Amyloidosis - Pathogenesis | Systemic amyloidosis

Amyloidosis is a disorder which is characterized by the extracellular deposition of insoluble fibrils called amyloids. It usually occurs in the systemic form, and the average age of diagnosed patients is 55-60 years. It is divided into:

- Primary
- Hereditary (familial)
- Secondary

The most common causes of secondary amyloidosis include: multiple myeloma (10-15%), rheumatoid arthritis (20-25%), tuberculosis (50%) or familial Mediterranean fever (26-40%).

Amyloidosis occurs more often in men than in women and more often in elderly patients. Amyloidosis has a poor prognosis, due to complications arising from the amyloid deposition in organs and disrupting their functions. Only 60% of patients with amyloidosis who are treated, survive more than a few years.

Amyloidosis is clinically a disorder caused by deposition of insoluble, extracellular, abnormal fibrils (also known as amyloids). The amyloid fibrils are formed by precipitation of soluble proteins normally found in an organism but have protein misfolding (an error in protein conformation). Protein folding is the process by which a protein folds into its characteristic and functional three-dimensional structure. If proteins do not fold into their functional structure, that leads to the formation of inactive proteins that are usually toxic. Twenty-three different proteins are known to form amyloid fibrils. Amyloids are composed primarily of proteins but they also may contain polysaccharides. Amyloids are formed only under pathological conditions due to overstimulation
by antigen, which is why this disease is considered as a hyperimmunization disease.³

Amyloids tend to precipitate in the functionally active organs (*kidneys, liver, myocardium, spleen*), and cause their functionality disrupted.⁴

Amyloidosis can be divided into two groups:

- Systemic amyloidosis
- Local amyloidosis

Systemic amyloidosis is divided into the following groups:

- **Primary systemic amyloidosis** (*idiopathic*), which is usually not associated with previous or existing illnesses, paraproteinemia, or plasma cells dyscrasias.
- **Hereditary amyloidosis** (*genetically determined*), which occurs due to genetic disorders of protein metabolism.
- **Secondary systemic amyloidosis**, which is associated with a previous or existing chronic inflammatory or infectious diseases.³⁴

Primary systemic amyloidosis is caused by deposition of insoluble immunoglobulin light chains (*L-fragment*) in different tissues⁵:

1. smooth and striated muscles
2. connective tissues
3. blood vessels walls and peripheral nerves

In primary systemic amyloidosis, amyloids are formed by blood cells in the bone marrow. In contrast to the normal immunoglobulin light chains, the immunoglobulin light chains in primary systemic amyloidosis are characterized by partial lysosomal proteolysis within macrophages. These amyloids are deposited as insoluble extracellular amyloid filaments attached to polysaccharides. Sometimes, instead of an intact immunoglobulin light chain, amyloid has a terminal amino group of the light chain.

Hereditary amyloidosis is caused by gene mutation or the inherited metabolic disorders of protein. This gene mutation leads to the formation of amyloid which can be precipitated in the kidneys, heart and nerves. It is divided into two groups:

1. **ATTR (transthyretin amyloidosis)**. This disorder occurs due to mutations in the TTR (*transthyretin*) gene and are inherited from parents. These genetic mutations make transthyretin (*protein that transports thyroxine*) unstable, causing an error in protein folding. Amyloid fibrils pass into the bloodstream and accumulate in nerves and other organs causing damage, depending on the type of TTR mutations the patient has. TTR is synthesized mainly in the liver. There are 126 different genetic variations of this type of amyloidosis. This type of amyloidosis is rare. There are different types of this amyloidosis, such as: familial amyloid polyneuropathy, and familial amyloid cardiomyopathy.⁶

2. **Non-TTR (non-transthyretin amyloidosis)**. Non-TTR amyloidosis is caused by other inherited genetic mutations, such as mutations in the:
   - apo lipoprotein A
   - fibrinogen
   - cystatin C and other proteins

   There are 53 different genetic variations of this type. Non-TTR amyloidosis is a rare and less frequent than ATTR.⁶

Secondary systemic amyloidosis is characterized by amyloid deposition in the reticular fibers.
Typically, it occurs along with some other infectious or chronic inflammatory diseases, such as: tuberculosis, bronchiectasis, osteomyelitis, and others. It may be accompanied by non-infectious inflammatory processes, such as: sarcoidosis, ulcerative colitis, Crohn’s disease, rheumatoid arthritis, Hodgkin’s lymphoma, multiple myeloma, and others. 

Amyloid is most often deposited in the kidneys, liver, and gastrointestinal tract. Secondary systemic amyloidosis is the most common type of amyloidosis.

Amyloidosis frequently affects the kidneys.

General symptoms of amyloidosis include:

- Skin color changes
- Stool color changes (clay color)
- Fatigue
- Malaise
- A feeling of fullness and consequently loss of appetite
- Joint pain
- Decreased number of red blood cells
- Difficulty breathing (shortness of breath)
- Swelling of the tongue
- Burning sensation
- Leg muscle stiffness

It often happens that in patients with rheumatoid arthritis (RA), some of these symptoms are incorrectly attributed to the progressive development of RA or to the side effects of medicines used in the treatment of RA. However, the presence of proteinuria in patients with rheumatoid arthritis should raise the suspicion of amyloidosis.

References

6. www.amyloidosis.org