Dialysis amyloidosis: clinical aspects and therapeutic approach

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Introduction

Long-term survival of patients with chronic renal failure treated with regular haemodialysis has recently been recognized to be associated with peculiar complications which involve the osteoarticular system [1]. Such complications are related to a new form of systemic amyloidosis which is due to β2-microglobulin (β2-M), a protein which is catabolized by normal kidneys and accumulates when renal failure occurs [2]. This protein has a beta pleated sheet structure and therefore is able to form amyloid filaments. More commonly, β2-M amyloid deposits are found in the osteoarticular system, where synovial structures are present.

Clinical presentation (Table 1)

Carpal tunnel syndrome, trigger finger and tenosynovitis are frequently associated with the disease and often represent its first clinical complications. Joint osteoarthropathies are also frequently observed in patients after the first decade of treatment; typical clinical manifestations include arthralgia, stiffness, swelling of capsules and tendons, non-inflammatory joint effusions and synovitis. In addition to these classical clinical aspects, patients on regular dialysis also frequently develop an additional articular syndrome called destructive spondyloarthropathy. This syndrome, initially described by Kuntz et al. [3], was better elucidated by Ohashi et al. [4] who recently showed that cervical vertebrae are particularly prone to β2-M amyloid deposition, often with invalidating consequences. Visceral involvement is less common, but may be clinically relevant.

Table 1. β2-M amyloidosis — clinical manifestations

<table>
<thead>
<tr>
<th>Targets of β2-M amyloidosis</th>
<th>Clinical and radiological aspects</th>
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</thead>
<tbody>
<tr>
<td>Common sites of deposition</td>
<td>Carpal tunnel syndrome</td>
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<tr>
<td>Periarticular bone</td>
<td>Cystic radiolucentics</td>
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<td>Tendons and ligaments</td>
<td>Arthralgias, tendon ruptures,</td>
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<td>Articular capsule and cartilage</td>
<td>joint effusions</td>
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<td>Synovia</td>
<td>Popliteal masses</td>
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<td>Intervertebral discs, vertebral bodies</td>
<td>Destructive arthropathy</td>
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<td>Tendon sheats</td>
<td>Tenosynovitis</td>
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<td>Rare sites of deposition</td>
<td>Bleeding, diarrhoea</td>
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<td>Intestinal mucosa</td>
<td>Villous macroglossia</td>
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<td>Tongue</td>
<td>Tumoral masses</td>
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<td>Subcutaneous fat</td>
<td>Hypocinesia</td>
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<td>Heart</td>
<td>Stones</td>
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<td>Kidney</td>
<td>Infection</td>
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</tbody>
</table>

Table 2. Diagnosis of β2-M amyloidosis: radiological assessment of bone cysts

- Significant cystic bone lesions affecting at least two joints, located at insertion sites of capsule or tendons
- Amyloid cyst: diameter > 10 mm (shoulder and hip) or > 5 mm (wrist)
- Normal joint space (to exclude osteoarthritic origin)
- Rapid growth (>30% per year) suggests β2-M amyloid

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Dialysis amyloidosis

Fig. 1. Villous macroglossia. The tongue of this 65 year old patient, who has been treated by haemodialysis for 22 years, presents peculiar villi which proved to be $\beta_2$-M amyloid deposits on biopsy.

Ultrasound (Table 3) has a major role in demonstrating thickened joint capsules, joint effusions and tendon involvement [7]. Computed tomography and nuclear magnetic resonance may be particularly useful in the assessment of destructive spondyloarthropathy. Besides these specific indications, they should be limited to clinical research, being very expensive.

A decade ago attempts to identify $\beta_2$-M amyloid localization using P component labelled with $^{123}$I were made by Hawkins et al. [8], and studies have been carried out more recently by Floege et al. [9], who used $^{131}$I-$\beta_2$-M as tracer. In both cases scanning was useful in detecting amyloid accumulation in vivo and theoretically this kind of methodology appears promising for staging the disease. However, there are some unsolved questions. The major concern is specificity: it is presumed that any inflamed articular synovial space could show a scintigraphic positivity when any labelled protein with a low molecular weight is injected in the blood stream of uraemic patients. In addition, both these costly and sophisticated methods are not able to accurately evaluate early stages of the disease, nor can they evaluate the pool of amyloid deposition in the body, and therefore adopted as a routine.

The gold standard for diagnosis of $\beta_2$-M amyloidosis is histology. The Congo Red staining is a common and specific method to identify amyloid deposition in tissues; however, the precise nature of the amyloid protein can be studied only using anti-$\beta_2$-M antibodies [10]; in this way capsulosecondynal infiltration due to other form of amyloid, such as AL, can be excluded. In both forms of amyloidosis deposits seem initially to involve synovial structures and, later on, capsules and ligaments with articular soft tissue swelling and bone erosion. Although the subchondral area is initially spared, amyloid infiltration induces bone erosions through possible cartilage defect. Cysts are the consequence of the progressive amyloid tissue infiltration into bone; again, even if standard X-ray analysis shows one or more cysts in a typical location (wrist, hip, shoulder), only histology combined with immunolabelling can give real evidence of the nature of amyloid deposits.

### Treatment

Several types of haemodialysis membranes which are capable of removing $\beta_2$-M from patients have been developed with the aim of preventing or treating dialysis-related amyloidosis. Also, new treatment modalities, such as haemodiafiltration with a large quantity of replacement fluid and continuous haemofiltration, have been created to increase $\beta_2$-M removal.

Plasma $\beta_2$-M concentrations of patients without residual renal function at the beginning of treatment with conventional dialysers [11] provide a mean value of 75.7 mg/l. Patients treated with synthetic membranes have a pre-haemodialysis plasma $\beta_2$-M that is approximately 30% lower [12], but in any case no pre-treatment plasma $\beta_2$-M concentration is ever lower than 20 mg/l. Therefore, all dialysis patients will have a plasma $\beta_2$-M many times greater than the normal concentration regardless of their treatment modality. Moreover, the plasma $\beta_2$-M concentration is not indicative of the severity of dialysis amyloidosis: plasma $\beta_2$-M concentrations do not increase with time spent on dialysis and are probably markedly influenced by
Fig. 2. CT scan of the femur neck of a 59 year old patient affected by $\beta_2$-M amyloidosis. The same two serial sections of two different scans (the first one, left panels, made in 1992, the second one, right panels, in 1995) are presented. The confluent bone cysts of the femur head and neck have obviously enlarged in the 3 years between the two scans. In particular, the right bottom panel shows that the cortical bone is interrupted for a large section. The risk of hip fracture in this patient is presumably very high.

the deposition rate into organs and tissues in the patient's body.

The deposition rate of $\beta_2$-M in uraemic patients on haemodialysis was studied using an interesting mathematical kinetic model by Kanamori and Sakai [13]. First, it is stated that there is no significant difference in the $\beta_2$-M generation rate between normal subjects and patients with renal disease [11,14–16] (Table 4). The model is based on the observation that even if a patient without residual renal function is treated with conventional dialysers incapable of removing $\beta_2$-M, the $\beta_2$-M concentration in the patient is maintained at a certain level, because the generation and extrarenal disappearance rates of $\beta_2$-M are evenly balanced. Assuming an extrarenal disappearance rate for $\beta_2$-M of 1 ml/min [14] and calculating the time-averaged concentration of $\beta_2$-M of intravascular fluids, these authors estimated the corresponding $\beta_2$-M deposition rate. For example, a time-averaged concentration of 76 mg/l corresponds to a deposition rate in the patient of about 29 g/year. This means that the lower the plasma concentration of $\beta_2$-M, the lower the deposition rate. However, the model does not take into account modifications induced by a different intradialytic removal rate of $\beta_2$-M; such theoretical modifications include an increase in the generation rate, decrease in the extrarenal disappearance rate and extrication from deposits due to a decrease in concentration. Moreover, considering that pre-treatment plasma $\beta_2$-M concentrations are always greater than 20 mg/l, regardless of the kind of dialysis treatment, deposition of $\beta_2$-M amyloid tissue will take place in all dialysis patients.

These results confirm the conclusions of Odell et al. [15], suggesting that $\beta_2$-M production is not increased in dialysis patients, that there is substantial non-renal $\beta_2$-M clearance, probably due to deposition in tissues, and that the amount of $\beta_2$-M that can be removed by extracorporeal therapy is therefore limited.

Keeping in mind the limitations of dialysis in the removal of $\beta_2$-M, the key question is whether the use of cellulosic membranes (as compared to synthetic membranes) is associated with an increased incidence of clinical manifestations of amyloid bone disease. This

<table>
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<tr>
<th>Reference</th>
<th>Normal subjects</th>
<th>CRF patients</th>
<th>HD patients</th>
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<tbody>
<tr>
<td>Maeda [11]</td>
<td></td>
<td>0.130±0.03</td>
<td>0.152±0.02</td>
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<tr>
<td>Karlsson [14]</td>
<td>0.131±0.02</td>
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<tr>
<td>Odell [15]</td>
<td></td>
<td>0.159±0.04</td>
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<tr>
<td>Floege [16]</td>
<td>0.100±0.03</td>
<td></td>
<td>0.129±0.03</td>
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</table>

CRF, chronic renal failure; HD, haemodialysis. Values given as means±SD.
issue has been addressed by many studies, with conflicting results. It has been suggested that the bioincompatibility of haemodialysis membranes may participate in the development of β2-M amyloidosis [17], but amyloid bone disease has been reported in a few patients before institution of haemodialysis [18], and in long-term peritoneal dialysis patients [19].

A large retrospective case-control study from the European Dialysis and Transplant Association [20] on the prevalence of signs and symptoms of dialysis osteoarthritis analysed data from 55 patients treated predominantly with polycrylonitrile (AN69) dialysers and 55 matched controls dialysed exclusively with cellulosic membranes. The authors concluded that they found little, if any, influence of the two types of membranes on the prevalence of signs and symptoms of β2-M amyloidosis. However, many of the AN69 patients had also been treated with cellulosic membranes for several years. Another European study [5] showed that the survival without amyloid bone disease was significantly shorter in patients dialysed with cellulosic membranes than in patients treated exclusively with the polycrylonitrile membrane. The difference in relative risk was greater the older the patient; for example, a 60 year old patient dialysed with a cellulosic membrane had 10 times the risk of developing amyloid bone disease compared to a similar patient on the polycrylonitrile membrane. A reduced prevalence of carpal tunnel syndrome and radiolucent bone cysts was also associated with the use of synthetic membranes [21,22].

There are, at present, no prospective randomized studies to judge the effects of different membranes on serious morbidity (including hospitalization and invalidating consequences of amyloid bone disease) and mortality of haemodialysis patients, although it is possible that the use of more permeable and biocompatible membranes could be associated with improvement in long-term morbidity. However, a clear clinical advantage should be established for one type of dialysis membrane before this can be chosen irrespective of its cost. At the moment the doctors' and patients' desire to eliminate uraemic toxins, prevent acute side effects and reduce long-term morbidity of the dialysis treatment is best achieved by a successful kidney transplant.

References

21. Chanard J, Bindi P, Lavaud S, Toupance O, Maheut H, Lacour F. Carpal tunnel syndrome and type of dialysis membrane before this can be chosen irrespective of its cost. At the moment the doctors' and patients' desire to eliminate uraemic toxins, prevent acute side effects and reduce long-term morbidity of the dialysis treatment is best achieved by a successful kidney transplant.

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