Hepatitis E Induced „Acute-On-Chronic” Liver Failure - Do We Transplant or Not?

„Acute-on-chronic” zatajenje jetre uzrokovano hepatitis E virusnom infekcijom - transplantirati ili ne?

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Abstract

Hepatitis E virus is a pathogen of worldwide significance. In developed countries, foodborne transmission of zoonotic genotypes is the most common route of infection. Transfusion transmitted infection is also an important source of infection, particularly in immunocompromised population. In most cases, HEV infection is asymptomatic or presents as an acute self-limiting hepatitis. Rarely it leads to fulminant hepatitis or „acute-on-chronic” liver failure in people with pre-existing chronic liver diseases. The aim of this report is to present the first documented case of HEV-related „acute-on-chronic” liver failure in Croatia in a patient with chronic liver disease listed for liver transplantation. Due to increasing incidence in industrialised countries, HEV infection should always be considered in the differential diagnosis of acute hepatitis and in patients with unexplained worsening of chronic liver disease.

Keywords:
hepatitis E
acute-on-chronic
liver transplantation

Introduction

Hepatitis E has a substantial impact on human health affecting 3 million patients and causing 70,000 deaths annually worldwide[1]. In developed countries, the most common route of infection is foodborne transmission of zoonotic genotypes (G 3 and 4) caused by consumption of raw and undercooked meat, and transfusion, which is important source of infection in immunocompromised population[2].

In most cases, HEV infection is asymptomatic or presents as an acute self-limiting hepatitis, rarely leading to fulminant hepatitis or „acute-on-chronic” liver failure (ACLF) in people with pre-existing chronic liver diseases (CLD)[3].

In the European general population HEV seroprevalence rate ranges from 0.6% to 86.4% with the highest prevalence reported in Arie’ge in France, while the incidence of an acute infection ranges from 0.2% to 3.2%[4]. However, the data on impact of acute HEV infection on the prognosis and survival of pre-existing CLD patients in Europe is limited[6-9].

We report the first documented case of HEV induced ACLF in Croatia in a patient with previously undiagnosed chronic liver disease.
Case report

A 67-year-old man with one-week history of fever and diarrhoea was admitted to the hospital. He had unremarkable medical history except for asymptomatic cholelithiasis and arrhythmia under good control with atenolol. He denied taking any drugs or herbal medicine, and he drank no more than two glasses of wine per day. A month before the onset of his symptoms, he travelled to Sicily.

After admission, his liver function rapidly deteriorated with worsening liver function tests, as indicated by rising bilirubin (total bilirubin 130 μmol/L), elevated transaminases (AST 3010 U/L, ALT 4000 U/L) and worsening coagulopathy (INR 3.1). Infectious work up was negative for hepatitis A, B, C, human immunodeficiency virus, cytomegalovirus, and herpes simplex virus and positive for previous EBV infection. Blood, urine and bacterial stool culture were negative as were Clostridium difficile antigen and toxins in stool. Deniga virus, enteroviruses, leptospirosis, adenoviruses and Coxiella burnetii, as well as autoimmune liver panel (antinuclear antibody, anti-smooth muscle antibody and anti-LKM) all tested negative.

Due to progressive deterioration of liver function the patient was urgently transferred to the Liver Transplant Centre. Abdominal ultrasound showed enlarged liver without focal lesions, normal bile ducts and normal hepatic blood vessels. Liver biopsy revealed acute hepatitis of unknown aetiology, non-specific chronic inflammation without severe necrosis but with marked microvesicular steatosis (with foaming of hepatocytes). The patient was transferred from the medical ward into the Intensive care unit (ICU) due to deterioration. Over the next few days he developed hepatic encephalopathy (grade III to IV) and required invasive mechanical ventilation. The Multislice Computed Tomography scan of the head excluded pathological intracranial processes and he was listed for liver transplantation with MELD score of 34.

His anti-HEV IgM and IgG resulted positive and the antiviral treatment with ribavirin (8mg/kg) was started, pending PCR analysis results. Since PCR HEV RNA resulted negative six days into treatment, ribavirin was discontinued. Management of critically ill patient consisted of respiratory support, parenteral antibiotics (cefuroxime and metronidazole), L-ornithine-L-aspartate, intensive insulin therapy, mechanical and pharmacological thromboprophylaxis, stress ulcer prophylaxis and enteral feeding. Intensive care therapy and supportive treatment resulted in the improvement of the liver function (AST 185 U/L; ALT 361 U/L, total bilirubin 127 μmol/L, INR1.6, V factor 0.7%). Three months after discharge from the hospital, the patient was well, without signs of liver disease and his liver function tests were normal. Furthermore, non-invasive evaluation of liver fibrosis was performed by implementing transient elastography with a median liver stiffness of 7.5 kPa indicating stage F2 fibrosis. Finally, he was removed from the liver transplant waiting list.

Discussion

This is the first documented case of HEV induced ACLF in Croatia, with severe clinical course which made him a candidate for liver transplantation. The vast majority of patients with HEV infection have favourable outcome and they rarely present with symptoms of acute hepatitis or with extrahepatic manifestations\(^6\). In contrast to several reports of HEV genotype 1 and 2 induced ACLF in Asia and Africa, the burden and prognosis of HEV genotypes 3 and 4 in developed countries is unknown. Available data indicate that some cases of severe liver injury with adverse outcome among CLD patients in Europe is related to autochthonous hepatitis E.

The first documented report of liver decompensation in cirrhotic patients with fatal outcome due to HEV infection was published in UK in 2007 by Dalton et al.\(^6\). Another study published in the same year in France described seven patients with fulminant liver failure due to HEV genotype 3 infection\(^2\). Six of them had CLD. Data from Switzerland reported severe clinical course in two patients with CLD and symptomatic acute HEV with fatal outcome\(^8\). However, a more recent large-scale study form the UK and France by Blasco-Perrin et al. found only minor (3,2%), predominantly in south-west France, number of HEV cases among 343 patients with decompensated CLD indicating it is an uncommon cause of liver decompensation. Moreover, mortality was estimated to be 27% and was not significantly different compared to patients without hepatitis E infection\(^9\). The incidence of HEV as a cause of decompensation in CLD patients considerably varies geographically and probably also changes over time, as a reflection of the amount of circulating virus in a given population at a given time.

In the presented case, risk factors for acute deterioration of liver function were male gender, age and underlying chronic liver disease considering liver histology which has shown nonspecific chronic inflammation with marked microvesicular steatosis (with foaming of hepatocytes) and FibroScan measurement indicating stage F2 fibrosis. Given the patient's medical data about his drinking habits and limited interpretation of histology in the setting of aetiology of underlying liver disease, it is very difficult to distinguish NAFLD from alcohol related CLD. In terms of making preliminary
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In conclusion, since HEV infection could be associated with significant morbidity and mortality, it is crucial to perform testing in all patients with symptoms consistent with acute hepatitis and patients with unexplained flares of chronic liver disease. Higher awareness of HEV in a differential diagnosis could reduce the number of cases of cryptogenic liver injury.

**REFERENCES**

[1] Murali AR, Kotwal V, Chawla S. Chronic hepatitis E: A brief review. World J Hepatol 2015; 7:2194–2201.

[2] Pavio N, Meng X-J, Doceul V. Zoonotic origin of hepatitis E. Curr Opin Virol 2015; 10:34–41.

[3] European Association for the Study of the Liver. EASL Clinical Practice Guidelines on hepatitis E virus infection. J Hepatol 2018; 68(6):1256-1271.

[4] Mansuy JM, Gallian P, Dimeglio C, et al. A nationwide survey of hepatitis E viral infection in French blood donors. Hepatology. 2016; 63(4):1145-54.

[5] Dalton HR, Hazeldine S, Banks M, Ijaz S, Bendall R. Locally acquired hepatitis E in chronic liver disease. Lancet. 2007; 369(9569):1260.

[6] Péron JM, Bureau C, Poirson H, et al. Fulminant liver failure from acute autochthonous hepatitis E in France: description of seven patients with acute hepatitis E and encephalopathy. J Viral Hepat. 2007; 14(5):298-303.

[7] Fraga M, Doerig C, Moulin H, et al. Hepatitis E virus as a cause of acute hepatitis acquired in Switzerland. Liver Int. 2018; 38(4):619-626

[8] Blasco-Perrin H, Madden RG, Stanley A, et al. Hepatitis E virus in patients with decompensated chronic liver disease: a prospective UK/French study. Aliment Pharmacol Ther. 2015; 42(5):574-81

[9] Peron JM, Dalton HR, Izopet J, Kamar N. Acute autochthonous hepatitis E in western patients with underlying chronic liver disease: a role for ribavirin? J Hepatol 2011; 54:1323–1324.