Systemic amyloidosis: getting to the heart of the matter

Just 10–15 years ago, amyloidosis was poorly understood, difficult to diagnose and type, and was widely thought to be inexorable. Specialist clinical services were not available and many patients did not receive any disease-modifying treatment. To the histopathologist, the inert appearance of amyloid deposits without any accompanying tissue reaction seemed to provide further evidence of their irreversibility. Patients with systemic AL (monoclonal immunoglobulin) amyloidosis, the most common and serious type, usually died within 2 years of diagnosis, and often within 6 months when the heart was involved. The symposium in this issue of the journal provides an update on systemic amyloidosis, with a focus on its pathogenesis and clinical management. Cardiac and renal amyloidosis are addressed specifically, given the frequency with which these two vital organ systems are involved.

What is amyloidosis?

The term amyloidosis describes a spectrum of clinical disorders caused by the extracellular accumulation of amyloid fibrils which can disrupt the structure and function of tissues and organs throughout the body (Pepys, 2006). Amyloid fibrils are derived from various normally soluble proteins through a process of misfolding and highly ordered auto-aggregation that results in their characteristic cross-beta quaternary structure. This conformational transformation confers amyloid precursor proteins with new biophysical properties including their ability to bind Congo red dye and the normal plasma protein serum amyloid P component (SAP), along with insolubility and marked resistance to degradation.

While more than 20 different unrelated proteins may form amyloid fibrils in vivo, and many others can be induced to do so in the laboratory, only a few are associated with significant disease. In systemic amyloidosis, amyloid deposits are present in the viscera and widely throughout blood vessel walls and connective tissues, and the resulting disease is usually fatal. Systemic amyloidosis is the cause of death in about one per thousand individuals in developed countries, and probably remains undiagnosed quite often. There are also localized forms of amyloidosis in which the deposits are confined to specific foci or a particular organ or tissue, which may be clinically silent or trivial, or associated with serious disease such as haemorrhage in the respiratory or urogenital tracts. In addition, there are various other important diseases in which local amyloid deposition occurs but in which the pathogenetic role remains unclear. Notable examples include the brain in Alzheimer's disease and the prion disorders, and the pancreas in type II diabetes mellitus.

Various developments including diagnostic SAP scintigraphy and precise biochemical and genetic characterization have led to substantial improvements in clinical management that now facilitate rational treatment of most patients. The NHS commissioned the National Amyloidosis Centre at the Royal Free Hospital in 1999, creating the world's largest and most diverse amyloidosis practice which has enabled knowledge of the amyloid diseases to develop at an ever-growing pace.

SAP scintigraphy exploits the specific binding between SAP and all kinds of amyloid fibril. Radiolabelled SAP provides a non-invasive method for imaging amyloid and quantitatively monitoring the deposits and their response to treatment (Hawkins et al, 1990). Contrary to previous expectations, serial SAP scintigraphy has shown that amyloid deposits exist in a state of dynamic turnover, which frequently regress when underlying disorders are treated. SAP scintigraphy is offered routinely to patients attending the National Amyloidosis Centre and, in conjunction with high sensitivity clinical chemistry assays that monitor production of the AA and AL amyloid precursor proteins, serum amyloid A protein and serum free light chains, anti-inflammatory treatment and chemotherapy respectively can now be delivered in a rational, patient-tailored and much safer manner than hitherto.

Hereditary forms

A crucial discovery has been that 10% of patients with amyloidosis have hereditary forms of the disease (Lachmann et al, 2002). This has major implications for clinical management including the need to perform DNA analysis routinely since a family history is often absent. Many new amyloidogenic mutations have been identified in transthyretin, apolipoprotein AI and fibrinogen Aα chain.

The most common form of hereditary amyloidosis occurs in Afro-Caribbean black individuals, 4% of whom possess the isoleucine 122 variant of transthyretin which is associated with cardiac amyloidosis after the age of 60 years. Discovery of hereditary lysozyme amyloidosis, which is exceptionally rare, has nevertheless been of pivotal importance as a laboratory model for elucidating fundamental mechanisms of protein misfolding and amyloidogenesis.

Diagnosis

Although histology remains the gold standard for diagnosis, demonstrating the characteristic red-green birefringence of amyloid deposits stained with Congo red, many non-invasive technologies are also informative. While only SAP scintigraphy is specific for amyloid, other anatomical and functional imaging modalities can strongly suggest the diagnosis. Echocardiography showing small, concentrically thickened ventricles, diastolic dysfunction, dilated atria and homogeneously echogenic valves coupled with reduced electrocardiographic voltages is characteristic of cardiac amyloidosis (Falk, 2005). Serum B-natriuretic peptide and troponin measurements and cardiac magnetic resonance imaging are being evaluated in cardiac amyloidosis with great promise.

A major clinical advance has been development of the serum free light chain (Freelite, The Binding Site, Birmingham) assay to detect and serially measure amyloidogenic immunoglobulin light chains in AL amyloidosis (Lachmann et al, 2003). In contrast to conventional serum immunofixation and electrophoresis, which have typical detection limits of 150–2000 mg/litre, this new high sensitivity immunoassay can quantify circulating free light chains with sensitivity of a few mg/litre. Before development of the serum free light chain assay, the AL amyloid precursor protein could not be measured accurately in most patients, to whom chemotherapy was empirically given for prolonged periods without evidence of its effect on the causative plasma cell dyscrasia. Nowadays, frequent serum free light chain assays enable chemotherapy to be given and monitored in a completely rational manner and, for example, to be discontinued or changed within two or three cycles if highly effective or completely ineffective as appropriate.

Management

Although no treatments are yet available that specifically promote clearance of amyloid, measures to support failing organ function while attempts are made to reduce the supply of the respective amyloid fibril precursor protein can be very effective. SAP scintigraphy in more than 3000 patients has shown that suppression of the underlying disease process often results in regression of amyloid deposits, although the process is slow and recovery of organ function is often much delayed. Ongoing production of the amyloid precursor protein should be monitored to help guide the requirement for and intensity of treatment for the underlying condition in the long term. In AA amyloidosis this necessitates regular estimation of serum amyloid A protein concentration, and long-term monitoring of serum free light chain concentration and other indicators of the underlying monoclonal plasma cell dyscrasia in AL amyloidosis.

Liver transplantation can ameliorate the underlying metabolic defect in selected patients with hereditary amyloidosis. It was first performed in familial amyloid polyneuropathy associated with transthyretin gene mutations and outcome is best among younger patients with the methionine 30 variant. Unexpectedly, paradoxical worsening of cardiac amyloidosis has occurred following liver transplantation in many older patients with other transthyretin variants, as a result of deposition of wild-type transthyretin amyloid on the existing template of variant transthyretin amyloid in the heart. Given the shortage of donor livers, functionally normal livers explanted from patients with variant transthyretin amyloidosis have been re-used in 'domino' liver transplants, in which they are given to patients with, for example, hepatic tumours who are not deemed eligible to receive standard healthy donor livers.

Supportive therapy remains critical in patients with amyloidosis, with the potential for delaying organ failure, maintaining quality of life and prolonging survival. Rigorous control of hypertension is vital in renal amyloidosis. Surgical resection of amyloidotic tissue is occasionally beneficial but, in general, a conservative approach to surgery, anaesthesia and other invasive procedures is advisable. Amyloidotic tissues may heal poorly and are liable to bleed. Vasoactive drugs should be used cautiously in cardiac amyloidosis because they can reduce cardiac output. Renal dialysis may be necessary, and cardiac, renal, and liver transplantation has been very successful in selected cases (Dubrey et al, 2004).

Finally, a range of novel therapies aimed specifically at inhibiting the formation of amyloid fibrils or promoting fibril regression are currently under development, some of which are already being evaluated clinically. These new approaches include amyloid-associated glycosaminglycans inhibitors, SAP depletion, stabilizing drugs that inhibit aberrant protein folding, RNA interference to reduce amyloid precursor protein production, and immunotherapy (Gillmore and Hawkins, 2006). There is every hope that amyloidosis will become much more readily treatable in the next few years. BJHM

Philip N Hawkins
Clinical Director
National Amyloidosis Centre
UCL Medical School
Royal Free Hospital Campus
London NW3 2PF

Dubrey SW, Burke MM, Hawkins PN, Banner NR (2004) Cardiac transplantation for amyloid heart disease: the United Kingdom experience. *J Heart Lung Transplant* **23**: 1142–53

Falk RH (2005) Diagnosis and management of the cardiac amyloidoses. *Circulation* **112**: 2047–60

Gillmore JD, Hawkins PN (2006) Drug Insight: emerging therapies for amyloidosis. *Nat Clin Pract Nephrol* **2**: 263–70

Hawkins PN, Lavender JP, Pepys MB (1990) Evaluation of systemic amyloidosis by scintigraphy with 123I-labeled serum amyloid P component. *N Engl J Med* **323**: 508–13

Lachmann HJ, Booth DR, Booth SE et al (2002) Misdiagnosis of hereditary amyloidosis as AL (primary) amyloidosis. *N Engl J Med* **346**: 1786–91

Lachmann HJ, Gallimore R, Gillmore JD et al (2003) Outcome in systemic AL amyloidosis in relation to changes in concentration of circulating free immunoglobulin light chains following chemotherapy. *Br J Haematol* **122**: 78–84

Pepys MB (2006) Amyloidosis. *Annu Rev Med* **57**: 223–41

KEY POINTS

- Systemic amyloidosis is a heterogeneous group of disorders which are responsible for the death of one per thousand of the population.
- Amyloidosis may be hereditary or acquired and is classified according to the respective fibril protein.
- Accurate diagnosis requires multidisciplinary investigation, frequently including DNA analysis.
- Management comprises treatment to reduce the supply of the respective amyloid fibril precursor protein where possible, along with supportive measures including organ transplantation in selected cases.
- Various new drug therapies are in development, some of which are already being evaluated in clinical trials.