Acute viral hepatitis, intravascular haemolysis, severe hyperbilirubinaemia and renal failure in glucose-6-phosphate dehydrogenase deficient patients

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Summary: Five patients with acute viral hepatitis developed severe intravascular haemolysis and unusually high levels of serum bilirubin (427 to 1368 $\mu\text{mol/l}$). All 5 had high fever, marked anaemia, reticulocytosis and neutrophilic leucocytosis. Three of them developed acute renal failure, which was of non-oliguric type in 2. The clinical course was protracted, but complete recovery occurred in 4 patients between 4 to 10 weeks. One patient with hepatic coma and oliguric renal failure died. Deficiency of the enzyme G-6-PD was confirmed in 4 cases. Massive haemolysis in the patients was probably induced by the administration of chloroquine and other drugs. Intravascular haemolysis should be suspected in patients with acute viral hepatitis, if they show unexplained anaemia and very high serum bilirubin levels, and measures to prevent renal failure should be instituted in such cases.

Introduction

Acute viral hepatitis is widely prevalent in Northern India. In a study by Tandon *et al.* (1984) in Delhi, 90% of the subjects over the age of 10 y were found to have antibodies against hepatitis A virus. Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency is also common in this region, the incidence being variously reported as 2.2 to 14% (Jolly *et al.*, 1972). A frequent association of these two conditions in the same patient would therefore be expected. This might not be clinically important, if both disorders occurred in a mild form. When hepatitis is complicated by severe intravascular haemolysis, serious problems may arise in the management of the illness and it may have a protracted course. We briefly report observations in 5 patients in whom such a situation developed. All of them had severe and prolonged jaundice with serum bilirubin levels of over 427 $\mu\text{mol/l}$, and 3 had acute renal failure.

Case reports

Case 1

A 9½ year old boy had moderately high, intermittent fever followed, a week later, by vomiting. After 3 days

he developed jaundice which rapidly increased. On examination, he was fully conscious but deeply jaundiced. The liver was palpable 4 cm below the costal margin and was firm and tender. The spleen was not palpable. The haemoglobin was 6.7 g/dl, reticulocytes 14% and total serum bilirubin 1111 $\mu\text{mol/l}$ with a direct fraction of 769 $\mu\text{mol/l}$. The results of other haematological tests and liver function tests are given in Table I. He was managed with supportive care including blood transfusions. The serum bilirubin increased to a peak value of 1368 $\mu\text{mol/l}$ (conjugated 821 $\mu\text{mol/l}$) on the third post-admission day but gradually declined to a normal level over the next 5 weeks. The blood urea levels were within the normal range throughout the course of illness.

Case 2

A 19 year old boy had continuous fever (37.5 to 40°C) for 9 days without any other significant feature. He was treated with antimalarial drugs and tetracycline. Five days later, he developed jaundice and persistent vomiting. He became unconscious a day before hospital admission. On examination he was in grade III coma and deeply jaundiced. Liver was palpable 3 cm below the costal margin. His haemoglobin was 6 g/dl, reticulocytes 9%, total serum bilirubin 752 $\mu\text{mol/l}$ with a direct fraction of 462 $\mu\text{mol/l}$ and the blood urea 10 mmol/l. Results of other tests and liver function tests are given in Table I.

During the hospital stay he continued to have high

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Table I Representative haematological and biochemical findings

No. of patient	Days of illness	Hb (g/dl)	WBC $10^9/l$ (% neutrophils)	Haemolysis*	Serum bilirubin ($\mu\text{mol/l}$) total/direct	Blood urea (mmol/l)	SGOT/SGPT (IU)
1	8	6.7	52.5 (80)	+	1111/769	N	1200/1200
	11	11.5	36.2 (70)	+	1368/821	N	860/760
	21	12.8	14.8 (66)	—	111/65	N	30/25
	58	13.5	13.2 (60)	—	20.5	N	44/53
2	9	6	20.5 (75)	+	752/462	10	660/1100
	15	8.9	13.5 (75)	+	653/499	25	75/65
	29	9.7	4.4 (60)	—	350/239	11	44/35
	41	12.8	6.2 (55)	—	200/128	4	50/35
3	5	7.9	12.8 (60)	+	448/282	N	180/180
	32	13.5	5.5 (56)	—	41/19	N	26/18
4	10	6.2	6.4 (70)	+	1265/838	43	600/600
	15†	8.4	6.2 (76)	+	752/445	30	500/600
5	7	5.5	56.0 (68)	+	688/479	20	1035/1645
	10	4.3	18.2 (84)	+	1026/598	25	860/920
	16	11.9	9.1 (58)	+	318/224	10	96/138
	37	13.7	8.5 (60)	—	41/20	5	39/46

Hb = haemoglobin; WBC: white blood cells; N = within normal range; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase. *Evidence of haemolysis = anaemia, reticulocytosis, haemoglobinuria. †Patient died the same day.

grade fever (up to 39°C) for 8 days, after which it gradually subsided over the next week along with sensorial improvement. Pedal oedema and ascites were seen on the fifth day which subsided over the next 3 weeks. He developed upper gastrointestinal bleeding which was managed with transfusion of 2 units of fresh frozen plasma and 4 units of blood. The blood urea level increased to a peak value of 24.9 mmol/l on the 8th day, after which it slowly came down to normal on the 20th day. Various clinical and biochemical features continued to show improvement (Table I). Urine output remained normal during this period. A percutaneous liver biopsy, done on the 30th day of illness, showed bridging necrosis and diffuse cholestasis. Two weeks later he was sent home in satisfactory condition, and on a follow-up visit after 1 month, his haemoglobin and liver function tests were normal.

Case 3

A 10 year old boy was diagnosed to have G-6-PD deficiency 1 year previously, when he had an episode of acute intravascular haemolysis after receiving chloroquine. On the present occasion, he had intermittent high fever for 5 days, which subsided following intake of some tablets, probably chloroquine. Fever recurred a few days later with nausea and vomiting. The urine was red-coloured and he showed yellow discolouration of sclera for 2 days before admission. On examination he was moderately jaundiced and

pale. The liver was enlarged 4 cm below the costal margin and was tender. His vital signs and systemic examination were normal. The haemoglobin was 7.9 g/dl, reticulocytes 7.5% and total serum bilirubin 445 $\mu\text{mol/l}$ with a direct fraction of 282 $\mu\text{mol/l}$ (Table I). He was treated with blood transfusion and increased fluid intake to keep a urine output of 2 to 3 litres/day. Haemoglobinuria stopped after 3 days, fever subsided within a week and jaundice gradually disappeared over the next 4 weeks.

Case 4

A 10 year old boy had moderately high fever. Five days later he developed jaundice, which rapidly increased over the next 4 days. He began to vomit 3 to 4 times a day; this was initially watery but later dark brown. The urine output decreased and he became drowsy. He had received antipyretics but there was no history of intake of antimalarial drugs. On examination the child was very ill and semiconscious. He was deeply jaundiced. The liver was palpable 4 cm below the costal margin. Haemoglobin was 6.2 g/dl, reticulocytes 10%, serum bilirubin 1265 $\mu\text{mol/l}$ with a direct fraction of 838 $\mu\text{mol/l}$, and the blood urea 43 mmol/l.

The child gradually became comatose. The urine output remained less than 100 ml/d throughout the course of the illness. He developed upper as well as lower gastrointestinal bleeding and haematuria. He

was managed with supportive care including administration of fresh blood and plasma, laevodopa, ampicillin and bowel washes. Peritoneal dialysis was performed on two occasions, but it did not result in a significant improvement in his condition. The child remained deeply comatose and died on the eighth hospital day. A post-mortem liver biopsy showed changes characteristic of severe viral hepatitis. Renal biopsy showed acute tubular necrosis with numerous haemoglobin and bilirubin casts in the tubules.

Case 5

An 8 year old boy had high fever and vomiting for which he was given chloroquine tablets. Three days later he passed dark brown urine and developed jaundice. Shortly thereafter he passed tarry stools and became drowsy. On examination he was semiconscious and deeply jaundiced. The vital signs were maintained. The liver was enlarged 3 cm below the costal margin. Haemoglobin was 5.5 g/dl, serum bilirubin 638 $\mu\text{mol/l}$ with a direct fraction of 479 $\mu\text{mol/l}$, reticulocytes 12% and blood urea 19.9 mmol/l. He was managed with standard supportive care. His sensorium gradually improved and melaena stopped over the next 7 d. The blood urea level had increased to 28 mmol/l on the third hospital day but subsequently it gradually declined. His urine output remained between 1.5 to 2.5 litres/day. Various biochemical tests showed normal results on the 40th hospital day.

Other investigations

In all cases examination of urine showed the presence of haemoglobin in early stages of the illness. Bilirubinuria, also present in all cases, persisted for several days and its intensity was related to the levels of conjugated bilirubin in the blood. Direct Coomb's test was negative and hepatitis B surface antigen absent in all. Kayser-Fleischer rings were absent in patients 1, 2, 3 and 5 on slit lamp examination. This examination could not be done in patient 4. In the former four patients, blood was examined for G-6-PD deficiency by the methaemoglobin reduction method (Brewer *et al.*, 1962) 6 to 12 weeks after they had completely recovered. The results indicated a severe deficiency state.

Discussion

The diagnosis of viral hepatitis in our patients was based on clinical features and laboratory evaluation of liver dysfunction, and liver histology in 2 cases. In all cases evidence of severe liver injury was present. Although jaundice may occur from severe intravascular haemolysis with normal liver function, it is

usually mild and of short duration (Schalm & Weber, 1964; Choudhry *et al.*, 1980).

Serum bilirubin levels of over 342 $\mu\text{mol/l}$ are uncommon in patients with uncomplicated viral hepatitis (Morrow *et al.*, 1968; Chan & Todd, 1975). Additionally, a decline in haemoglobin of more than 1 to 2 g/dl is also rare in this condition unless there is associated blood loss, severe haemolysis or bone marrow suppression. Mild haemolysis, associated with decreased red cell survival, is commonly present in viral hepatitis (Pitcher & Williams, 1963), but is of little clinical importance. Our patients had severe intravascular haemolysis as evidenced by marked anaemia, reticulocytosis and haemoglobinuria. They also had high fever with chills and rigours and neutrophilic leucocytosis, which are seldom observed in uncomplicated viral hepatitis, but are typically associated with acute intravascular haemolysis (Choudhry *et al.*, 1980). The haemolysis was in all likelihood related to G-6-PD deficiency, which was confirmed in four cases. Other important causes of haemolysis, such as infections, immunological abnormalities and chronic haemolytic states were excluded.

It is of interest that Wilson's disease (hepatolenticular degeneration) may rarely present initially with acute hepatic failure and acute intravascular haemolysis (Roche-Sicot & Benhamou, 1977), which may be further complicated by acute renal failure (Hamlyn *et al.*, 1977). Such cases present difficult therapeutic problems and the outcome is usually fatal. It is therefore important to look for Wilson's disease by examination for Kayser-Fleischer rings in patients with acute liver disease and intravascular haemolysis, since this condition would require prompt institution of specific therapy.

The presence of high levels of serum bilirubin in patients with viral hepatitis and intravascular haemolysis due to G-6-PD deficiency has been observed earlier (Clearfield *et al.*, 1959; Salen *et al.*, 1966; Morrow *et al.*, 1968; Philips & Silvers, 1969; Kattamis & Tjortjatou, 1970; Chan & Todd, 1975). Usually such values are proportional to the degree of haemolysis and the severity of hepatic involvement, but sometimes unexplainably high levels may be encountered (Salen *et al.*, 1966). Chan & Todd (1975) and Kattamis & Tjortjatou (1970) reported a direct correlation of reticulocyte cell count and haemoglobin values with levels of serum bilirubin in patients with viral hepatitis and G-6-PD deficiency. This observation would suggest that increased bilirubin load, resulting from haemolysis, was the main factor to influence the serum bilirubin levels. In massive haemolysis, however, hepatic excretion of bilirubin may be a limiting factor (Snyder *et al.*, 1967) and pronounced hyperbilirubinaemia may result.

Jaundice, besides being more severe, has been observed to persist for longer periods in patients with

viral hepatitis and associated G-6-PD deficiency, than in those with normal G-6-PD levels (Morrow *et al.*, 1968). Three of our patients (no. 1, 2 and 5) had jaundice while serum transaminase values had come down to near normal. An increased occurrence of canalicular cholestasis has been suggested to account for unusually prolonged jaundice in such patients (Morrow *et al.*, 1969).

In patients with viral hepatitis and G-6-PD deficiency, massive haemolysis is usually precipitated by exposure to oxidant drugs (Chan & Todd, 1975). The most noxious of these are primaquine, nitrofurantoin and sulphonamides, but a number of other drugs, including chloroquine, may also be responsible (Brewer *et al.*, 1962). Exaggerated haemolysis may, however, occur in patients with viral hepatitis and G-6-PD deficiency without the intake of such drugs (Salen *et al.*, 1966; Kattamis & Tjortjatou, 1970). Pitcher & Williams (1963) reported decreased values of reduced glutathione in the red cells of patients with acute viral hepatitis, which returned to normal after the patients had recovered. Such an abnormality could result from accumulation of oxidants due to hepatic dysfunction and, in conjunction with G-6-PD deficiency, lead to increased haemolysis.

Despite the alarmingly high levels of serum bilirubin in patients with viral hepatitis and intravascular haemolysis, the prognosis is usually favourable, and chiefly related to the severity of hepatic injury (Wong, 1966; Clearfield *et al.*, 1969). One of our patients who

died had fulminant hepatitis and renal failure. The development of acute renal failure in these patients is a serious complication (Salen *et al.*, 1966; Philips & Silvers, 1969; Chan & Todd, 1975). Although acute viral hepatitis is rarely associated with significant renal dysfunction, renal failure may occasionally develop in this condition (Wilkinson *et al.*, 1978). The underlying basis may be acute tubular necrosis or it may resemble the hepatorenal syndrome observed in patients with advanced cirrhosis of the liver. Acute renal failure is not an uncommon complication of severe intravascular haemolysis in patients with G-6-PD deficiency (Choudhry *et al.*, 1980). It is understandable that association of hepatitis and severe haemolysis could result in increased susceptibility to renal failure (Green *et al.*, 1984). Mechanical blockage of the tubules by haematin and bilirubin plugs may play a more important role in the pathogenesis of acute renal failure in such a situation. It is important to note that renal failure may be of the non-oliguric type in some of these patients. Thus, unless the blood chemistry and urinary sodium and osmolal excretion are monitored, renal insufficiency may be overlooked, or elevated blood urea values considered to be due to pre-renal factors.

Preventive measures against the development of renal failure, such as correction of anaemia, hypotension, avoidance of nephrotoxic drugs and maintenance of a high urine output, should be instituted in patients with viral hepatitis and haemolytic anaemia.

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