Pathology, diagnosis and pathogenesis of AA amyloidosis

Abstract  Amyloid is defined as a proteinaceous tissue deposit that shows a typical green birefringence in polarised light after staining with Congo red, the presence of non-branching linear fibrils of indefinite length with an approximate diameter of 10–12 nm and a distinct X-ray diffraction pattern consistent with Pauling’s model of a cross-β fibril. Approximately 45% of generalised amyloidoses are secondary or reactive (AA) amyloidosis. Among the causes of AA amyloidosis are rheumatic diseases, idiopathic diseases, inherited diseases, infectious diseases and malignant tumours. Recent decades have provided significant advances in our understanding of the pathology and pathogenesis of AA amyloidosis. Its pathogenesis is multifactorial involving many variables such as primary structure of the precursor protein, acute phase response, the presence of non-fibril proteins (e.g. amyloid P component, apolipoprotein E, glycosaminoglycans, proteoglycans and basement membrane proteins), receptors, lipid metabolism and proteases. Study of the pathogenesis of AA amyloidosis has provided many insights into the nature of conformational diseases, which may help in the understanding of other members of this particularly heterogeneous group of diseases, such as Alzheimer’s disease and transmissible spongiform encephalopathies.

Keywords  Amyloid · Serum amyloid A

Conformational diseases

Carrell and Lomas [7] introduced the term “conformational diseases” to include Alzheimer’s disease, Creutzfeldt-Jacob disease, transmissible spongiform encephalopathies and amyloidoses. According to Carrell and Lomas a conformational disease “…arises when a constituent protein undergoes a change in size or fluctuation in shape, with resultant self-association and tissue deposition.” At least part of the protein is correctly folded when it is released in its physiological form, and the conformational disease arises from post-translational modification. This is influenced by genetic variables and the primary structure of the protein. Much of our knowledge and understanding of conformational diseases stems from research on amyloidosis.

Amyloid

Amyloid is defined as a proteinaceous tissue deposit showing: (1) a typical green birefringence in polarised light after staining with Congo red (Fig. 1), (2) the presence of non-branching linear fibrils of indefinite length with an approximate diameter of 10–12 nm (Fig. 1) [66] and (3) a distinct X-ray diffraction pattern consistent with Pauling’s model of a cross-β fibril. High resolution electronmicroscopic studies provided evidence that the amyloid fibril contains a core composed of pentosomal particles that have the characteristics of amyloid P component (AP, Fig. 1). Wound around this is a “double-tracked” ribbon-like structure identified as chondroitin sulphate proteoglycan (CSPG) [22]. Covering the surface of this structure is a further ribbon-like double-tracked structure, characterised as heparan sulphate proteoglycan (HSPG, Fig. 1). The fibril protein forms the outermost surface. The basic architecture of amyloid fibrils is similar to that of microfibrils of elastic tissue [22]. The origin of amyloid is diverse, and over 20 different fibril proteins have been described. The precursors of most fibril proteins differ from each other with respect to primary structure and function; fibril proteins are derived from apolipoproteins (apolipoprotein AI, apolipoprotein AII and serum amyloid A), proteohormones (atrial natriuretic peptide, calcitonin, insulin, islet amyloid polypeptide and prolactin), immunoglobulins (λ and κ-light chain, heavy chain), proteases (lysozyme),...
protease inhibitors (cystatin), transmembrane proteins (amyloid precursor protein), transport proteins (transthyretin) and others (gelsolin, fibrinogen, lactadherin, lactoferrin, β2-microglobulin). The only feature common to all these proteins is their ability to form aggregates under specific circumstances, which leads to the formation and deposition of amyloid. Deposits may be local, organ-limited or generalised, and they can affect any organ or tissue type. However, the distribution pattern of amyloid depends on the origin and type of fibril protein deposited.

**Amyloidosis**

**Epidemiology**

Amyloidosis denotes the disease state that results from the deposition of amyloid. Symptoms depend on the distribution pattern and quantity of the deposits. Although a particular combination of clinical symptoms may be highly indicative of amyloidosis in a given patient, the clinical pictures of different amyloid diseases can be variable. Moreover, a single patient may suffer from different amyloid diseases simultaneously. This review will only focus on the reactive or secondary type of amyloidosis (AA amyloidosis).

**AA amyloidosis**

Approximately 45% of all generalised amyloidoses are AA amyloidosis. The onset is usually explosive and among its causes are rheumatic diseases (ankylosing spondylitis and rheumatoid and juvenile arthritis), idiopathic diseases (sarcoidosis, Crohn’s disease, ulcerative colitis and Rosai-Dorfman disease), inherited diseases