Pathology - Topic 9 - Amyloidosis

Pathogenesis of Amyloidosis

- **Amyloidosis** is a group of disorders in which misfolded proteins form insoluble fibrils that accumulate mainly outside cells.

Protein Deposits and Tissue Effects

- The deposits disrupt tissue structure and function, but the precursor protein differs between diseases.
- Amyloid is not one chemically identical substance and is not simply an excess of ordinary connective tissue.
    - Identifying the deposited protein is essential because the underlying cause and management differ between types.

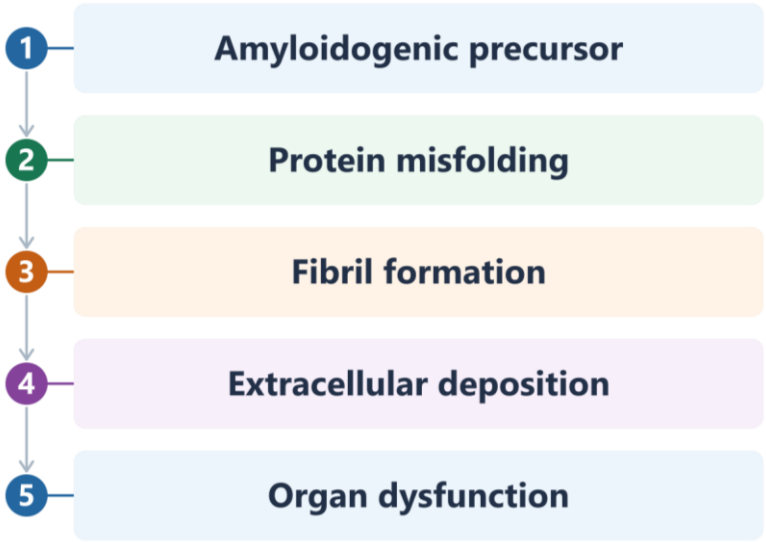
Fibril Structure and Associated Components

- The fibrils share a **cross-beta-sheet** structure that contributes to their stability and characteristic staining properties.
    - Associated components include serum amyloid P and extracellular-matrix molecules.

Protein-based Nomenclature

- Amyloid nomenclature uses A followed by an abbreviation of the precursor, which is more informative than the older labels primary or secondary alone.

Mechanisms of Deposition



- A normal protein may accumulate in excessive amounts, or an altered protein may be particularly prone to misfolding.
    - Ageing, chronic inflammation, plasma-cell disorders and inherited variants produce different settings for fibril formation.
- Misfolded protein aggregates into fibrils that resist normal removal and deposit in tissues.

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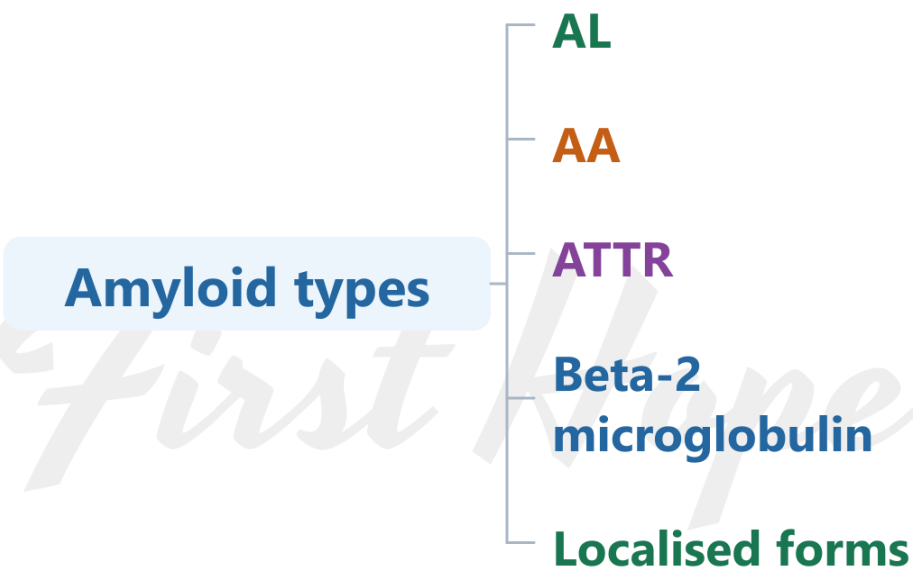
- Both deposits and smaller toxic protein aggregates may contribute to organ dysfunction.

- Progressive accumulation can compress cells, narrow vessels and alter the physical properties of an organ.
    - The amount and location of deposition influence the clinical effects more directly than the colour of the tissue alone.

Major Types of Amyloidosis

- Amyloidosis is classified by the protein forming the fibrils and by whether deposition is systemic or localised.

Classification by Precursor Protein



1. AL Amyloidosis

- **AL amyloid** is derived from immunoglobulin light chains produced by a clonal plasma-cell population.
    - The clone may be small, and systemic AL amyloidosis does not require overt multiple myeloma.
- The kidneys, heart, peripheral nerves, gastrointestinal tract and other organs may be involved.
    - Abnormal protein folding allows light-chain-derived material to form amyloid fibrils.

Light-Chain Structure and Toxicity

- Light-chain-derived fibrils often contain variable-region fragments, and the producing clone may be detected by marrow studies and sensitive monoclonal-protein testing.
- Disproportionate organ dysfunction may occur even with a small clone because misfolded light chains can exert direct toxicity in addition to forming deposits.

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2. AA Amyloidosis

Precursor and Mechanism

- **AA amyloid** is derived from serum amyloid A, an acute-phase protein produced during inflammation.
- Persistent high production in chronic inflammatory or infectious disease can promote deposition in susceptible patients.

Associated Diseases and Renal Involvement

- Associated settings include chronic inflammatory arthritis, inflammatory bowel disease, certain chronic infections and inherited autoinflammatory disorders.
- Not every person with prolonged inflammation develops amyloidosis.
- Renal involvement is particularly important and can present with substantial proteinuria.
- Longstanding bronchiectasis, chronic osteomyelitis and tuberculosis are traditional infectious associations, while chronic inflammatory and autoinflammatory diseases are important noninfectious causes.
- The risk reflects prolonged inflammation and host susceptibility rather than a short isolated rise in an acute-phase marker.

3. ATTR Amyloidosis

- **ATTR amyloid** is derived from transthyretin, a transport protein produced mainly by the liver.
  - An inherited variant can destabilise the protein, while wild-type transthyretin can also form amyloid with ageing.
- The heart and peripheral or autonomic nerves are important targets, with the pattern depending on the type of ATTR disease.
  - Wild-type ATTR commonly presents as a cardiac disorder in older adults rather than a widespread inflammatory disease.
- Destabilisation permits transthyretin tetramers to dissociate, allowing their subunits to misfold and aggregate.

4. Dialysis-Related Amyloidosis

- Long-term accumulation of beta-2 microglobulin can produce amyloid in patients with markedly reduced renal clearance.
  - Deposition often affects joints, bones and periarticular tissues and can contribute to carpal-tunnel symptoms.
- This mechanism differs from the light-chain and inflammatory precursor mechanisms.

5. Other Amyloid Precursors

- Amyloid can remain localised near the cells producing its precursor protein.

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- Examples include islet amyloid derived from islet amyloid polypeptide in type 2 diabetes and calcitonin-related amyloid in medullary thyroid carcinoma.

➢ Amyloid-beta deposition occurs in the brain in Alzheimer disease and cerebral amyloid angiopathy.

- These localised deposits do not automatically indicate systemic AL or AA amyloidosis.

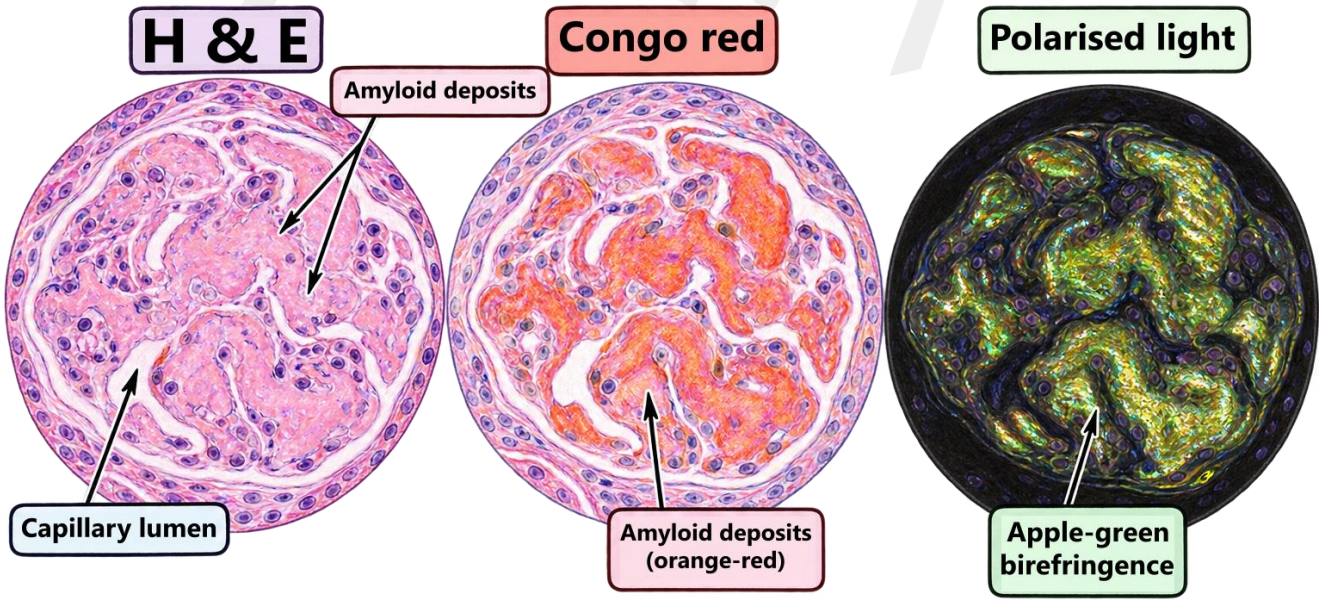
Systemic and Localised Distribution

- **Systemic amyloidosis** involves multiple organs or reflects a precursor capable of circulating and depositing at distant sites.
  - The clinical presentation may still be dominated by a single organ.
- **Localised amyloidosis** is confined to a particular tissue or organ region.
  - A tissue diagnosis should prompt appropriate typing and assessment rather than an assumption that every patient has systemic disease.

Pathology and Clinical Effects of Amyloidosis

- Amyloid deposits alter tissue structure and may impair organ function through their location and extent.

Routine Microscopy and Congo Red Staining



Amyloid expands the glomerular mesangium and capillary walls and shows characteristic Congo red staining

- On haematoxylin and eosin sections, amyloid appears as extracellular amorphous eosinophilic material.
  - It may expand tissue spaces, surround vessels or replace normal structures.
- Amyloid stains orange-red with **Congo red** and shows characteristic birefringence under polarised light, classically described as apple green.

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- Correct staining technique, adequate tissue and careful interpretation are necessary because artefacts and other materials may mislead.

- Electron microscopy shows randomly arranged, non-branching fibrils approximately 7–12 nm in diameter rather than the organised bundles of ordinary collagen.
    - Specialised protein typing is still needed because fibril appearance alone does not identify the precursor.

Distinguishing Amyloid from Other Eosinophilic Deposits

- Collagen forms organised bundles and usually differs from the amorphous distribution of amyloid.
- Fibrin, hyalinised vessels and light-chain deposition disease can produce extracellular eosinophilic material but do not share the complete Congo-red and ultrastructural pattern of amyloid.
- An appropriate positive staining control and adequate section assessment help avoid a false interpretation of weak or artifactual birefringence.

Organ Distribution and Clinical Effects

1. Renal Amyloidosis

- Amyloid commonly accumulates in glomeruli and can also involve vessels and the interstitium.
    - Mesangial expansion and capillary-wall deposition disturb the filtration barrier.
- Proteinuria may progress to nephrotic syndrome and impaired renal function.
    - The kidneys may initially be enlarged and pale, while later chronic damage can produce scarring and reduced function.
- The distribution and severity vary between amyloid types, so a single gross appearance is not universal.

2. Cardiac Amyloidosis

- Interstitial and vascular deposits can make the myocardium thickened and stiff.
    - Impaired relaxation and filling can produce a restrictive pattern of heart failure.
- Conduction-system involvement can produce arrhythmias or heart block.
    - The apparent increase in wall thickness reflects infiltrative material rather than ordinary myocyte hypertrophy alone.
- AL and ATTR are important causes of cardiac amyloid disease.

3. Liver and Spleen

A. Liver

- Hepatic deposits often develop in the spaces of Disse and around vessels.

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