Amyloidosis

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Abstract

Amyloidosis is a group of diseases due to pathologic deposition of various insoluble fibrilllar proteins having an identical secondary structure (ß-pleated sheet) in the extracellular compartments of the body. When diabetes mellitus type II and Alzheimer's disease are taken into account, the prevalence of amyloidosis is obviously quite high. There are four types of amyloidosis: AL (light chain) amyloidosis, AA amyloidosis (secondary to chronic inflammation), $Aß_2M$ amyloidosis (secondary to long-term hemodialysis) and heredofamilial (ATTR and other) amyloidoses. The process may be focal, local or generalized whose clinical consequences are reflections of the involved organ(s). Some clinical features such as macroglossia (AL), nephrotic syndrome (AA), arthropathy ($Aß_2M$) or familial peripheral neuropathy (ATTR) may imply the type of deposit to a certain extend. A definitive diagnosis requires not only tissue confirmation (Congo Red staining with green birefringence under polarized light) but also genomic DNA and protein analyses and immunohistochemistry. Suitable tissue samples can be obtained from subcutaneous fat pad aspiration, rectal mucosa or renal biopsy. Neural or myocardial biopsies are rarely necessary. Serum amyloid P component (SAP) scintigraphy can visualise and demonstrate the amyolid burden of the patient; this procedure may also be useful to measure the response to treatment.
Amyloidosis is not regarded as an irreversible pathology anymore. Detection of the precursor protein such as SAA or mutated transthyretin is an important step in therapeutic decision making since further progression of the deposits can thus be halted. There are several treatment options available to the clinicians, while the efficacy of some of these modalities has not yet been definitely established.

Keywords: amyloidosis, pathogenesis, treatment, familial mediterranean fever

Introduction

Amyloidosis is a heterogeneous group of diseases. Misfolding and deposition of certain soluble proteins as insoluble fibrils in the extracellular compartments of the body cause variety of organ dysfunctions. They have an identical secondary structure (ß-pleated sheet) but there are 21 different proteins causing amyloidosis. The majority of amyloid cases are due to acquired pathologic processes but a substantial minority is hereditary.

Historically, the term "amyloid" (starch-like) was first used by Schleiden, a German botanist, in 1838. Virchow introduced it to medical jargon in 1858 for the autopsy findings which were later demonstrated that they had nothing to do with starch but were proteinaceous in nature. Congo Red staining was first used by Divry in 1927 and the ultrastructure of amyloid fibrils was identified by Cohen and Calkins in 1959 (1).

Types of amyloidosis and their prevalence

Amyloidosis may be localized or systemic. There are four types of systemic amyloidosis:

1. AL amyloidosis is due to plasma cell dyscrasia related to multiple myeloma where the precursor protein is either λ or κ immunoglobulin.
2. AA amyloidosis is secondary to chronic inflammation and the precursor protein is serum amyloid A protein.
3. $Aß_2M$ amyloidosis is secondary to long-term hemodialysis and the precursor protein is $ß_2$ microglobulin.
4. ATTR and other heredofamilial amyloidoses where the precursor protein is usually abnormal transthyretin (previously called prealbumin). The precursor of other rarer forms may be apolipoprotein A-I, lysozyme, or fibrinogen A α-chain.

It is estimated that amyloidosis is the cause of death of about 6,6/10,000 people in the United Kingdom annually (2) and age-adjusted incidence of AL amyloidosis is around 8 per million person-years in USA where the ratio of ATTR amyloidosis rate is 10-20 percent of AL cases (3). AA type is relatively more prevalent in under-developed countries since untreated chronic infections such as tuberculosis are still not exceptional; other chronic inflammatory diseases (rheumatoid arthritis etc) are outstanding sources of new cases universally. Familial Mediterranean fever (FMF) needs mentioning since it is quite prevalent in Turkey (0,1 percent) and in Greece and may be encountered in other Balkan countries to a certain extend. Migration of populations from the Middle East in the twentieth century has transformed FMF into a universal disease. It was recently observed that about 13 percent of nearly 3000 FMF patients had AA amyloidosis in Turkey and it is the most frequent cause of amyloidosis in that country (4, 5). $Aß_2M$ amyloidosis is potentially important source because there are approximately 1 million people on dialysis programs worldwide and the development of amyloidosis approaches to 100 percent after 20 years (6).

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When diabetes mellitus type II and Alzheimer's disease are taken into account, the prevalence of amyloidosis is obviously quite high. Amyloidosis is not systemic but localized to pancreatic islet cells and cerebrum in these diseases and their pathogenetic implications are not well established.

Pathogenesis

The newly synthesized polypeptides enter a funnel-like pathway of conformational modification in the cytoplasm under physiological conditions. Some polypeptides may however misfold and aggregate as insoluble fibrils, which is a pathologic process leading to amyloidosis. The first step in amyloidogenesis is the change in the precursor protein that starts the process of fibrillar autoaggregation. Production of the precursor protein is quantitatively and/or qualitatively pathologic. There are specific amino acid substitutions in the precursor light chain in AL amyloidosis or transthyretin in ATTR and it is thought that such changes destabilize the molecule and facilitate fibrillogenesis. A third mechanism is proteolytic remodelling of the precursor protein.

Since not every person with the same mutation develops amyloidosis and there is a very wide time range in AA amyloidosis, other genetic and macro and microenvironmental factors may be operational. Certain genotypes such as being M694V homozygote and SAA1 alpha/alpha and a positive family history for amyloidosis have significantly higher risk of amyloidosis in FMF (7). The concentration of urea in the inner renal medulla or the pH level of the tissues may enhance fibrillogenesis. It is also well recognized that once amyloid deposition starts, progression is easier ("amyloid begets amyloid"). This may explain the concentration of amyloid in certain organs but the tissue specificity of each protein (joints, peripheral nerves etc.) is not well understood (1, 3, 8).

Diagnosis

Every patient must be evaluated for extend of organ involvement and family history and the type of precursor protein must be determined. A definitive diagnosis requires not only tissue confirmation (Congo Red staining with green birefringence under polarized light) but also genomic DNA and protein analyses and immunohistochemistry, otherwise some hereditary forms may be misdiagnosed as AL type (2, 9). Suitable tissue samples can be obtained from subcutaneous fat pad aspiration, rectal mucosa or renal biopsy. Neural biopsy is not very reliable because of the focal distribution of amyloid. Myocardial biopsy is rarely necessary. Serum amyloid P component (SAP) scintigraphy can visualise and demonstrate the amyolid burden of the patient; this procedure may also be useful to diagnose sub-clinical disease in progress or measure the response to treatment (1, 10).

Clinical aspects

Some clinical features such as macroglossia (AL), nephrotic syndrome (AA), arthropathy ($A\beta_2M$) or familial peripheral neuropathy (ATTR) may imply the type of deposit to a certain extend but the clinical picture is rarely conclusive.

AL type is the most diverse in clinical picture but the central nervous system is spared. Kidney and heart are frequently involved and the absence of hypertension despite severe renal failure should alert the physician. Heart failure is particularly an ominous sign. Easy bruising and spontaneous periorbital purpura ("racoon eyes"), hard hepatomegaly with elevated alkaline phosphatase and macroglossia (about 20 percent of the patients) are prominent features (3).

AA amyloidosis almost always presents with proteinuria which may be intermittent initially. Other organ involvements such as hepatomegaly, splenomegaly, malabsorption, thyroid or heart failure are exceptional features of the average patient.

$A\beta_2M$ amyloidosis is always secondary to prolonged dialysis and the commonest complaint is severe joint pain in the absence of radiological changes of arthritis, the shoulders usually being the most affected. Carpal tunnel syndrome (usually bilateral) is also frequently encountered (5).

Heredeofamilial amyloidosis is probably more frequent than perceived (2). Peripheral and autonomous nervous system involvements are outstanding features while renal failure is rare and macroglossia has not been reported. The most frequent mutation of ATTR causes cardiac conduction disturbances while other mutations may cause cardiac failure indistinguishable from AL type. Generally heart failure is less common and more benign in ATTR type (3).

Treatment

Amyloidosis is not regarded as an irreversible pathology anymore. Detection of the precursor protein such as SAA or mutated transthyretin is an important step in therapeutic decision making since further progression of the deposits can thus be halted. Another main objective is to support the failing organ while transplantation may be the definitive therapy (11, 12).

AL amyloidosis may respond to oral melphalan and prednisone but high dose IV melphalan with autologous stem cell transplantation is more effective. The trials with IDOX (4'-iodo-4'-deoxydoxorubicin) have been disappointing.

AA amyloidosis can respond favourably to specific treatment of the primary disease. SAA determinations with aim of values lower than 10 mg/L would be appropriate. It has been shown that colchicine can slow the progression of amyloidosis and regress the proteinuria in FMF (13, 14), where drug dosage must be escalated to tolerated maximum which is usually 2-2.5 mg/day. Patients with amyloidosis secondary to inflammatory arthritides may respond to anti-TNF treatment (infliximab or etanercept) particularly when combined with methotrexate (15). CPHPC is a promising drug which removes SAP from the circulation and amyloid deposits (9, 11). Sodium-I,3-propane-disulfonate (Fibrillex) is an investigational drug whose phase II/III results will soon be available.

Liver transplantation is the definitive therapy of ATTR amyloidosis. If the liver of the affected patient is transplanted to another patient (so-called "domino liver transplantation") systemic ATTR amyloidosis may sometimes develop in the recipient. Renal transplantation is the only effective treatment of $A\beta_2M$ amyloidosis.

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