Amyloid heart disease – the continuing enigma

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Amyloid heart disease is comparatively rare, frequently missed and often mimics other clinical conditions. It often carries a very poor prognosis. Nonetheless, healthcare professionals should be aware of 'the amyloidoses' and advances in their diagnosis and treatment.

The amyloidoses form a collection of diseases that are part of the wider category of protein-folding disorders. Within this spectrum, proteins comprising both normal plasma constituents and mutations of such proteins, undergo a change in conformation. Such proteins become 'insoluble' and form highly ordered fibrillar aggregates. In amyloidosis, a process of self-assembly occurs in various tissues to form a beta-pleated sheet. While a comparatively rare condition, it is frequently not recognised or misdiagnosed. Patients presenting with advanced cardiac involvement have an extremely poor prognosis, with survival measureable in terms of only a few months. Healthcare professionals need to be aware of the classic stigmata, systemic nature and diagnostic facilities in order to avoid late recognition of this devastating disease.

Although amyloid heart disease is the archetypal infiltrative cardiomyopathy, it remains an unusual disease for most hospital physicians, let alone general practitioners (GPs). The experience of one busy West London district general hospital (DGH), with an interest in cardiac amyloidosis, is that of 'identifying' approximately one or two new cases per year. A GP might have had one patient with cardiac amyloidosis on their list.

Many patients remain undiagnosed, particularly among the elderly. The usual reason is that thickening of heart structures, due to infiltration, is mistaken as left ventricular hypertrophy. A low-voltage electrocardiogram (ECG) will rule out most recognised causes of true myocardial hypertrophy and make the diagnosis likely to be an infiltrative cardiomyopathy (e.g. amyloidosis, Fabry's, myxoedema and Pompes). The most common being one of the amyloidoses and usually in its most devastating form as immunoglobulin light chain (AL) amyloid. Multi-organ involvement, often with renal, gastrointestinal or neurological features, also provides the clue that this 'thickening of the heart' is part of a more sinister systemic disorder.

History

Landmark events in the management of amyloid disease include the development of serum amyloid P scanning (^{123}I-SAP scintigraphy) in 1988. This allowed estimation of whole body disease load, specific organ involvement and monitoring of response to treatment. In 1991 liver transplantation was introduced as a treatment for patients with hereditary forms of amyloidosis and remains useful for some mutations to this day.

In the early 1990s it became apparent that melphalan might be capable of curing patients with AL amyloid, but only if patients could survive long enough to receive a therapeutic course of treatment. It was not until 1996 that patients with AL amyloidosis were for the first time availed of a possible cure. This involved the use of high-dose intravenous melphalan with autologous stem-cell support (rescue transplantation).

Current management

Treatment of the amyloid disease process, of whatever type, necessitates removal of the protein at source. In the case of AL amyloid, where immunoglobulin light chains are deposited, the plasma cell clone responsible must be eradicated. In hereditary forms of the disease, the protein is predominantly produced by the liver and hence usually necessitates liver transplantation. With current treatments ranging from bone marrow ablative doses of chemotherapy through to solid organ transplantation, which can include liver, kidney and heart, one appreciates how critical an exact diagnosis becomes. These complex treatments have significant morbidity when applied appropriately and more so with any misdiagnosis of amyloid type.

A further complication is the fact that the amyloid matrix forms a 'nidus' to begat further deposition.

In the case of hereditary disease due to transthyretin, it has been shown that wild-type (normal) molecules of transthyretin are also deposited and can continue to do so even when the mutant source is removed. This situation mirrors the process in senile systemic amyloidosis, where wild-type transthyretin is deposited in the heart. It remains unclear as to what triggers normal circulating proteins to assemble.

The future

More recent additions to the established chemotherapy regimens include encouraging results using thalidomide in combination with dexamethasone. A new approach, currently under trial, is using the proteasome inhibitor bortezomib that acts by preventing destruction of ubiquinated (labelled for catabolism, via proteasome mediated proteolysis) molecules within the cell. Further advances focus on drugs that target the serum amyloid P (SAP) component, found in all amyloid deposits, with an expectation that removal of this molecule might reduce deposition or accelerate clearance. Small molecule ligands, an example of which is the non-steroidal anti-inflammatory diflusinal, have also shown some promise in treating familial amyloidosis due to transthyretin mutations.

We have now achieved a position of being able to 'turn-off' the supply (bone marrow plasma cell eradication or liver transplantation are examples) of the monomer subunits for several types of the disease and in a proportion of patients. Our understanding of amyloid structure and additional constituents has provided more targets for therapeutic attack. We now know that amyloid deposits are not insoluble and that reduction of the supply of the protein monomer units in itself may allow some regression. The associated non-fibril constituents of amyloid are also under increasing attention for their contribution to this vast spectrum of protein-folding disorders.

The vast potential of these strategies also beckons for the treatment of Alzheimer's disease, Parkinson's disease, Huntingdon's chorea, human Prion diseases, type 2 diabetes and atherosclerosis in which amyloid deposition is also intimately related

Conflict of interest

SD has received support from Johnson & Johnson Pharmaceuticals for drug trial research in amyloid disease.

Editors' note

An extensive review of amyloid heart disease, by Simon Dubrey, will be featured in a future issue of the journal.