Case Report

Non-oliguric acute renal failure associated with hepatitis E

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Introduction

Hepatitis E usually presents as a self-limiting, acute icteric disease similar to hepatitis A [1]. Jaundice is usually accompanied by malaise, anorexia, abdominal discomfort and liver enlargement. The hepatitis E virus is enterically transmitted and frequently spread by feecally contaminated drinking water.

Hepatitis E is endemic in developing countries of the Indian subcontinent, Asia, Africa and South America [1,2]. The infection is recognized as a significant health problem in these areas and so far outbreaks have been described and serologically confirmed in 29 countries [2].

Hepatitis E is rare in the so-called developed countries and mostly restricted to immigrants from endemic areas or travelers returning from endemic areas [2]. Also in the Netherlands most cases of hepatitis E are described in immigrants and visitors of third world countries [3]. Although in general hepatitis E runs a benign course, death may follow. In endemic areas the case-fatality rate is estimated to be 0.5–4%, although in pregnant women these rates are much higher i.e. 10–40% [1,2]. Death is most often due to acute liver failure with resulting coma and bleeding. Renal failure however may be of additional importance.

Renal failure in liver disease is most often caused by hepatorenal syndrome or acute tubular necrosis [4,5]. Other causes of renal failure in viral hepatitis are acute glomerulonephritis as seen in hepatitis B [6], and interstitial nephritis, which has been reported in hepatitis A [7]. Renal failure complicating hepatitis E has, to our knowledge, never been described. We describe a patient with fulminating hepatitis E, who developed an acute non-oliguric renal failure.

Case report

A 34-year-old female was referred to our unit with acute hepatitis. From September 1994 until May 1995 she travelled through Thailand, Malaysia, Singapore, Nepal, India, and Bhutan. Before leaving The Netherlands she received immunoglobin for hepatitis A prophylaxis. During her travels she used mefloquine as malaria prophylaxis, and oral contraceptives. She suffered some short periods of self-limiting diarrhoea. In India, a few weeks before her return, she once drank water from a river. There was no history of unprotected sexual intercourse.

Five weeks after her return she was admitted to a local hospital with fever, nausea, vomiting, muscle pains, and diffuse abdominal pains. The next day she was transferred to our hospital because of serious liver failure, possibly requiring liver transplantation.

At admission physical examination revealed an icteric young female with grade 1 encephalopathy. Temperature was 34.9°C, blood pressure 140/80 mmHg and the central venous pressure was normal. We found diffuse tenderness of the abdomen, a palpable liver and spleen, but no ascites.

Laboratory test results at admission were as follows: Hb 13.4 g/dl, leucocytes 11.7 x 10^9/l, platelets 108 x 10^12/l, Na 133 mmol/l, K 4.2 mmol/l, urea 7.9 mmol/l, creatinine 179 μmol/l, uric acid 0.40 mmol/l, APH 170 U/l, LDH 15495 U/l, ASAT 9766 U/l, ALAT 7712 U/l, gamma GT 125 μmol/l, albumin 33 g/l, pH 7.39, bicarbonate 17.5 mmol/l, lactate 2.8 mmol/l, ammonia 102 μmol/l. Prothrombin time 25 s prolonged, APTT 10 s prolonged, fibrinogen 2.5 g/l, anti-thrombin III 64%, and coagulation factor V 18%.

Urine analysis showed many erythrocytes, 0–5 leucocytes and many granular casts per high powered field. Urine sodium was low: 12 mmol/l; there was no proteinuria.

Serologic tests for hepatitis B, hepatitis C, Epstein-Barr virus, cytomegalovirus, human immuno-deficiency virus, herpes viruses, leptospirosis, Q fever, toxoplasma and schistosoma were negative. There were no serological features of auto-immune hepatitis. However IgM antibodies against hepatitis E virus were
repeatedly strongly positive. IgG-antibodies against hepatitis E virus were initially borderline but later positive in high titers (anti-HEV EIA, Abbott Laboratories, Delkenheim, Germany).

Treatment was started with glucose, fresh frozen plasma, and ranitidine intravenously; in addition, vitamin K, lactulose and neomycine were given by nasogastric tube.

The first hours after admission urine production appeared low (10 ml/h). As we suspected vascular underfilling 1000 ml of 0.9% saline was given in 4 h. This resulted in an increase of diuresis to 30 ml/hour.

The following days the patient remained haemodynamically stable with blood pressures never below 90/60 mmHg. With more than 3 l infusion per day, plus 10 mg furosemide per hour the diuresis and sodium excretion remained good (Figure 1). The liver function started to improve with decreasing bilirubin levels from day 4 onwards. There were no longer signs of encephalopathy after 4 days. However, despite the improving liver function non-oliguric renal failure persisted (Figure 1). Creatinine rose from 179 µmol/l to 926 µmol/l. Eight days after admission dialysis had to be started. Because of impaired coagulation a renal biopsy was postponed until day 9. After the biopsy was performed it was decided not to wait for the definite result but to start without further delay with prednisone 1 mg/kg because of suspected interstitial nephritis. Hereafter gradually the renal function recovered and dialysis could be discontinued at day 12 (Figure 1).

The renal biopsy showed 8 normal glomeruli, no interstitial oedema and some tubuli with debris and erythrocytes. No vascular abnormalities were seen. Immune-fluorescence for IgA, IgG, IgM, heavy chains, κ and λ chains and complement C3 were negative.

Since the histological result was not compatible with the presumed diagnosis of interstitial nephritis the prednisone was rapidly tapered and discontinued.

Three weeks after admission the patient could be discharged. Follow-up revealed complete recovery of liver and kidney function.

**Discussion**

In our patient with a serologically proven acute hepatitis E the cause of the renal failure is not immediately clear. Renal failure in advanced liver disease is a well known feature. Most often hepatorenal syndrome with oliguric renal failure is seen. Other possible causes of acute renal failure in hepatitis are acute tubular necrosis, glomerulonephritis, and interstitial nephritis [4–7].

Hepato-renal syndrome is caused by circulating vasoactive toxins which cause vasodilatation, shunting, renal vasoconstriction and sodium and fluid retention. This condition is completely reversible when liver function is restored. If however hypoperfusion of the kidney is severe enough, this can, even in absence of hypotension, lead to acute tubular necrosis. Our patient had a low urine sodium and urine output at admission. These

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![Fig. 1. Clinical course and temporal relationship between liver and renal function.](image-url)
parameters however rapidly improved after infusion of normal saline. So hepatorenal syndrome at this point seems unlikely. In case of hepatorenal syndrome one would also have expected renal function to restore simultaneously with hepatic function. It improved days later so hepatorenal syndrome alone is an unlikely explanation in our patient.

The urine sediment contained many erythrocytes, some leucocytes and many granular casts. This suggests a renal cause of the acute renal failure. Glomerulonephritis is ruled out, since the renal biopsy showed normal glomeruli. Interstitial nephritis has been described in viral hepatitis [7]. The urine findings of our patient are compatible with this diagnosis. Also renal function began to improve after the start of prednisone. The renal biopsy however, taken before the prednisone therapy, showed no signs of interstitial nephritis. Due to the bleeding tendency the renal biopsy had been postponed. However some time delay cannot, in our view, explain that interstitial nephritis may have been missed.

Some tubuli contained necrotic debris and erythrocytes. This is compatible with a recovery phase of acute tubular necrosis. So in our view this patient developed an acute tubular necrosis. This may explain why the recovery of renal function occurred later than the normalization of the liver function.

The cause of ATN in this patient is unclear. As far as we know the patient had no evidence of seriously underfilling and there was also no strong evidence for serious hepatorenal syndrome. There was also no history of administration of nephrotoxic medication. Whether the ATN is directly related to the hepatitis E virus is unknown. If so, in addition to the sequela of a fulminant course of hepatitis E, acute renal failure as described here may well contribute to the mortality rate of hepatitis E virus infection, especially in less developed areas.

In conclusion we report a patient with fulminant hepatitis E who developed a non-oliguric acute renal failure due to acute tubular necrosis of unknown origin. It is possible that this complication is directly related to the virus. Acute renal failure may contribute to the mortality rate of hepatitis E virus infection.

References


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