Ubiquitin in Dialysis Amyloidosis

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Dear Sir,

β 2-Microglobulin (β 2-M) amyloidosis is a serious complication of long-term dialysis therapy. The major clinical manifestations of this amyloidosis are carpal tunnel syndrome (CTS) and arthralgia. Low molecular weight plasma proteins, such as β 2-M, are catabolized mainly in the kidney; hence these proteins tend to accumulate in patients with renal insufficiency. It has been assumed that prolonged elevation of β 2-M levels is a possible pathogenetic factor for amyloidosis. Serum levels of β 2-M in patients with CTS did not differ from those in other patients who received dialysis therapy, suggesting the involvement of other pathogenic mechanisms in β 2-M amyloidosis [1]. In an experimental model of amyloidosis using mice, an amyloid-enhancing factor peptide has been purified. This peptide was found to be ubiquitin, a low molecular weight protein. Furthermore, this peptide was codeposited with the murine amy-

loid [2]. These findings raise the possibility that ubiquitin acts as an amyloid-enhancing factor in β 2-M amyloidosis during prolonged dialysis therapy.

Our recent work [3] supports this possibility by the following three relevant points. (1) Ubiquitin is codeposited with β 2-M in synovial tissue from dialysis patients with CTS. (2) Plasma ubiquitin levels in patients who had dialysis treatment with cuprophane membrane were about 13 times higher than those in normal subjects. (3) Plasma concentrations of ubiquitin in dialysis patients with CTS were significantly higher than those in patients unaccompanied by CTS. Nevertheless, as noted above, serum β 2-M levels were comparable in these groups. Thus, prolonged increase in plasma ubiquitin levels may enhance the amyloidogenesis in patients on dialysis treatment.

There are two types of dialysis membrane materials: cellulose and synthetic polymers. Cuprophane is the most commonly used cellulose membrane. Synthetic membranes are highly porous and more permeable to proteins than cuprophane. In fact, dialysis therapy using these artificial membranes can reduce serum β 2-M levels markedly compared with cuprophane membranes. The relationship between incidence of amyloidosis and type of membrane used for dialysis is widely investigated, and the development of amyloidosis appears to be influenced by membrane characteristics [4-6]. In the case of ubiquitin (fig. 1), the plasma concentrations were also significantly lower in patients on regular dialysis treatment with synthetic membranes than in those receiving dialysis therapy with cuprophane

membranes. Consequently if ubiquitin is associated with dialysis amyloidosis, the choice of the dialysis membrane would be crucial.

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Fig. 1. Different plasma ubiquitin concentrations observed in patients on dialysis with respect to the type of dialysis membrane used. Each value shows the mean ($\pm$ SD) plasma concentration of ubiquitin in normal subjects (normal) and dialysis patients using various membranes. Blood was sampled immediately before ($\square$) and after ($\blacksquare$) dialysis treatment. Plasma concentrations were measured using a radioimmunoassay specific for ubiquitin [3]. The mean age and the mean duration of dialysis therapy were comparable among the different groups; cupro = Cuprophane; PAN = polyacrylonitrile; PMMA = polymethylmethacrylate; PS = polysulfone. * $p < 0.01$, ** $p < 0.001$ vs. cuprophane, Student's t test.

cupro PAN

N=29 N=9

normal

N=10

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\$8.00/0

Based on these observations, we recommend that clinical studies on the incidence of β 2-M amyloidosis should include a systematic test of the dialysis membrane type and the assay of plasma ubiquitin levels. The purpose of this approach is twofold. First, the most useful membrane can be identified for dialysis therapy. Second, the possible involvement of ubiquitin in β 2-M amyloidosis can be examined directly.

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