinal tract
- peripheral nerves
- liver

A special - but not completely unusual - form of amyloid deposition is **amyloidoma**, a tumorous accumulation of amyloid anywhere in the body, including the brain. If the heart is affected, the prognosis of patients is significantly worse.

The clonal expansion of plasma cells described above is usually not accompanied by clinically manifest multiple myeloma, usually less than 10% of myeloma cells in the bone marrow. The reason for the overproduction of light chains is that light and heavy chains are also produced independently in non-tumor cells but a balanced ratio. In tumor cells, this ratio can be disrupted, usually in favor of light chains, which can be synthesized three to four times as much as heavy chains. This results in free light chains in an amount sufficient to form and grow amyloid deposits. The mere presence of light chains in serum and possibly also in urine is demonstrable in a relatively large number of people over the age of 50, so it is not sufficient for the development of clinically manifest amyloidosis. The actual amyloidogenesis is conditioned by the interaction of biophysical properties of a particular precursor protein and the microenvironment in the target tissue. Due to their sequence, light chains are a relatively heterogeneous group of proteins; some variable domains have been shown to produce amyloid significantly more frequently.

When primary amyloidosis develops, the blood vessels are affected first. In practically all patients with primary amyloidosis, an endothelial microcirculatory disorder can be demonstrated, which leads, for example, to demonstrable ischemic changes in the myocardium. The mechanisms by which microcirculation is disrupted are unknown; however, it is clear that this is not only a passive barrier to the diffusion of important substances, but that amyloid also affects the reactivity of blood vessels.

Suspected primary amyloidosis should be triggered by the finding of otherwise unexplained nephropathy, heart failure, peripheral or autonomic neuropathy, hepatomegaly, splenomegaly, or involvement of multiple organ systems. About 50% of cases are manifested by kidney disease with proteinuria and nephrotic syndrome. Patients may develop acquired factor X deficiency, which can complicate biopsy, among other things. Congestive heart failure due to heart disease occurs in about 15-30% of patients. Postural hypotension can be a direct result of heart failure, but can also be caused by amyloid neuropathy or changes caused by nephrotic syndrome. Liver involvement is almost the rule, but the clinical manifestation is usually less pronounced and does not dominate the clinical picture.

The prognosis of untreated primary amyloidosis is very poor; median survival is between 6 and 15 months, 10-year survival is less than 5%. The current therapy is aimed at stopping the production of free light chains. Organ suppression does not continue to suppress clonal expansion by chemotherapy, and several cases of remission of amyloid deposits have been reported. Significant improvement in survival is associated with early intervention. Chemotherapy is chosen according to experience with multiple myeloma therapy. Experience with autologous stem cell transplantation is contradictory because the procedure itself is burdened by high mortality.

An integral part of therapy is the symptomatic treatment of complications. Therapy for heart failure and the nephrotic diuretic syndrome is vital. The involvement of the autonomic nervous system is difficult to deal with, sometimes it can respond well to fludrocortisone and midodrine. Patients are more susceptible to infectious diseases, so vaccination against seasonal flu is appropriate and indications for antibiotics should be much looser. Failing organ transplantation remains a controversial issue.

Secondary amyloidosis

Secondary amyloidosis, usually referred to as AA amyloidosis, is a relatively rare complication of virtually any chronic inflammatory disease, chronic infection, or cancer. The causative factor is the long-term elevation of acute-phase proteins, specifically SAA protein.

In the past, tuberculosis was the most common cause of chronic inflammation, today secondary amyloidosis most often occurs as a complication of rheumatic diseases, especially rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and juvenile idiopathic arthritis. Secondary amyloidosis accompanying rheumatic diseases accounts for about 50-70% of all cases. On the other hand, the frequency of involvement in rheumatological patients is lower, eg according to the autopsy findings in patients treated with rheumatoid arthritis, less than 6% of patients developed secondary amyloidosis. However, secondary amyloidosis is a serious complication, with an estimated 3% of patients with rheumatoid arthritis dying from complications of secondary amyloidosis. Compared with studies performed in the past, there is a declining trend in the incidence of secondary amyloidosis in rheumatology patients. In developing countries, the spectrum of causes is different, chronic infections are more pronounced.

List of conditions associated with secondary amyloidosis:

- **Rheumatic diseases**
  - Rheumatoid arthritis
  - Ankylosing spondylitis
  - Juvenile idiopathic arthritis
  - Still's disease, adult form
  - Psoriatic arthritis
  - Reactive arthritis
  - Behçet's disease
  - Large cell arteritis
  - Polyarteritis nodosa
  - Takayasu's arteritis
  - Bottoms
  - Oxalate arthritis
  - Systemic lupus erythematosus (rare)
  - Systemic sclerosis (rare)
  - Sjögren's syndrome
- **Tumors**
  - Carcinoid
  - Castleman's disease
  - Hairy cell leukemia
  - Hepatocellular adenoma
  - Kidney cancer
  - Mesothelioma
  - Lymphoma (Hodgkin's and non-Hodgkin's)
  - Ovarian cancer
  - Gastrointestinal stromal tumor
  - Liver sarcoma
  - Waldenström's macroglobulinemia
- **Hereditary periodic fevers**
  - Familial Mediterranean fever
  - TNF receptor-associated periodic syndrome
  - Muckle-Wells syndrome
  - Hyperimmunoglobulinemia D
  - FCAS (Familial Cold Autoinflammatory Syndrome)
- **Inflammatory bowel disease**
  - Crohn's disease
  - Ulcerative colitis
- **Chronic infections**
  - Bronchiectasis
  - Chronic skin ulcerations and pressure ulcers
  - Chronic pyelonephritis
  - Leprosy
  - Osteomyelitis
  - Tuberculosis
  - Whipple's disease
  - Subacute bacterial endocarditis
- **Other conditions**
  - AIDS
  - CVID (Common Variable ImmunoDeficiency)
  - Cyclic neutropenia
  - Sex-linked agammaglobulinemia
  - Hypogammaglobulinemia
  - Epidermolysis bullosa
  - Sarcoidosis
  - Cystic fibrosis
  - Atrial myxoma
  - Rosai-Dorfman disease
  - Sickle cell disease
  - Schnitzler's syndrome
  - Idiopathic retroperitoneal fibrosis

At the time of diagnosis, secondary amyloidosis usually (up to 95% of cases) manifests as proteinuria or renal failure with varying rates of progression, reaching approximately Stage Renal Disease (ESRD) in approximately 10% of patients. Liver and spleen involvement can be demonstrated, for example, by radiolabeled SAP, but it rarely manifests clinically. Clinical involvement of the spleen can be clinically manifested by more frequent infections; Amyloid can infiltrate the submucosa of the gastrointestinal tract, and any involvement is clinically manifested by malabsorption syndrome, pseudoobstruction, vomiting or diarrhea. Gastrointestinal vascular infiltration increases the risk of gastrointestinal bleeding and wall perforation. Any infiltration of the thyroid gland manifests itself clinically as goiter. Only rarely is the myocardium affected and cardiomyopathy develops; it is prognostically a bad condition. Amyloid neuropathy from peripheral nerve infiltration is also a rare complication.

The prognosis of patients with secondary amyloidosis is improving. E.g. in 1991, the median survival of patients was 24 months, with studies published at the end of the first decade of the 21st century already pushing the median survival to around 10 years. Prognostic unfavorable factors are older patient age, lower serum albumin levels and ESRD at the time of diagnosis.

The level of SAA as an indicator of ongoing inflammation is a very good prognostic factor with a direct link to the biology of the disease. When SAA levels are reduced by treatment of the underlying disease below 5 mg / l, regression of all organs except the kidneys is relatively common. Renal impairment is usually irreversible and therefore preservation of function and non-deterioration can be expected at most.

Amyloidosis of chronically dialysis patients

Chronically dialysis amyloidosis (β2M amyloidosis) is a serious complication of chronic hemodialysis. Fibrils are formed from β2 microglobulin, part of HLA. β2 microglobulin may accumulate because its degradation occurs in a relatively unusual manner. The protein normally crosses the glomerular membrane into the primary urine and is resorbed and degraded in the proximal renal tubules. If ESRD (End Stage Renal Disease) develops, the protein accumulates and the level from physiological values of 1-2 mg / l may rise to 50-70 mg / l.

The development of the disease is gradual, usually occurring 10 years after the start of dialysis. β2M amyloid is deposited mainly in the musculoskeletal system, usually manifesting as carpal tunnel syndrome, arthralgia, spondylarthropathy, subchondral bone cysts and pathological fractures.

Senile systemic amyloidosis

Senile systemic amyloidosis (ATTRWT amyloidosis) is a disease of the elderly, more common in men. The precursor protein of amyloid fibrils is normal transthyretin. This is probably a relatively common condition, amyloid is evident in roughly 25% of autopsies over the age of 80.

Deposits usually occur in the heart, usually asymptomatic deposits. When senile amyloidosis reaches the clinical stage, it manifests as restrictive cardiomyopathy and congestive heart failure. Clinically silent deposits can be detected in a number of other organs, especially in the lungs, intestine, bladder and small artery wall.

Familial amyloid polyneuropathy

Familial amyloid neuropathy (hereditary transthyretin amyloidosis, ATTR amyloidosis, FAP) is the most common hereditary amyloidosis. The basic clinical manifestation is progressive peripheral and autonomic neuropathy. Approximately 100 point mutations in the transthyretin (prealbumin) gene, which are responsible for the development of FAP, have been described. The clinical manifestation usually occurs in the third decade, but the age of onset and the extent of other manifestations depend on the specific mutation. Overall, progressive disease is fatal, with a life expectancy no longer than 10 years from the onset of symptoms. The earlier onset of symptoms is usually associated with a worse prognosis. In addition to nervous tissue, the heart is often affected.

- **The Portuguese form** (ATTRV30M, amyloidosis of the Portuguese type) is the most common, it is caused by the replacement of valine at position 30 with methionine (V30M). The disease most often manifests itself between the ages of 30 and 40, and differs from other forms in that the heart disease is exceptional. Most patients are in Portugal, but the same mutation has been demonstrated in Sweden.
- **The T60A** is the most common in Ireland and the United Kingdom. It usually manifests around the age of 50 with disorders of the autonomic nervous system. Myocardial involvement at the time of diagnosis does not dominate the clinical picture but is demonstrable in almost all cases.
- **The V122I** variant occurs in about 3-4% of blacks and manifests clinically over the age of 60 as having a myocardial infarction. Neuropathy is usually not part of the clinical picture.

Orthotopic liver transplantation plays a key role in therapy, as most mutant transthyretin is produced in the liver. The timing of the transplant itself is still a matter of debate.

The research focuses on other therapeutic strategies, especially the stabilization of soluble transthyretin in the blood and the attenuation of transthyretin expression.

Hereditary gelsolin amyloidosis

Hereditary gelsolin amyloidosis (Finnish-type amyloidosis) is caused by a mutation in the gelsolin gene. Most of the cases described are from Finland. Two mutations have been described: G645A and G645T. It is usually presented as lattice corneal dystrophy in middle age, gradually developing a slowly progressing but severely damaging cranial nerve neuropathy. The disease practically does not shorten life expectancy. Amyloid deposits in the kidneys are usually detectable at the time of diagnosis, but usually do not lead to clinical manifestations. Rarely, sick homozygotes also occur, in which, on the contrary, renal function deteriorates very rapidly.

Diagnosis of systemic amyloidosis

The diagnosis is complicated by a clinically highly heterogeneous picture of the disease, so the diagnosis is usually made relatively late, and it is not uncommon for amyloidosis to be an unexpected finding on histopathological examination.

Histopathological diagnostics

Congo red staining and birefringence detection are the gold standards for histopathological diagnostics, and immunohistochemical examination plays a role in determining the type of fibrils. However, the immunochemical examination is relatively insensitive and specific, because amyloid fibrils can relatively often lose antigenic

specificity and, conversely, relatively non-specific staining can occur, especially in the case of primary amyloidosis. Mass spectroscopy of samples obtained by laser microdissection could probably be an effective method for typing amyloids.

Bone marrow examination may be appropriate to rule out multiple myeloma as a cause of AL amyloidosis.

Imaging techniques

A specific technique for detecting amyloid deposits in a patient's body is a scintigraphic examination using a radiolabeled SAP protein, usually 123I-SAP. SAP binds reversibly to all known types of amyloid, equilibrium is reached very quickly. The method is not suitable for the examination of small or mobile structures, so it is not suitable for the assessment of heart and nerve damage.

Echocardiography is appropriate to assess the severity of heart disease. Cardiac amyloidosis is characterized by thickening of the ventricular wall, valve thickening and diastolic restriction. Cardiac involvement is likely if the mean left ventricular wall thickness is greater than 12 mm in the absence of factors that could cause hypertrophy, i.e., in the absence of hypertension in particular.

Magnetic resonance imaging of the heart can reveal a relatively characteristic late gadolinium amplification subendocardially or diffusely.

X-ray examination of the skeleton is a suitable supplement to rule out multiple myeloma.

Laboratory examination

Biochemical indicators serve primarily as a marker of the severity of the involvement of individual organs.

In the case of primary amyloidoses, monoclonal production of the pathological protein can be demonstrated in serum and usually in urine. Quantitative highly sensitive light chain level analysis is one of the most sensitive indicators of response to chemotherapy in AL amyloidosis.

Genetic testing

It is estimated that 5–10% of all systemic amyloidoses occur on an inherited basis, so it is appropriate to supplement genetic testing.

Histological specimens

Soubor:Cerebral amyloid angiopathy - very high mag.jpg

Soubor:amyloidosis kidney amyloidoza ledviny HE 20x.jpg

Soubor:amyloidosis kidney amyloidoza ledviny HE 20x.jpg

Soubor:amyloidosis kidney amyloidoza ledviny HE 4x.jpg

Soubor:amyloidosis liver amyloidoza jater HE 20x.jpg

Soubor:amyloidosis liver amyloidoza jater HE 4x.jpg

Soubor:amyloidosis liver amyloidoza jater kongo 20x.jpg

Soubor:amyloidosis liver amyloidoza jater kongo 4x.jpg

Links

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Extern links

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