Factor VIII levels during the course of acute hepatitis in a haemophiliac

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SYNOPSIS A 51-year-old patient with haemophilia since childhood (usual factor VIII level 14%) developed acute viral hepatitis type B two months after an operation which had been covered by cryoprecipitate. The course of the hepatitis following admission was severe with encephalopathy and ascites. Evidence of intravascular coagulation with an increased radioactive fibrinogen turnover was also present.

The factor VIII level measured by a one-stage clotting factor assay rose rapidly to 200% of normal and remained at this level for two weeks, and factor-VIII-related antigen as measured by electroimmunoassay also became greatly elevated (900% of normal). The possible mechanisms underlying those surprising changes are discussed.

The syndrome of fulminant hepatic failure, caused by viral hepatitis or toxic liver damage, is characteristically accompanied by a severe coagulation disturbance. Bleeding, which was the direct cause of death in 35% of the patients in a recent series (Clark *et al*, 1973), is caused in part by the failure of the liver to synthesize clotting factors, aggravated by consumption of these factors in the process of intravascular coagulation (Rake *et al*, 1970). Levels of many clotting factors are low with the exception of factor VIII, which may become elevated for reasons not currently known (Meili and Straub, 1970). The finding that the same elevation of factor VIII could occur in a haemophiliac patient with acute hepatitis was rather unexpected, and in this paper we describe the changes found in the serial coagulation tests during the course of the illness.

Clinical History

The patient, a 51-year-old musician, was found to have haemophilia in childhood. All through his life he had suffered from excessive bleeding from wounds and following dental extractions. There was no family history of the disorder. Two months before the admission with hepatitis, the patient had been

given cryoprecipitate therapy at the time of an inguinal hernia repair. Six weeks later the patient became nauseated and shortly afterwards jaundiced. His condition deteriorated with the appearance of drowsiness and disorientation due to hepatic encephalopathy, which led to his admission on 2 January 1972. He was treated with neomycin and lactulose, and the encephalopathy improved, although subsequently he became deeply jaundiced, the serum bilirubin level rising to a maximum of 450 $\mu\text{mol/l}$ (figure). A further manifestation of the

Figure The changes in liver function tests in relation to treatment given: (●—●) serum aspartate amino transferase and (○—○) serum bilirubin.

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severe hepatocellular dysfunction was the presence of ascites, requiring diuretic therapy. Hepatitis B antigen detected in the patient's blood by immunodiffusion was present for the first month of the illness. Prednisone (50 mg/24 hr), started after the first four weeks in hospital because of the deep jaundice and poor general condition, was continued for one month, by which time the prothrombin time had returned to normal and the bilirubin had fallen to 150 μ mol/l. The patient was able to leave hospital after four months.

Eighteen days following admission he developed pain in the buttocks, axilla, and abdomen. As well as large haematomas in the axilla and both gluteal muscles, one in the retroperitoneal area was suspected, his haemoglobin falling from 12 to 6 g/100 ml over a 12-hour period. He was given a six-pint blood transfusion, and there was no further progression of the bleeding.

Coagulation Tests and Factor Assays

Standard methods were used for the one-stage prothrombin time with human brain thromboplastin, partial thromboplastin time with kaolin, and thrombin clotting time (Hardisty and Ingram, 1965). The results were expressed as a ratio with a normal control. Fibrinogen was estimated gravimetrically (Ingram, 1961). Serum FR antigen was measured by the human tanned red cell haemagglutination inhibition technique (Merskey *et al*, 1969), and circulating plasminogen activator was measured on bovine fibrin plates (Astrup and Müllertz, 1952). The presence of fibrin strands in the plasma after protamine precipitation was assessed by the serial dilution of protamine sulphate (SDPS) test (Gurewich and Hutchinson, 1971). The turnover of 125 I-labelled fibrinogen was measured on three occasions, as described by Rake *et al* (1970). The coagulation activity of factor VIII and of factor IX was measured by the one-stage method of Hardisty and Ingram (1965). Factor-VIII-related antigen was measured by the method of Denson (1973).

Results

The level of factor VIII shortly before the inguinal herniorrhaphy was 14% of normal. Following the infusion of 15 units of cryoprecipitate this rose to 65%. No antibody to factor VIII was detectable in his plasma then or subsequently.

During the first week of his readmission, following the development of hepatic encephalopathy, there was evidence of intravascular coagulation with a low fibrinogen level, raised levels of serum fibrin(ogen) degradation products, and a persistently positive SDPS test (table). However, fibrin plates showed no lysis when treated with fresh plasma from the patient. The plasma disappearance rate of a tracer dose of 125 I fibrinogen injected intravenously was abnormally rapid at this time, with a marked increase in the calculated fractional catabolic rate of 64%/day (normal 22-28%/day; Tytgat, 1971). This was still slightly raised one month later (30.4%) but had fallen to within the normal range at six months (23%). An attempt was made to control the intravascular coagulation during the first six days by the administration of a combination of fresh frozen plasma (300 ml 6-hourly) and heparin given by continuous infusion so as to maintain a level of 0.5 mg/100 ml, as assessed by titration against protamine sulphate (O'Shea *et al*, 1971).

At the time of admission with hepatitis, but before the administration of FFP, the factor VIII level was 100%. The next day the factor VIII activity had risen to 217% following 600 ml of FFP and remained above 200% for two weeks, despite the cessation of replacement therapy at six days. One month later, the activity was still 91% of normal, but by seven months it had fallen to 23%. Factor-VIII-related antigen was greatly elevated for two months (table).

Subsequent repeated estimations of the bleeding time, platelet adhesion, and platelet aggregation have failed to reveal any abnormality.

Discussion

The hepatitis B infection in this patient was almost

Test	Initial	1 wk	2 wk	4 wk	8 wk	7 m
Prothrombin time ratio	3.8	1.8	1.8	1.3	1.1	1.0
Partial thromboplastin time ratio	3.0	3.9	2.0	2.0	1.3	—
Thrombin clotting time ratio	2.3	2.0	1.3	1.2	1.0	1.0
Plasma fibrinogen (mg/dl)	70	250	140	280	220	400
Plasma plasminogen (casein units/ml)	0.4	2.2	1.0	—	—	—
Serum FR-antigen (μ g/ml)	128	2	2	2	2	2
Factor IX (% normal)	13	24	28	68	70	90
Factor VIII assay (% normal)	100	200	275	65	100	23
Factor-VIII-related antigen (% normal)	480	800	800	900	900	430

Table Results of coagulation tests performed on admission before administration of FFP, and at serial intervals thereafter including the recovery phase (4 weeks onwards)

certainly acquired *via* the cryoprecipitate therapy. This is a recognized, although rare complication of such treatment (Lewis, 1970). The rise in factor VIII level observed has not previously been documented to our knowledge in a patient with haemophilia suffering from hepatitis. The possibility that this patient suffered from von Willebrand's disease rather than haemophilia, which could account for the rise in factor VIII levels following infusion of plasma, seems unlikely. No abnormality has been detected in bleeding time or platelet function; no such rise has been observed previously when the patient was given cryoprecipitate. Furthermore, the factor VIII levels were also raised before the start of replacement therapy. The levels of factor VIII measured in this patient by a one-stage technique could have been elevated because of the presence of activated clotting factors in the plasma as a result of disseminated intravascular coagulation, the similar one-stage assay for the measurement of factor IX being much less affected by these activated factors (Niemetz and Nossel, 1969). However, the factor VIII levels remained elevated for a considerable period when there was no other evidence of intravascular coagulation, and the levels of factor-VIII-related antigen were also greatly increased.

The factor-VIII-related antigen is present in normal amounts in patients with classical haemophilia, and increases in healthy people are observed following all kinds of stress (Denson, 1973). The rise observed in the present patient during acute hepatitis might suggest that a similar response to stress could also occur in haemophilia.

Several explanations have been proposed for the rise in factor VIII occurring in patients with fulminant hepatic failure. These include the possibility of increased synthesis, impaired physiological clearance which is normally *via* the liver, or leakage of factor VIII from damaged cells (Meili and Straub, 1970). In our patient with haemophilia, the genetic defect may not have been in the synthesis of the clotting factor but in its release from hepatocytes. Another possibility is that he had a defective 'operator' gene which was 'turned on' by the hepatitis virus. If this were so, the rise in factor VIII levels in other patients

with fulminant hepatic failure due to viral hepatitis could be explained by increased synthesis following interference with a normal negative feed-back mechanism, but patients with hepatic necrosis produced by toxins would not be expected to have raised levels of factor VIII. Indeed, Meili and Straub (1970) found low levels of factor VIII in two patients with *Amanita phalloides* poisoning, although patients with paracetamol-induced liver injury have, in our experience, high levels of this clotting factor.

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