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Loss of Fibronectin in Plasma of Patients with Shock and Septicaemia and after Haemoperfusion in Patients with Severe Poisoning

Fibronectin concentrations in plasma in human diseases, II.[1] [2]

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Summary: Plasma fibronectin is diminished in patients with shock and septicaemia, probably as a result of a decreased function of the reticuloendothelial system (RES) of liver, spleen and bone marrow. A loss of plasma fibronectin was also observed after haemoperfusion of patients with severe poisoning. The deposition of fibronectin on the surface of cultured mouse liver *Kupffer* cells and the possible role of fibronectin in RES function are discussed.

Verlust von Fibronectin im Plasma von Patienten mit Schock und Septicaemie sowie nach Hämoperfusion von Patienten mit schweren Vergiftungen

Zusammenfassung: Fibronectin im Plasma ist vermindert bei Patienten mit Schock und Sepsis, vermutlich in Zusammenhang mit verminderter Funktion des retikuloendothelialen Systems (RES) von Leber, Milz und Knochenmark. Ein Verlust von Fibronectin im Plasma wurde auch nach Hämoperfusion von Patienten mit schweren Vergiftungen beobachtet. Es wird über die Verteilung von Fibronectin auf den Zelloberflächen kultivierter *Kupffer*-Zellen von Mäuselebern und über die Bedeutung von Fibronectin für die RES-Funktion berichtet.

Introduction

The high molecular weight glycoprotein fibronectin from plasma, cell-surface and intercellular connective tissue matrix, has been shown to have various functions, e.g. in cell attachment and in connective tissue formation.

Fibronectin seems to be identical with the LETS factor (large external transformation sensitive factor), cold-insoluble globulin and anti-gelatin factor. Furthermore fibronectin is closely related to or identical with α-opsonic glycoprotein. Fibronectin is an opsonin, for example, it enhances endocytosis of bacterial toxins (1–4), collagens, fibrinogen and cells. Depressed levels of α-opsonic glycoprotein have been found in plasma of patients with shock and septicaemia (1, 5), indicating that fibronectin supports the function of the reticuloendothelial system. Further evidence to support this suggestion is given elsewhere (1). In a previous contribution we reported an easily-handled immuno-test to measure fibronectin in human plasma (6). Using this laser nephelometry assay, we have estimated fibronectin in the plasma of patients with septicaemia and/or shock, before and after haemoperfusion for the treatment of severe poisoning.

[1] I. l.c. (6).

[2] Supported by Deutsche Forschungsgemeinschaft, Bonn-Bad Godesberg (SFB 104, A4).

Patients, Materials and Methods

Fibronectin was measured in 8 patients with cardiogenic shock, in 12 patients with pancreatogenic shock and in 16 patients with septicaemia. In five patients with septicaemia caused by staphylococcal infection and in four patients with cardiogenic shock, a follow-up study was performed; fibronectin was measured and various other laboratory and cardiopulmonary tests were carried out. In four patients with severe poisoning (2 × paraquat, 2 × bromocarbamide) fibronectin was determined before and after haemoperfusion.

Fibronectin in plasma was determined as described in earlier literature (6). Briefly, the final test consists of: 100 µl plasma, dilution 1:10 in 0.15 mol/l NaCl, 200 µl antiserum, dilution 1:5 (Behring-Werke); 1:10 (own preparation) in 0.15 mol/l NaCl.

Fibronectin was purified and antibodies were raised in rabbits as described elsewhere (6). For the routine assay an antibody against fibronectin (from Behring-Werke, Marburg/Lahn, FRG) was used, which did not cross-react with fibrinogen. The common laboratory tests, including blood clotting tests and cardiopulmonary function tests, were carried out as described (5). Repeated haemoperfusion with coated charcoal (Gambro, Hechingen, FRG) was done according to *Yatzidis* (7).

Results and Discussion

Fibronectin levels in plasma of patients with shock from different causes or with septicaemia are markedly depressed (fig. 1). In follow-up studies the survivors showed an increase to normal concentrations, whereas

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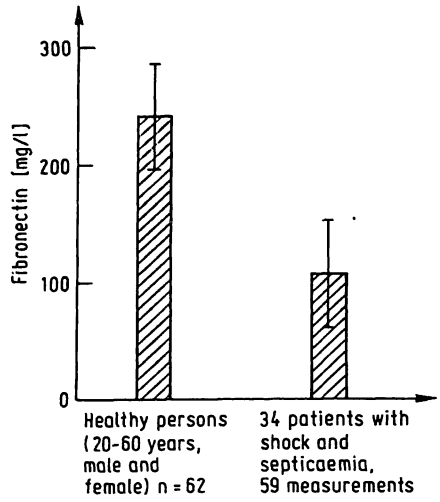

Fig. 1. Fibronectin concentrations in the plasma of patients with shock and septicaemia. n = normal healthy controls. $I = \bar{x} \pm 1S$.

the non-survivors had depressed levels until their deaths (fig. 2). Plasma fibronectin is also depressed after haemoperfusion (fig. 3). Depressed levels of α-opsonic glycoprotein, which may be identical with fibronectin have been reported by *Saba* et al. and by *Blumenstock* et al. (2, 8).

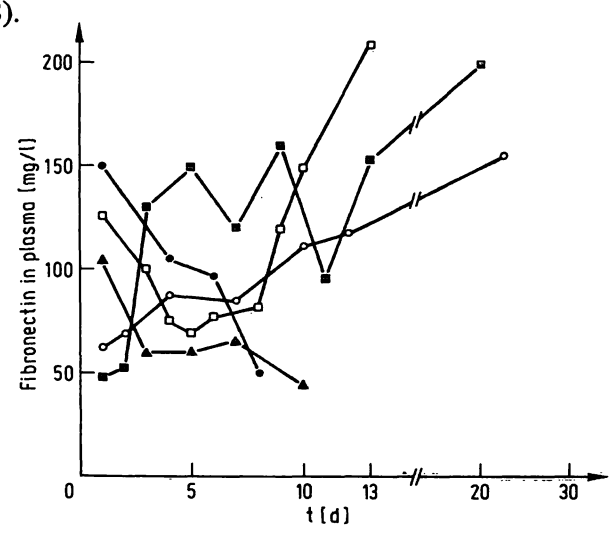

Fig. 2. Follow-up observations in patients with shock and septicaemia.
- □ acute liver failure
- ○, ●, ■ septicaemia, caused by *Staphylococcus* infection
- ▲ septicaemia, bacterial infection not identified
- ●, ▲ non-survivors

The fact, that fibronectin is depressed in patients with septicaemia provides further evidence that these proteins may be identical or very closely related. Endothelial cells (1), hepatocytes and macrophages (9) contain and synthesize large amounts of fibronectin. Conditions of phagocytosis of coated and labelled particles in the blood flow mediated by fibronectin have been published recently (reviews l.c. (2, 10)).

From studies with mouse *Kupffer* cells (9), and hepatocytes (11) it is concluded that these cells produce fibronectin which is deposited as a meshwork on the cell surface; this site of deposition of fibronectin is presumably related to its role in phagocytosis. We have observed depression of fibronectin in plasma not only in cases of septicaemia but also in patients with shock. This may be due to the fact that under shock conditions the function of the reticuloendothelial system is also depressed. This supports the evidence that fibronectin may be an indicator of the functional efficiency of the reticuloendothelial system.

In this connection, the observation that fibronectin decreases after haemoperfusion of patients with various types of poisoning may be significant. It could be due to adhesion of fibronectin, like other plasma proteins (7) to the coated charcoal. Work is in progress, using immuno-fluorescence, to investigate whether fibronectin is bound to the coated charcoal after haemoperfusion.

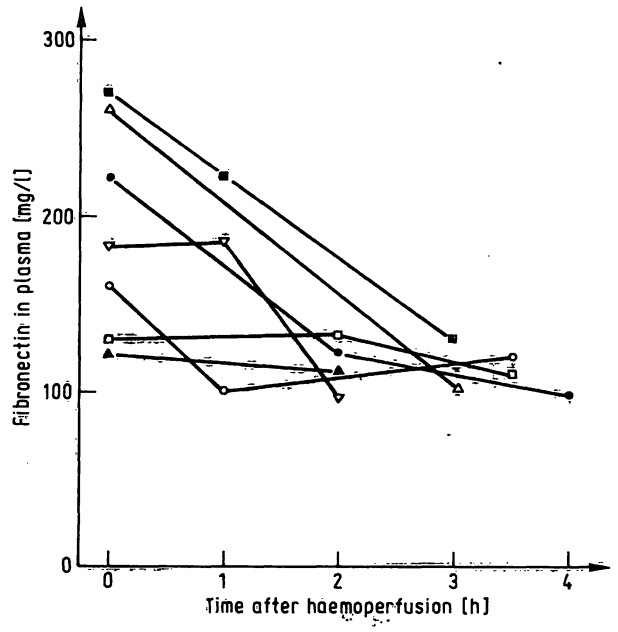

Fig. 3. Fibronectin concentrations in the plasma of patients before and after several haemoperfusions.
- ■, ○, ▲ paraquat poisoning
- □, ○, △, ▽ bromocarbamide poisoning

Conclusions

Our results support the hypothesis that fibronectin may play an important role in the function of the reticuloendothelial system. This may be the fact not only in patients with septicaemia but also in patients with shock, as a sign of depressed phagocytosis of the reticuloendothelial system. This supports the evidence that it might be necessary to substitute fibronectin in patients with depressed levels. Initial treatments with cryoprecipitate (2) by *Saba & Blumenstock* demonstrate a dramatically improved survival rate compared with non-treated patients. Cryoprecipitate contains high concentrations of fibronectin.

These therapeutic measures should be continued with highly purified fibronectin, and consideration should also be given to the use of fibronectin infusions in patients undergoing haemoperfusion and showing a marked fall in fibronectin concentrations in the plasma.

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