Case report: Acute hepatitis E infection with coexistent glucose-6-phosphate dehydrogenase deficiency

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Hepatitis E virus is one of the leading causes of acute viral hepatitis in India but usually manifests as a mild self-limiting illness. Viral hepatitis in the presence of glucose-6-phosphate dehydrogenase (G6PD) deficiency may be associated with complications such as severe anemia, hemolysis, renal failure, hepatic encephalopathy and even death. The incidence of G6PD deficiency in the general population of northern India is reported to be between 2.2% and 14%. Despite both hepatitis E infection and G6PD deficiency being common, their impact on patient illness has only recently been reported. The present study reports a case of severe hemolysis in a patient with G6PD deficiency and hepatitis E infection.

Key words: *Glucose-6-phosphate dehydrogenase; G6PD; Hemolysis; Hepatitis E*

Exposé de cas : Hépatite E aiguë en présence d'un déficit en glucose-6-phosphate-déshydrogénase

Le virus de l'hépatite E est l'une des principales causes d'hépatite aiguë en Inde, mais il s'agit en général d'une maladie bénigne, spontanément résolutive. Par contre, une hépatite virale en présence d'un déficit en glucose-6-phosphate-déshydrogénase (G6PD) peut donner lieu à des complications comme une anémie grave, l'hémolyse, l'insuffisance rénale, une encéphalopathie porto-cave et même la mort. L'incidence du déficit en G6PD dans la population en général dans le Nord de l'Inde varie entre 2,2 et 14 %. Même si l'hépatite E et le déficit en G6PD sont deux affections fréquentes, on ne fait état de leur influence sur l'évolution de la maladie que depuis peu. Voici un cas d'hémolyse grave chez un patient atteint à la fois d'un déficit en G6PD et d'une hépatite E.

Hepatitis E is an enterically transmitted virus and is one of the most common causes of acute viral hepatitis in India (1). Glucose-6-phosphate dehydrogenase (G6PD) deficiency is found in 2.2% to 14% of the general population in North India (2). The coexistence of viral hepatitis and G6PD deficiency has been reported to be associated with severe jaundice and other complications (3,4). Hepatitis E infection with G6PD deficiency has been associated with more severe illness in only one previous report (5). We report an additional case.

CASE REPORT

A 35-year-old man with no history of alcoholism or liver disease presented with low grade fever, upper abdominal pain, fatigue and loss of appetite for eight to 10 days. He had noticed a yellow discolouration of the eyes for three days and dark coloured urine for five to six days. On examination, he was deeply icteric. Abdominal examination revealed a soft, tender liver, palpable 4 cm below the costal margin. There was no splenomegaly and the remainder of the physical examination was normal.

Laboratory investigations revealed a hemoglobin mass concentration of 126 g/L, a total leucocyte count of 12.2×10^9/L, and a total serum bilirubin of 198 μmol/L with a conjugated fraction of 141 μmol/L. The serum aspartate aminotransferase (AST) concentration was 376 U/L and the alanine aminotransferase (ALT) concentration was 270 U/L. The prothrombin time was 15 s (control: 12 s). Immunoglobulin (Ig) M anti-hepatitis A virus, hepatitis B surface antigen, IgM anti-hepatitis B core and anti-hepatitis C virus were negative, while IgM anti-hepatitis E virus (HEV) was positive. A diagnosis of HEV hepatitis was made and the patient was managed conservatively.

Over the next three weeks, the serum bilirubin peaked at 964 μmol/L (conjugated fraction: 533 μmol/L), AST peaked at 1415 U/L, and ALT peaked at 2184 U/L. The hemoglobin mass concentration decreased to 80 g/L. The peripheral blood smear showed polychromasia, anisopoikilocytosis and reticulocytosis (the reticulocyte count was 14.6%). Urine was positive for hemoglobinuria. The serum lactate dehydrogenase concentration was 696 U/L (normal: 200 to 500 U/L) and serum haptoglobin was undetectable. Direct and indirect Coomb's tests were negative. Both the peripheral blood smear and the antigen-test were negative for malaria. Normal serum ceruloplasmin levels and the absence of Keyser-Fleischer rings on slit lamp examination excluded Wilson's disease. The G6PD level was 3.9 U/gHb (normal range: 4.6 U/gHb to 13.5 U/gHb).

The patient was managed conservatively, including avoiding all hepatotoxic, nephrotoxic and oxidant drugs, and maintaining an adequate urine output. The metabolic parameters

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gradually improved over the subsequent five weeks. The hemoglobin mass concentration increased to 98 g/L, bilirubin fell to 161 μmol/L (conjugated fraction: 99 μmol/L), AST fell to 176 U/L, ALT fell to 281 U/L and reticulocyte count fell to 4.4%. The patient was discharged to be followed in the outpatient department. Ten weeks after the onset of illness the patient's G6PD level was 1.1 U/gHb, and his serum bilirubin and aminotransferase levels were nearly normal. About one month after the onset of illness, the patient's wife, who nursed him through the course of this illness, also developed jaundice and was diagnosed with HEV hepatitis.

DISCUSSION

Mild hemolysis associated with decreased red blood cell survival may be commonly seen with viral hepatitis, but is seldom of clinical significance (6,7). However, when viral hepatitis occurs in G6PD-deficient patients, hemolysis may be severe (7,8).

The patient described in this case had severe intravascular hemolysis as evidenced by a fall in hemoglobin, reticulocytosis, unconjugated hyperbilirubinemia, hemoglobinuria and undetectable serum haptoglobin levels. The presence of severe hyperbilirubinemia in patients with viral hepatitis and G6PD deficiency has been previously reported (9-11). In a case control study, Gotsman and Muszkat (12) evaluated the impact of G6PD deficiency on patients with Hepatitis A virus infection. They found that although patients with G6PD deficiency had a more severe initial clinical presentation, the clinical outcome was not affected. Abid and Khan (5) recently reported a cohort of five patients from Pakistan with G6PD deficiency and Hepatitis E viral infection. All five patients had severe and protracted illness, and four developed acute renal failure.

Profound hemolysis in G6PD-deficient individuals is usually precipitated by exposure to selected drugs. However, as in this case, viral hepatitis may precipitate massive hemolysis even without the intake of such drugs (5,7,10). The mechanism of hemolysis is thought to occur through decreased levels of reduced glutathione in red blood cells (6). Reduced glutathione levels could result from the accumulation of oxidants due to hepatic dysfunction and lead to increased hemolysis in the presence of G6PD deficiency. Despite the high levels of bilirubin in these patients, the prognosis is mainly related to the severity of hepatic injury (9). Acute renal insufficiency, though uncommon in uncomplicated acute viral hepatitis, can occur as a fatal complication of severe intravascular hemolysis in these patients (3). Excess hematin and bilirubin may result in the obstruction of renal tubules, leading to acute renal insufficiency with increased morbidity. Renal failure may be non-oliguric,; therefore, kidney function should be assessed by regularly monitoring blood chemistry, and urinary sodium and osmolarity. Measures to prevent renal failure include maintaining good hydration and adequate urine output, and avoiding nephrotoxic drugs.

HEV infection is transmitted through the feco-oral route but, unlike other enteric agents, does not generally spread from infected persons to their close contacts (13). In the present case, one month after the onset of jaundice in the patient his wife also contracted HEV. Because the incubation period of HEV ranges from 14 to 60 days, it is likely that she contracted the virus from her husband, rather than from a common source.

In patients with acute viral hepatitis and unexplained anemia with very high serum bilirubin levels, intravascular hemolysis should be considered and investigated. Wilson's disease may present with jaundice and hemolysis and must be excluded. Tests for G6PD deficiency may be negative during and immediately after a hemolytic episode because the old red blood cells deficient in G6PD have been hemolysed and the higher content of G6DP in the new red blood cells may lead to false normal levels. A repeat test should be done eight to 10 weeks after the disease resolves. When G6PD deficiency is suspected, treatment with vitamin K should be avoided because it may further aggravate hemolysis (14). Finally, all G6PD-deficient individuals should be vaccinated against Hepatitis A and B. Universal immunization against HAV and HBV for communities with high prevalences of G6PD deficiencies (eg, Vataliya-Prajapati community in western India [15], Muria gonds of central India [16], etc) should also be considered.

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