Acta Medica et Biologica
Vol. 39, (Suppl.) 67-73, 1991

AB-Amyloidosis and Monokines*

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Summary. **AB-amyloidosis, characterized by the presence of β_2-microglobulin in the amyloid fibrils, has become a major complication of long-term therapy in chronic hemodialysis or peritoneal dialysis patients. The pathogenesis of AB-amyloidosis is incompletely understood, but most likely is based on the uremic retention of β_2-microglobulin. In addition, posttranslational modification of the molecule also seems to be an important step in the amyloidogenesis, since in addition to intact β_2-microglobulin, fragmented β_2-microglobulin or β_2-microglobulin with altered isoelectric properties can be detected in the AB-amyloid fibrils. The occurence of these β_2-microglobulin species could be linked to a chronic intermittent stimulation of monokine release or other subclinical inflammatory processes during renal replacement therapy. Thus, it is possible that, as a consequence of repeated cellular activation, subsequent protease release and/or intracellular processing of β_2-microglobulin occurs. Renal transplantation, though effective in preventing dialysis associated amyloidosis or arresting its progress, does not help to dsistinguish between the relative importance of retention of β_2-microglobulin or inflammatory events. Retrospective studies on AB-amyloid related symptomatology in patients on chronic hemodialysis with synthetic high-flux membranes have suggested a lesser prevalence in these patients as compared to patients chronically treated with standard cellulosic membranes. However, a possible benefical effect of chronic treatment with synthetic membranes also might be of multifactorial orgin. To further evaluate this issue and to test whether non-transplant therapies indeed may play a role in the prevention of AB-amyloidosis, prospective studies will be needed. Recently introduced non-invasive scanning methods, employing radiolabelled β_2-microglobulin or amyloid P component, may provide an objective, sensitive and specific basis for such studies.**

INTRODUCTION

With increasing numbers of long-term hemodialysis patients and with increasing awareness of the treating physicians it has become apparent that AB-amyloidosis is an important complication of chronic dialysis therapy. The designation "AB-amyloidosis" is derived from the precursor protein of this type of amyloidosis, which has been shown to be β_2-microglobulin,[1)] the light chain of the HLA class I complex. The disease has mainly been described in chronic hemodialysis patients. While clinical symptomatology of the disease is exceptional before 5 years of chronic hemodialysis treatment, the reported prevalences of AB-amyloidosis in patients treated for more than 10 years range from 30 to 100%.[2-4)] Furthermore, in the meantime it has been noted that AB-amyloidosis is not confined to patients on chronic hemodialysis, but that it may also occur in patients exclusively treated by either long-term hemofiltration of CAPD.[5,6)] Due to the low numbers of patients on either long-term CAPD or hemofiltration no data on the disease prevalence in these groups are available. Some reports published within the last two years have shown, that AB-amyloidosis may be a systemic amyloidosis with possible clinical manifestations of organ failure,[7-9)] but in the vast majority of patients the clinical manifestations are restricted to articular and periaticular sites[2-4,7)] (Table 1). In these patients the disease shows similarities with a rare clinical manifestation of the immunoglobulin light chain amyloidosis (AL-amyloidosis), which is known as "pseudorheumatoid arthritis". In this short review

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*Footnote to the title:
Synonyms used for AB-amyloidosis amongst others include: dialysis-related amyloidosis, dialysis amyloidosis, AB2M-amyloidosis.

Table 1. Predominant clinical manifestations of AB-amyloid deposition in long-term dialysis patients

Sites of AB-Amyloid Deposition	Clinical and Radiological Correlates
Carpal ligament, carpal tendon sheaths, carpal epineurium	Carpal tunnel syndrome (Median nerve compression).
Periaticular bone	"Cystic" bone radiolucencies, pathological fractures.
Synovial membrane, articular capsule articular cartilage	Arthralgias (humero- scapular periarthritis): tendon ruptures; destructive arthropathies with recurrent joint effusion; acute arthritis.
Intervertebral discs, vertebral bone, small intervertebral joints	Intervertebral narrowing and destructive changes; lumbago; cervicobrachialgia; paraplegia.
Tendonsheaths	Tenosynovites

we will not deal further with clinical symptomatology, as this topic has been discussed in recent reviews.[2-4] Rather we will focus on some findings, which have been published during the last two years and which may be of relevance to the pathogenesis, the diagnosis and possibly the therapy or prevention of AB-amyloidosis.

PATHOGENESIS: RETENTION OF AN AMYLOIDOGENIC MOLECULE

β_2-microglobulin, like most low molecular weight proteins, is eliminated nearly exclusively via the kidney. Accordingly the removal of this protein is markedly diminished in end stage renal failure.[10] Since all HLA-bearing cells continue to produce and shed β_2-microglobulin, considerable retention of the molecule occurs in uremic patients and plasmal levels are elevated up to 60-fold.[10] This retention is presumed to be a basic requirement for the development of AB-amyloidosis. In line with this concept therapeutic and preventive considerations initially have been centered around the question whether it would be possible to normalize the β_2-microglobulin balance in patients with terminal renal failure. The prospects in this regard are bleak: We recently obtained data in 11 chronic hemodialysis patients, showing that the synthetic rates (1107-2087 mg/week) of these patients were not significantly different from those measured in 5 normal controls (932-1814 mg/week). In order to fully compensate a production of this magnitude one can estimate, based on the data available from the literature,[11-13] that a continuous 6-days/week high-flux hemofiltration would be necessary to normalize uremic β_2-microglobulin plasma levels. Furthermore it can be predicted that even the inclusion of recently described β_2-microglobulin sorbing devices[14] in such a treatment would not significantly alter this time requirement unless the capacity of such devices is increased by several orders of magnitude. On the other hand, however, the data on AB-amyloid prevalences that have been published so far do not allow to address the question of whether e.g. a 50% reduction of the total body burden of β_2-microglobulin might serve to at least retard the onset of the disease.

POSTTRANSLATIONAL MODIFICATION OF β_2-MICROBLOBULIN AND ITS ROLE IN THE AMYLOIDOGENESIS

Several recent findings suggest that AB-amyloidosis is not only a consequence of retention of an amyloidogenic protein, but that its pathogenesis also may involve posttranslational modification of this protein (Table 2). Thus, a study on the amino-acid sequence of AB-amyloid fibrils disclosed intact β_2-microglobulin molecules as well as fragmented β_2-microglobulin molecules.[15] This suggests that a limited proteolysis of a circulating precursor molecule may be involved in the development of AB-amyloid deposits, which would be in accordance with current concepts on the pathogenesis of several other types of amyloidosis.[16] Another study showed by two-dimensional electrophoresis that "novel β_2-microglobulin" with reduced molecular weight occurred in solubilized amyloid fibrils in addition to intact β_2-microglobulin.[17] The "novel β_2-microglobulin" was also detected in a circulating form in the plasma of long-term hemodialysis patients with clinical manifestations of AB-amyloidosis.[17] The origin of the circulating "novel β_2-microglobulin" remains

Table 2. Comparison of the characteristics of the various β_2-microglobulin species detected in chronic hemodialysis patients

	Native β_2-Microglob. (19,20)	"Novel" β_2-Microglob. (17)	Cleaved β_2-Microglob. (15,21)
Molecular weight	11.8 kDa	reduced	reduced
Isoelectric point	5.3-5.7	4.8-5.2	?
N-terminal sequence	intact	intact*	cleaved
Present in AB-amyloid	yes	yes	yes
Present in serum	yes	yes	no
Correlation of serum concentration with the presence of AB-amyloid	no	?	?

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hypothetical. It is conceivable that it either represents processing of plasma β_2-microglobulin by proteases released from circulating blood cells into compartments with restricted access for anti-proteases such as the cell-dialyzermembrane interface or that it represents spillage of altered β_2-microglobulin from within the tissues. Alternatively, however, it might even reflect the production of two different β_2-microglobulin species, and would thus not be related to posttranslational modification at all, since restriction fragment length polymorphism has been reported for human β_2-microglobulin, indicating that at least two alleles are present on chromosome 15.[18] The role of the "novel" β_2-microglobulin in the amyloidogenesis remains unknown up to date.

POSSIBLE INVOLVEMENT OF ACTIVATED CELLS AND MONOKINES IN THE DEVELOPMENT OF AB-AMYLOIDOSES

Activation of cells and the release of inflammatory mediators during or following the process of renal replacement therapy has been postulated since the early '80s as part of the "interleukin-hypothesis"[22] and has been widely documented in the meantime. Thus it has been shown that during hemodialysis blood cells may be induced to release several mediators, including interleukin-1,[23-25] tumor necrosis factor,[25] reactive oxygen species[26] or prostaglandins.[27] Furthermore, complement activation occurs on some dialysis membranes,[28] which in turn may induce cellular activation and, under certain circumstances, increased cellular monokine production.[29] Besides the dialysis membrane, acetate as dialysate buffer and especially endotoxin in the dialysate have been demonstrated to be potent inducers of cellular monokine release.[30,31] In addition, it is worthwhile mentioning that cellular release of proteases[32] can also be demonstrated during hemodialysis with several different dialysis membranes. Some of these mechanisms may also be operative in CAPD patients as illustrated by two recent reports suggesting that the act of peritoneal dialysis itself may already be enough stimulus to induce local activation of cells, i.e. cytokine production, in asymptomatic CAPD patients.[33,34]

After having established that cellular activation and monokine release may occur repeatedly in dialysis patients and having made the observation that dialysis patients develop AB-amyloidoses, the question arises, whether these are independent or causally related events. Theoretically a number of ways can be envisaged to link inflammatory events and the development of AB-amyloid deposition:

a) Resident or blood-derived cells in the tissue, especially macrophages, may be activated by mediators released from circulating cells during renal replacement therapy and consecutively may express an increased proteolytic activity either on their surface or in intracellular compartments (amyloid fibrils have repeatedly been shown to be present in intracellular compartments of macrophages surrounding the deposits although it is not known so far, whether this represents intracellular amyloid formation or rather phagocytosis of amyloid fibrils).

b) Alternatively intravascular cellular activation may lead to increased release of proteases which in turn may lead to the limited proteolysis or modification of β_2-microglobulin (vide *supra*). Such cellular activation may take place on the dialyzer membrane or in tissue adjacent to the peritoneal membrane respectively.

c) Chronic intermittent stimulation of the acute phase response may lead to biochemical alterations

of the interstitial matrix of the (peri-) articular tissues, thereby predisposing these sites for amyloid deposition. In this respect a theory raised by Kissilevsky et al.[35] is of importance, in which they suggest that alterations of the glycosaminoglycan composition of a certain tissue may be a crucial step in the localization of amyloid deposits.

d) Monokines such as interleukin-1 or tumor necrosis factor as well as endotoxin have been shown to increase the cellular release of β_2-microglobulin.[37] While on an average level our finding of similar β_2-microglobulin synthesis rates in Cuprophan hemodialysis patients and normal controls[11] argues against a significant influence of hemodialysis on the β_2-microglobulin synthesis rate, we can not exclude that on an intraindividual level the institution of dialysis may increase the synthesis rate, thereby augmenting the total body burden of β_2-microglobulin.

Up to date no direct evidence is available to link any of these events to the development of amyloid deposition. Indirect evidence might, however, be derived from the analysis of factors aggravating or improving AB-amyloidosis. Some investigators have described an augmentation of shoulder pain during hemodialysis, subsiding after the end of treatment.[37] However, this is not a universal observation and the shoulder pain has only been assumed but not proven to be due to amyloid deposition in these patients. Furthermore, even if the pain were due to an AB-amyloidosis, it seems more likely that the aggravation of the pain during treatment is related to intradialytic water shifts rather than to an acute progression of the disease. Other than this no factors which aggravate the amyloidosis have been described. Concerning strategies which improve the course of an AB-amyloidosis or even prevent it, two treatment modes of end stage renal failure deserve consideration: renal transplantation and chronic treatment with synthetic dialysis membranes (as opposed to the standard cellulose-based Cuprophan membranes).

RENAL TRANSPLANTATION AND AB-AMYLOIDOSIS

It seems justified to assume that a successfully transplanted kidney will prevent the occurrence of the amyloid deposition. Furthermore, in cases with already established amyloid deposits, renal transplantation has been demonstrated to arrest the progression of the deposits.[38] A successful transplantation not only abolishes the retention of β_2-microglobulin within a few weeks,[39] but it also avoids the problems associated with dialysis. Finally an immunosuppressive treatment is instituted which will counteract inflammatory precesses. However, as all this takes place simultaneously, the clinical "experiment" of renal transplantation does not distinguish between the relative importance of retention of β_2-microglobulin and the effects of dialysis-induced cell activation or monokine release.

SYNTHETIC MEMBRANES AND AB-AMYLOIDOSIS

The standard hemodialysis with Cuprophan membranes has been shown to induce more complement-activation as well as protease- and mediator-release than that with newer, synthetic high flux membranes. A transient improvement of subjective parameters such a shoulder pain has been described to follow the switch from Cuprophan hemodialysis to hemodialysis with synthesic high-flux membranes.[40] However, an improvement of pain is not supported by personal experience and in the study cited objective parameters of articular disease showed little or no improvement.[40]

On the other hand, synthetic high flux membranes could have a role in the prevention of AB-amyloid deposition. This seems to gather support from a recent, preliminary report of a large multicenter study,[41] which, in contrast to some earlier and non-conclusive studies,[42–44] showed significantly less carpal tunnel syndromes and/or radiological signs of AB-amyloidosis in patients treated chronically with the highly permeable acrylonitrile membrane. Removal of β_2-microglobulin employing the acrylonitrile membrane (when used in the hemodialysis mode) is in the range of 400–600 mg/week or less.[11,13] Accordingly it has been shown that patients on long-term treatment with this membrane have about 30% lower β_2-microglobulin plasmal levels than patients treated with β_2-microglobulin impermeable membranes.[11] However, other mechanisms may also account for a lesser disease prevalence in patients on chronic treatment with acrylonitrile membranes: This may include reduced release of proteases from blood cells during treatment with this membrane,[45] low complement activation,[46] low induction of phagocyte oxidative metabolism[26] and the high adsorptive capacity of the membrane for cytokines.[47] Thus, as in the case of renal transplantation, a possible beneficial effect of high flux synthetic membranes could be a multifactorial one and would not allow to define the importance of single mechanisms

in the amyloidogenesis. Furthermore, in contrast to renal transplantation the beneficial effect of synthetic membranes is far less established and it will require future prospective studies to evaluate whether such treatment indeed has a role in the prevention of AB-amyloidosis.

FUTURE RESEARCH STRATEGIES

Based on the above considerations studies on the prevention of AB-amyloid deposition by non-transplant therapies may be designed. Such strategies may attempt to reduce the retention of β_2-microglobulin. Alternatively or in addition, preventive strategies may be directed towards the use of least cell/complement-activating membranes, the avoidance of acetate as a dialysate buffer, the identification (and avoidance) of cell-activating factors in CAPD and the avoidance of endotoxin contamination in dialysate solutions, substitution fluids etc. In this context one may worry, whether the increasingly popular treatment with highly permeable dialysis membranes, intended to counterbalance retention of β_2-microglobulin, might not even contribute to the disease as they may facilitate the passage of endotoxin from dialysate to blood, as long as the preparation of sterile, pyrogen-free on-line dialysate is not routinely available. Thus, it has been shown that certain high-flux dialyzers have the potential to permit the passage of large amounts of cytokine inducing substances through the membrane upon challenge of the dialysate side with endotoxin.[48]

The prospective evaluation of preventive strategies hitherto has suffered from the problem of the non-availability of an early, easily accessible and sensitive parameter to indicate the presence of amyloid anywhere in the body. Amyloid related clinical symptomatology or bone cysts are late occurrences in the process of the syndrome,[2-4] and biopsies of non-selected tissues may at best yield chance findings of amyloid.[49-51] Two procedures, which most often seem to yield positive results, i.e. a synovial biopsy or the aspiration of a joint effusion respectively,[52] certainly do not have the potential to become routine diagnostic procedures. In this respect two recent reports are very promising, describing the diagnostic radionuclide tracing and imaging of AB-amyloid deposits by injection of either ^{125}I-labelled serum amyloid P component (SAP)[53] or ^{131}I-labelled β_2-microglobulin.[54,55] SAP is a minor constituent of AB-amyloid, amounting to about 5-15% of the total amyloid mass.[16] Injection of the radiolabelled molecule allowed the non-invasive detection of amyloid deposits in the carpal tunnel region and metacarpophalangeal joints of two long-term hemodialysis patients.[53] However, currently it is not known, whether the scan will also detect minor, asymptomatic, early stages of amyloid deposition. An alternative to scanning with radiolabelled SAP is offered by the injection of the radiolabelled AB-amyloid precursor molecule β_2-microglobulin.[54] Using this technique, is has been possible to image AB-amyloid deposits in the shoulders, hands, knees, pelvis and vertebral column of 23 long-term hemodialysis patients with and without clinical correlates of AB-amyloidosis.[55] Furthermore, this study showed, that a considerable number of sites of increased tracer accumulation in patients with >6 years of hemodialysis were not associated with any clinical symptomatology or radiological alterations. Currently this radiodiagnostic method therefore seems to offer the most sensitive and objective non-invasive way to demonstrate AB-amyloid deposits. It may not only allow a more complete description of the incidence of AB-amyloidosis, but by repeated scanning, they may permit the evaluation of the influence of certain therapeutic strategies on the de novo appearance of amyloid deposits or on the fate of already deposited amyloid.

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