Clinical Significance of Fibrinuria with Fibrinogen Split-Product E following Kidney Allotransplantation¹

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Introduction

Since the work of Brun nd Merrill (1), Antoine (2) and from our laboratory (35), several other investigators have pointed out the importance of fibrinuria following kidney allotransplantation as an early sign of impending rejection episodes. In further studies we could demonstrate (6) that in addition to fibrinuria, typical findings of disseminated intravascular coagulation (DIVC) with secondary compensatory fibrinolysis could be detected in patients with renal allografts, and that these findings also preceded other well-known clinical signs of rejection crises. In this study we demonstrate that fibrinogen split-product E constitutes to fibrinuria.

Materials and Methods

The finding of fibrinuria is based on immunological analyses of 228 24-hour urine concentrates of 25 patients who received cadaveric kidney allografts. e-Amino caproic acid was added to all urine samples to suppress fibrinolytic activation processes by urokinase. Fibrinogen degradation products were detected using double diffusion in agar gel, micro-immunoelectrophoresis, and the Mancini technique with Partigen plates (Behring-Werke, Marburg/Lahn, FRG) (46). In addition, in order to further characterize the split products in the urine of these patients, two-dimensional crossed immunoelectrophoresis according to Lurell (7) in a modification of Clrke nd Freemn (8), was used on 60 urine samples of ten patients with a monospecific antifibrinogen split-product E serum (Behring-Werke, Marburg/Lahn, FRG).

Prior to this, the final lysate of 500-mg fibrinogen was split with streptokinase plasmin and separated in pevikon electrophoresis, resulting in a pure split-product E in fraction 12. Coagulation studies in 96 different plasma samples and 56 different serum samples of ten kidney-transplanted patients were performed by applying the ethanol test, protamine-sulfate test, precipitin test, radial immunodiffusion, and the haemagglutination-inhibition immune assay for fibrinogen split products in serum samples (46).

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Results

Within the first 14 days following kidney transplantation all patients examined revealed fibrinogen split products in the urine. The pattern of these fibrinogen degradation products varied, however, heat-labile fragment D of -immunoelectrophoretic mobility and heat-stabile fragment E with -immunoelectrophoretic mobility being found quite frequently. Whereas during the first 14 days fibrinuria was found constantly, later in the post-transplantation course it is an early and quite reliable sign of impending rejection and correlates positively in 70% with all observed rejection crises. Furthermore, in several instances, fibrinogen-split products could be detected several days prior to other well-known clinical and laboratory signs of rejections.

According to the overall content of fibrin degradation products in the urine samples a parallel excretion pattern was observed for split-product E which constitutes a minor part of the fibrinogen degradation products in the urine. The mean value of split-product E in the urine during the first 14 days following transplantation was 1015 µg/ml, declining to almost undetectable levels during periods of stable renal graft function, but rising immediately with the onset of a rejection crisis as shown in figure 1. Figure 2 and 3 demonstrate that split-product E excretion within the 14-day period after transplantation may even rise to values of more than 20 µg/ml during an early rejection crisis on day 7, but declined again after successful treatment until on day 215 with a new rejection crisis the levels of split-product E rose again. Figure 3 shows results of the

Fig. 1. During the first 14 days following kidney allotransplantation, fibrinogen split-product E was regularly elevated to levels of 10-15 µg/ml; later on in the post-transplantation course elevated levels only were found during a rejection crisis.

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Fig. 2. Correlation of FSP-E in the urine with the clinical course of a patient with kidney allotransplantation. Note the sharp rise of FSP-E excretion in the urine during a rejection crisis on day 6 and again during a second crisis on day 215,

Fig. 3, Two-dimensional electrophoreses of urine concentrates of a kidney-allografted patient with monospecific antifibrinogen split-product-E serum during an acute rejection crisis, The increasing and decreasing amounts of FSP-E are shown. See also figure 2, which shows the clinical data of this patient.
crossed immunoelectrophoretic technique during the first rejection crisis from days 3-9 on this patient. These results are in agreement with those of Hnen et al. (9) and Clarkson et al. (10) who also demonstrated that the low molecular weight split-product E constitutes not insignificantly to fibrinuria in patients with kidney transplants and those with glomerulonephritis, respectively. In addition to these urinary fibrinogen split products our clotting analyses of plasma and serum samples of these patients revealed definite signs of disseminated intravascular coagulation with secondary compensatory fibrinolysis. Fibrin monomer complexes as well as fibrinogen-fibrin monomer complexes and fibrin monomer-fibrinogen split-product complexes were positive in 44 and 69%, respectively, of all plasma samples examined, but negative in normal controls after provoking the paracoagulation phenomenon by means of the ethanol and protamine-sulfate test. Fibrin-fibrinogen split products in serum, detected by haemagglutination-inhibition immune tests, revealed a mean value of 8 µg/ml during periods of normal transplant function, a value of 75 µg/ml during the first 14 days after

Fig. 4. Mean values of serum fibrinogen split-product levels in patients with kidney allografts. There is especially a sharp increase in FSP in the serum of these patients during periods of acute rejections (see also text).

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kidney transplantation, but a significant increase to 350 µg/ml during rejection crisis (fig. 4). These split products in serum were again detectable several days earlier than other signs of a rejection reaction.

Discussion

That the finding of fibrinogen degradation products in the urine of kidney-transplanted patients during rejection crises may serve as an important additional diagnostic tool was reported from several laboratories (1-3, 5). Our studies show that one major component of these split products is the low molecular weight substance E. In addition, typical signs of disseminated intravascular coagulation were found in these patients, both phenomena arising several days prior to other clinical signs of rejection episodes. Brun and Merrill explain fibrinuria by lysis of fibrin deposits by plasmin within the kidney, since activity of urokinase as activator of plasminogen seems to be quite high in renal tissue and urine. Clarkson (11), however, could demonstrate that urokinase activity is rather low in the urine of kidney-grafted patients. Local secondary fibrinolysis of fibrin deposits within the kidney has to be anticipated in these cases. Furthermore, corticoste-
roids may play a role since Antoine et al. (2) and Hnén et al. (9) found a positive correlation between the degree of fibrinuria and the dose of corticosteroids employed. Experimental work by McKy (12) may explain this, since in the presence of disseminated intravascular coagulation, corticosteroids lead to formation of microthrombi, especially within the kidney.

In our studies there is a significant increase in fibrinogen split products in the serum during rejection crises, an observation which also was seen by Nilsson (13), Csh and Clarkson (14) and Hnén et al. (9). Even though the detection of fibrin-fibrinogen split products in serum, and fibrin monomer complexes in plasma, points to intravascular coagulation with compensatory secondary fibrinolysis in patients with rejection crises of allografted kidneys, resulting in fibrinuria with moderate amounts of split-product E being excreted in the urine, these events only can be interpreted as secondary events of primary immunological reactions within the kidney graft during the rejection reaction, which itself is caused by complex antigen-antibody reactions with possible endothelial lesions, which again can be considered as releasing factors for disseminated intravascular coagulation processes (15).

Summary

Typical findings of disseminated intravascular coagulation were found in patients following kidney allotransplantation where quantitative determinations revealed fibrin degradation products in the urine. Split-product E, which was quantitatively determined in urine samples, contributes to this fibrinuria. Elevated levels of fibrinogen split products in serum as well as in urine are detectable several days prior to clinical signs of rejections and serve as an early indicator of impending rejection in patients with renal allografts.

References


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