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MiniReview

Review Article of Cardiac Amyloidosis

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Abstract

Cardiac amyloidosis is a term that means the deposit of abnormal proteins in the myocardium leading to global thickening of the heart walls. The clinical character is that of infiltrative cardiomyopathy. AL amyloidosis is the most common type that involves cardiac failure. Cardiac amyloid precedes clinical congestive heart failure, especially right-sided heart failure. Laboratory investigations have identified the amyloid fibril proteins deposited in the organ tissues. Immunofixation tests are the most sensitive that recognize the paraprotein mean light chain protein or immunoglobulin subtype deposit. Prognosis is poor if AL amyloidosis is untreated. Treatment of systemic involvement in AL amyloidosis is via chemotherapy such as melphalan and prednisolone. UK experts have reported the results of treatment in AL amyloidosis. Regardless of the use of adjunctive chemotherapy, the five-year survival after heart transplantation was generally poorer for AL (20 % at five years), but similar for non-AL amyloidosis (64 % at five years), than heart transplants in other cases. Progression of the systemic disease contributed to increased mortality. A specific treatment that increases the chances of survival is unknown.

Keywords: Amyloid, AL amyloidosis, cardiac amyloid

Introduction

The amyloidoses comprise a collection of proteins disorders and are deposited in tissues. These proteins self-assemble to form an ordered fibrillar matrix termed amyloids. Currently, more than 20 different proteins have been identified, the most common with as many as 100 different mutations per protein. This article describes the features, diagnosis and treatments for the different types of amyloid that affect the heart. Several types of amyloidosis involve the heart often with devastating consequences. In many cases, the prognosis is further worsened by systemic multi-organ involvement. For the physician, two types are important to identify as they are often present in the heart. These include AL amyloid (previously termed primary) and some of the hereditary forms of amyloid. The remaining forms rarely involve the heart, such as secondary amyloid (AA) or rather late in life as in cases of senile systemic amyloid (SSA) and isolated atrial amyloid (IAA). These latter forms are still capable of causing significant mechanical dysfunction and rhythm disturbance. Many disorders can be confused with amyloid heart disease: most commonly forms of intrinsic hypertrophic cardiomyopathy (HCM), other deposition diseases and in some cases of Fabry's disease [1].

Cardiac involvement is usually firstly suspected from the appearances on echocardiography. The heart walls are usually globally thickened and characteristically this often includes the interatrial septum. The myocardium demonstrates an increased scintillation pattern (granular sparkling) although this is certainly not specific for amyloids. Valve leaflets and the pericardium may be thickened and modest pericardial effusion may be found. While both atria will usually be dilated, the ventricular chambers are rarely dilated. Doppler interrogation of ventricular inflow will show the characteristic

restrictive features of an infiltrative cardiomyopathy. A low or normal voltage electrocardiogram (ECG) in the presence of apparent left ventricular hypertrophy is very suggestive of heart involvement, as are Q-waves without prior history of myocardial infarction. Tissue Doppler techniques have proved helpful in distinguishing amyloid from other causes of true hypertrophy and in characterising ventricular dysfunction [2]. Myocardial velocity profiles in patients with amyloid heart involvement show characteristics that differ from hypertrophied ventricular walls due to hypertension or HCM. Imaging amyloid heart disease using magnetic resonance imaging (MRI) with gadolinium enhancement, can also help differentiate amyloid from other causes of wall thickening, particularly HCM [3]. The extent of amyloid deposition can be assessed by serum amyloid P component (SAP) scintigraphy [4]. SAP is a normal plasma protein that binds reversibly to amyloid deposits of any type. While useful for imaging and quantifying amyloid in the liver, kidneys, spleen and bone marrow, it is not useful for identifying amyloid in the heart, due to the large blood pool and cardiac motion.

Histological and Genetic Diagnostic Procedures

A formal histological diagnosis is made from either a screening biopsy, such as rectal or abdominal fat biopsy, or from an affected organ, for example kidney, liver or nerve. Amyloid deposits stain with Congo red and produces red-green birefringence when viewed under cross-polarised light. Cardiac biopsy may be indicated when there is no suggestion of extra-cardiac amyloid or when the diagnosis is uncertain. In AL amyloid, serum and or urine electrophoresis and immunofixation will detect monoclonal immunoglobulin in 80 - 90 % of cases. The availability of techniques to estimate free light chains has revolutionised the diagnosis and management of AL amyloid disease. In cases where there remains doubt about the amyloid fibril type, DNA analysis to exclude hereditary amyloidosis and even amyloid fibril protein sequencing may be required. A bone marrow biopsy should be performed to quantify the plasma cell population, exclude myeloma and also stain for amyloid, which if present is strongly suggestive of AL type.

AL Amyloidosis

AL amyloidosis is the most commonly recognised form of amyloid in the UK. AL amyloid fibrils are derived from monoclonal immunoglobulin light chains produced by a plasma cell dyscrasia. While organ dysfunction is probably due to the disruptive physical presence of amyloid deposits, there is good evidence that these light chains are inherently cytotoxic [5,6]. AL amyloid presenting with heart failure has a very poor prognosis, with a median survival reported as low as four months [7]. In the absence of treatment, the natural history of AL amyloidosis is that of a progressive and fatal disease within two years in about 80 % of patients [8]. The disease is usually renal or cardiac dominant in character with death an early outcome in the absence of treatment [7,9]. AL amyloidosis may be associated with myeloma or other B cell malignancy, but in most cases the underlying plasma cell dyscrasia is subtle and non-proliferating, and can be considered to be a form of monoclonal gammopathy of undetermined significance (MGUS). The cytogenetic abnormalities that commonly occur in multiple myeloma and MGUS, such as 14q translocations and 13q deletion, have also been observed in AL amyloidosis. A concurrent diagnosis of myeloma or other B-cell malignancy is made at diagnosis in patients with AL amyloidosis when the diagnostic criteria for these conditions are fulfilled. Coexistent AL amyloidosis is diagnosed either at presentation or at some time during the course of the disease in approximately 10 - 15 % of patients with myeloma and more rarely in Waldenström's macroglobulinaemia and other lymphoid malignancies. AL amyloid deposits demonstrated histologically during the course of investigations in patients with these disorders may not be clinically significant but this can only be determined following comprehensive clinical and laboratory evaluation. It is rare for AL amyloidosis to progress to overt myeloma probably because of the short survival of patients with AL amyloidosis. AL amyloid fibrils are derived from the N-terminal region of monoclonal immunoglobulin light chains and consist of the whole or part of the variable (V_L) domain. Intact light chains are rarely found, and the molecular weight therefore varies between about 8,000 and 30,000 Dalton. All monoclonal light chains are unique and the propensity for certain ones to form amyloid fibrils is an inherent

property related to their particular structure. Monoclonal light chains that can form amyloid are able to exist in partly unfolded states, involving loss of tertiary or higher order structure. These readily aggregate with retention of β-sheet secondary structure into protofilaments and fibrils. Once the process has started, 'seeding' may also play an important facilitating role, so that amyloid deposition may progress exponentially as expansion of the amyloid template 'captures' further precursor molecules. Only a small proportion of monoclonal light chains are amyloidogenic, but it is not possible to identify these from their class or abundance.

Incidence and Epidemiology

The incidence of AL amyloidosis is difficult to define precisely. The age-adjusted incidence of AL amyloidosis in the United States is estimated to be between 5.1 and 12.8 per million persons per year [8], which is equivalent to approximately 600 new cases per year in the UK. AL amyloidosis is estimated to be the cause of death in 1 per 1,500 deaths in the UK (Office of National Statistics data). Among 474 patients seen at the Mayo Clinic [7], 60 % patients were between 50 and 70 years old at diagnosis and only 10 % were less than 50 years. Similarly, among 800 patients with AL amyloidosis who have been evaluated at the UK National Amyloidosis Centre (NAC), 66 % were aged between 50 and 70 years old at diagnosis, and 17 % were aged less than 50; thirty of these patients (4 %) were aged less than 40 and 3 were aged less than 30 years. The male:female ratio was equal. The relatively lower fraction of patients older than 70 as compared with the age incidence of myeloma and MGUS probably reflects referral practice to tertiary centres and undiagnosed disease in the elderly.

Clinical Features

The most common clinical features at diagnosis are nephrotic syndrome with or without renal insufficiency [8], congestive cardiomyopathy, sensorimotor and/or autonomic peripheral neuropathy and hepatomegaly. Fatigue and weight loss are extremely common presenting symptoms but the diagnosis is rarely made until symptoms referable to a particular organ appear.

Cardiac Amyloid

About 20 % of patients have dominant symptomatic cardiac amyloid at diagnosis. Abnormalities on ECG, notably low voltages in the standard leads, may precede clinical congestive cardiac failure. Clinical signs are mainly of right-sided heart failure (raised JVP, right sided third heart sound, peripheral oedema and hepatomegaly) or those associated with a low cardiac output, including orthostatic hypotension. In severe cases atrial thrombi may be present in sinus rhythm [9]; the onset of atrial fibrillation may be associated with an abrupt deterioration in cardiac performance and a high risk of thromboembolism. The cardiomyopathy in amyloidosis is restrictive in nature. Hence the cardiac silhouette on chest X-ray is often not enlarged and the clinical differential diagnosis may include pericardial disease or tamponade.

Localised AL Amyloidosis

AL amyloidosis can occur in a localised form that is most often identified in the upper respiratory, urogenital and gastrointestinal tracts, the skin and the orbit. In such circumstances the amyloidogenic light chains are produced by a subtle focal infiltrate of clonal lymphoplasmacytoid cells in proximity to the amyloid deposits. This type of amyloid is frequently nodular in character, but can occur quite diffusely throughout a particular tissue when it is associated with a more contiguous infiltrate of clonal cells. The AL nature of localised amyloid can often be confirmed immunohistochemically or by sequencing the fibril protein but it may not be possible to characterise the associated clonal cells due to their scanty nature. Monoclonal immunoglobulin cannot be detected in the serum or urine of most patients with localised AL amyloidosis, even when using highly sensitive assays. The phenotype of hereditary systemic amyloidosis associated with certain apolipoprotein AI variants can mimic localised laryngeal AL amyloidosis. The course of the disease is relatively benign in most patients, but severe damage to the affected organ can ultimately occur. Treatment is generally confined to local surgical intervention according to symptoms.

Laboratory Abnormalities

Common laboratory findings on routine investigation include:

- Glomerular proteinuria (predominantly albuminuria) in 90 % of patients.
- Hypercholesterolaemia is common in patients with nephrotic syndrome.
- Abnormal liver function tests - usually just elevation of alkaline phosphatase until liver amyloidosis is very advanced.
- A monoclonal immunoglobulin can be detected in serum in approximately 50 % of patients by routine electrophoresis and in serum or urine in 80 % by immunofixation. When an intact whole paraprotein is present in serum the concentration is less than 10 g/l in 30 % of patients, less than 20 g/l in over 70 % of patients and very rarely above 30 g/l [7,9]. When patients with myeloma are excluded, fewer than 10 % patients have a serum paraprotein of > 10 g/l (NAC data, unpublished).
- Anaemia is uncommon unless the amyloidosis is associated with myeloma, bleeding or chronic renal failure.
- Bone marrow aspirate and trephine biopsy is usually reported to be normal or to show only a mild increase in the percentage of plasma cells, unless the patient has overt myeloma.
- Abnormal clotting screen. A prolonged thrombin time is the most frequent abnormality, but this has no clinical association with a bleeding diathesis [9]. A prolonged prothrombin time is the only coagulation abnormality associated with bleeding.

Diagnosis and Investigation

Many patients with AL amyloidosis have multi-system involvement at diagnosis. AL amyloidosis should be considered in any patient who presents nephrotic range proteinuria with or without renal insufficiency, non-dilated cardiomyopathy, peripheral neuropathy, hepatomegaly or autonomic neuropathy whether or not a paraprotein can be detected in the serum or urine. Particular vigilance should be maintained in patients with multiple myeloma or MGUS. If suspicion of the diagnosis is based on symptoms in one organ system, evidence for involvement at other sites should be sought e.g. low voltage ECG, proteinuria or hepatomegaly, but multiple organ biopsies are potentially hazardous and are not recommended.

Diagnostic Investigations

Initial investigation should confirm the diagnosis of amyloidosis on tissue biopsy and this should be followed by investigations to establish the type of amyloid present and the extent of organ involvement. It is not always easy to be certain that amyloidosis is of an AL type because immunohistochemical staining for immunoglobulin light chains in amyloidosis is unreliable and the presence of a paraprotein does not per se confirm a diagnosis of AL amyloidosis; hereditary forms of amyloidosis are more common than previously thought and may co-exist with MGUS. This can lead to misdiagnosis [13]. In cases of doubt, DNA analysis and/or amyloid fibril sequencing may be necessary. Imaging using SAP scanning is helpful because demonstration of bone marrow involvement is strongly correlated with amyloidosis of AL type. In addition, SAP scanning may confirm the diagnosis of amyloidosis when tissue biopsy is not feasible.

Histology

Amyloid deposits stain with Congo red and produce pathognomonic red-green birefringence under cross-polarised light microscopy. Biopsy of an affected organ is usually diagnostic but less invasive alternatives are possible e.g. subcutaneous fat aspirate. Abdominal fat aspirate and rectal and labial salivary gland biopsies yield positive results in up to 80 % of cases in reported studies [8] but are non-diagnostic in up to 50 % of patients in routine clinical practice. Bone marrow biopsy should also be stained with Congo red for the presence of amyloid, and involvement of the bone marrow is strongly suggestive of AL type.

Immunohistochemistry

Antibodies are available against most known amyloid fibril proteins but definitive results are obtained in less than 50 % of patients with AL amyloid due to the presence of background normal immunoglobulin, and because light chain epitopes that are recognised by antisera to kappa or lambda light chains may be lost during fibril formation and tissue fixation. In contrast, immunohistochemistry in experienced hands can confirm or exclude amyloidosis of AA type in virtually all cases.

DNA Analysis

This is principally used to distinguish AL amyloidosis from hereditary forms of amyloid. Hereditary amyloidosis is an autosomal dominant disorder caused by mutations in the genes for transthyretin, fibrinogen A alpha-chain, lysozyme or apolipoprotein AI, but a family history is often masked due to incomplete penetrance. The clinical features may be indistinguishable from AL amyloidosis. Hereditary transthyretin and fibrinogen A alpha-chain amyloidosis are much more common than previously thought, and 31 out of the 34 patients in whom hereditary amyloidosis was misdiagnosed as AL amyloidosis in a British series of 350 cases had amyloid of either variant transthyretin or fibrinogen A alpha-chain chain type [10]. Hereditary transthyretin amyloidosis presented with polyneuropathy and/or amyloid cardiomyopathy in each case, and there should be a low threshold for sequencing the gene for transthyretin in patients with this phenotype. Features suggestive of variant fibrinogen A alpha-chain amyloidosis are its almost exclusively renal presentation coupled with a distinctive appearance on renal biopsy. This type of amyloid accumulates very selectively and substantially within the glomeruli, but is characteristically absent from blood vessels and the interstitium. DNA analysis is available at the NHS National Amyloidosis Centre.

Amyloid Fibril Protein Sequencing

Amyloid fibrils can be isolated from tissue biopsy samples and characterised by amino acid sequencing. This is the only uniformly definitive method for determining the amyloid fibril type, and can be performed to identify the type of amyloidosis when other methods have failed. This is the method by which the genes associated with hereditary amyloidosis have been identified, and is available at the NHS National Amyloidosis Centre.

Evaluation of Plasma Cell Dyscrasia

While the presence of a paraprotein does not necessarily mean that amyloidosis is of AL type, evidence of a plasma cell dyscrasia would be supportive evidence for a diagnosis of AL amyloidosis. Relevant investigations are as follows.

Serum and Urinary Protein Electrophoresis and Immunofixation

A paraprotein is detectable in the serum or urine by routine electrophoresis in approximately 50 % of patients. When an intact whole monoclonal immunoglobulin is present in serum the concentration is less than 10 g/l in 30 % of patients, less than 20 g/l in over 70 % of patients and above 30 g/l in less than 10 % [8]. It is therefore essential to perform immunofixation, as the level of paraprotein in AL amyloidosis is usually very low and routine electrophoresis is often negative. However, even on immunofixation no paraprotein is detectable in serum or urine in 20 % of cases.

Serum Free Light Chain Estimation

A new immunoassay can detect and quantify free light chains (FLC) in serum with remarkable specificity and sensitivity. The assay gives a positive result (raised level of either kappa or lambda together with an altered ratio of free kappa to free lambda light chain) in 98 % of patients with systemic AL amyloidosis [10], including those in whom a monoclonal immunoglobulin cannot be demonstrated by conventional means. This assay is not specific for AL amyloidosis, and monoclonal FLCs are present in about one-half of patients with uncomplicated MGUS, and in virtually all patients with multiple myeloma.

Bone Marrow Aspirate and Trephine Biopsy

Immunophenotyping may help to establish clonality when only small numbers of plasma cells are present.

Differential Diagnosis

The possibility of the following alternative diagnoses should be considered in all patients:

- Systemic non-AL amyloidosis including hereditary forms and AA amyloidosis. Patients with AA amyloidosis may not have an overt underlying inflammatory disorder, and that non-AL amyloidosis may co-exist with MGUS.
- Localised AL amyloidosis.

Other paraprotein-associated diseases including peripheral neuropathy and immunoglobulin deposition diseases.

Evaluation of Organ Involvement

Once a diagnosis of AL amyloidosis has been made, investigations are required to evaluate the extent and severity of organ involvement, along with further evaluation of the underlying monoclonal plasma cell dyscrasia to exclude a diagnosis of myeloma or other lymphoid malignancy.

SAP Scintigraphy

This investigation is available at the NHS National Amyloidosis Centre, and is performed routinely in most patients who are referred for evaluation of proven or suspected amyloidosis. Radiolabelled serum amyloid P component (SAP) localises rapidly and specifically to amyloid deposits in proportion to the quantity of amyloid present, allowing diagnosis and quantification of deposits by whole body scintigraphy [11]. It is used mainly to assess the extent and distribution of organ involvement by amyloid, and for evaluating the effects of treatment. It can also be used as supporting evidence for a diagnosis of amyloidosis when tissue biopsy is not possible. But cardiac amyloid is poorly visualised by this technique.

ECG and Echocardiography

Cardiac amyloid is poorly visualised by SAP scintigraphy but ECG and echocardiography provide essential information about the extent of involvement, cardiac function and prognosis. Characteristic features of cardiac amyloid on ECG include low voltages and a pattern suggestive of myocardial infarction without evidence of ischaemic damage on echocardiography. The echocardiographic features of amyloid include concentrically thickened ventricles, normal or small cavities, thickened valves and dilated atria. The ejection fraction is frequently normal, or even increased. Doppler flow studies are required to identify diastolic dysfunction, which is frequently missed in routine studies, and tissue Doppler imaging may provide further useful information. There is a poor correlation between echocardiographic and ECG findings, one or other of which may occasionally appear normal in the presence of clinically significant cardiac amyloidosis. The World Health Organisation (WHO) has described a grading system for cardiac amyloid and the New York Heart Association (NYHA) has developed a functional classification for patients with cardiac disease that can be applied to patients with cardiac amyloid.

Chest X-ray

Chest X-ray in patients with pulmonary amyloidosis may show reticulo-nodular shadowing and there may be impaired CO diffusion on pulmonary function testing.

Nerve Conduction Studies

These may be required where neuropathy is the dominant presenting symptom. Nerve biopsy may be required to establish the diagnosis.

Criteria for Defining Organ Involvement

There are no universally agreed or validated criteria for defining organ involvement. Most groups use similar but not identical criteria and only two have reported these in detail [10-12].

Prognostic Factors

Prognosis is variable but is generally poor if AL amyloidosis is untreated. Patients with systemic AL amyloidosis have a median survival of 1 to 2 years [13-15]. Few studies have specifically addressed prognostic variables. The natural history varies with the extent and nature of organ involvement but fewer than 5 % of all AL amyloidosis patients survive 10 or more years from the time of diagnosis. A poor prognosis is associated with:

- symptomatic or substantial echocardiographic evidence of cardiac amyloid; this is associated with a median survival of only approximately 6 months [11,13,16,19].
- a large whole body amyloid load on SAP scintigraphy, and evidence of accumulation of amyloid on serial SAP scans [13].
- autonomic neuropathy.
- liver involvement with hyperbilirubinaemia.
- lack of suppression of underlying clonal disease by chemotherapy.
- associated multiple myeloma**.**

A better prognosis is associated with:

- proteinuria or peripheral neuropathy (without autonomic neuropathy) as the dominant clinical feature [8].
- substantial suppression of underlying clonal disease by chemotherapy.
- regression of amyloid deposits on serial SAP scintigraphy.

A recent study characterised the repertoire of immunoglobulin light chain variable genes used by the clonal B cell in 58 AL amyloid patients and found an association between the use of certainVL germline genes and clinical presentation and outcome.

Treatment and Assessment of Response

Principles of Treatment

No treatment is yet available that specifically targets the amyloid deposits, and therapy is therefore aimed at suppressing the underlying plasma cell dyscrasia along with supportive measures to support and possibly preserve organ function. Chemotherapy regimens used in AL amyloidosis are based on those that have proven to be effective in patients with multiple myeloma, although little is known about any differences in sensitivity of the clonal plasma cells between the two disorders. Amyloid deposits exist in a state of dynamic turnover that varies markedly between patients, but gradual regression of AL amyloid is often seen when the supply of monoclonal light chains is suppressed. Furthermore, organ function may improve even when the deposits merely stabilise rather than regress. The degree by which the clonal disease needs to be suppressed to produce clinical benefit varies substantially between patients and depends on many factors, notably the turnover rate of the amyloid deposits. Clinical benefit from chemotherapy typically does not occur for many months after the underlying plasma cell dyscrasia has been adequately suppressed. Patients who receive slow-acting chemotherapy regimens often do not live long enough to derive benefit and it is therefore important to try to suppress the clonal disease as rapidly as is reasonably possible. However, more intensive chemotherapy in patients with AL amyloidosis is associated with much greater treatment-related toxicity than that seen in patients with myeloma. This is because of multiple organ impairment, which may not be evident clinically or from the results of routine laboratory investigations prior to treatment. Selecting appropriate treatment for individual patients is complicated and is compounded by the paucity of randomised controlled trials in this disorder.

Monitoring Treatment

The disease needs to be assessed in terms of response of:

Plasma Cell Dyscrasia

- assessment of the clonal B-cell disease by sensitive measurements of monoclonal immunoglobulin. This is often difficult in patients with amyloid because of the generally low amount of paraprotein. The situation has improved with the introduction of the serum free light chain assay, which appears to be the most effective method for monitoring the clonal disease in AL patients (see below).

- Follow-up bone marrow examinations are frequently unhelpful or misleading due to the subtle nature of the plasma cell dyscrasias in most patients and inherent sampling error.

Amyloid Deposits

- SAP scintigraphy.

- assessment of organ size clinically or by imaging techniques.

Organ Function

- ECG / echocardiography.

- routine measurements of renal function, including 24 h urine protein excretion and creatinine clearance.

- liver function tests.

- assessment of other organ function as indicated.

Use of serum free light chain concentration (FLC) in Monitoring Disease raised levels of serum FLC are detectable in most patients with AL amyloidosis, and since FLC have a circulating half-life of several hours as opposed to many weeks for intact immunoglobulins, their measurement enables response to chemotherapy to be evaluated effectively and rapidly, for example on a monthly basis during cyclical treatments. A study of 137 patients with AL amyloidosis who were followed-up at the NAC demonstrated that outcome correlated strongly with changes in concentration of circulating FLC following chemotherapy [13]. Following chemotherapy, for those patients who survived 6 months, the abnormal FLC concentration fell by more than half in 86 out of 137 patients. Changes in the amyloid load correlated positively with changes in FLC concentration, and survival at 5 years was 88 % among patients whose FLC fell by more than half, but only 39 % among patients whose FLC remained above this value ($p < 0.0001$).

Chemotherapy and Other Agents

Chemotherapy currently used in AL amyloidosis can be classified as:

Low Dose: Single agent melphalan or cyclophosphamide (with or without prednisolone). Clinical benefit occurs in only about 20 - 30 % of patients, and only after a median of 12 months treatment. The combination chemotherapy regimen vincristine, carmustine, melphalan, cyclophosphamide and prednisone (VBMCP) is not more effective.

Intermediate Dose: Monthly courses of VAD and similar regimes, or intravenous intermediate dose melphalan 25 mg/m^2 (IDM) with or without dexamethasone.

High Dose: High dose therapy (HDT) with intravenous melphalan (100 - 200 mg/m^2) and stem cell rescue.

Other Approaches

- Pulsed high dose dexamethasone.
- thalidomide (with or without dexamethasone) with or without other agents.

Intermediate and high dose chemotherapy are thought to be clinically beneficial in more than 50 % of patients, but have not been compared in randomised trials either with each other, or with low dose chemotherapy, or with no treatment.

Standard and Intermediate Dose Therapy

Colchicine

Colchicine is effective in the treatment of AA amyloidosis complicating familial Mediterranean fever by suppressing the underlying inflammatory disease, but has no role in AL amyloidosis. In a randomised controlled trial [14], studied 220 patients who were treated with colchicine alone, melphalan and prednisolone, or melphalan and prednisolone and colchicine. Median survival was 8.5, 18 and 17 months respectively ($p < 0.001$).

Recommendation

There is no role for colchicine in the management of AL amyloidosis (Grade A recommendation; level Ib evidence).

Melphalan and Prednisolone Regimen

Histological regression of amyloid has been documented on repeat liver biopsy after therapy with melphalan and prednisolone [14]. It is the only chemotherapy regimen that has been evaluated in randomised controlled clinical trials. Several studies using slightly different regimens of melphalan and prednisolone have confirmed the efficacy of this treatment over no therapy or colchicine alone. The first of these trials was a placebo-controlled, double blind study of 55 patients with AL amyloidosis [15], which showed benefit in terms of organ function for those patients receiving melphalan and prednisolone. A randomised trial confirmed that MP was superior to colchicine alone in terms of response and survival. Response assessed by organ function and paraprotein levels, was seen in 28 % of patients on MP and only 3 % of those on colchicine. Survival in patients receiving MP was 18 months compared to 8.5 months for colchicine alone. It has also been shown that the addition of colchicine to melphalan and prednisolone did not confer any extra benefit over melphalan and prednisolone alone [15]. In a later study comparing MP with VBMCP, the median survival of patient's randomised to MP was 25 months. Patients who respond to MP survive significantly longer than non-responders (89 vs. 14 months) [15]. The median time to response in this study was 12 months. Patients must therefore live long enough to receive several cycles of chemotherapy before any survival benefit is seen. Patients with symptomatic cardiac amyloid rarely benefit from treatment with standard MP but encouraging results have recently been reported with continuous oral melphalan in patients with cardiac amyloidosis who were unfit for more aggressive therapy [16]. The adverse effects of melphalan include myelotoxicity, and in patients who survive longer than 3.5 years, there is a 20 % risk of myelodysplasia often leading to secondary leukaemia [14].

Recommendations

- Melphalan with or without prednisolone may be considered as initial treatment of choice for patients in whom intermediate or high-dose therapy is not considered appropriate (Grade A recommendation; level Ib evidence).
- Treatment should be continued when feasible until the clonal disease has been substantially suppressed, i.e. by at least 50 - 75 %, or until plateau, and should be monitored where possible by the serum FLC assay (Grade C recommendation; level IV evidence).
- The evidence of benefit from steroids in standard doses has not been evaluated in AL

amyloidosis. In myeloma the evidence of benefit from steroids in standard doses is controversial. It may therefore be reasonable not to include prednisolone, particularly in patients at risk of steroid-related side effects (Grade C recommendation; level IV evidence).

- high dose therapy and PBSCT is not recommended in patients with any of the following:
  - symptomatic cardiac amyloid
  - symptomatic autonomic neuropathy
  - history of GI bleeding due to amyloid
  - dialysis-dependent renal failure
  - age over 70 years
  - more than 2 organ systems involved
- PBSCT may be considered in other selected patients, including.
  - good-risk patients (no cardiac involvement, 1 - 2 organs involved and GFR > 50 ml/min).
  - patients treated with VAD or other initial therapy who have not responded.
  - patients with early relapse of plasma cell dyscrasia after VAD or other treatment.
- transplantation should be performed according to an agreed protocol in centres with particular expertise/interest.
- caution is required during mobilisation and harvesting of stem cells prior to transplantation and this should also be performed according to an agreed protocol in centres with particular expertise/interest.

Allogeneic BMT

The first successful allogeneic BMT for AL amyloidosis was reported in 1998 [16] and was associated with complete clinical recovery at 3 years post-BMT. This supports the hypothesis that as in myeloma a small proportion of patients may derive significant clinical benefit from the procedure but at present it remains experimental, and is likely to be associated with extremely high treatment related mortality. There is currently no data on the use of reduced-intensity conditioning in AL amyloid.

Management of Amyloid Heart Disease

Patients with AL (and non-AL) forms of cardiac involvement may benefit symptomatically from conventional heart failure therapies. Careful titration of diuretics remains the mainstay of management. Orthostatic hypotension may require support stockings and sometimes the use of fludrocortisone. The alpha agonist midodrine can be very effective as a pressor agent. Calcium channel blockers and beta blockers should be used with caution due to their negative inotropic effects. Reports suggest digoxin can bind to amyloid fibrils with increased toxicity, but judicious low dose treatment can sometimes be beneficial. Permanent pacing, resynchronisation pacing and automatic implantable cardioverter defibrillator (AICD) implantation may prove useful in a small proportion of cases.

Congestive Cardiac Failure

The presence or absence of cardiac amyloidosis is the most important factor affecting survival. Sudden death is common and is usually not presaged by evidence of arrhythmias. The mainstay of treatment for congestive heart failure is diuretics and increasing doses are required as progression of cardiomyopathy occurs. The addition of spironolactone to loop diuretic therapy is very effective in some cases. Cardiac amyloidosis is a restrictive cardiomyopathy, and an adequate cardiac output depends crucially on maintaining relatively high filling pressures. It has not been established whether angiotensin-converting enzyme inhibitors are beneficial, and low cardiac output or orthostatic hypotension may limit their use. Calcium-channel blockers and beta-blockers are contra-indicated in cardiac amyloidosis. Digoxin may cause toxicity at therapeutic levels but is not necessarily contra-indicated in the management of patients with cardiac amyloidosis and supraventricular tachyarrhythmias.

Cardiac Transplantation

Where AL amyloidosis is limited to the heart, death usually occurs suddenly or as a result of progressive heart failure. Cardiac transplantation has been performed in a small number of these patients [16,19,22] although the procedure remains controversial because of the scarcity of donor hearts, the high transplant-related mortality (due to extra-cardiac amyloid) and the likelihood of amyloid deposition in the graft. Chemotherapy used in association with cardiac and other organ transplantation is required to prevent recurrence of amyloid or its progression in other organ systems.

Recommendations

- Congestive cardiac failure should be treated predominantly with diuretics, and angiotensin-converting enzyme inhibitors should be used with caution (Grade C recommendation, level IV evidence).
- Calcium-channel blockers and beta-blockers are best avoided in cardiac amyloidosis (Grade C recommendation, level IV evidence).
- Cardiac amyloidosis is a relative contraindication to the use of digoxin (Grade C recommendation, level IV evidence).

In patients where cardiac manifestations are the predominant or only signs/symptoms of cardiac amyloidosis, patients should be considered for heart transplantation but this procedure should be followed by chemotherapy treatment to prevent re-accumulation of amyloid in the transplanted heart (Grade C recommendation, level IV evidence).

Specific Management of AL Amyloid

Treatment of AL amyloidosis comprises chemotherapy directed towards the underlying clonal plasma cell disease, with the objective of reducing production of amyloidogenic monoclonal immunoglobulin light chains. Combined oral melphalan and prednisolone is of proven but very modest benefit in AL amyloidosis [10] and more dose-intensive regimens are now usually pursued. Recent British guidelines favour intermediate dose chemotherapies, such as vincristine, adriamycin and dexamethasone (VAD) or monthly intravenous melphalan with dexamethasone [11]. Chemotherapy that reduces circulating free immunoglobulin light chain (FLC) concentrations can greatly enhance survival [12,13]. In a recent study, the five-year survival of AL patients was 88 % in those with more than a 50 % reduction in their FLC, compared to 39 % in those whose FLC did not fall by half ($p < 0.0001$) [13].

High-dose Chemotherapy and Autologous Stem Cell Transplantation

High-dose chemotherapy with melphalan supported by autologous stem cell transplantation has been used increasingly in AL amyloidosis [14]. Response rates in terms of clonal disease remission are encouraging with centres reporting a complete haematologic response in as many as 40 % of eligible patients. However, mortality rates are appreciable with experienced centres reporting values between 13 and 20 % [15,16]. The overall impression is that patients with advanced disease, and particularly those with cardiac decompensation, tolerate this therapy poorly.

Additional and Alternative Therapies

Following success with its use in myeloma, the drug thalidomide has been tried both alone and in combination with chemotherapy [17], although high dose thalidomide is not well tolerated by subjects with AL amyloid [18]. Recently, the combination of thalidomide and intermediate-dose dexamethasone has been shown to be effective in a proportion of patients (48 %) who are refractory to therapy. Again, as with high-dose thalidomide, treatment-related toxicity was frequent (65 %) [19]. The tumour necrosis factor inhibitor etanercept has been trialled in a small cohort with advanced AL amyloidosis, with 50 % of patients appearing to benefit objectively and 88 % reporting subjective benefit in symptoms [20]. Clonal disease remission is encouraging with centres reporting a complete haematologic response in as many as 40 % of eligible patients. However, mortality rates are appreciable with experienced centres reporting values between 13 and 20 % [15,16]. The overall impression is that patients with advanced disease, and particularly those with cardiac decompensation, tolerate this therapy poorly. As yet there is no specific treatment for amyloid that has been proven to promote its regression, though many candidate drugs have been tested over the years. Recent studies of a doxorubicin derivative (I-DOX), a cytotoxic anthracyclin, suggested promise [21], but subsequent data were inconclusive [22,23], and it is notably toxic.

Heart Transplantation for AL Amyloid Heart Disease

The UK experience was reported in 2004 for a total of 24 patients (17 AL and 7 non-AL amyloid) [24]. Regardless of the use of adjunctive chemotherapy, the five-year survival after heart transplantation was generally poorer for AL (20 % at five years), but similar for non-AL amyloidosis (64 % at five years), than following heart transplantation for other indications. Progression of the systemic disease contributed to the increased mortality. Experience from the United States is similarly disappointing in AL patients undergoing heart transplants [25].

The Non-AL Amyloidoses

Within the non-AL categories of amyloid, of the 75 mutations known to express a clinical phenotype, around 44 (59 %) involve the heart with a cardiomyopathy. Some deposited proteins cause cardiac compromise on a par with AL amyloid. The true frequencies of these individual types of amyloid are very difficult to estimate, largely due to the fact that many patients remain undiagnosed or misdiagnosed, and it may be of relatively late onset in life. In the non-AL types, inquiry about a family history, with particular attention to any neurological diseases, is important. The caveat to this is that penetrance of these autosomal dominant genes is not always 100 %. Patients with many of the non-AL forms of inherited amyloidosis frequently present with a progressive sensorimotor neuropathy. Macroglossia is not a feature, although carpal tunnel syndrome may be an early indicator of the disease. Clinical features will depend on the protein sub-unit, the actual mutation and, frequently, the kindred within which the mutation is 'embedded'. As in AL amyloid heart disease, a restrictive cardiomyopathy is often the ultimate cause of death, and fatal cardiac arrhythmias are also a feature. Echocardiographically, a hereditary form of amyloidosis may be indistinguishable from AL amyloidosis [26]. Autosomal dominant hereditary amyloidosis is probably the second most common type of amyloid encountered by cardiologists, though the familial etiology is often not obvious. Usually these forms are associated with a mutation of the plasma protein transthyretin (TTR). Around 100 different amyloidogenic missense point mutations of TTR have already been described. One such is particularly common in patients of black African origin. Heart involvement is not uncommon and can also occur with variants of hereditary fibrinogen and apolipoprotein-AI amyloid.

Management of Hereditary Amyloidosis

In patients with hereditary amyloidosis, where the amyloidogenic protein is predominantly produced by the liver (TTR and fibrinogen mutations), orthotopic liver transplantation provides a treatment by removing the source of the mutant protein [27,28]. Initial hopes for liver transplantation as a cure have been tempered by reports of progression of amyloid deposition in native hearts and donor hearts simultaneously transplanted with livers [29]. It appears that wild-type TTR may continue the amyloid deposition, after liver transplantation has eliminated the TTR variant that initiated the amyloidogenic process [30]. Experience with apolipoprotein AI amyloidosis and cardiac involvement is less well described. Patients with mutations of the apoprotein AI molecule, may require combined heart and kidney transplants, because of a predilection for apoprotein AI amyloid deposition in the kidneys with resultant renal failure.

Additional and Alternative Therapies

A drug is already being tested in patients that targets SAP with the goal of eliminating SAP from amyloid deposits, in the hope that this may reduce amyloid deposition and/or accelerate amyloid clearance. Small molecule ligands that stabilise the native tetrameric structure of TTR and prevent its fibrillogenesis are being actively investigated for prophylaxis and therapy in TTR amyloidosis. Diflusinal has recently been found to stabilise the structure of TTR. This action reduces tetramer dissociation and subsequent monomer misfolding and aggregation into the amyloid. A trial of its clinical efficacy is in progress and several similar, and possibly more potent, agents are in development. Senile systemic amyloidosis normal wild-type TTR is in itself weakly amyloidogenic and wild-type TTR amyloid deposition is remarkably common in individuals over 70 - 80 years of age. Unlike genetically variant forms, wild-type TTR amyloid deposits are largely confined to the heart [31]. Cardiac deposition of wild-type TTR may sometimes be massive, resulting in severe heart failure [32]. The echocardiographic appearance is typical of other forms of amyloidosis, but there is no neuropathy or other major extracardiac involvement. It is almost exclusively a disease of elderly men. A recent report comparing patients with AL and senile amyloid heart involvement found that patients with senile cardiac amyloid had ventricular walls even thicker than those with AL [33]. However, despite thicker walls and being older, the senile amyloid patients had less severe heart failure and a much longer median survival (75 vs. 11 months). Treatment is directed at symptom relief with conventional heart failure therapies. Heart transplantation is a reasonable consideration in patients with advanced SSA heart involvement, but only if they present at a young enough age. Despite

the terminology ('senile' amyloid), occasionally patients are under 60 years of age and eligible for transplantation [24].

Secondary Amyloidosis

AA amyloidosis is a rare complication of chronic inflammatory disorders. The fibrils are derived from the acute phase reactant serum amyloid A protein. Although cardiac deposits are often present at histology, echocardiographic abnormalities and clinical symptoms of cardiac AA amyloidosis are extremely rare, occurring in about 2 % of cases. The prognosis is substantially better than in cases of AL amyloid [34]. Treatment involves suppressing the underlying inflammatory disease.

Isolated Atrial Amyloid

Atrial natriuretic peptide (ANP) is synthesised locally by atrial myocytes [35], and can be deposited locally within the atria as an amyloid. It may be important in the development of atrial conduction abnormalities and atrial fibrillation. IAA is a disease of the elderly, with a female preponderance that contrasts with an almost male exclusivity of senile TTR amyloid [33]. The incidence of IAA in elderly hearts is high, with one autopsy study describing IAA in 91 of 100 hearts [36]. No specific therapy exists to treat IAA and management centres on controlling rhythm disturbance.

Conclusion

Late diagnosis remains one of the main hindrances to the management of amyloidosis. Once identified, it is vital to precisely determine the type of amyloid as both the prognosis and treatment differ very considerably among the types. The goal remains, to prevent production and deposition of constituent monomer building blocks, to destabilise assembled fibrils and solubilise the amyloid deposits into nonpathogenic constituents. In cardiac amyloidosis may be identified for localised or systemic involvement. The rational treatment in localised cases is controversial but the treatment for the systemic form is chemotherapy and cardiac transplantation.

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