Anticardiolipin Antibodies in Patients on Regular Hemodialysis: An Epiphenomenon?

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was calibrated against an international standard from the Rayne Institute London. Results are expressed as units/milliliter, 1 U being defined as the cardiolipin-binding activity of 1 µg of affinity-purified IgG-aCL. Plasma samples giving 2 or more SD above the mean of normal controls were considered as positive (> 15 U/ml).

The proportion of subjects shown to have positive tests for IgG-aCL was significantly ($p < 0.05$) higher among patients undergoing regular hemodialysis (9 of 54) than in patients on CAPD (1 of 19) or in healthy blood donors (2 of 50; table 1). However, the mean aCL concentration of these three groups did not differ significantly. The prevalence of positive aCL did not differ between patients dialyzed exclusively with cellulose-based membranes (5 of 29) or with more biocompatible

Hemodialysis (n = 54) 17*

Biocompatible Membrane (n = 25) 16

Cellulose-based Membrane (n = 29) 17

Thrombotic Episode (n = 10) 10

Dear Sir,

Patients with end-stage renal disease have been found to be associated with a higher frequency of raised anticardiolipin (aCL) antibodies than the general population [1¹]. The presence of these autoantibodies has been related to the occurrence of thrombotic complications [2-Q. However, the clinical significance of aCL antibodies as markers for a high risk of recurrent thrombosis and the therapeutic implications of this association are still far from established, and the data reported by several studies are discordant. The objectives of our investigations were (a) to characterize the aCL antibody status in patients with end-stage renal disease treated with different methods of dialysis; (b) to investigate possible causes of aCL antibody synthesis, and (c) to find out whether aCL of IgG isotype are additional risk factors for vascular events in dialysis patients.

73 patients with end-stage renal disease (26 females, 47 males, aged 25-86 years) were selected for the study, 50 healthy blood donors served as controls. The major causes of chronic renal failure were chronic glomerulo-nephritis in 38, diabetic nephropathy in 8 and interstitial nephritis in 7 patients; 54 patients with end-stage renal disease were maintained on hemodialysis, 19 patients were treated with continuous ambulatory peritoneal dialysis (CAPD). The two subgroups had comparable demographic characteristics and did not differ in the underlying cause of renal failure. None of the patients had systemic lupus ery-

thematosis (SLE) or other autoimmune disorders known to be associated with aCL [5]. Plasma concentration of IgG-aCL was measured by a quantitative solid-phase enzyme-linked immunosorbent assay. This commercial assay (ELIAS, Freiburg, FRG)

Table 1. aCL

antibodies in patients on hemodialysis in comparison with patients on CAPD or normal subjects

synthetic membranes (4 of 25). Only one of 10 hemodialysis patients with a history of thrombotic events had raised aCL (table 1).

The meta-analysis of the major results of all published studies of antiphospholipid antibodies in hemodialysis patients reveals that the proportion of patients shown to have positive tests for IgG-aCL varies greatly between 0.7 and 69% [1-4,6]. The majority of hemodialysis patients with positive aCL showed only slightly elevated aCL antibody concentrations [1-2]. Extremely high values comparable with SLE patients have been reported in 1 study [3].

Technical differences in the assays used may bias some of the published trials, and different characteristics of the patients may account for many of the conflicting results. Some authors have selected patients with clinical manifestations

Positive aCL, %	aCL concentration U/ml (mean $\pm$ SD)
8 $\pm$ 7	9 $\pm$ 7
8 $\pm$ 7	8 $\pm$ 7
8 $\pm$ 7	8 $\pm$ 9

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believed to be related to positive aCL [7], or have included patients with immune disorders, such as SLE, rheumatoid arthritis or HIV infection known to be associated frequently with aCL [2, 3].

The causes of enhanced antiphospholipid antibody synthesis remain obscure. All studies, including our own, were unable to explain the presence of IgG-aCL by differences in age or sex distribution or by duration of hemodialysis treatment [1, 2]. Whether chronic glomerulonephritis as underlying nephropathy may predispose to positive aCL antibodies is discussed controversially. A higher prevalence of aCL in patients with chronic renal failure due to glomerulonephritis was only found in 1 study [2] and not confirmed by others [1].

Quereda et al. [8] have demonstrated that the incidence of aCL antibodies in nonuremic chronic glomerulone-

phritis is similar to that in the general population. Comparison of hemodialysis patients with CAPD patients revealed that uremia did not account for the differences observed in our patients but points to origins derived from the technical procedure of hemodialysis. In contrast to the study of Garcia-Martin et al. [1], we were unable to show any effect of dialysis membranes on the synthesis of aCL antibodies. But even in this study, the majority of hemodialysis patients undergoing dialysis with cuprophane membranes had negative aCL levels. Nevertheless, each of these studies provides independent evidence that higher aCL levels may be related to some kind of bioincompatibility associated with hemodialysis.

There is controversy whether the presence of higher aCL concentrations correlates significantly with thrombosis in hemodialysis

patients [1-3,6]. However, all studies demonstrated that not every patient with a positive result in the aCL test has had or will have a clinical event. We followed 4 patients with

persistently elevated aCL for up to 3 years, but none of them developed thrombosis. Equally, patients may have thrombotic events without ever showing antibody. In all published series, the number of events has been too small to calculate risks with any accuracy and especially to make definitive statements about the presence or absence of any correlation. At the moment, it must be said that there is no direct evidence that aCL antibodies in patients on hemodialysis are good markers for a high risk of thrombosis. In this context, it should be emphasized that aCL are typical autoantibodies which in general are epiphenomena rather than pathogenetic agents.

References

Garcia-Martin F, De Arriba G, Carrascosa T, Moldenhauer F, Martin-Escobar E, Val J, Saiz F: Anticardiolipin antibodies and lupus anticoagulant in end-stage renal disease. *Nephrol Dial Transplant* 1991;6:543-547.

Grönhagen-Riska C, Teppo AM, Helanterä A, Honkanen E, Julkunen H: Raised concentrations of antibodies to cardiolipin in patients receiving dialysis. *Br Med J* 1990; 300:1996-1997.

Kirschbaum B, Mullinax F, Curry N, Mallory J: Association between anticardiolipin antibody and frequent clotting problems in hemodialysis patients (abstract). *J Am Soc Nephrol* 1991 ;2: 332.

Bala Subramanian V, Smith D, McMillan MA, Macdougall AI: Anticardiolipin antibodies in long-term dialysis patients (abstract). *Nephrol Dial Transplant* 1992;7:459.

Cameron JS, Frampton G: The 'antiphospholipid syndrome' and the 'lupus anticoagulant'. *Pediatr Nephrol* 1990;4:663-678.

Koblmueller A, Breitenfellner P, Leitner E, Stummvoll HK, Kapiotis S: Antikardiolipin-antikörper bei Dialysepatienten (abstract). *Nieren-Hochdruckkrankh* 1991 ;20:235.

Page B, Yazbeck F, Zingraff J, Zins B, Bourque-Iot P: Clotting of vascular access in dialysis patients associated to anticardiolipin antibodies (abstract). *Nephrol Dial Transplant* 1992;7:733.

Quereda C, Garcia-Otero G, Gonzalo A, Rivera M, Orte L, Pascual J, Ortuno J: Antiphospholipid antibodies in glomerulopathies: A prospective study (abstract). *J Am Soc Nephrol* 1991;2:273.

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