Amyloidosis

- what is amyloidosis?
  Amyloidosis is a condition associated with a number of inherited and inflammatory disorders in which there's **accumulation of fibrillar proteins** (amyloid) in the extracellular space that damages surrounding tissues.
  It is not a single disease but rather, there's a group of diseases characterized by amyloid deposit.
  The abnormal fibrils are produced by the aggregation of misfolded proteins which then organize into beta-pleated sheets, that are insoluble. These protein aggregates bind glycosaminoglycans and proteoglycans which under the microscope, when stained with hematoxylin and eosin stain, gives them the appearance of starch: eosinophilic, amorphous, hyaline-like. Hence, the name "amyloid".
  Amyloid deposits were identified by Virchow in 1854. He discovered that these deposits had the property to **react with iodine** with a similar reaction of the starch. To recognize the starch we use an iodine solution but Virchow discovered that these misfolded proteins can react with the same iodine solution, for that reason he called them amyloid deposits. Although these proteins have nothing to do with starch.
  Two general categories of proteins that form amyloid:
    - **normal proteins produced in enormous amounts, and a small fraction of them fold incorrectly.**
    - **abnormal proteins with incorrect amino acid sequences are produced in normal amounts, and they fold incorrectly**
- About 23 different proteins can form amyloids.
  These accumulations are very dangerous as they compromise both morphological and functional points of view. They can compress the tissue and organ, compromising the blood vessels and causing a reduction in the distribution of the blood in the organs. The final result is that the cell starts to suffer and die causing atrophy of the tissue.
- what types of amyloidosis are there?
  We can distinguish two types of amyloid depositions:
  1. **Systemic amyloidosis:** Deposits are in various organs which are compromised from a morphological and functional point of view
     - **primary systemic amyloidosis**: associated with B cell disorders: **AL AMYLOIDOSIS**
     - secondary systemic amyloidosis: underlying chronic inflammatory process
       - **AA AMYLOIDOSIS**
       - **AH (Hemodialysis-associated amyloidosis)**

2. **Localized amyloidosis:** Deposits only at the level of a specific organ
    - Primary ****(idiopathic)
    - Secondary ****to other pathological conditions
3. **Hereditary or familial amyloidosis** constitute a separate, although heterogeneous group, with several distinctive patterns of organ involvement.

- describe the chemical and physical composition of amyloid
  The fibrils are rigid, unbranched, variable length, diameter about 10 nm
  4-6 fibrils joined together by hydrogen bonds form an amyloid fiber with an unusual β-sheet conformation that makes them unaffected by tissue enzymes
  95% of amyloid is protein, 5% are glycoprotein (called amyloid P component) and glycosaminoglycans.
  Amyloid p component is a pentameric glycoprotein of the **pentrassins** class that binds to fibrils with a calcium-dependent mechanism
- where in the body is amyloid deposited?
  Amyloids are present in the **extracellular space** of various tissues and organs.
  Preferential deposition of amyloid: **vessel wall and interstitial compartment**
  Commonly affected organs:
    - peripheral nerves
    - skin
    - tongue
    - joints
    - heart
    - liver
    - spleen
    - kidneys
    - adrenal
    - lymph nodes
    - thyroid
- Organs affected by **chronic inflammatory diseases or tissue necrosis** are more at risk
- Describe the pathogenesis of the systemic forms of amyloidosis
  SYSTEMIC AMYLOIDOSIS:
    1. **AL amyloidosis**, (primary): “L”: In B cell disorders, like multiple myeloma, plasma cells in the bone marrow produce more light chains than heavy chains, and those **excess light chains leak out into the blood**. Since there are so many light chains, **some** (the ones with a.a compatible with beta configuration) **misfold into AL proteins, and build up in various tissues (heart, kidneys, liver, spleen, etc.)**

2. **AA amyloidosis**, or **secondary**: the misfolded protein comes from serum amyloid A, an acute phase reactant (secreted by the liver when there's inflammation). In **chronic inflammation**, like in rheumatoid arthritis, IBD, cancer, there's **lots** of serum amyloid A in the blood. A small **portion spontaneously misfold into AA amyloids,** which accumulate in tissues→ amyloidosis. MMPs (monocyte-derived) are important for SAA degradation, if enzyme defect or insufficient →incomplete breakdown of SAA.Histological diagnosis with anti-AA antibodies. Targets: mainly kidneys, liver and spleen
3. **Hemodialysis-associated amyloidosis (AH),** secondary: after years of hemodialysis patients may develop **bilateral carpal tunnel syndrome** (deposition of amyloid in the carpal ligament → compression of the median nerve), and **cystic bone lesions** (amyloid deposition in the bone). **AH fibril protein** is a ****beta-2-microglobulin, that accumulates in the blood with renal dysfunction (not filtered by dialysis). It binds to collagen and settles in the connective tissue. Targets: skeletal and muscular system.
4. **Familial amyloidosis (primary)**
    1. **Familial amyloidotic Polyneuropathies (FAP)** autosomal dominant. ****Genetic defects of protein synthesis: mutant transthyretin (TTR) → prone to misfolding → **ATTR (amyloid transthyretin)** • Target: kidneys, thyroid, and peripheral and autonomic nerves.
    2. **Familial Mediterranean fever**: autosomal recessive defects of neutrophil function: excessive IL-1 production that cause attacks of fever, associated with inflammation of serosal surfaces (peritoneum, pleura, synovial membrane) and cause abdominal pain, arthritis. There's an accumulation of **AA fibril**. Targets: kidneys, blood vessels, spleen, respiratory tract.

- Describe the pathogenesis of the localized forms of amyloidosis
    - **Amyloid of aging (AS fibrils**)**:** localized amyloid deposition in older populations. The target organs are brain and heart
        - **Alzheimer's disease:** APP
        - **Prion encephalopathy:** accumulation of abnormal prion proteins indicated as PrPc. This is responsible for severe damages in the central nervous system. This disease is fatal in a short time.
        - **Senile cardiac amyloidosis :** increased levels of normal, non mutated, transthyretin (TTR)
    - **Endocrine amyloid (AE fibrils):** localized amyloid deposition associated with metabolic disorders or tumors of endocrine glands. It may be found in:
        - Medullary carcinoma of the **thyroid** gland

        - Islet tumors of the **pancreas**
        - Islet of Langerhans in type II diabetes mellitus, etc.
    - Protein component: locally produced peptides: precursor of calcitonin, precursor of amylin (IAPP, islet amyloid polypeptide) produced by the beta cells of the pancreas
- summary table with classification of amyloidosis

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- What are the clinical manifestations of amyloidosis?
  It is possible to have amyloidosis that does not cause clinical manifestations and at the same time, some cases of amyloidosis cause serious clinical problems and even death.
  The clinical manifestations are rather unspecific, especially in the beginning, there may be **weakness, weight loss, light-headedness, syncope, etc.** It all depends on which type of amyloidosis it is and thus, which organ/s it affects.
  With progression of the condition we might start seeing other signs that are more specific and useful for the diagnosis such as problems with the kidneys, heart, GI tract.
  In general, prognosis is very poor with systemic amyloidosis.
    - **Kidney** manifestations (timeline):
        - normal size and color → may progress to **atrophy** due to ischemia of renal arteries caused by amyloid deposition in arterial wall
        - early **glomerular dysfunction** (its architecture is obliterated by the massive accumulation of amyloid)
        - later issues in the **tubules** (peritubular space) and **arterioles**
        - signs: from modest **proteinuria** to **nephrotic syndrome**
        - progressive **uremia (high levels of urea in the blood)** →kidney failure → death
        - therapy: dialysis and transplant
    - **Liver**
        - Initial deposition in the **perisinusoidal space** and progressive growth that causes deformity, pressure atrophy → replacement of large areas of liver parenchyma.
        - deposits of amyloid in the walls of sinusoids and in Kupffer cells
        - hepatomegaly, portal hypertension, diminished liver function
        - average survival with liver amyloidosis is 9 months.
    - **Heart**
        - initial deposits between muscle fibers in the myocardium → progressive expansion → thickening and stiffening of ventricular wall, as well as damage to the conduction system → hypomobility

        - it may involve valves and pericardium
        - heart may appear firm and enlarged
        - cardiomegaly, cardiomyopathy and arrythmias → heart failure
    - **Endocrine system**: no significant clinical manifestations.
    - **Spleen**: deposition may be limited to the follicles (tapioca-like granules) or it may involve the walls of the sinuses and connective tissue framework in the red pulp→ splenomegaly. Fusion of deposits → lardaceous spleen.
    - **Skin**: involved mainly in AL amyloidosis (55%) or AA amyloidosis (42%). Papules in the axilla, inguinal region, face, neck, and on mucous membranes. small hemorrhages and purpura.
    - **GI tract:** Obstructions, disturbances in digestion, ulcerations, malabsorption, hemorrhages, diarrhea. Nodular depositions in the tongue may cause macroglossia. (AL both primary and associated with myeloma)
    - **Nervous system**: neuropathies, alzheimer, carpal tunnel syndrome, etc.
    - **Joints**: Deformation of joints and synovial membrane that lead to arthritis
    - **Respiratory tract**: may be involved locally or diffusely.
- is there a treatment for amyloidosis?
  Ongoing clinical trials with new drugs to:
    - decrease the chronic antigenic stimulus that produces amyloid
    - correct protein misfolding
    - inhibit the formation of amyloid fibrils
    - modify/eliminate its extra-cellular deposition
    - stimulate lysis and mobilization of fibrils