Lethal acute HEV superinfection on hepatitis B cirrhosis

Hépatite virale E responsable du décès d’un patient suivi pour cirrhose virale B

Hepatitis E virus (HEV) associated acute liver failure has been reported in populations in the developing countries that are exposed to this virus in endemic or epidemic settings [1]. We report a fatal case of HEV superinfection with hepatitis B cirrhosis.

A 50-year-old white man was admitted in November 2008 for jaundice and ascites. The patient had a previous history of hepatitis B cirrhosis, diagnosed in 2006 associated with hypertension and type 2 diabetes. The complications of cirrhosis included portal hypertension with stage 2 oesophageal varices and hypersplenism. When hepatitis B cirrhosis was diagnosed, the hepatitis B virus (HBV) DNA viral load was below 100 IU/mL and no HBV treatment was initiated. Ligature of varices was performed twice and every 6 months, the patient underwent screening for hepatocellular carcinoma with ultrasound or computed tomography.

At admission in November 2008, the patient had a Glasgow score of 15 without fever, diffuse icteria and ascites without encephalopathy. Cardiac examination revealed a regular rate and rhythm and no cardiac failure (blood pressure of 100/45 mmHg).

The patient had not travelled in the past year and had not consumed uncooked or poorly cooked meat. Cholangio magnetic resonance imaging showed hepatic dysmorphism. The biliary tree was normal.

At day 0, alanine aminotransferase was 2430 IU/L (N < 45), aspartate aminotransferase 1822 IU/L (N < 35), total bilirubin 215 µmol/L (N < 20), gamma glutamyltransferase 58 IU/L (N < 55). The patient developed hepatic failure with a prothrombin index of 36% and factor V 41%. No bacterial infection was detected in ascites. HBV DNA was below 100 IU/mL. Anti hepatitis Delta virus antibodies were negative. The patient was immunized against hepatitis A virus, herpes simplex virus, Cytomegalovirus and Epstein Barr Virus. Tests for autoimmune hepatitis were negative (negative for anti Nuclear, anti Liver Kidney Microsomal type 1, anti smooth muscle antibodies). Dosing for paracetamol was negative, ceruleoplasmin was normal. The second line of etiological factors led to investigate hepatitis E markers.

The serum sample collected at the onset of clinical signs (November 2008) was reactive against anti HEV IgG (EIAgen HEV IgG®, Adaltis, Optical density/Cut off [OD/CO] = 7) and IgM (EIAgen HEV IgM®, Adaltis, OD/CO = 11). HEV RNA was detected in both serum and stools [1]. Direct sequencing of 340 nucleotide fragments in the Open reading Frame 2 gene (Fr-118) identified a sub genotype 3f close to the genotype mainly involved in autochthonous hepatitis E in France and the European countries (Fig. 1). No professional or personal exposure (pork consumption, contact with wild reservoir) was reported.

One month later, the patient had stage I encephalopathy. Biological tests showed stabilization of cytolysis and worsening of jaundice (total bilirubin 748 µmol/L, conjugate bilirubin 585 µmol/L). Liver Function tests showed liver failure (prothrombin index 27%, factor V 25%). HEV RNA was not detected in stools at this time. The patient was placed on the list as a candidate for emergency liver transplantation because of the severity of HEV superinfection on hepatitis B cirrhosis.

Two months later after admission, clinical signs included worsening ascites, jaundice and encephalopathy with asters. After being transferred to the intensive care unit, biological tests showed hyponatremia at 126 mmol/L, creatinine level at 181 µmol/L, prothrombin index at 25%. HEV RNA was not found in serum and the sample collected at this time (Fig. 2). There was no bacterial superinfection in the ascites fluid. Symptomatic treatment with glypressin and albumin perfusion was begun. Three days later, the patient had a variceal haemorrhage. An initial endoscopy was performed with five oesophageal varice ligations. Six hours later, the patient had a new episode of bleeding. A second endoscopy revealed an active bleeding varice that could not be controlled by endoscopic treatment. Despite blood transfusions and noradrenaline, multiorgan failure occurred and the patient died. No liver biopsy was performed.

Discussion

In European countries, fulminant HEV has been described in a few indigenous cases involving patients with chronic liver
disease. In France, four cases of fatal HEV infection and two subfulminant HEV were diagnosed from 2003 to 2008 [2,3].

Different factors related to the host (patients) or virus (HEV) have been associated with acute liver failure. This includes alcoholic liver disease with consumption of over 40 g of alcohol per day [3], hepatitis C virus infection, hepatitis B virus infection, auto-immune hepatitis and coexistent Wilson’s disease.

Middle age and old age have been documented as a major prognostic marker of severe hepatitis and liver failure. A rate of 8—11% of fulminant hepatitis has been reported in HEV infected patients with a mean age of 65 in Europe and Japan [4]. This risk factor is probably correlated to factors of comorbidity and also makes patients unavailable for transplantable. Also, the outcome can be poor in immunsuppressed patients. Chronic HEV infection has been documented in 50 to 60% of solid organ transplant patients and bone marrow recipients in the industrialized countries [4]. In India, the mortality rate ranged from 4% with most deaths due to liver failure in pregnant women, to 70% in patients with chronic liver disease [4].

Pregnancy is considered to be a risk factor for hepatitis E associated acute liver failure in the developing countries. However, recent data have shown that the overall prognosis of acute liver failure did not seem to be worse compared to age-matched non-pregnant patients [5]. The prognosis was better if the delay between symptoms and admission was reduced and renal function was preserved or improved.

The role of genotype with the development of fulminant hepatitis E is questionable. Genotype 4 HEV was isolated from fulminant hepatitis in Japan although both genotypes 3 and 4 are present. In Europe, HEV isolates associated with acute liver failure belonged to genotype 3f and genotype 1 was the only genotype found in Indian patients [4]. It has also been suggested that mutations located in the coding regions RNA for helicase and the capsid were also associated with the development of fulminant hepatitis but more samples should be tested. In the present study, this analysis was not performed because the sequences of amplicons were located in another HEV region. The influence of viral load has not been evaluated in any studies because of the lack of international standard for HEV.

Finally, the mechanisms of HEV associated fulminant hepatitis have not been clearly elucidated although hepatocytes are the main target of HEV infection. However, other replicative sites have been documented in model experimental infection.

In conclusion, acute sporadic hepatitis E may develop with encephalopathy. Different host factors (such as underlying chronic liver disease, age, pregnancy, coadministration of other hepatotoxic drugs) or HEV (such as genotype and mutation location) have been associated with acute liver failure.

Conflict of interest statement

None.

References


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Progressive multifocal leukoencephalopathy in a patient with alcoholic cirrhosis

Leucoénphalopathie multifocale progressive chez un patient ayant une cirrhose alcoolique

Progressive multifocal leukoencephalopathy is a central nervous system infection caused by JC virus, a DNA virus from the polyomavirus family, resulting in demyelination and significant neurological disorders. It occurs in immunodeficient patients affected by any process, which decreases cellular immunity. The diagnosis can be made with cranial magnetic resonance imaging (MRI) and by detection of JC virus DNA in cerebrospinal fluid with polymerase chain reaction (PCR). The prognosis is usually poor. We report the first published case of progressive multifocal leukoencephalopathy in a patient with cirrhosis.

Case report

A 51-year-old man was admitted to our unit in October 2008 because of progressive right-sided weakness, dysarthria and gait instability. This patient had been followed for alcoholic cirrhosis for 8 years. His medical history included three hospitalizations for tense ascites in the past year. The most recent episode in September 2008 was triggered by spontaneous bacterial peritonitis. He was not on waiting list for liver transplantation at admission because he was still actively consuming alcohol. Corticosteroids were not administered in the absence of proven severe acute alcoholic hepatitis. The patient had never been diagnosed with hepatic encephalopathy. He belonged to Child C class.

The patient’s current medications associated norfloxacin and spironolactone. Alcohol had been discontinued since the last hospitalization 5 weeks before. There was no illegal drug use and the patient had not travelled recently. Clinical examination showed dysarthria related to a central right-sided facial droop and right hemiparesia.

Cranial computed tomography (CT)-scan was performed and showed a hypointense lesion in the left subcortical frontal white matter, extending from the left centrum semiovale to the left external capsula. No mass effect was observed. Cranial MRI confirmed the presence of a single lesion, which was hypointense on diffusion-weighted images, hyperintense on T2-weighted images and hypointense on T1-weighted images, with no contrast enhancement after gadolinium administration (Fig. 1). This lesion was strictly limited to the white matter suggesting an old cerebral infarct, a brain tumor or a demyelinating disease.

Blood test results were as follows: haemoglobin 10 g/dL, platelet count 45 000/mm³, and lymphocyte count 456/mm³. Child-Pugh score was C13 with a prothrombin index at 37%, serum albumin at 26 g/L and serum bilirubin at 133 µmol/L. There was no renal failure or inflammation. Liver tests included: gamma glutamyltransferase 71 IU/L (N < 60), aspartate aminotransferase 90 IU/L (N < 240), alanine aminotransferase 42 IU/L (N < 45), alkaline phosphatases 146 IU/L (N < 240).

In the next few weeks, the patient’s deficit fluctuated considerably. Several electroencephalograms were performed during that period but did not confirm either seizure or metabolic encephalopathy. One week later, the right side motor deficit and aphasia worsened. A second cranial MRI study showed that the left frontal lesion had the same magnetic properties but had grown extending through the splenium of the corpus callosum to the right side parietal white matter (Fig. 2). Spectrometry showed an increase in choline to creatinine ratio, a decrease in the N-acetyl-aspartate peak and a lactate doublet. Perfusion sequences suggested an increase in neoangiogenesis. Lumbar puncture yielded clear, colorless cerebrospinal fluid with a normal cell count. The glucose level was normal and total protein levels were 0.56 g/L (N: 0.18–0.53). PCR analysis showed the JC virus in the cerebrospinal fluid. Blood sample analysis confirmed lymphopenia with only 132 CD4+ (N: 500—1200) and 100 CD8+ (N: 230–900) lymphocytes. Antibodies against HIV, hepatitis B virus and hepatitis C virus were all negative. Chest and abdominal CT-scan did not show any tumors or abnormal lymph nodes excluding any underlying solid tumour or lymphoma. Based on these results progressive multifocal leuoencephalopathy was diagnosed linked to immunosupression secondary to alcoholic cirrhosis. The patient died 70 days later.

Discussion

Progressive multifocal leukoencephalopathy is a severe demyelinating disease of the central nervous system caused by reactivation of the polyomavirus JC, which affects immunosuppressed individuals. Asymptomatic seroconver-