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REVIEW

Diagnostic and therapeutic approach of systemic amyloidosis

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ABSTRACT

Amyloidosis is a group of diseases, all characterised by deposition of protein fibrils with a β-sheet structure. This structure generates affinity of amyloid for Congo red dye and is resistant to proteolysis. Three types of systemic amyloidosis are important for the clinician: AA (related to underlying chronic inflammation), AL (related to underlying monoclonal light chain production) and ATTR amyloidosis (related to old age or underlying hereditary mutations of transthyretin). Signs and symptoms vary considerably among the three types and the choice of treatment differs completely.

A stepwise approach in diagnosis and therapy is presented. When amyloidosis is suspected the first step is histological proof of amyloid and the second is proof of systemic involvement. The next two steps are determination of the type of amyloid followed by detection of the precursor protein. The fifth step is a thoughtful clinical evaluation, necessary for assessment of prognosis and therapy. Subsequently, the choice of therapy is based on the 'precursor-product' concept. In the final step, the effects of therapy on the underlying disease as well as on the amyloidosis are assessed during follow-up. In this evaluation serum amyloid P component (SAP) scintigraphy helps to show organ involvement and therapy response.

INTRODUCTION

Amyloidosis is a group of diseases all characterised by deposition of proteinaceous fibrils with a molecular β-sheet structure.[1] This structure of the fibrils is responsible for their insolubility, resistance to proteolysis and binding affinity for Congo red dye and the consequent green birefringence with polarised light. Amyloid fibrils are derived from different protein precursors. Extracellular deposition of amyloid fibrils in organs and tissues results in loss of organ function and may cause prominent swelling of the affected organ or tissue. Deposition of amyloid can be localised (restricted to one organ or site of the body) or systemic (in various organs and tissues throughout the body). The various clinical pictures of systemic amyloidosis are related to the type of precursor protein involved.[1,2] Terms such as primary and secondary amyloidosis have become obsolete, because all types of amyloid are secondary to the production of a specific precursor. Therefore the old nomenclature has been replaced by a new one based on the protein precursor.[2] In this article the clinician will find a stepwise approach to diagnosis, clinical evaluation and background of therapy in patients with suspected systemic amyloidosis. Readers who want to know more about clinical aspects and molecular mechanisms of the systemic amyloidoses are referred to the review articles of Falk *et al*[1] and Merlini and Belotti.[3]

CLASSIFICATION

Although localised deposition of amyloid plays an important role in the development of widespread serious diseases such as Alzheimer's disease (β-protein in the plaques) and diabetes mellitus type II (amylin in the islands of Langerhans), this article focuses on the systemic types of amyloidosis. There are four major types.[1,3]

AA amyloidosis
This type is caused by longstanding inflammation. Serum amyloid A protein (SAA), an acute phase reactant, is the precursor protein. Renal manifestations, such as proteinuria (progressing to nephrotic syndrome) and loss of renal function (progressing to renal failure), are observed very frequently (about 90% of cases). Less frequent manifestations are autonomic neuropathy, hepatomegaly and cardiomyopathy.

AL amyloidosis
AL amyloidosis is caused by a plasma cell dyscrasia. Lambda or kappa immunoglobulin light chain is the precursor protein of this type. Clinical manifestations are very diverse, such as cardiomyopathy, hepatomegaly, splenomegaly, nephrotic syndrome, renal failure, orthostatic hypotension, diarrhoea, peripheral and autonomic neuropathy, arthropathy, carpal tunnel syndrome (CTS) and glossomegaly. The diversity of manifestations (and their combinations) depends on the severity of deposition in the various organs and tissues.

ATTR amyloidosis
Various autosomal dominant hereditary point mutations of the precursor protein transthyretin (TTR) cause this type. Transthyretin, formerly called prealbumin because of its electrophoretic profile, is an acronym of a transport protein of thyroid hormone and retinol-binding protein. More than 80 of these mutations have been described. Prominent clinical manifestations are (familial) peripheral and autonomic neuropathy, but cardiomyopathy, renal failure and eye involvement (vitreous opacities) are also often observed. Severe cardiomyopathy can be the presenting sign in some of the TTR mutations. In very old age, normal ('wild-type') TTR can also behave as precursor protein. This so-called senile systemic amyloidosis is characterised by a slowly progressive cardiomyopathy.

Aβ2M amyloidosis
This type is caused by renal failure and longstanding (i.e. at least 5 to 10 years) dialysis with decreased clearance of beta-2-microglobulin (β2M). β2M is the precursor protein of this type. Clinical manifestations are arthropathy, such as tenosynovitis, shoulder pain, CTS, periarticular cysts, pathological fractures and destructive spondyloarthropathy. Synovial tissue biopsy is the method to detect amyloid. Kidney transplantation stops the disease.[4,5]
Aβ2M amyloidosis is a disabling disease that should be recognised and treated. This article, however, describes only the first three types (AA, AL and ATTR) of systemic amyloidosis because these types are often unexpected, difficult to diagnose, with variable involvement of many different organs and tissues and often pose the problem of finding the most appropriate therapy.

PROOF OF AMYLOID

The first step is to detect amyloid. The diagnosis of amyloid is based on proof of its presence in tissue. This can be shown in a positive Congo red stained tissue specimen with the characteristic apple-green birefringence in polarised light (see *figure 1*). The abdominal subcutaneous fat aspiration is the most elegant and least inconvenient method for this purpose, with a sensitivity ranging between 54%[6] and 82%[7,8] and a specificity of 100%.

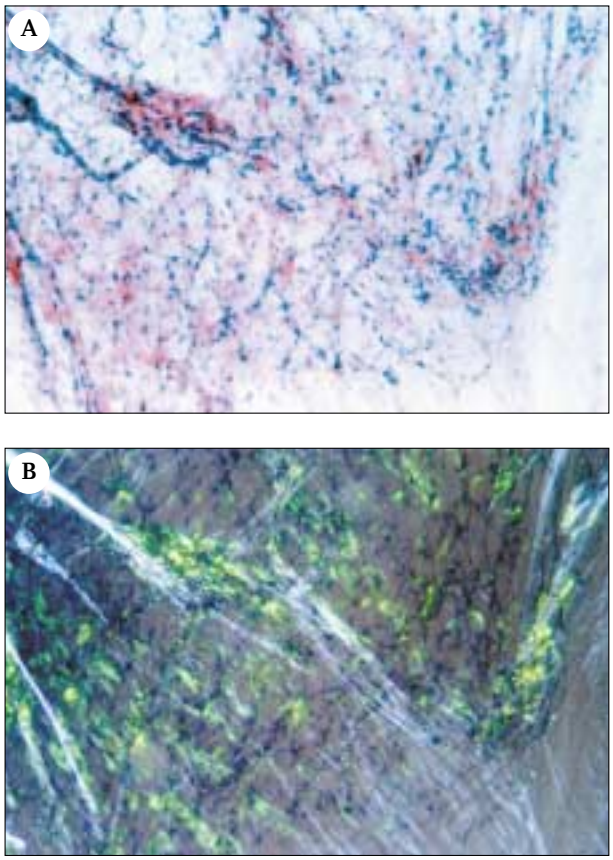

Figure 1A and B
Example of an abdominal subcutaneous fat aspirate, stained with Congo red, magnification 30x.
A: When viewed in normal light, amyloid is stained red.
B: The same specimen viewed in polarised light: amyloid shows apple-green birefringence.

These figures are similar to those of the well-known rectum biopsy.[8] If the primary biopsy site (fat or rectum) is negative for amyloid and there is strong suspicion of amyloidosis, a biopsy of the other tissue is useful to increase the chance of detecting amyloid. A bone marrow biopsy can also be used, but has a disappointingly low sensitivity of 50 to 60%.[8] When all biopsies are negative but a strong suspicion of amyloidosis still exists, a biopsy of the affected organ or tissue is indicated.[1,9]

SYSTEMIC DEPOSITION

Amyloid deposition can be local or systemic. Therefore the second step is to check for systemic deposition. Some sites are exclusively involved in systemic amyloidosis, such as kidneys, liver, nerves, abdominal fat and spleen. If such a site is positive for amyloid, systemic involvement is established. Localised amyloid can often be found in other sites of the body, including the eyelid, cardiac atria, larynx, ureter and skin. In these cases amyloid must be undetectable elsewhere in the body to confirm localised amyloidosis. Most other sites (bone marrow, heart, bowel, lung, joint, etc.) are nearly always involved in systemic amyloidosis. In this situation it is recommended to demonstrate amyloid in two different organs or tissues. For this demonstration, however, it is sufficient to have histological proof at one site (such as bone marrow, skin or rectum) and clinical involvement (such as nephrotic syndrome, hepatomegaly, macroglossia, or cardiomyopathy) at the other site.[10]

TYPE OF AMYLOID

After verification of presence of systemic amyloid, the third step is determination of the type of amyloid. In many cases the type of amyloid can be assessed with high probability from the medical history and clinical picture. Amyloidosis in a patient with longstanding rheumatoid arthritis and nephrotic syndrome is almost certainly the AA type. Someone with polyneuropathy who belongs to a family with hereditary amyloidosis probably has ATTR amyloidosis. And in a patient with characteristic shoulder pads and glossomegaly it is hard to imagine something other than AL amyloidosis. Nevertheless, even in these patients with strong clinical evidence for a particular type of amyloid, more solid confirmation of the specific type of amyloid should be determined. The clinical consequences of incorrect typing of amyloid can be considerable: prognosis and therapy of the three major types of systemic amyloidosis are completely different.
Immunohistochemistry of a biopsy is helpful to characterise the type of amyloid by using specific antibodies (see *figures 2* and *3*). In AA amyloidosis this technique is sufficient, provided sensitive and specific monoclonal antibodies are used, such as mc1[10] and Reu.86.2.[11,12]

However, in ATTR amyloidosis and especially in AL amyloidosis this method is less reliable than in AA amyloidosis. This is caused by heterogeneity of amyloid deposits, loss of epitopes in the fibril structure, lower sensitivity and specificity of (polyclonal) antibodies and nonspecific adherence of immunoglobulins to amyloid deposits or the background.[10] Lack of a positive family history does not exclude ATTR amyloidosis as shown by a considerable number of 'sporadic' cases that have been described.[13] Therefore presence of a TTR mutation (by DNA analysis) must be established in all cases of ATTR amyloidosis. The only exclusion for this requirement is old age (>80 years) and a typical clinical picture of senile systemic amyloidosis (i.e. slowly progressive cardiomyopathy). In patients with AL amyloidosis, a monoclonal plasma cell dyscrasia with overproduction of lambda or kappa light chain must be present. It can be detected in bone marrow (clonal dominance by immunophenotyping of plasma cells), urine (Bence Jones proteins, immunofixation of concentrated urine) and blood (M-protein, immunofixation and the free light chain assay). However, a monoclonal gammopathy of undetermined significance (MGUS) is frequently present in healthy older persons,

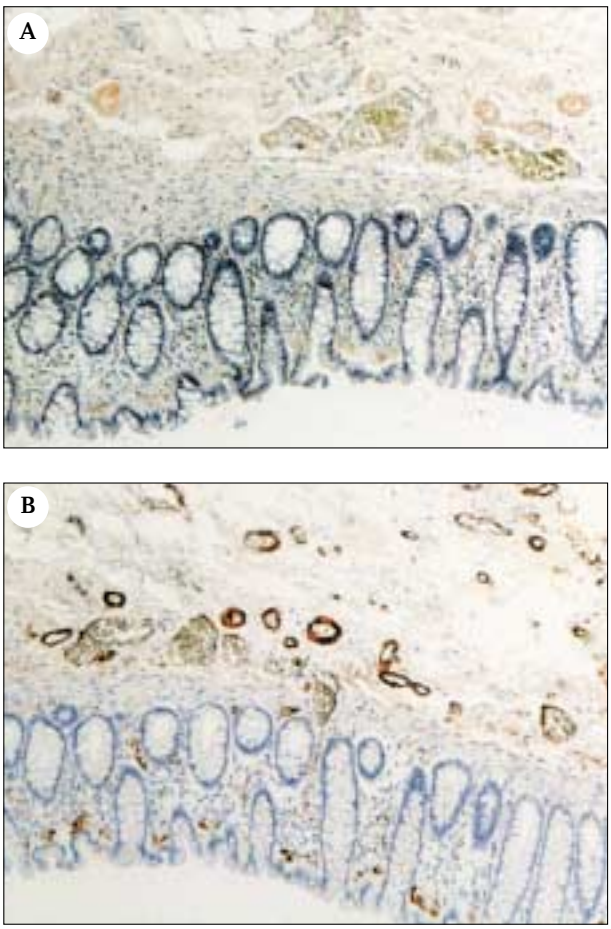

Figure 2A and B
Rectum biopsy of a patient with AA amyloidosis, magnification 30x. Small deposits of amyloid can be seen in the epithelial border and in the submucosa in the walls of blood vessels.
A: Amyloid is red in the Congo red stain.
B: Amyloid is brown in the immunoperoxidase stain with monoclonal antibodies against SAA (Reu.86.2).

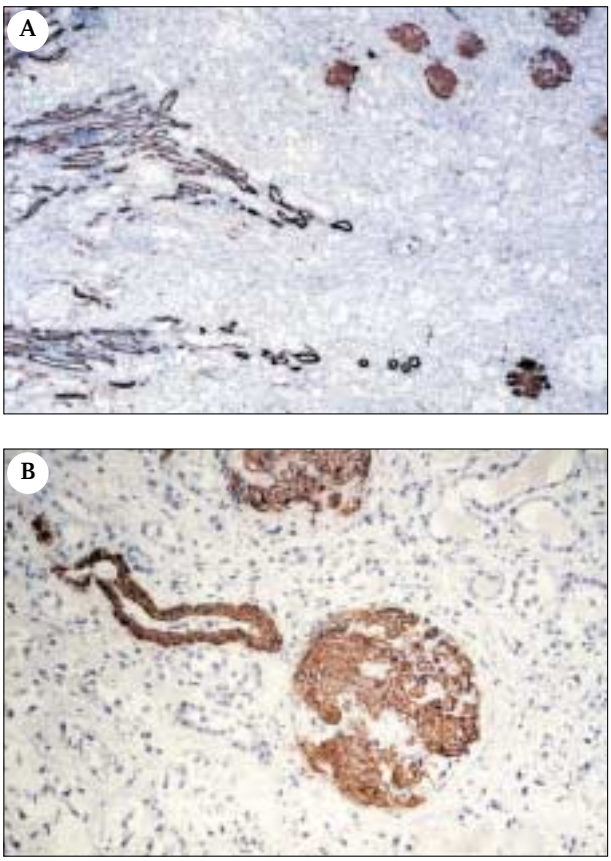

Figure 3A and B
Kidney tissue of a patient with AA amyloidosis. Amyloid is brown in the immunoperoxidase stain with monoclonal antibodies against SAA (Reu.86.2).
A: Overview with glomeruli and vasa recta, magnification 10x.
B: Detail, glomerulus, magnification 40x.

ranging from 2% in persons of 50 to 3% in persons of 70 years.[14] Thus detection of MGUS does not exclude other types than AL amyloidosis. It is important to notice that the clinical picture of ATTR amyloidosis and AL amyloidosis can sometimes be similar, such as in cases with polyneuropathy, autonomic neuropathy, cardiomyopathy and carpal tunnel syndrome. In such a clinical picture it is therefore not sufficient to show the presence of a plasma cell dyscrasia but also necessary to exclude a TTR mutation before AL amyloidosis can be diagnosed.[13]

PRECURSOR PROTEIN

After establishing the type of amyloid it is time for the fourth step, i.e. to look for a precursor protein in the blood. Detection of a precursor protein and measuring its serum concentration is important for therapy. In AA amyloidosis the precursor protein is SAA, an acute phase reactant. The behaviour of SAA during inflammation is comparable with C-reactive protein (CRP), a protein that can be assessed in routine clinical practice. In ATTR amyloidosis the precursor protein is a mutated TTR. This can be detected by isoelectric focusing.[1] In AL amyloidosis a recently described assay shows the presence of free lambda and kappa precursor proteins in blood using specific antibodies raised against normally hidden epitopes in the complete immunoglobulin.[15]

CLINICAL EVALUATION

The fifth step is to obtain a reliable understanding of the 'amyloid load', i.e. affected organs and tissues and severity of amyloid deposition in vital organs (such as heart, liver and kidneys). One should not forget to ask about the family history, impotence, orthostatic complaints, loss of sensibility, fatigue, weight loss and bowel problems. Physical examination should also focus on signs such as orthostatic blood pressure, friability of skin, glossomegaly, arthropathy, hepatomegaly, splenomegaly, oedema, cardiac failure and loss of sensibility and muscle strength of extremities.
A thoughtful systematic clinical approach is helpful. The heart can be examined with electrocardiography (signs of low voltage and pseudo-anteroseptal infarction), chest X-ray (normally sized heart despite signs of cardiac failure), echocardiography (thickness of septum and ventricular walls), 24-hour Holter registration (conduction, rhythm and heart rate variability) and a MUGA scan (ejection fraction). The kidneys can be examined with serum albumin, creatinine clearance, urine sediment and proteinuria, whereas serum albumin, liver enzymes such as alkaline phosphatase, bilirubin, coagulation tests and cholinesterase can be used to examine the liver. Thyroid-stimulating hormone can be used for the thyroid and fasting cortisol for the adrenal glands. Autonomic function tests ('Ewing battery') and heart rate variability are ways of evaluating autonomic neuropathy.[16,17] Electromyography can be used to assess peripheral neuropathy. Abdominal ultrasound may be helpful to evaluate size and echogenecity of liver, spleen and kidneys. Not all of the examinations mentioned above need to be employed because often it is obvious that clinical organ involvement is not present at all. However, echocardiography should be considered in all patients, even in those without cardiac symptoms.
Serum amyloid P component (SAP) scintigraphy is a technique that has been developed in London by Pepys and Hawkins for specific evaluation of amyloidosis.[18,19] All amyloid deposits contain SAP, a glycoprotein that belongs to the pentraxin family and binds in a calcium-dependent way to all amyloid deposits independently of the protein of origin. The ^{123}I-labelled SAP scan can show specific uptake in organs such as liver, spleen, kidneys,

adrenals, bone marrow and joints (see *figure 4* for some examples). However, myocardium does not show specific uptake, probably because of the combination of high background activity of tracer still present in the blood pool and decreased permeability in cardiac tissue of this tracer with a high molecular weight.[18] Measurement of SAP retention after 24 or 48 hours combined with the intensity of organ uptake on images provides a quantitative estimate of amyloid load in an individual patient that might be used to monitor effect of therapy in this patient.[19] The technique is only available in a few centres.

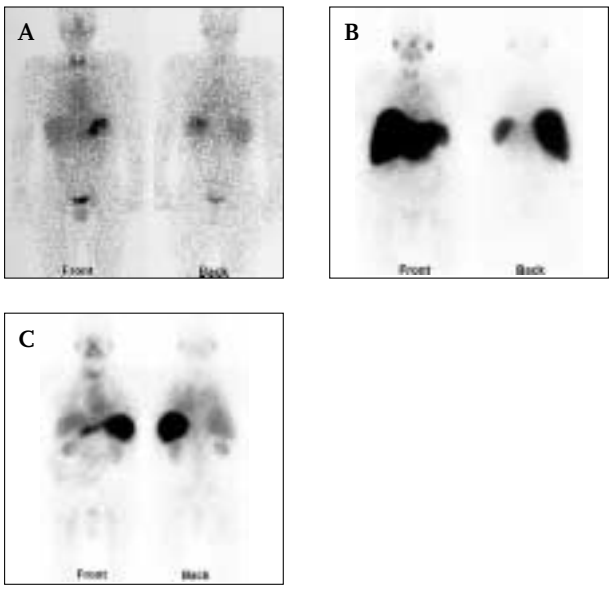

Figure 4A, B and C
SAP (Serum Amyloid P component) scintigraphy 24 hours after intravenous injection of ^{123}I-SAP, total body uptake front (left images) and back (right images).
A: Healthy control with minor nonspecific uptake (radioactive degradation products including free iodine) in stomach, bladder and minimal uptake in the (blocked) thyroid.
B: Intense uptake in liver and spleen in a patient with AL amyloidosis.
C: Uptake in spleen and kidney in a patient with AA amyloidosis.

PROGNOSIS

The last step before determining therapy is assessment of prognosis. Generally prognosis is poor if the disease is untreated. The prognosis depends upon the type of amyloid, severity of amyloid deposition, number of vital organs affected, presence of symptomatic cardiomyopathy, severity of the underlying disease and response to therapy of the underlying disease. Patients with untreated AL amyloidosis have the worst prognosis, with a median survival of less than one year.[1,9] Median survival in AL amyloidosis in case of symptomatic cardiomyopathy is four to six months, with kidney involvement about two years and with CTS more than three to four years. Patients with AA amyloidosis have a median survival of two to four years.[1,9] However, survival depends greatly on the activity of the underlying inflammation.[20] Patients with ATTR amyloidosis may survive up to 10 to 15 years.[1]

THERAPY

The current basis of therapy is the so-called 'precursor-product' concept.[21] The central idea of this concept is that further growth of amyloid deposits will cease when the supply of necessary precursor proteins is put to a stop. Therefore, in AA amyloidosis the treatment is aimed at decreasing SAA serum levels to normal basal values (below 3 mg/l). This aim can only be achieved by a complete suppression or eradication of the underlying chronic inflammation. Examples are surgical treatment of chronic osteomyelitis and antibiotic treatment of infectious diseases such as tuberculosis and leprosy. In chronic inflammatory diseases such as rheumatoid arthritis and Crohn's disease effective suppression of inflammation (resulting in a substantial decrease of serum SAA levels below 10 mg/l) can be difficult, but should be attempted.[20] To achieve this goal, cytostatic drugs can be used (such as methotrexate, azathioprine, cyclophosphamide, or chlorambucil), but also anti-TNF (tumour necrosis factor) drugs (such as infliximab, adalimumab and etanercept). In patients with TRAPS (TNF-receptor-associated periodic syndrome) etanercept (acting as a soluble TNF receptor) seems to be a rational treatment because of the abnormal function of the mutated TNF receptor.[22] The interleukin-1-receptor antagonist anakinra may be highly effective in cryopyrin-related diseases such as familial cold urticaria and Muckle-Wells syndrome.[23] Colchicine has a central place in the treatment of familial Mediterranean fever (FMF), not only by reducing the frequency and severity of attacks, but also by preventing the development of AA amyloidosis.[24] Dimethylsulphoxide (DMSO) was first thought to dissolve amyloid fibrils, but turned out to be an anti-inflammatory agent.[25] The antiamyloid effect in AA amyloidosis appeared to be mediated by lowering SAA serum levels.[21,25,26]

In AL amyloidosis the aim of treatment is to eradicate the underlying plasma cell dyscrasia by chemotherapy. High-dose melphalan with autologous stem cell transplantation is favourable in a group of well-selected patients.[27,28] In patients with hereditary ATTR amyloidosis liver transplantation is nowadays the only way to remove the source of 99% of the mutated TTR in the blood.[29]

SUPPORTIVE TREATMENT

Beside treatment aimed at the underlying disease, it is necessary to give supportive treatment for loss of organ function caused by amyloid deposition. In cardiac involvement the clinician should be extremely careful when using digoxin and calcium-channel blockers (their affinity to amyloid in the heart may enhance toxicity) and with cisapride for bowel motility problems (because of the risk of 'torsade des pointes'). Amyloid involvement of the heart primarily leads to right-sided heart failure; therefore the clinician should be careful with volume depletion (the problem is more an inflow than an outflow problem). Patients with symptomatic bradycardia may need implantation of a pacemaker. Nephrotic syndrome can be treated with salt restriction, careful use of diuretics and angiotensin-converting enzyme (ACE) inhibitors or nonsteroidal anti-inflammatory drugs. Orthostatic hypotension is difficult to treat. Fludrocortisone should be tried first and sometimes erythropoietin may also be helpful to treat this condition. Amitryptilline can be used for neuropathic pain; however, it should be used with caution (because of its possible effects on blood pressure and rhythm) in patients with cardiomyopathy. Adequate oral or intravenous feeding is mandatory in patients with significant weight loss, debilitating diarrhoea, absorption problems, or intestinal pseudo-obstruction. Various problems can cause diarrhoea, such as disturbed bowel motility, bacterial overgrowth, bile salt malabsorption and massive bowel wall infiltration with amyloid. Multisystem involvement results in a mix of serious problems and in such a situation it is almost impossible to find an appropriate treatment for all symptoms.[1]

EFFECT OF TREATMENT

The final step after the establishing therapy is the measurement of effect. This is especially true for patients with such an intangible disease as systemic amyloidosis.[30] The essence of the 'precursor-product' concept is that no further accumulation of amyloid deposits will occur after successful standstill of the supply of precursor proteins. Besides, the hope is that the body will be able to remove some of the amyloid deposits still present. Repeated measurements after specific time intervals can give an idea of the effect of therapy. It is important to note that two different processes should be monitored in this way.
Firstly, the underlying process with its precursor protein should be monitored: serum SAA, free kappa or lambda light chain and mutated ATTR in AA, AL and ATTR amyloidosis, respectively. If treatment is successful SAA levels should fall below 10 mg/l, free kappa and lambda levels and kappa/lambda ratio should return to normal reference ranges and mutant TTR should not be detectable in the blood. Secondly, the process of amyloid accumulation should be assessed by measuring the 'amyloid load'. For this measurement quantitative abnormal clinical signs should be monitored, such as serum albumin, alkaline phosphatase, bilirubin, creatinine clearance, proteinuria, ventricular wall thickness, ejection fraction, conduction and rhythm, heart rate variability, Ewing battery results and the size of enlarged organs, such as liver, spleen and kidneys. The abdominal subcutaneous fat aspiration can be repeated at each time point to get an idea of the severity of the presence of amyloid or its disappearance from tissue.[30] SAP scintigraphy, if abnormal at presentation, is the method of choice to monitor amyloid load in the individual patient.[18,20,30,31] Although differences among the leading research groups are small, response criteria are currently not standardised. Comparing results of therapy will become much easier if the international amyloid community is able to create a generally accepted set of criteria for response, stable disease and progressive disease for the different types of systemic amyloidosis.

TREATMENT PERSPECTIVES

The 'precursor-product' concept focuses on the prevention of further deposition of amyloid. Clinical research is directed to developing new drugs that can interfere with amyloid deposition or can stimulate the removal of amyloid deposits. A promising new drug for patients with AA amyloidosis is sodium-1,3-propane-disulfonate (Fibrillex). This drug is a glycosaminoglycan-mimetic drug that binds to SAA. This binding may prohibit binding of SAA to glycosaminoglycans in tissue.[32] A multinational phase II/III trial started in 2001 and results are to be expected in the summer of 2005. In AL amyloidosis 4'-iodo-4'-deoxydoxorubicin (IDOX) may have effect in soft tissue involvement, although definite proof has to be awaited.[33] CPHPC is another drug that leads to depletion of SAP from the circulation.[34] If this mechanism indeed stops accumulation of amyloid, it may be very useful for all types of systemic amyloidosis. However, clinical results are not available yet. Diflunisal is worth mentioning, which might be useful as stabilising ligand in patients with ATTR amyloidosis. This drug stabilises *in vitro* the TTR tetramer in blood and prohibits its degradation into amyloidogenic dimers and monomers.[35]
A completely different approach is vaccination. Research has been focused on conformational epitopes present in all types of amyloid that might be used for vaccination.[36] If this hypothesis turns out to be valid, it can be used for patients with all types of systemic amyloidosis. What is more, in the future preventive vaccination might be considered in people at risk for the development of amyloidosis.

CONCLUSION

A systematic, stepwise evaluation of patients with systemic amyloidosis helps to get a grip on this intangible disease. Histological proof of amyloid, verification of systemic involvement, assessment of the particular type of amyloid and its precursor form the background for a thoughtful clinical evaluation. New techniques such as ^{123}I-SAP scintigraphy may have a place in this evaluation. The 'precursor-product' concept is still the current basis of treatment, but research is aimed at finding new ways to attack amyloid.

NOTE

Most data were presented at the Immunology symposium on Systemic Diseases in Groningen, 14 February 2003 and at the Internal Medicine Congress in Maastricht, 15 May 2003.

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