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Fibronectin in fulminant hepatic failure

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Abstract

Thirteen out of 17 patients with fulminant hepatic failure had plasma fibronectin concentrations below the normal range (194-472 µg/ml), the mean concentration in all 17 patients being $117.9 \pm \text{SE } 19.4$ µg/ml. There was a significant negative correlation between plasma fibronectin concentration and aspartate aminotransferase activity, suggesting that fibronectin is consumed during clearance of hepatocyte debris.

The reduced availability of fibronectin may be an important factor in the impaired function of Kupffer cells in patients with fulminant hepatic failure.

Introduction

Fibronectin is an important plasma glycoprotein that plays a part in opsonising cell debris, fibrin, and denatured protein before phagocytosis.^{1,2} Reduced concentrations of fibronectin in patients with sepsis and trauma may be responsible for the reported impairment of reticuloendothelial cell function.³

Patients with fulminant hepatic failure also have impaired function of Kupffer cells,⁴ and this might be related to changes in fibronectin concentration. We report here serial measurements of fibronectin concentration in 17 patients with fulminant hepatic failure in relation to laboratory variables of liver damage.

Patients and methods

The 17 patients studied had grade 3-4 encephalopathy due to fulminant hepatic failure after a paracetamol overdose (11 patients), viral hepatitis (five: four presumed non-A non-B, one hepatitis B virus), and halothane-associated hepatitis (one). Initial blood samples were taken on admission and, in eight of the patients, daily until recovery or death. On admission blood cultures in all patients were sterile; overt evidence of septicaemia (*Staphylococcus aureus*) developed in only one patient (case 2), on day 3 (see figure).

Blood was freshly collected into plastic tubes containing citrate (3.8% w/v) with aprotinin (1000 U/l) added to prevent proteolysis. Samples were kept on ice and spun immediately to obtain plasma, which was stored at -20°C. Fibronectin concentrations were determined by an automated immunoturbidimetric method⁵ using an assay kit (Boehringer Mannheim). Plasma (5 µl) was incubated with the reaction mixture (500 µl) in a LKB reaction-rate analyser at 25°C, with the change in absorbance at 340 nm being measured after 280 s. Control values were obtained in 64 normal healthy subjects (31 men, 33 women; age range 20-81 years).

Routine biochemical variables were determined daily, including liver function tests, using a Technicon Auto-Analyser (SMAC), and the prothrombin time.

Results

On admission 13 of the 17 patients had fibronectin concentrations below the lower limit of the normal range (± 2 SD, 194-472 µg/ml); the mean concentration in all patients was significantly lower than that in the control subjects ($117.9 \pm \text{SE } 19.4$ v 332.9 ± 8.6 µg/ml; $p < 0.001$, Student's *t* test). In the four patients with concentrations

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within the normal range the fulminant hepatic failure was due to viral hepatitis; the mean concentration in this group was higher than that in patients with fulminant hepatic failure due to paracetamol overdose (214.0 ± 15.0 v 80.5 ± 17.0 $\mu\text{g/ml}$; $p < 0.001$).

No correlation was found between the initial fibronectin concentration and the depth of coma or final outcome. In four of the five patients who died and in whom serial values were obtained, however, the fibronectin concentration decreased further in the first 24 hours after admission, whereas in three patients who survived the concentration increased. Two of the patients who survived (after paracetamol overdose; cases 2 and 3) had very low initial concentrations of fibronectin, which slowly returned to normal during the course of the illness (figure). One patient (case 5), who died, was given fresh-frozen plasma on the third day, after which the concentration rose. Another patient (case 6), who had hepatitis B virus, died despite stable fibronectin concentrations.

Serial fibronectin concentrations in two patients with fulminant hepatic failure who recovered (●) and two patients who died (○).

A significant negative correlation was found between fibronectin concentration and aspartate aminotransferase activity ($r = -0.766$, $p < 0.001$) and a positive correlation between fibronectin concentration and plasma total bilirubin concentration ($r = 0.654$, $p < 0.01$). In contrast, no correlation was found with serum albumin concentration ($r = -0.034$) or the prothrombin time ($r = 0.213$). The initial fibronectin concentration tended to be lower in patients in whom renal failure developed (urine output < 300 ml/24 h, creatinine concentration > 400 $\mu\text{mol/l}$ (4.5 mg/100 ml)) compared with those with normal renal function (96.5 ± 26.1 v 148.6 ± 26.6 $\mu\text{g/ml}$), and a significant inverse correlation was found between serum creatinine and fibronectin concentrations ($r = -0.509$, $p < 0.05$).

Discussion

This is the first report of reduced plasma fibronectin concentrations in patients with fulminant hepatic failure. In a recent study Matsuda *et al*⁶ found increased fibronectin concentrations in patients with uncomplicated acute hepatitis but the severity of the liver damage was considerably less than that in our patients with acute liver failure. Reduced fibronectin concentrations were found only in patients with decompensated cirrhosis. Other workers have also reported raised plasma concentrations of fibronectin in various types of liver disease including obstructive jaundice and primary biliary cirrhosis,⁷ and we have found normal concentrations in patients with alcoholic cirrhosis (unpublished observations).

The reduced plasma fibronectin concentration correlated most

closely with the activity of aspartate aminotransferase, a cytosolic enzyme released when liver cells are damaged. There was no correlation with either the prothrombin time or serum albumin concentrations, which agrees with the findings of Matsuda *et al*⁶ in patients with acute hepatitis. The most likely explanation for the low fibronectin concentrations in fulminant hepatic failure is the increased consumption of fibronectin during phagocytosis of particulate matter after hepatic necrosis. The difference in fibronectin concentrations between patients after paracetamol overdose and those with fulminant viral hepatitis may be related to the slower time course of hepatitis,⁸ which allows time for further production or release of fibronectin so that plasma concentrations are maintained. Decreased production of fibronectin by endothelial cells⁹ is less likely to be the cause, since other products of endothelial cells including factor VIII¹⁰ are appreciably increased in patients with acute liver failure. The absence of overt sepsis on admission makes this an unlikely reason for the low concentrations, as reported in patients with severe shock.¹¹

The lack of availability of fibronectin for opsonisation of particulate material may be a major factor responsible for the impaired function of Kupffer cells in patients with fulminant hepatic failure.⁴ This may lead to endotoxaemia as a result of failure of the damaged liver to clear gut-derived endotoxin from portal blood. Endotoxin has been implicated in the pathogenesis of renal failure in these patients,¹² and, interestingly, in our study there was a significant correlation between low fibronectin concentration and renal function as assessed by the plasma creatinine concentration. The patient given fresh-frozen plasma showed a rise in plasma fibronectin concentration. The effect on the function of Kupffer cells of therapeutic replacement of fibronectin remains to be evaluated.

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