Diagnosis and treatment of amyloidosis

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Amyloidosis has lately emerged from the backwaters of pathological curiosity into the mainstream of clinical science. This has principally arisen following characterisation of the cerebral β-protein amyloid deposits that are a pathological hallmark and very likely the cause of Alzheimer's disease. For scientists, as well as the British population at large, bovine spongiform encephalopathy, Creutzfeldt-Jakob disease, and their association with prion protein amyloid have provided additional food for thought. At the same time much progress has been made in our understanding of systemic amyloidosis, which has revolutionised the clinical management and outcome of many affected patients.

Amyloid deposits consist mainly of amyloid fibrils.[1] A prerequisite for developing amyloidosis is the sustained supply of an amyloid fibril precursor protein—that is, one which can undergo 'off-pathway' folding into an abnormal conformation that facilitates its incorporation into fibrillar aggregates. In many situations the fibril precursors are produced in abnormal abundance or with abnormal primary structure, or both. Many such proteins can form amyloid fibrils in vitro, their amino acid sequence appearing to determine their amyloidogenicity, but little is known about the factors that govern the anatomical distribution of the deposits or their clinical effects, and why certain forms of amyloid are deposited in some people but not in others. Despite the heterogeneity of their respective precursor proteins, the structure and biochemical properties of all amyloid fibrils are remarkably similar, including relative resistance to proteolysis. The fibrils associate in vivo with certain glycosaminoglycans and also with the normal plasma protein serum amyloid P component (SAP)[2] via a specific calcium dependent ligand binding interaction. The latter is the basis for our development of radiolabelled SAP as a diagnostic nuclear medicine tracer. Amyloid deposits probably exert much of their pathological effects directly through their physical presence, although this may not necessarily explain how they might cause disease in cerebral amyloidosis where the deposits are often scanty.

Amyloidosis is now classified according to the fibril protein, the previous clinical descriptions often proving to be misleading. Amyloid deposition is by no means rare and may be apparently incidental or associated with disease in virtually any organ. Focal deposits of amyloid are common in the elderly, including at least some β-protein amyloid in the brain. Whether this is the harbinger of Alzheimer's disease is unknown, but is a significant concern as life expectancy increases. Systemic AA amyloidosis, in which the fibrils are derived from the acute phase reactant serum amyloid A protein, occurs in about 5% of European patients with chronic inflammatory diseases, most commonly rheumatoid arthritis. AL amyloidosis, in which the fibrils are derived from monoclonal immunoglobulin light chains, is now the most commonly diagnosed systemic form of the disease in the developed world and probably causes the death of 1 in 2000 people. Symptomatic β_2M amyloid deposition in the bones, joints, and soft tissues eventually affects most people receiving long term haemodialysis. Hereditary amyloidosis associated with genetically variant proteins is extremely rare, but important as a model for studying amyloidogenesis.[3]

AA amyloidosis usually presents with proteinuria or renal dysfunction, or both. Clinical involvement of the liver, spleen, and sometimes gut may occur at a late stage. In contrast, AL amyloidosis is extremely variable in its presentation with any number of organs systems other than the brain being directly involved.[4] The underlying monoclonal gammopathy may not be demonstrable. Cardiac AL amyloid producing a restrictive cardiomyopathy is common and has a poor prognosis. Polyarthropathy that can mimic inflammatory synovitis is an occasional manifestation. Clinically significant amyloid in the heart, lungs, skin, nerves, muscles, gut, tongue, lymph nodes, and disorders of clotting points very strongly to AL type.

Amyloidosis can only be confirmed by demonstrating amyloid in the tissues.[5] The type must be determined and any underlying disorder characterised. Congo red staining remains the histological gold standard and immunohistochemistry is the most direct method for identifying fibril type, although it may not be definitive in AL amyloid. However, amyloid can be patchy and small biopsy specimens are open to sampling error and provide limited information on the distribution and extent of amyloid generally, and even less on its progress. The development of radiolabelled SAP as an agent that specifically targets amyloid deposits in vivo has therefore been welcome.[6–8] As SAP interacts with amyloid fibrils reversibly, the ligands to which radiolabelled SAP bind are always available validating serial studies for monitoring amyloid throughout all stages of its evolution. Although ^{123}I-labelled SAP scintigraphy is now used routinely at Hammersmith Hospital for diagnosis and quantitative monitoring of amyloid (fig 1), the technique is not yet available commercially; our success in labelling SAP with ^{99m}Tc,[9] an inexpensive and universally available isotope, may bring this closer.

No treatment specifically causes amyloid deposits to regress and the natural history of systemic amyloidosis is usually of a progressive disease with fatal outcome. This,

Table 1 Reducing the supply of fibril precursors in systemic amyloidosis

Disease	*Aim of treatment*	*Example of treatment*
AA amyloidosis	Suppress acute phase response (Monitor serum amyloid A protein)	Immunosuppression in rheumatoid arthritis, juvenile rheumatoid arthritis (for example, chlorambucil). Colchicine for familial Mediterranean fever. Surgery for resistant osteomyelitis, and rare cytokine producing tumours
AL amyloidosis	Suppress production of monoclonal immunoglobulin light chains	Chemotherapy for myeloma and monoclonal gammopathy
Hereditary amyloidosis	Eliminate source of genetically variant protein	Orthotopic liver transplantation for variant transthyretin associated familial amyloid polyneuropathy
Haemodialysis amyloidosis	Reduce plasma concentration of β_2M	Renal transplantation

along with the relative resistance of amyloid fibrils to proteolysis in vitro, has given rise to the popular notion that accumulation of amyloid is irreversible. However, it has long been known that control of underlying conditions can improve clinical outcome, and there have also been anecdotal reports of histological regression of amyloid in these circumstances. These findings, coupled more recently with the results of systematic serial radiolabelled SAP scintigraphy in over 1000 patients indicate that amyloid is, in fact, a remarkably dynamic process and suggest that mobilisation of the deposits may be the usual mechanism through which clinical improvements occur.[10]

The treatment of amyloidosis depends on the type, distribution, and clinical effects of the deposits. Supportive treatment is essential, while every means to reduce the supply of the respective fibril precursor should be considered. Under favourable circumstances further amyloid deposition will be prevented, existing deposits will regress, and organ function may improve. Unfortunately, a paucity of clinical trials means that treatment remains somewhat empirical [11] and relatively radical approaches may be justified when the prognosis is otherwise poor (table 1). Prospective SAP scintigraphy has systematically demonstrated regression of amyloid after such treatment in AA,[10 12] AL,[13–15] β_2M,[16] and hereditary TTR[17] amyloidosis. Indeed, regression of amyloid occurred in most patients whose fibril precursor supply was substantially reduced although, for reasons we can only now begin to study, the rate varied considerably from patient to patient. Under the best circumstances the whole body amyloid load can decrease by some 50% per year, and in the worst, there may be no detectable regression after five years of follow up. As clinical benefits may be delayed for many months after treatment has been started, it is important to reduce the precursor supply as quickly as possible. The alkylating agent chlorambucil was introduced by Barbara Ansell and her colleagues 30 years ago as treatment for AA amyloidosis complicating juvenile chronic arthritis,[18] and was associated with a 90% reduction in the 10 year mortality of her patients.[19] In view of its potential to induce rapid and complete remission of inflammatory disease in many cases, along with its relative freedom from kidney or liver toxicity, we continue to use chlorambucil in patients with AA amyloidosis complicating rheumatoid arthritis and juvenile chronic arthritis. Counselling should be undertaken before this drug is prescribed in view of the unlicensed indication and its adverse effects on fertility.[19] Monthly monitoring of the full blood count is ideally accompanied by estimation of serum amyloid A protein concentration.[20]

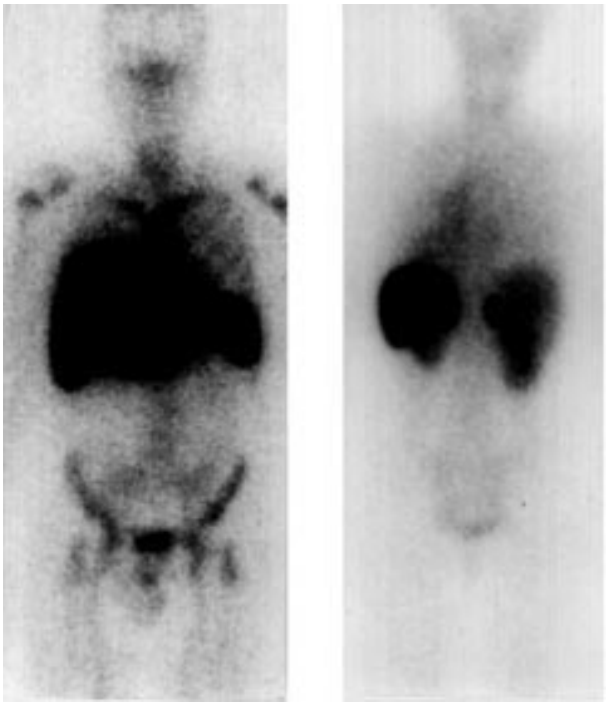

Figure 1 Whole body ^{123}I-SAP scintigraphy in amyloidosis. Left: anterior image of a 26 year old man showing uptake of tracer into substantial liver, spleen, and bone marrow amyloid, a distribution diagnostic of systemic AL amyloidosis. Right: posterior scan showing AA amyloid deposits in the spleen, adrenals, and kidneys of a 34 year old woman with rheumatoid arthritis.

Treatment of AL amyloidosis is based on experience in myeloma,[11] although the plasma cell dyscrasias are usually more subtle and may be less chemosensitive. Most patients have such a poor prognosis that they will die before low intensity cytotoxic regimens can produce clinical benefit, although some 20 per cent of patients respond well after one year of treatment with oral low dose melphalan and prednisolone.[21] Dose intensive chemotherapy regimens such as vincristine, doxorubicin (Adriamycin), and dexamethasone (VAD), and autologous peripheral blood stem-cell transplantation are presently being evaluated, with very promising early results.[22 23] An anthracycline derivative, 4'-iodo-4'-deoxydoxorubicin (I-DOX), has been identified that binds to amyloid fibrils and which may have beneficial effects in AL amyloidosis independent of its cytotoxic action.[24]

An important message to have emerged from prospective SAP scintigraphy is that there is a poor correlation between the amount of amyloid in an organ and accompanying impairment of function, especially with respect to proteinuria. Regression of amyloid does not always lead to clinical improvement, typically when organ failure is very advanced, and, conversely, improvement in organ function may sometimes occur when the progression of amyloid has merely been halted rather than reversed.

Supportive treatment remains critical, with the potential for delaying target organ failure, maintaining quality of life, and prolonging survival while the underlying process can be treated. Replacement of vital organ function, notably dialysis, may be necessary and cardiac,[15] renal,[25] and liver[26] transplant procedures have a role in selected cases. Rigorous control of hypertension is vital in renal amyloidosis. Surgical resection of amyloidotic tissue[27] is occasionally beneficial but, in general, a conservative approach to surgery, anaesthesia, and other invasive procedures is

advisable. Should any such procedure be undertaken, meticulous attention to blood pressure and fluid balance is essential. Amyloidotic tissues may heal poorly and are liable to haemorrhage. Diuretics and vasoactive drugs should be used cautiously in cardiac amyloidosis because they can reduce cardiac output substantially. Dysrhythmias may respond to conventional pharmacological treatment or to pacing.

Amyloidosis can be prevented in some circumstances. Deposition of AA amyloid can be almost completely inhibited in familial Mediterranean fever by the long term prophylactic use of colchicine, and β_2M amyloidosis is avoided by early renal transplantation. Mutant genes associated with hereditary amyloidosis can now be identified in utero and orthotopic liver transplantation has the potential to halt the development of familial amyloid polyneuropathy.

In conclusion, major progress in our biochemical knowledge of amyloid has led to significant improvements in diagnosis and evaluation of clinical cases, but there is still no treatment that specifically causes amyloid deposits to regress. Supportive measures remain a mainstay of management, particularly with respect to renal and heart failure, which are common causes of death. Encouragingly however, prospective studies with SAP scintigraphy have confirmed that amyloid deposits regress in a substantial proportion of patients in whom the supply of the amyloid fibril precursor proteins can be reduced, and regression of amyloid is often associated with improvement in organ function. As this strategy is not possible in cerebral amyloidosis, and may fail in others, new approaches to inhibit fibril formation, and the persistence and pathological effects of amyloid deposits are being pursued.

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