

# Factor VII levels as a guide to prognosis in fulminant hepatic failure

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**SUMMARY** Levels of clotting factors II, V, and VII were measured on admission and then daily in 12 patients with grade IV hepatic coma due to fulminant hepatic failure. Factor VII levels obtained within 36 hours of the development of grade IV coma were not of value in predicting which patients would subsequently recover consciousness. Four of the latter group had levels below 9% at this time while the levels in three of the seven fatal cases were higher. Serial determinations were of more value and levels rose rapidly in those patients who ultimately made a complete recovery.

The mortality in fulminant hepatic failure is closely related to the degree of encephalopathy which develops and is over 80% in those who deteriorate to deep coma—that is, grade IV encephalopathy—(Trey and Davidson, 1970). Within this fatal group there may well be cases with such extensive hepatic necrosis that recovery of the liver is impossible and the only conceivable treatment is liver transplantation. In others, recovery is a possibility provided that they can be brought through the acute phase of the illness by some means of temporary liver support. If these two groups of patients could be differentiated at an early stage, then this would clearly be of help in considering their possible management.

Raised levels of  $\alpha$  foetoprotein indicate a good prognosis but these are found only later in the course of the illness (Karvountzis and Redeker, 1974). The galactose elimination test also appears to be of some value as a prognostic test but is relatively difficult to perform (Tygstrup *et al.*, 1975). Recently, Dymock *et al.* (1975) have suggested that reductions in levels of clotting factor VII to less than 9% of normal carry a very poor prognosis. However, these results were obtained in a series of patients with hepatic encephalopathy of varying severity ranging from slight to severe, and it is well known that the prognosis is very much better in patients in whom the encephalopathy is relatively mild. The purpose of the present study therefore was to determine whether the measurement of factor VII levels would also be of value in patients with grade IV hepatic coma, in whom the problem of prediction is much more difficult.

## Methods

The 12 patients were admitted to King's College Hospital between September 1973 and January 1975. All of them had been in grade IV coma for up to 36 hours before arrival. In addition to intensive supportive therapy, including bowel sterilisation with neomycin, they were subsequently treated by daily four hour periods of charcoal haemoperfusion (Gazzard *et al.*, 1974).

All patients had blood withdrawn for clotting factor assays on admission and then daily. The plasma was separated immediately by centrifuging at 4°C and then stored for up to three weeks at -20°C. Five of the 12 patients received fresh frozen plasma (300 ml) intravenously every six hours as treatment for the coagulation disturbance. In these patients samples were initially withdrawn before its use and then on successive days three hours after the infusion.

Blood platelets were counted manually (Brecher and Cronkite, 1950). Plasma fibrinogen levels were determined by a gravimetric technique (Ingram, 1961) and serum fibrin degradation products were estimated by the method used by Merskey and colleagues (1969). Assays of clotting factors II (Biggs and Douglas, 1953), V (Denson, 1972), and VII (Denson, 1972) were performed in duplicate on the stored plasma samples.

The number of surviving liver cells in the patients who died was estimated by a morphometric technique on a liver biopsy taken with the Tru-cut needle immediately after death. A Weibel graticule was fitted into the eyepiece of a microscope and the points on the graticule which coincided with a hepatocyte were counted in 60 high power fields (Weibel *et al.*,

1966). Thus, the percentage of the liver area occupied by hepatocytes could be calculated, which gave a hepatocyte volume fraction (HVF) when related to the total area. In our laboratory the normal HVF is 85% ( $\pm$  SD 10).

## Results

Five of the 12 patients recovered consciousness after an average of three charcoal haemoperfusions. Four of them eventually returned home. The fifth died two weeks later of multiple lung abscesses when liver function was improving. The results of standard haematological and biochemical tests carried out on admission were of no value in predicting which patients would recover (Table). In six of the seven fatal cases the HVF was less than 20% indicating greatly reduced numbers of hepatocytes. The immediate cause of death in these six was a complication of acute hepatic failure, either cerebral oedema, pancreatitis, or a major haemorrhage. The seventh case with a higher HVF died of cerebral oedema.

Measurement of the factor VII levels at the time of admission showed values below 9% of normal in four of the five patients who eventually recovered consciousness (Fig. 1). The patient who recovered consciousness but later died of infection showed a factor VII level of 28%. However, subsequent levels for the factor VII concentrations obtained in the other four patients increased to 9% or above (Fig. 2). In two this increase may have been related to the fresh frozen plasma they received, but in the other two patients this increase was probably a reflection of improving liver function, as they did not receive replacement therapy.

In three of the seven patients who did not recover consciousness the factor VII levels on admission were greater than 9% of normal (Fig. 1). Subsequently, however, readings showed that they fell

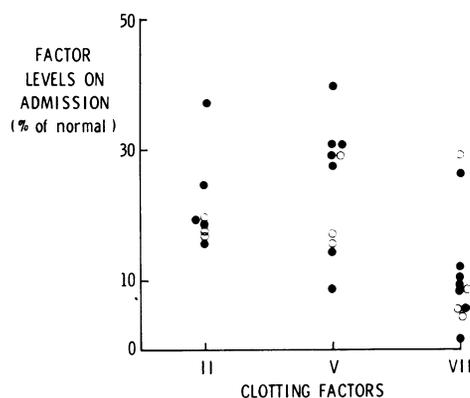


Fig. 1 Levels of clotting factors II, V, and VII on admission shown separately for those who subsequently recovered consciousness (○) and those who did not (●).

below 9% in two of these three patients (Fig. 2). The third patient, in whom the factor VII level was above 9% initially and also on the following day, suffered from a respiratory arrest 36 hours after admission. Necropsy showed cerebral oedema with herniation of the cerebellum. Morphometric analysis of hepatic histology showed there were practically no surviving liver cells (HVF 0.8%). We could not detect any differences in the levels of clotting factors II and V obtained on admission or serially between those who recovered consciousness and those who did not.

## Discussion

The low levels of clotting factors found in patients with fulminant hepatic failure are due to a decrease in liver synthesis aggravated by increased consumption consequent on intravascular coagulation (Rake *et al.*, 1971). As factor VII has a short half-life of about three to 5½ hours, plasma levels fall rapidly

Table Haematological and biochemical values in 12 patients on day of admission in grade IV hepatic coma

Case	Age (yr)	Aetiology	Serum bilirubin ( $\mu$ mol/l)	Aspartate amino transferase (IU/l)	Prothrombin time (s prolonged)	Fibrinogen (g/l)	Fibrin degradation products ( $\mu$ g/ml)	Platelet count ( $\times 10^9/l$ )
1	32	Acute hepatitis	>240	262	23	2.50	4	54
2	24	Acute hepatitis	320	1010	65	3.20	<2	165
3	62	Halothane-associated hepatitis	200	5440	40	0.85	8	126
4	44	Acute hepatitis	460	570	37	0.50	8	101
5	32	Acute hepatitis	640	1650	11	—	—	82
6	16	Acute hepatitis	—	>2000	55	0.50	8	214
7	26	Acute hepatitis	320	900	42	1.00	8	209
8	24	Acute hepatitis	280	2320	26	1.20	8	285
9	31	Fatty liver of pregnancy	320	450	11	1.50	4	119
10	30	Acute hepatitis	216	9120	63	3.50	2	135
11	36	Acute hepatitis	164	>2000	52	—	2	143
12	26	Acute hepatitis	146	>1000	42	—	<2	240

Cases 1-7 died; cases 8-12 recovered consciousness. Of those with acute viral hepatitis only in case 1 was HBsAg detected by radio-immunoassay.

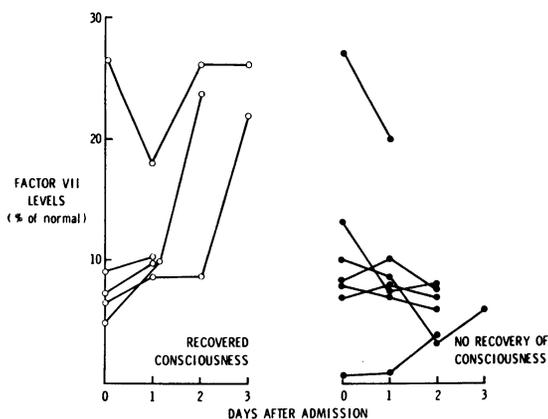


Fig. 2 Serial measurements of factor VII separated as in Fig. 1 according to the ultimate outcome.

after hepatocellular damage (Roberts and Cederbaum, 1972). Also, plasma levels are less likely to be affected by intravascular coagulation, since factor VII is part of the extrinsic clotting system and is not destroyed by thrombin (Roberts and Cederbaum, 1972). Thus, of all the coagulation factors, factor VII is probably the most sensitive index of hepatic synthetic function. In the series of 12 patients with fulminant hepatic failure investigated by Dymock *et al.* (1975), the factor VII levels were obtained either on admission or as soon as the patients developed encephalopathy. All those with levels of 8% or less of normal died, whereas none died with higher levels. However, only five of those patients were in grade III or IV coma at the time the measurements were carried out and it would appear from the data reported that the degree of encephalopathy was almost as good a prognostic guide. Thus, all those with grade III or IV coma died, whereas all but one of the patients with grade II coma survived.

In contrast, the present series comprised patients who had already deteriorated to grade IV coma and it is clear from the results that the initial factor VII levels were not of such good discriminatory value. Serial readings were more useful, as the levels fell to less than 9% in those who died whereas a rise was observed in those who recovered.

It would be of interest to compare the value of serial determinations of factor VII with other tests of hepatocellular function such as the galactose elimination test (Tygstrup *et al.*, 1975) and the conjugation of a radioactive tracer dose of bile acid (Horak and Waldram, 1975) which have been reported as useful in distinguishing those with the

greatest chance of recovery from fulminant hepatic failure. It seems most unlikely, however, that any one single test will ever be completely reliable in this respect and to withhold treatment from cases of fulminant hepatic failure because of a low factor VII level or some other test result would be quite unjustified on the present evidence.

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